# Production, Quality Control and Clinical Applications of Radiosynovectomy Agents

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# PRODUCTION, QUALITY CONTROL AND CLINICAL APPLICATIONS OF RADIOSYNOVECTOMY AGENTS

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# PRODUCTION, QUALITY CONTROL AND CLINICAL APPLICATIONS OF RADIOSYNOVECTOMY AGENTS

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# FOREWORD

Therapeutic radiopharmaceuticals play a major role in today's nuclear medicine, especially in the treatment of cancer. They have long been applied in 'radiation synovectomy', or, more briefly, 'radiosynovectomy' (RSV). In recent decades, the production and quality control of radiopharmaceuticals for use in RSV has moved from simple $^{32}$P colloids to recently developed matrixes labelled with short and medium range beta emitters. RSV is a well established technique with growing applications worldwide. However, the lack of generic and peer reviewed production, quality control and clinical application guidelines and recommendations is a major concern for their application in human patients.

Given both the IAEA's global efforts in supporting Member States in the application of nuclear techniques in radiopharmacy and health and several requests from Member States as well as professional societies in recent years, the need for an IAEA technical publication on the subject became apparent. Currently, there is a lack of international standardized regulations for RSV production and clinical use. This publication is intended for professionals in the field. It outlines ideal quality control and quality assurance procedures in the production of several radiopharmaceuticals for performing RSV, as well as the standard operating procedures needed to achieve successful therapeutic effects in patients.

# CONTENTS

# 1. INTRODUCTION

## 1.1. BACKGROUND

Radiopharmaceuticals have had an incrementally positive impact in the health sector since the 1950s, especially in the diagnosis and treatment of diseases. In particular, radiation synovectomy, known more briefly as radiosynovectomy (RSV), has been used as an alternative minimally invasive treatment for joint inflammation. A common manifestation of this is rheumatoid arthritis, which, despite recent therapeutic advances, remains incurable. RSV has been used for over 50 years as an adjunct to conventional treatment (e.g. corticosteroids, arthroscopic synovectomy, arthrodesis) of refractory painful and disabling synovitis in patients with rheumatoid arthritis and other inflammatory synoviopathies, such as activated osteoarthritis and haemophilia. RSV is a local treatment with ionizing radiation involving the coupling of the right unsealed beta emitting radioisotope with a suitable colloid applied intra-articularly to irradiate the pathological superficial synovial membrane. A multidisciplinary approach involving rheumatologists, orthopaedists and nuclear medicine physicians, as well as a good understanding of the pathophysiology of synoviopathy, are essential for selecting the most appropriate treatment for individualized joints in order to optimize the result of this minimally invasive local therapy. Hence, RSV production and application ought to be handled and administered carefully, as there are several requirements to meet to deliver successful outcomes.

RSV response rates range from 60 to 80%, depending on the joints involved, any underlying disease and the stage of the disease. The best results are reported for haemophilic arthropathy with a response rate of approximately 90%. RSV is the preferred choice for the treatment of patients with refractory haemarthrosis in haemophilia [1–3]. Well designed double-blind trials have assessed the effectiveness of RSV as an alternative local treatment option for pain relief in patients with synovitis due to rheumatoid arthritis or other arthropathies that cause swollenness and inflammation [1]. RSV obtains comparable results to surgical synovectomies, and it is well tolerated, has few side effects, costs less, allows patients to be ambulatory, and can repeated and performed simultaneously in multiple joints [1]. The use of radiopharmaceuticals to treat RSV is well established and has a high rate of positive outcomes across different diseases and applications.

RSV radiopharmaceuticals are not commonly available globally because of production complications and difficult access to cost effective strategies. For example, $^{169}$Er is recommended for the treatment of finger and toe joints but is available in Europe only for patients with polyarthritis and is not available at all in many other parts of the world. Some countries in Latin America, the Middle East and Asia use alternative radionuclides, such as $^{188}$Re (obtained from a radioisotope generator), $^{177}$Lu and $^{153}$Sm, which differ from European recommendations, but yield good results, because of their availability and the cost of clinical studies. This publication has the potential to address the possible neglect or misuse of these radiopharmaceuticals. This creates an opportunity for the IAEA to provide guidance on international standards for the successful production and application of radiopharmaceuticals in RSV as well as a platform for scientific knowledge sharing for Member States and potential improvement of healthcare delivery.

## 1.2. OBJECTIVES

Because of the diverse applications of RSV and the new RSV radiopharmaceutical candidates entering the clinical field worldwide, this publication will present recommendations and suggestions for quality control and quality assurance procedures for the Member State laboratories in charge of radiopharmaceutical production, with a new look at the latest RSV agents. It also provides proposed standard operating procedures for RSV application in patients. This publication aims to create an

international standard for both newcomers in the field and those currently working in the field so that they have established and comparable levels of international regulations for successful practices.

Only limited companies worldwide produce these agents, and the required long distance transportation (which is affected by the short shelf life of radiopharmaceuticals due to their half-lives), together with the lack of commercial availability and high prices, have influenced some Member States to produce their own products according to their local capacities and regulations. This has presented a challenge for several reasons, including a lack of international guidelines on production and quality control, and a lack of resources and personnel to meet RSV standards. It is important to emphasize proper care and attention regarding production and administration, as well as to avoid negative consequences, such as radioactive leaks, secondary infection and inflammation.

## 1.3. SCOPE

The purpose of this publication is to provide a general overview on the following:

(a)     Evaluating appropriate patients for radiosynovectomy;
(b)     Understanding the pathophysiology of underlying diseases that cause synovitis;
(c)     Understanding RSV's mechanism of action and appropriate radiopharmaceuticals;
(d)     Providing appropriate facilities for performing RSV;
(e)     Preparing technical prerequisites and utensils for RSV;
(f)     Pre-therapeutic imaging;
(g)     Evaluating indications and contraindications of RSV;
(h)     Preparing patients about the procedure and any possible adverse effects;
(i)     Administering radiopharmaceuticals intra-articularly;
(j)     Notifying patients about post-radiosynovectomy procedures and instructions;
(k)     Following up with patients to monitor the treatment's effect;
(l)     Providing radiation protection.

## 1.4. STRUCTURE

This publication aims to help radiopharmaceutical production centres and nuclear medicine units to understand the background and standard operating procedures for production, quality control and clinical applications. The publication is divided into eight chapters. Section 1 explains the background, objective, scope and structure of this publication. Section 2 defines RSV and provides a history of its use in treating synovitis and five other diseases that affect the joints. Section 3 describes the conditions for selecting patients for the administration of RSV, including required actions, indications, contraindications and adverse effects. Section 4 specifies the characteristics of the radionuclides used in RSV. Section 5 covers production of radiopharmaceuticals using the mentioned radioisotopes. Section 6 explains four methods used in preparing particles for RSV: precipitation, emulsion, the sol-gel process and spray drying. Section 7 goes into more detail regarding regulatory and manufacturing issues, especially the required quality assurance, quality control and documentation procedures. Finally, Section 8 illustrates the implementation of processes for RSV, including examples of consent forms, diagnosis, facilities, patient preparations, utensils and post-RSV procedures. The two annexes contain a sample informed consent form and a medical questionnaire. This publication aims to include the most relevant aspects for the production procedures and clinical uses of RSV radiopharmaceuticals.

# 2.  RADIOSYNOVECTOMY IN THE TREATMENT OF SYNOVITIS

## 2.1.  DEFINITION

The original name, 'radio-synovi-orthesis', means restoration of the synovial membrane with radiation, and reflects the nature of this treatment exactly. RSV is a minimally invasive local treatment using nuclear particles (mainly beta emitting radioisotopes) embedded in a suitable colloid applied intra-articularly to treat the inflamed synovial membrane.

The interest in continuation and practice of RSV is attributable primarily to the following factors [1, 3]:

— It is a local, alternative and minimally aggressive treatment option.
— It is generally performed on an outpatient basis though it might involve an overnight hospital stay.
— It is useful for all joints, including small and peripheral ones.
— It has a favourable cost–benefit ratio.
— It precludes the need for postoperative physical therapy to prevent and relieve joint stiffness associated with surgical synovectomy.
— It has a lack of surgical/anaesthetic risk.
— It provides an alternative treatment choice for inoperable patients.
— It has a recuperation period of minimal length and intensity.
— It requires only a low radiation dose for effective outcomes.
— It is possible to treat multiple joints concurrently by performing the procedure on an outpatient basis.
— It can be repeated after 6 months in case of failure.
— It is generally more reliable and quicker at deactivating the synovium than chemical synovectomy.
— It has minimal side effects.
— It offers satisfactory control of synovitis.

## 2.2.  HISTORY

Ishido first reported on irradiation ofe the synovial membrane to treat synovitis in animals in 1924 [4]. Fellinger and Schmid described the first use of radiation synovectomy treatments in the knee joints of patients with rheumatoid arthritis in 1952 [5]. In 1963, the first clinical study was performed to treat synovitis of the knee in patients with rheumatoid arthritis with colloidal $^{198}$Au [1, 6].

Today, $^{90}$Y, $^{186}$Re and $^{169}$Er are the most preferred beta emitter radioisotopes in Europe [7], and have been used for over 50 years for local treatment of refractory synovitis of non-responding individual joints after long term systemic pharmacotherapy and intra-articular steroid injections [8–17].

RSV is commonly recognized as a beneficial alternative to surgical synovectomy in treating rheumatoid arthritis and other inflammatory synoviopathies, such as osteoarthritis and haemophilic arthropathy [1, 3]. Ideally, it ought to be employed before radiological signs of joint destruction occur. However, it is unusual to have a referred patient in the clinic who has not previously been treated by a general physician, orthopaedist or rheumatologist, and most patients have already had symptoms for many months, despite prolonged conservative treatment, multiple applications of intra-articular corticosteroid, and in many cases, prosthetic surgery. In other words, RSV is unfortunately considered to be the option of last resort by musculoskeletal disease specialists. On the other hand, the increasing demand for this procedure is also a result of the ageing population worldwide, especially in European Union (EU) countries [18].

## 2.3. SYNOVIAL JOINTS

Before delving deeper into RSV, a brief discussion of synovial joints is relevant, since they provide the foundations for synovitis.

The skeletal system contains the following six different types of synovial joint [19]:

(1) The plane or intertarsal joints of the tarsal bones in the foot offer limited gliding movements. The most important intertarsal joints are the subtalar, the talocalcaneonavicular and the calcaneocuboid.
(2) The hinge (elbow) joint is between two bones and only allows movement along one axis for flexion or extension.
(3) The pivot joint (C1 to C2 vertebral joint) allows rotary movement around a single axis and some bending.
(4) The ellipsoid/condyloid joint (radius to carpal joint; wrist) is where the articular surface of one bone has an ovoid convexity sitting within an ellipsoidal cavity of the other bone that permits two planes of movement, and allows flexion, extension, adduction, abduction and circumduction.
(5) The saddle (base of the thumb) joint is where one of the bones forming the joint is shaped like a saddle with the other bone resting on it like a rider on a horse, which allows movement in the sagittal and frontal planes.
(6) The ball and socket (hip) joint is where the ball-shaped surface of one rounded bone fits into the cup-like depression of another bone to allow rotary motion in every direction within certain limits, and it is the most mobile of the synovial joints.

A schematic representation of the different types of synovial joints is provided in Fig. 1.
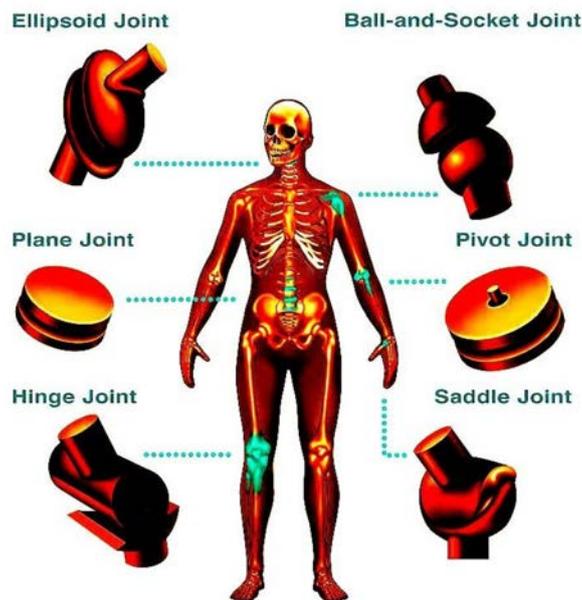


*FIG. 1. Types of synovial joint.[1]*

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[1] Figure 1 is available at https://fineartamerica.com/featured/human-joint-replacements-illustration-gwen-shockey.html

The internal structure of each of these joints is essentially the same, even though they vary in their number of ligaments and tendons and other specialized attributes. Each joint contains:

(a) An articular cartilage that allows smooth pain-free movement of the bones with very little friction.
(b) A synovial membrane, which is a layer of connective tissue that lines the cavities of the joint and joint cavity, filled with synovial fluid to provide lubricant for the joint to move smoothly and painlessly.
(c) Outside of their articulating surfaces, the bones are connected by ligaments made up of bundles of dense regular connective tissue that hold them in the joint together and help to restrict movement of that joint.
(d) Although not part of the structure of a joint, muscle tendons are the next layer around joints and may have a bursa (pad for cushioning) at key points of friction, providing the joint with free movement. Bursas reduce friction by separating the adjacent structures and preventing them from rubbing directly against each other.
(e) Some joints also have a meniscus consisting of elastic collagen fibre tissue to offer a cushion within the joint. The meniscus is also responsible for shock absorption and joint lubrication and provides stability of the entire joint. It is normally found in joints that bear large loads, such as the knee.

A schematic representation of a synovial joint is provided in Fig. 2.

## 2.4. SYNOVITIS

The joint capsule consists of an outer fibrous membrane and an inner synovial membrane that produces synovial fluid, which lubricates the joint during movement and supplies a vascular cartilage. The inner synovial membrane is essential for maintaining joint homeostasis [20]. The synovial membrane is a highly specialized, multifunctional structure consisting of an inner layer made up of intima, a thin (20 to 40 µm) but highly cellular lining containing synovial fibroblasts and synovial macrophages [20, 21], and an outer subintima layer (5 mm), containing loose connective tissue with fibroblasts. It is a rich network of sympathetic and sensory nerves, in which blood and lymphatic vasculature supply oxygen/nutrients and immune mediated response [22].

Synovial fibroblasts provide the extracellular matrix that supports the structure of the synovium and secrete hyaluronic acid and lubricin into the synovial fluid [20, 21]. Synovial tissue macrophages are constitutively resident in the healthy synovium. However, other immune cells, such as lymphocytes, mast cells and dendritic cells, are scarce in the normal synovium and are mainly localized in perivascular areas
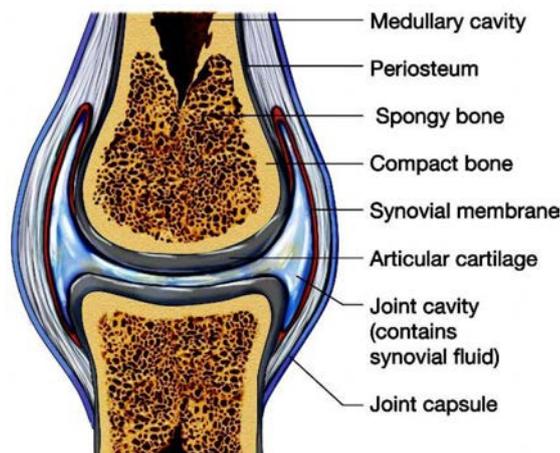


*FIG. 2. Schematic representation of a synovial joint. Reproduced with permission from Ref. [19].*

of the subintima [23]. In patients with rheumatoid arthritis, the synovial membrane becomes hypertrophic due to synovial fibroblast proliferation, increased blood–lymphatic vasculature and an inflammatory influx of immune cells from the circulation, resulting in the destruction of cartilage and bone, and pain and loss of joint function [24–26].

Histopathological analysis of the synovium in patients with osteoarthritis (OA) reveals abundant inflammation in the majority of cases [27]. While traditionally considered to be primarily a disease of hyaline cartilage with associated bone involvement, caused by overload or overuse, the pathophysiology of OA development is now known to be more complex. Mounting evidence suggests that synovitis and the resultant proinflammatory mediators are important in the pathogenesis of OA, with effects on articular cartilage [28, 29]. Recently, synovitis was reported to be a common feature of symptomatic and pre-radiographic OA criteria [30], indicating that chronic, early stage joint inflammation occurs well before significant radiographic changes.

In contrast, haemophilia is a bleeding disorder caused by a deficiency of clotting factor VIII [31]. Approximately 50% of patients suffer from severe haemophilia and bleeding, and without suitable treatment, the condition can become an irreversible haemarthropathy [32–36]. Bleeding in the joint may result in iron-mediated synoviopathy and irreversible haemarthropathy. Experimental joint bleeding is reported to cause progressive degenerative joint damage [34, 36].

The prerequisite for RSV response is a homogenous distribution of radiopharmaceuticals in the joint cavity, phagocytosis and radiopharmaceuticals retention to obtain the highest radiation dose for the synovialis by direct radiation or by a crossfire radiation effect [31]. Different colloid particle sizes have been suggested to be appropriate for RSV. Most studies in Europe performed on patients with rheumatoid arthritis have employed colloid sizes ranging between 2 and 10 $\mu$m based on the hypothesis that they need to be small enough to be engulfed by phagocytes and large enough not to leak rapidly from the joint [37]. In contrast, the preferred particle sizes for the colloids utilized to couple isotopes (in general $^{32}$P) for RSV to treat haemophilia in the United States of America (USA) are approximately 10 times larger.


## 2.5. RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic inflammatory autoimmune disease associated with multisystemic manifestations, characterized by persistent inflammatory synovitis of peripheral joints in symmetric distribution. It destroys diarthrodial or synovial joints, increases levels of disability, reduces quality of life and causes pain [38–41]. In addition, patients suffering from rheumatoid arthritis (RA) display a variety of other clinical features, such as pain, morning stiffness, weakness, fatigue, fever, weight loss and depression [20, 42, 43].

Rheumatoid arthritis is one of the most prevalent autoimmune diseases. The annual incidence of rheumatoid arthritis is estimated to be between 20 and 50 cases per 100 000 people in northern European countries [44]. Recent studies have suggested that more than 2 300 000 individuals have been diagnosed with rheumatoid arthritis in Europe [45]. The prevalence of rheumatoid arthritis varies by population, with Europe yielding prevalence rates of 0.32% in France and 0.83% in the UK [44], with somewhat larger prevalence rates of ~1% being reported for the USA [46]. Typically, females are affected approximately two to three times more often than males [46, 47]. Rheumatoid arthritis can develop at any age, but typically manifests between 40 and 70 years of age, peaking at 56 years in Germany [48].

Diagnosis is made by studying the patient's history and symptoms, and conducting joint examinations, blood tests and diagnostic imaging. However, a gradual onset of clinical symptoms is common in rheumatoid arthritis, and often contributes to a delay in referral and diagnosis [49].

Local and systemic drug treatment, physiotherapy and lifestyle changes are considered to be the primary treatments. In cases of persistent and refractory synovitis after non-invasive strategies, surgical, chemical, or radiation synovectomy may be an option.

Three main groups of drugs are used for the management of rheumatoid arthritis: painkillers, including non-steroidal anti-inflammatory drugs (NSAIDs); corticosteroids; and disease modifying

anti-rheumatic drugs (DMARDs) [50, 51]. Recent advances in rheumatoid arthritis therapies mainly target the mediators of inflammation (e.g. tumour necrosis factor (TNF), interleukin (IL-6R)) or block the adaptive immune response (e.g. T cell stimulation or B cell function). These treatments are expensive and have to be received continuously and permanently, with inadequate responses being observed in 30–50% of cases [52, 53]. In addition, half of responders will relapse within months of treatment cessation [22, 52, 53].

From 1951, the reduction of localized pain by using chemical synovectomy with intra-articular injection of several chemicals, such as thiotepa and osmic acid, has shown limited success rates [54–59]. In addition, massive haemorrhaging has been reported after chemo-synovectomy with osmic acid in haemophilic patients with recurrent haemarthrosis [60]. In contrast, open and surgical synovectomy to remove inflamed synovial membrane is reported to be successful in 40–90% of treated patients, with a remission time of several months up to more than 10 years [61–67].


## 2.6. OSTEOARTHRITIS

Osteoarthritis (OA) is the most common form of arthritis and a leading cause of disability worldwide, largely due to pain, the primary symptom of the disease. The aetiology of pain in osteoarthritis is recognized to be multifactorial [68], with both intra-articular and extra-articular risk factors and systemic and local biomechanical factors identified [69]. Nonetheless, greater insights into the pain mechanisms in osteoarthritis are required to enable rational mechanism based management of pain. The consequences of pain related to osteoarthritis contribute to a substantial socioeconomic burden.

People with OA typically experience joint pain, stiffness and swelling over long periods, resulting in progressive physical disability and pain. In the hip and knee, OA often causes progressive joint damage, with growing numbers requiring joint replacement surgery. Approximately 27 000 000 US adults and 8 500 000 UK adults are estimated to have clinical OA, based on symptoms and physical findings, accounting for 25% of visits to primary care physicians [70–72].

Symptomatic OA indicates the presence of both radiographic OA and symptoms (i.e. pain, aching, stiffness) in the same joint attributable to OA; as such, its prevalence is generally lower than that of radiographic OA. For example, the prevalence of radiographic knee OA was reported to be 19 and 28% among adults aged ≥45 years in the Framingham study and Johnston County Osteoarthritis Project, respectively, while the prevalence of symptomatic knee OA was 7% in the Framingham study and 17% in the Johnston County Osteoarthritis Project [73, 74]. "The prevalence of symptomatic knee OA in two UK studies ranged from 11–19%, and estimates of 5–15% were noted in surveys undertaken in other countries" [69, 75].

As a result of various degenerative knee diseases, approximately 25% of people over 45 years of age experience pain and other symptoms that may be severe and negatively affect their quality of life [72, 76]. Total knee arthroplasty is the only definitive therapy available but is reserved for patients with severe disease who fail conservative management. In the USA, arthroscopic knee surgery in people with degenerative knee disease is the most common ambulatory orthopaedic procedure, and is the ninth most commonly performed ambulatory procedure overall [77, 78]. Such surgery results in transient increase in pain and the necessity for restricted activity for a period of 2 to 12 weeks. Randomized clinical trials comparing arthroscopic surgery with a conservative management strategy in patients with degenerative knee disease revealed no benefits of arthroscopy as compared to conservative management [79]. The review of 13 randomized clinical trials and 12 observational studies included in this analysis identified high certainty evidence that knee arthroscopy results in a very small reduction in pain up to three months after the procedure (mean difference = 5.4 on a 100 point scale, 95% confidence interval (CI): 2.0–8.8) and very small or no pain reduction up to two years later (mean difference = 3.1, 95% CI: −0.2–6.4) when compared with conservative management [79]. With respect to function, the review identified with moderate certainty evidence that knee arthroscopy results in a very small improvement in the short term (mean difference = 4.9 on a 100 point scale, 95% CI: 1.5–8.4) and very small or no improved function up

to two years later (mean difference = 3.2, 95% CI: −0.5–6.8) [79]. Low certainty evidence suggested a very low probability of serious complications after knee arthroscopy. Recently, an expert panel made a strong recommendation against the use of arthroscopy in nearly all patients with degenerative knee disease [80].

Modern diagnostic modalities have confirmed the role of synovitis as an active component of the OA process, associated with both pain and structural progression, as noted by the following:

(a)  Clinical hallmarks of painful synovitis in patients with osteoarthritis such as effusion and swelling of joint [29, 81, 82];
(b)  Histologically observed synovial hypertrophy and hyperplasia [27, 83–87];
(c)  Increased periarticular perfusion and blood pool detected by three phase bone scan and contrast enhanced hypertrophic synovial membrane visualized by magnetic resonance imaging (MRI) [31, 88–95];
(d)  Production and release of pro-inflammatory cytokines; (TNF, IL-1$\beta$, IL-6, IL-8, IL-15, IL-17, IL-18, IL-21);
(e)  Response to anti-inflammatory therapy with intra-articular corticosteroids and RSV [1, 7, 96–102].

Thus, non-operative treatments directed at managing inflammation and future trials targeting the synovial tissue for treatment ought to consider pain and structural progression as potential inclusion criteria [30].

## 2.7. HAEMOPHILIA

Haemophilia is the most common bleeding disorder. Haemophilia is an X chromosome linked disease caused by mutation of clotting factor genes resulting in a deficiency of clotting factors VIII (haemophilia A) and IX (haemophilia B) [103]. The most common complication and primary morbidity of haemophilia is musculoskeletal bleeding, particularly in target joints [104]. Haemophilic patients, particularly those suffering from moderate to severe haemophilia, often experience serious joint involvement. Such a condition, called 'haemophilic arthropathy', is the result of a vicious circle that starts in the target joints as a response to the first episode of haemarthrosis, generally during childhood [105]. The presence of blood within the joint triggers the synovial tissue and induces direct damage to the cartilage [106]. The result is a progressive and irreversible arthropathy, which affects the bone early on and ultimately develops into a disabling and painful condition for the daily life activities of generally young subjects [107, 108]. Arthropathy involves mainly synovial joints, such as elbows, ankles and knees, and from a clinical point of view it may present differently according to the stage of the disease [109]. Inadequate replacement of factor VIII and IX, and lack of patient education regarding simple techniques (application of ice or ice packs, immobilization of affected joints, use of slings), physiotherapy and new therapy methods such as radiation synovectomy, have contributed to the fact that more than 50% of these patients suffer from physical disability and crippling arthropathy [110].

Haemophilic arthropathy in one or more joints, mainly the ankles, elbows and knees, affects about 90% of haemophilia patients by 20–30 years of age. Recurrent bleeding into joints (haemarthroses) results in progressive proliferative and degenerative articular changes. Regular factor replacement therapy of factor VIII and IX from an early age is key to prevent synovitis and haemophilic arthropathy and avoid these complications [111]. However, despite primary prophylaxis, some patients suffer from clinical bleeding due to an insufficient dosing regimen or non-adherence, while others may experience subclinical joint bleeding. Although the pathogenesis of haemophilic arthropathy is not fully understood [112], it is generally assumed that primary prophylaxis prevents bleeding and haemophilic arthropathy [107, 113].

A diagnosis of haemophilic synovitis is usually made following examination of a knee with typical signs of joint swelling and warmth but with or without painful symptoms and reductions in motion [111]. Ultrasonography can be used to demonstrate hypertrophy of the synovium and the presence of fluid [114].

Chronic haemophilic synovitis and cartilage destruction are the main findings for haemophilic arthropathy, with both phenomena occurring because of severe or recurrent haemarthroses. Experimental studies have also demonstrated that after a major haemarthrosis the joint cavity is filled with a dense inflammatory infiltrate, and the tissues become stained brown because of hemosiderin deposition following the breakdown of erythrocytes [115, 116]. Vascular hyperplasia takes place, resulting in tenuous and friable vessels prone to bleeding, creating a vicious cycle of bleeding–vascular hyperplasia–bleeding. The articular surface becomes rugose with pannus formation and the subchondral bone becomes dysmorphic. After about one month, erosion of both cartilage and bone is evident [111].

Loading of the affected joint with blood and blood breakdown products may play a role in the mechanism of cartilage degeneration in haemophilia, as shown in an experimental murine model, and blunt trauma injury causes joint inflammation, synovitis and haemophilic arthropathy [117, 118]. Molecular changes induced by iron in the blood are reported to increase cell proliferation in the synovial membrane, causing chronic inflammation of synovium.

The main therapeutic approach is to prevent articular damage, and this is achieved by controlling bleeding episodes, by factor replacement and by physiotherapy in the initial period. However, in cases with refractory chronic haemarthrosis, open surgical or arthroscopic options are used in addition to the non-surgical methods, using either chemical or radioisotope agents [119]. RSV is less invasive than surgical synovectomy because it requires minimal factor replacement prior to the procedure and it can be performed as an ambulatory procedure with a lower cost [1, 120–122]. Bleeding episodes and pain are significantly reduced following radiosynovectomy, and improvement in range of motion is noted [123–127].

## 2.8. PIGMENTED VILLONODULAR SYNOVITIS

Pigmented villonodular synovitis is a rare benign joint disorder characterized by a slowly progressive proliferation of synovial tissue and deposit of intracellular hemosiderin [14, 128]. The peak age of affected patients is the second and fourth decade of life, and the knee is the most frequently involved joint. Complete excision of the mass in the affected joint is the treatment of choice in the localized form. More common extensive diffuse cases are treated by total synovectomy; however, it is almost impossible to achieve complete remission. The main goal is to eradicate the synovial disease, while avoiding the need for joint replacement in this young patient population. RSV has been reported to be effective in reducing the rate of local recurrence without relevant joint destruction [129].

# 3. PATIENT SELECTION FOR RADIOSYNOVECTOMY

## 3.1. MECHANISM OF ACTION

RSV "is a local selective treatment with intra-articullar [sic] application of a proper unsealed beta-emitting radioisotope to irradiate a pathological synovial membrane that may be causing fibrosis and reducing joint effusion" [1]. The radiopharmaceuticals currently used for this purpose in Europe are mainly $^{90}$Y citrate (for the knee), $^{186}$Re sulphide (for shoulder and ankles), $^{169}$Er citrate (for interphalangeal joints) and $^{32}$P colloid (also for knee joints in many countries). The major indications are haemarthropathy in haemophilia, synovitis in rheumatoid arthritis and exudative OA [130, 131].

After the discovery of radioactivity by Henri Becquerel and Marie Curie, a number of radioisotopes, such as $^{131}$I, $^{32}$P, $^{90}$Sr and $^{90}$Y, were used to treat various malignancies and for pain management [132]. Since the first RSV performed by Fellinger using $^{198}$Au colloid, a large number of radioisotopes in different chemical forms have been utilized to find the ideal compound [5]. Today, RSV is developing

rapidly as an alternative treatment for synoviopathies with different underlying diseases. The low invasiveness of this procedure and relatively low level of complications in comparison with conventional surgical synovectomy make RSV an attractive and realistic alternative in the treatment of patients with refractory joint inflammation.

The major physical characteristics of radionuclide therapy include the physical half-life, types of emission, energy of the radiation, daughter product, method of production and radionuclide purity [133–135]. The biochemical aspects of ideal radiopharmaceuticals include in vivo stability, toxicity, target uptake, spatial and temporal distribution, retention, metabolism, clearance and excretion within the body [136, 137].

With a half-life ranging from 3 to 10 days, the commercially available radiopharmaceuticals used for RSV (Table 1) can continuously irradiate the synovial membrane for several weeks [138]. High energy $\beta^-$ emitters can ultimately cause damage to the absorbing cells of the synovial membrane, resulting in the ionization of the molecules inside the medium and the generation of secondary particles. The generated free radicals result in biochemical effects involving apoptosis and subsequent ablation by fibrosis and necrosis of inflamed synoviocytes in the synovial membrane [138]. Monte Carlo simulation has shown absorbed doses per unit activity of 0.01–2 Gy/MBq in the synovial membrane, resulting in an accumulated dose of up to 100 Gy, depending on the radionuclide and the disease state [13, 17, 139]. This process inhibits the progression of synovitis and diminishes the serious exudative inflammation of the joint [140].

Autoradiography after intra-articular application reveals that colloid particles labelled with beta emitting isotopes are incorporated and rapidly phagocytized by macrophages located in the inflamed intima layer of the synovial membrane [141]. In synovial biopsies, colloidal particles are abundant in vacuolar cavities in the cytoplasm of the cell lining [142]. The use of an appropriate radiopharmaceutical is essential to avoid significant leakage of the isotope from the joint cavity. Thus, a beta emitting isotope for RSV ought to be coupled to a particle that is small enough to be phagocytized and large enough to avoid leakage from the joint before being phagocytized; the appropriate size range is usually considered to be from 2–10 μm when phagocytized [143, 144]. Binding between radioisotopes and particles ought to be stable during the application of the RSV, which is determined by the physical and biological half-life of the radioisotope [1–3].

To achieve an optimal target/non-target ratio, the energy of the selected ß⁻ radiation ought to be high enough to reach the whole depth of the inflamed synovial membrane without damaging the adjacent cartilage or the subchondral bone tissue, as well as the skin. The radiopharmaceuticals used in RSV have very limited tissue penetration, depositing more than 90% of their energy within a maximum of 11 mm from the point of origin, thus almost exclusively affecting the joint cavity. Most of the radiation is absorbed by the synovium, synovial fluid, superficial layers of cartilage and articular capsule. Subchondral bone and other para-articular tissues receive negligible doses of radiation [145]. Appropriate energy for radiosynovectomy is provided by the commercially available radiocolloids (Table 1).

The mean and maximum penetration depths of $^{90}$Y $\beta^-$ rays are 3.6 and 11 mm, respectively. The penetration depths of $^{186}$Re $\beta^-$ rays are 1.2 and 3.7 mm, and those of $^{169}$Er $\beta^-$ rays are only 0.3 and 1.0 mm. Because of these penetration rates, $^{90}$Y colloid is used for RSV of the knee, $^{186}$Re colloid is used for medium sized joints such as shoulder, ankle, elbow, radiocarpal and hip joints, and $^{169}$Er colloid is used for finger and toe joints.

In the USA, gold $^{198}$Au, $^{32}$P chromic phosphate and $^{165}$Dy ferric hydroxide macroaggregate are the most used radiopharmaceuticals [1]. Since these radiopharmaceuticals have disadvantages with respect to high lymphatic transport, they are no longer included in the guidelines of the European Association of Nuclear Medicine and the German Society of Nuclear Medicine [60, 130, 146].

It is difficult to determine the exact amount of activity of any radionuclide needed to achieve a therapeutic response. The absorbed dose is not only dependent on the type of radionuclide and the amount of activity used, but also on various other factors, such as the type and size of the joint cavity, the underlying pathophysiology of the synovial membrane, synovial thickness, the distribution of colloids in the joint fluids and the inflammatory activity of the joint. Approximately 100 Gy per 100 g of synovial

tissue ought to be absorbed to have an optimal effect [1]. The standard radiopharmaceuticals used in the EU and the USA are listed in Table 1.

RSV is usually performed as an outpatient procedure and is minimally invasive compared to surgical synovectomy. After 48 hours, moderate rehabilitation enables for daily activity.

TABLE 1: RADIONUCLIDES USED TO TREAT JOINT PAIN

| Radionuclide (particle) | Vol. (mL) | Particles ($\mu$m) | Half-life (d) | $\beta$ max. energy (MeV) | $\beta$ particle penetration (mm) | Gamma energy (keV) | Activity (MBq) | Joint |
|---|---|---|---|---|---|---|---|---|
| Yttrium-90 (citrate) | <2 | 3–6 | 2.7 | 2.2 | 3.8–11 | n.a.[a] | 185–275 | Knee |
| Re-186 (colloid/ sulphide) | <1 | 5–10 | 3.7 | 1.07 | 1.2–3.7 | 140 | 110–185 | Shoulder |
| Er-169 (citrate) | <0.2 | 3–8 | 9.4 | 0.34 | 0.3–1.0 | n.a. | 9–18.5 | Proximal interphalangeal |
| P-32 (chromic) | 10 | 20 | 14 | 1.7 | 2.6–7.9 | n.a. | n.a. | Knee |
| Dy-165 (FHMA) | n.a. | 3–10 | 0.09 | 1.3 | 1.4–5.6 | 95 | n.a. | Knee |
| Re-188 (tin colloid) | 0.5 | n.a. | 0.7 | 2.12 / 1.96 | 11.0 | 155 | 370 | Proximal interphalangeal |
| Ho-166 (FHMA) | n.a. | 5–10 | 1.2 | 1.8 | 2.2–8.7 | 81 | n.a. | Knee |
| Sm-153 (particulate hydroxyapatite) | n.a. | n.a. | 1.9 | 0.67 / 0.81 | 2.5 | 103 | 218–840 | Knee |
| Au-198 (colloid) | n.a. | 2.7 | 0.96 | n.a. | 1.2–3.6 | 411 | n.a. | Knee |
| Lu-177 (particulate hydroxyapatite) | n.a. | 1.7 | 6.7 | 0.48 | 1.7 | 208 | 333 ± 46 | Elbow |
| Pd-109 | —[b] | — | 0.56 | 1.03 | 0.42 | n.a. | — | No human report |
| Yb-175 | — | — | 4.2 | 0.47 | n.a. | 396 | — | No human report |
| Sn-177m | — | — | 13.6 | 0.151 | 0.3 | 158.6 | — | No human report |

**Note:** The radionuclides depicted in Table 1 can be used for the treatment of joint pain arising from arthropathies, including RA, spondyloarthropathy, other inflammatory joint diseases (Lyme disease, Behçet's disease), persistent synovial effusion, haemophilic arthritis, calcium pyrophosphate dihydrate arthritis, pigmented villonodular synovitis and undifferentiated arthritis [1, 7, 131].

[a]   n.a.: not applicable.
[b]   —: data not available.

## 3.2. INDICATIONS

According to the guidelines for radiosynovectomy published by the German Society of Nuclear Medicine and the European Association of Nuclear Medicine, the major indications for RSV are rheumatoid arthritis, spondylarthropathy (e.g. reactive or psoriatic arthritis), other inflammatory joint diseases, e.g. Lyme disease, Behçet's disease, persistent synovial effusion, haemophilic arthritis, calcium pyrophosphate dihydrate, arthritis pigmented villonodular synovitis, persistent effusion after joint prosthesis and undifferentiated arthritis (where the arthritis is characterized by synovitis, synovial thickening or effusion). However, the common basic target among all the listed diseases making a patient eligible for RSV is synoviopathy, which is an inflammatory reaction of the synovial membrane. Indeed, RSV is not a systemic or specific treatment for any of the specified maladies and is not indicated as a first line of treatment. Thus, it can be concluded that RSV is a local therapy option in patients with refractory synovial inflammation.

Irrespective of the underlying disease, the higher the inflammation signs for synovitis, and the lower the degeneration signs for arthrosis, the more successful RSV appears to be [147]. Thus, the best results of intra-articular radionuclide therapy can be achieved at an early stage of synoviopathy, when systemic anti-rheumatoid therapy appears to be insufficient.

Indications for RSV in patients with refractory synoviopathy include [1]:

(a)    Haemarthropathy: haemophilia.
(b)    Arthritis:
    (i)    Rheumatoid arthritis;
    (ii)   Other accompanied inflammatory joint diseases, for example, Lyme disease, Behçet's disease, psoriatic arthritis, ankylosing spondylitis.
(c)    Exudative synoviopathy:
    (i)    Exudative osteoarthrosis;
    (ii)   Postoperative effusion.
(d)    Villonodular synovitis.

In addition, RSV is indicated for:

(a)    Relapsing synovitis after surgical synovitis;
(b)    Inoperable or multi-morbid patients with clinically relevant synovitis;
(c)    Patients who express a preference for it.

Assessments ought to be performed with respect to age, affected joint, stage of disease to estimate ratio of target/non-target (inflammation/degeneration) radiation, multi-morbidity and laboratory status. Good understanding of the pathophysiology of the disease and interdisciplinary collaboration for decision making is mandatory for individualized risk/benefit analysis and justification of treatment.

Ultrasound may be useful in cases of RSV for the shoulder joint because it provides information on abnormalities in and around the joint cavity, such as the presence and extent of effusion, rotator cuff rupture, bursitis subdeltoid, tenosynovitis and enthesitis. The success rate for RSV of olecranon bursitis is reported to be between 50 and 80%, depending on the localization and the amount of inflammatory activity [148–150]. In patients with bursal disease, RSV ought to be attempted on the basis of an individual treatment trial. The ß radiation is expected to affect the epithelium cells of the cysts, reducing effusion.

## 3.3. PATIENT PREFERENCE

Patient centredness has become increasingly important in healthcare delivery and is justified on both humane [151, 152] and medico-legal grounds [153]. Shared decision making is used when there is

no clear 'right' or 'wrong' treatment, as in cases of equivocal benefit or where there is uncertain evidence regarding benefit [154]. The physician and patient are considered to be equal partners who go through the process of decision making together, sharing information and preferences so that the patient is able to evaluate the trade-offs between the advantages and disadvantages of an alternative treatment [155, 156]. Thus, both jointly arrive at a consensus on treatment [157]. This is in contrast to other models, where decisions are made solely by the clinician (paternalistic model) [158] or solely by the patient (autonomous model) [159]. Physicians involved in the treatment of patients with persistent synovitis are committed to informing patients about alternative therapy options.

## 3.4. INDICATION FOR REPEATING RADIOSYNOVECTOMY

In contrast to surgical synovectomy, with surgical removal of the inflamed synovial membrane, radiosynoviorthesis aims to 'restore' the synovial membrane by irradiating the pathological superficial inflamed membrane. The protracted continuous irradiation of inflamed layers and restoration of the synovial membrane after radiosynovectomy is reported to occur after a period of six to eight weeks, and in some cases, it can be achieved up to six months after the treatment. To avoid any overtreatment, the results of RSV ought to be evaluated three to six months after the treatment. Fractionated RSV can be useful in cases with proliferating synovitis, for example, pigmented villonodular synovitis. However, cumulative activity ought not to exceed 14.8 GBq for $^{90}$Y.

Prompt response after RSV is less likely to be attributed to the radiation effect and most likely results from co-injected corticosteroids and/or immobilization of the joint, and this usually only lasts for a short duration. In contrast, temporarily increased signs of inflammation come from radiation synovitis and do not indicate unresponsiveness to RSV. Patients ought to be informed of the RSV healing process to avoid excessive expectations after prompt but short term healing. Radiation induced synovitis generally does not require medication or local intervention and can easily be alleviated by a cooling pad.

In cases of persistent radiation synovitis, the treated joint ought to be checked for any complications. It is preferable that the responsible nuclear physician perform and document an emergency aspiration biopsy in cases of severe acute synovitis with swelling of the joint [130, 131, 160, 161].

## 3.5. CONTRAINDICATIONS

According to the guidelines of the German Society of Nuclear Medicine and the European Association of Nuclear Medicine, in several cases RSV is absolutely and/or relatively contraindicated; thus, any decision to perform RSV ought to be made with caution. In cases of suspicious bacterial infection in the joint and infection or skin disease around the proposed injection site, RSV is absolutely contraindicated. Furthermore, in patients with highly advanced joint and bone destruction, and increased joint instability, radiation synovectomy is less likely to be successful. Also, lack of intra-articular retention may lead to lymphatic transport of the radiopharmaceutical, resulting in undesirable side effects.

In children and adolescents (patients younger than 20 years of age), the benefits of the treatment are considered to be greater than the potential hazards resulting from RSV [1]. However, lack of a calm attitude and non-compliance in children may result in leaking of the radiopharmaceutical from the joint after RSV. This may be the case in haemophiliac patients and some patients with severe juvenile rheumatoid arthritis.

Indication for RSV in the presence of a Baker's cyst is controversial. A Baker's cyst of the knee joint may be missed by clinical examination and would be ruptured due to radiation induced synovitis after RSV [162]. Thus, the presence of Baker's cyst ought to be clarified before performing RSV of the knee joint. The prevalence of a Baker's cyst among 980 cases of knee joints treated with RSV — assessed by arthrosonography — has been reported to be 25% [163]. A prominent Baker's cyst ought to be aspirated by ultrasound guided puncture following instillation of corticosteroids prior to radiosynovectomy. There

are reports on successful recovery from simultaneously presenting Baker's cysts after treatment of the knee joint [102]. However, direct puncture of a popliteal cyst ought to be avoided in these cases. In general, there is no indication for RSV of Baker's cysts alone.

Absolute contraindications for RSV include [1]:

(a)  Pregnancy;
(b)  Breastfeeding;
(c)  Ruptured Baker's cyst (knee);
(d)  Local skin infection;
(e)  Massive haemarthrosis;
(f)  Joint infection;
(g)  Shoulder rotator cuff defect.

Relative contraindications for RSV include [1]:

(a)  Patients younger than 20 years of age;
(b)  Evidence of significant cartilage loss;
(c)  Joint instability with bone destruction;
(d)  Bursal disease;
(e)  Post-RSV joint immobility not warranted after RSV.

## 3.6.  ADVERSE EFFECTS OF RADIOSYNOVECTOMY

In cases of proper joint puncture and impeccable intra-articular instillation of the radiopharmaceutical, side effects are rarely expected. Reactive radiation induced synovitis after RSV may cause transient increase of the swelling and pain within the first few days. These symptoms can easily be relieved by conventional measures and are reported to occur in up to 24% of patients treated with RSV [164]. However, other studies report lower frequency of side effects, and some report no local adverse reactions. A needle tract burn, which is a radiation burn of the needle tract caused by backflushing of the radioisotope is a rare adverse effect of RSV, sometimes resulting in a fistula [165].

Thrombosis and joint infection are two rare but serious adverse effects [166]. Extra-articular administration of radiopharmaceuticals leads to skin necrosis, especially when using $^{90}$Y. This is considered to be a serious but rare side effect, occurring at an estimated rate of less than 1:1000 [18]. It can also have an iatrogenic effect through extra-articular instillation or leakage of the radiopharmaceutical during injection; this can be avoided by radiographic guided application of the radiopharmaceutical.

Inappropriate application of higher activities or radioisotopes with higher energy (e.g. $^{90}$Y for the ankle joint) may also cause necrosis and is considered to be medical malpractice. The majority of post-therapeutic skin necrosis cases are, however, non-iatrogenic and caused by non-compliance of patients and premature mobilization of the treated joint. The quality of the radiopharmaceuticals may also cause necrosis due to degradation and/or diffusion of the radiopharmaceutical from the joint. Post-RSV skin necrosis merits special attention. Conservative treatment is highly recommended, accompanied by patience. Surgical excision ought to be avoided, since the radiogenic lesions show a delayed healing tendency. Wait and watch is recommended until the necrosis recedes by itself; however, a secondary infection ought to be prevented using ointment.

The high incidence of radiation induced skin reactions in radiotherapy has generated interest in methods of preventing and effectively treating such reactions [167]. Nevertheless, no general accord has been achieved across radiotherapy centres regarding the treatment of radiation skin toxicities.

The causes of necrosis are:

(a) Directly related to the administration of RSV owing to:
    (i) Extra-articular instillation of radiopharmaceuticals;
    (ii) Leakage in the injection channel through non-proper injection or multiple insertions of the needle by puncture;
    (iii) Higher activities than recommended;
    (iv) Radioisotopes with higher energy for smaller joints (e.g. $^{90}$Y instead of $^{186}$Re for the ankle joint).
(b) Indirectly related to the administration of RSV owing to:
    (i) Non-compliance of patients and premature mobilization of the treated joint;
    (ii) Degradation of the radiopharmaceutical;
    (iii) Extra-articular diffusion of the radiopharmaceutical.

Septic arthritis of the knee is one of the known complications of intra-articular corticosteroid injection. The incidence of septic arthritis of the knee after intra-articular corticosteroid injection ranges from 1 in 3000 to 1 in 50 000, and may be higher in immunocompromised patients [168]. In patients with RA undergoing long term immune suppressive treatment, the incidence of septic arthritis increases to 1 in 2000 within 3 months [169]. Skin is the most common source of infection in patients with RA, accounting for 75% of infections.

The treatment of iatrogenic septic arthritis requires multiple joint washout and debridement, long term antibiotic therapy and prolonged inpatient hospital stay. A higher rate of infectious complications following intra-articular injection can be expected in immunocompromised patients [170]. However, due to the extremely high local radiation dose of more than 100 Gy over the superficial layers of the inflamed synovial membrane, a pyarthrosis is less likely to occur after RSV [171].

Lymph node swelling and pain can be the result of insufficient immobilization and high extra-articular outflow of the beta emitter during the first 48 hours after RSV. For $^{186}$Re, an effective dose of 27 mSv was measured at an administered activity of 70 MBq. A total activity of 30 MBq $^{169}$Er resulted in an effective dose of less than 1mSv [172].

Cytogenetic analyses after radiosynovectomy with $^{90}$Y did not reveal any significant radiation doses for the peripheral lymphocytes in children with a high cancer risk [123]. The risk of malignancy remains theoretical, but there has been no report of cancer induced by RSV. There are no indications of increased incidence of cancer after radiosynovectomy in the literature [166, 173]. Animal studies revealed no histological or genetic damage to cartilage [174]. The rate of chromosomal aberration before (0.25%) and after (0.41%) RSV with $^{90}$Y colloid did not differ in studies published by Voth et al. and Vuorela et al. [164, 166], where no significant risk of cancer was observed among 143 patients treated with $^{90}$Y colloid as compared with 1085 patients in the control group.

In a German survey of 260 nuclear medicine physicians and 20 insurance companies between 1998 and 2003 (with a response rate of only 25.7%), only 53 severe complications were reported: 28 cases with skin necrosis, 13 intra-articular infections and 12 thromboses were reported [175]. The frequency of thrombosis can be reduced by anticoagulation during the period of immobilization.

The late effects of normal application have not yet been fully determined. Experimental animal data show some mild effects in the form of morphological changes to the cartilage, supported by in vitro cultured chondrocytes, after exposure to $^{90}$Y [176]. Changes to the cartilage after $^{90}$Y radiation could represent a factor predisposing the treated joint to a subsequent development of osteoarthrosis. Long term clinical trials are needed to evaluate this issue.

In the lower limb joints, long time immobilization of joints may cause deep vein thrombosis [37]. Inflammatory joints and long term corticosteroid treatment in patients with rheumatoid disease are risk factors for deep vein thrombosis. Thus, further anticoagulation therapy is strongly advised [177]. Post-RSV, low molecular weight heparin administered for 3–5 days may be sufficient for prophylaxis. However, there are no guidelines for anticoagulation therapy after RSV and any type of any duration ought to be managed by the responsible nuclear medicine physician. It ought to be noted that in patients

receiving oral anticoagulants, joint punctures do not increase the risk of bleeding and haemarthrosis [178]. RSV can be performed on an outpatient basis. The patient has to be informed about the RSV and the need for continuous treatment with DMARDs [37].

# 4. PRODUCTION OF RADIONUCLIDES REQUIRED FOR RADIOSYNOVECTOMY

## 4.1. INTRODUCTION

The production of radionuclides is not only the first step in the preparation of therapeutic radiopharmaceuticals, but also the cornerstone of the success and sustainable growth of radionuclide therapy [179]. Therapeutic radionuclides are produced through nuclear reactions either in a reactor or from charged particle bombardment in cyclotrons and accelerators. Depending on the production route, either no carrier added (NCA) or carrier added (CA) radionuclides are obtained. The reactor offers large volume for irradiation, simultaneous irradiation of several samples, economy of production and the ability to produce a wide variety of radioisotopes. Accelerator produced isotopes constitute a smaller percentage of total use. Accelerators are generally used to produce those isotopes that cannot be produced by reactors or have unique properties.

## 4.2. TARGETING

An important step in the production of radionuclides is the preparation of reactor samples and/or accelerator targets for irradiation. The targets used for neutron/charged particle activation constitute one of the most important aspects of the production of a desired radionuclide. The selection of a target for reactor irradiation is based on a number of considerations, such as the following [110]:

(a) Cost effective target material is essential to make the radionuclide more affordable.
(b) The target material ought to be sufficiently chemically pure.
(c) The chemical form of the target ought to be such that it remains stable under irradiation conditions, resists any physical or chemical change during irradiation and enables easy post-irradiation processing — usually targets in metallic forms or oxides are preferred.
(d) The physical or chemical form of the target material ought to be such that it contains as much as possible of the target nuclide in unit volume.
(e) It ought to be possible to handle the target material without any special precautions.
(f) The chemical form of the target material ought to be such that it contains those elements that will only produce negligibly small amounts of unwanted radionuclides, compared with the required nuclide during irradiation, or generate radioactive impurities that can easily be removed from the product.
(g) The physical form of the target ought to be compatible with reactor/accelerator irradiation.
(h) The purity of the targets has to be ensured to avoid the coproduction of unwanted radionuclides.
(i) While the use of enriched target materials constitutes a positive step to augment the production yield as well as the specific activity (SA) of radionuclides recycling of the enriched target is essential, wherever feasible, to make the radionuclides cost effective.

With a view to ensuring the safety of the reactor/accelerator, calculation of the reactivity effects, nuclear heating effects and radioactivity produced in the target is necessary [2]. These data are also helpful for the safe handling and transport of the irradiated materials [2]. For neutron irradiation, the most

preferred targets are metals or inorganic salts, usually oxides, carbonates, nitrates or sulphates, but not halides. When the sample size for irradiation is large, self-shielding is essential.

For accelerator production, considerable effort is warranted when preparing the targets for charged particle irradiations. The chemical and mechanical designs of the targets are crucial because of the high rate of energy loss of charged particles in matter. In general, irradiation is performed in a vacuum; thus, irradiation of liquid and gas targets is more involved but surmountable. The target materials used for accelerator production ought to possess favourable thermal properties such as a high melting point or high boiling point and good heat transfer coefficients. It is necessary to provide a cooling system to dissipate the heat energy deposited in the target material during irradiation [180]. Additionally, the target ought to have adequate corrosion and radiation resistance. Solid targets in the form of thin foils or deposits on thin backing material with a thickness of ~0.1–5 mg/cm2 are generally preferred, but this depends on the rate of energy loss of the projectile passing through the target material [181]. Various methods have been developed for the preparation of accelerator targets, including evaporation, vacuum deposition, electrospraying, electrodeposition and molecular plating [179].

### 4.2.1. $^{198}$Au

The production route of $^{198}$Au is primarily based on neutron irradiation of $^{197}$Au targets by the $^{197}$Au(n,$\gamma$)$^{198}$Au reaction [182]. This direct (n,$\gamma$) activation route offers the prospect of producing $^{198}$Au of adequate SA owing to the very high thermal neutron capture cross-section (26 500 b). The use of a gold foil or metallic gold bead target is desirable due to their ability to remain stable under harsh irradiation conditions. The chemical processing of irradiation usually consists of dissolving irradiated targets in aqua regia (3:1 HCl/HNO$_3$), followed by evaporating them to near dryness and reconstituting them with dilute HCl (normally 0.05 M) to obtain H$^{198}$AuCl$_4$ in dilute HCl [182]. In order to reduce coproduction of $^{199}$Au as a result of a $^{198}$Au(n,$\gamma$)$^{199}$Au reaction, a short irradiation period is advised. In light of the perceived need to remove trace radionuclide impurities, the prospect of extracting $^{198}$AuCl$_4^-$ into an organic solvent that includes chloroform, dichloromethane, or ethyl acetate as its tetrabutyl ammonium salt, TBA(AuCl$_4$) is an effective strategy [183, 184].

### 4.2.2. $^{165}$Dy

$^{165}$Dy is produced by the nuclear reaction $^{164}$Dy (n,$\gamma$) $^{165}$Dy through the irradiation of either Sm$_2$O$_3$ or Sm(NO$_3$)$_3$ targets in a nuclear reactor, as seen in Fig. 3. Both natural and enriched $^{164}$Dy are used. The thermal neutron radiative capture cross-sections ($\sigma_{th}$) and epithermal neutron ($\sigma_{epith}$) values of $^{164}$Dy(n,$\gamma$)$^{165}$Dy process are 2400±200 barn and 932 barn, respectively [185].

Naturally occurring dysprosium comprises seven stable isotopes: $^{156}$Dy(0.056%), $^{158}$Dy(0.095%), $^{160}$Dy(2.329%), $^{161}$Dy(18.889%), $^{162}$Dy(25.475%), $^{163}$Dy(24.896%) and $^{164}$Dy(28.260%), with $^{164}$Dy being the most abundant. Neutron irradiation of a natural dysprosium target as a result of a (n,$\gamma$) nuclear reaction will produce radioactive isotopes such as $^{157}$Dy(T$_{1/2}$=8.14 h), $^{159}$Dy(T$_{1/2}$=144.4 d), $^{165}$Dy(T$_{1/2}$=2.334 h) and $^{166}$Dy(T$_{1/2}$=81.6 h). Owing to the low isotopic abundance of $^{158}$Dy and longer half-life of $^{159}$Dy, the production yield of $^{159}$Dy is not significant. Additionally, both$^{156}$Dy and$^{159}$Dy decay by electron capture mode and will not pose any problem as far as radiation dose burden is concerned.

Owing to the relatively high thermal ($\sigma_{th}$=3600 b) and epithermal ($\sigma_{epith}$=22000 b) neutron capture cross-sections of a $^{165}$Dy(n,$\gamma$)$^{166}$Dy reaction, a significant amount of $^{166}$Dy will be formed due to second neutron capture reaction [182]. Additionally, the availability of efficient chemical separation methods to remove $^{166}$Ho from macroscopic amounts of $^{166}$Dy is desirable [182]. By judicious optimizing neutron irradiation parameters, it is possible to minimize concomitant production of $^{166}$Dy.
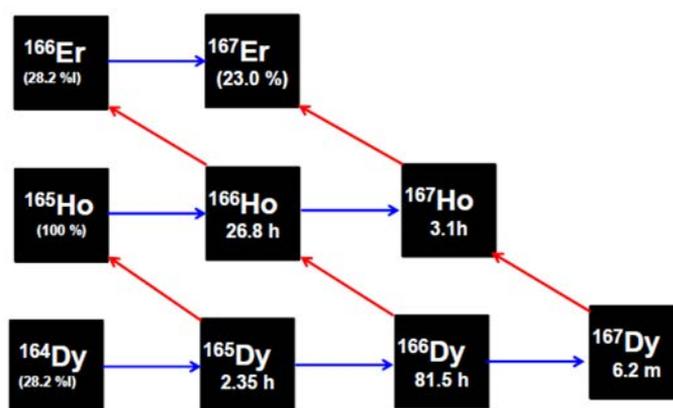
FIG. 3. Reactor production of $^{165}$Dy. Reproduced from Ref. [184].

### 4.2.3. $^{169}$Er

The 9.4 day half-life of $^{169}$Er is sufficiently long to offer easy transport to centres far from a reactor site [3]. $^{169}$Er could be produced by the nuclear reaction $^{168}$Er(n,$\gamma$)$^{169}$Er through irradiation of $^{168}$Er in a nuclear reactor. Naturally occurring erbium comprises six stable isotopes: $^{162}$Er(0.14%), $^{164}$Er(1.61%), $^{166}$Er(33.6%), $^{167}$Er(22.95%), $^{168}$Er(26.8%) and $^{170}$Er(14.9%) [186]. The use of natural erbium target to produce $^{169}$Er following direct (n,$\gamma$) activation results in concomitant production of $^{165}$Er and $^{171}$Er. In this context, the use of an isotopically enriched $^{168}$Er target is not only an interesting prospect, but also necessary to mitigate such disadvantages [182].

The low neutron capture cross-section of $^{168}$Er ($\sigma$=1.95 b) results in the production of $^{169}$Er of low SA, which can be circumvented by target irradiation at higher possible flux [182]. Although the use of an isotopically enriched $^{168}$Er target can provide $^{169}$Er of acceptable SA for the preparation of RSV agents, concomitant production of $^{169}$Yb (T$_{1/2}$=32 d) due to the presence of $^{168}$Yb impurity during the enrichment process of $^{168}$Er constitutes a roadblock and needs to be addressed [182].

During the enrichment process of $^{168}$Er, the level of $^{168}$Yb in the target increases, which, on activation, leads to concomitant production of $^{169}$Yb due to the very high thermal neutron capture cross-section (2300 b) of $^{168}$Yb. $^{169}$Yb with a half-life of 32.026 days decays by the electron capture route (100%) followed by the emission of high abundance gamma photons (E$\gamma$=177 keV (22.5%), 197 keV (35.9%)) to stable $^{169}$Tm. The gamma photons emitted by $^{169}$Yb not only offer unnecessary dose to non-target organs, but also affect the dosimetric evaluation of the administered activity. Moreover, measurement of the activity of $^{169}$Er following gamma spectrometry is a problem as its lone low abundant gamma photon (110.5 keV) is masked by the same energy gamma peak emitted by $^{169}$Er of much higher abundance (14%). Therefore, complete removal of $^{169}$Yb prior to radiolabelling is not only necessary, but is also a major determinant for its utilization in RSV. A viable method for the reactor production of $^{169}$Er with acceptable SA that follows the electrochemical pathway has been developed and demonstrated. It is based on the mercury pool cathode to provide $^{169}$Er in a radionuclidically pure form that is suitable for radionuclide therapy [186].

### 4.2.4. $^{166}$Ho

$^{166}$Ho can be produced via a relatively easy route involving thermal neutron irradiation of $^{165}$Ho using a natural Ho$_2$O$_3$ (100% $^{165}$Ho) target in research reactors. It precludes the use of an enriched target and obviates the formation of radionuclide impurities by radiative capture during neutron activation. The high thermal neutron capture cross-section of $^{165}$Ho ($\sigma$=66 b) offers scope for the production of $^{166}$Ho of

adequate quantity and sufficient SA [3] for use in radiosynovectomy [187, 188, 189]. The dependence on neutron flux in the production of $^{166}$Ho is shown in Fig. 4.

A method has been reported for the production of high-SA $^{166}$Ho that exploits hot atom reactions through neutron irradiation of the organometallic compound tris(cyclopentadienyl)holmium $(C_5H_5)_3$Ho. A chemical separation method was developed to separate the recoil $^{166}$Ho from the irradiated compound [191].

Production of NCA $^{166}$Ho can be carried out following an alternative path. In this mode, $^{166}$Dy can be produced following a $^{164}$Dy(2n,$\gamma$) $^{166}$Dy reaction using an isotopically enriched $^{164}$Dy target, which then decays by $\beta^-$ emission to yield $^{166}$Ho [182]. While this indirect production route offers the potential to provide $^{166}$Ho of the highest possible specific activity, the requirement for elaborate radiochemical separation, as well as a purification procedure for the effective separation of micro amounts of $^{166}$Ho from macro amounts of the irradiated Dy target, is challenging. Owing to the relatively high thermal ($\sigma_{th}$=2731 b) and epithermal ($\sigma_{epith}$=932 b) neutron capture cross-sections of a $^{164}$Dy(n,$\gamma$)$^{165}$Dy reaction, a significant amount of $^{165}$Dy($T_{1/2}$=2.33h) will be formed. The relatively short half-life of $^{165}$Dy is not an impediment because of the high thermal ($\sigma_{th}$=3600 b) and epithermal($\sigma_{epith}$=22000 b) neutron capture cross-sections of a $^{165}$Dy(n,$\gamma$)$^{166}$Dy reaction [182]. It was possible to produce close to the theoretical yield of 44.4 GBq of $^{166}$Dy when 1 mg of enriched $^{164}$Dy was irradiated over 155 h at a thermal flux of $4 \times 10^{14}$ n·cm$^{-2}$·s$^{-1}$ and an epithermal flux of $1.6 \times 10^{13}$ n·cm$^{-2}$·s$^{-1}$ at the University of Missouri Research Reactor (MURR) [192].

The applicability of reversed phase ion exchange chromatographic methods for the separation of carrier-free $^{166}$Ho from milligram quantities of $^{164}$Dy$_2$O$_3$ irradiated targets has been reported using a metal-free high performance liquid chromatography (HPLC) system with Dowex AG 50WX12 or Aminex A5 cation exchangers and $\alpha$-hydroxy-isobutyric acid ($\alpha$-HIBA) as the eluent (0.085 M, pH=4.3, adjusted with NH$_4$OH). The Aminex A5 column gave a separation factor of $\sim10^3$ between Ho and Dy. Subsequent to the acidic destruction of the Ho–HIBA complex, Ho$^{3+}$ was further purified on a small cation exchange column from acidic chloride solutions [193]. A similar HPLC radiochemical separation method has also been reported using Aminex A7 ion exchanger resin and $\alpha$-HIBA as the mobile phase [194].
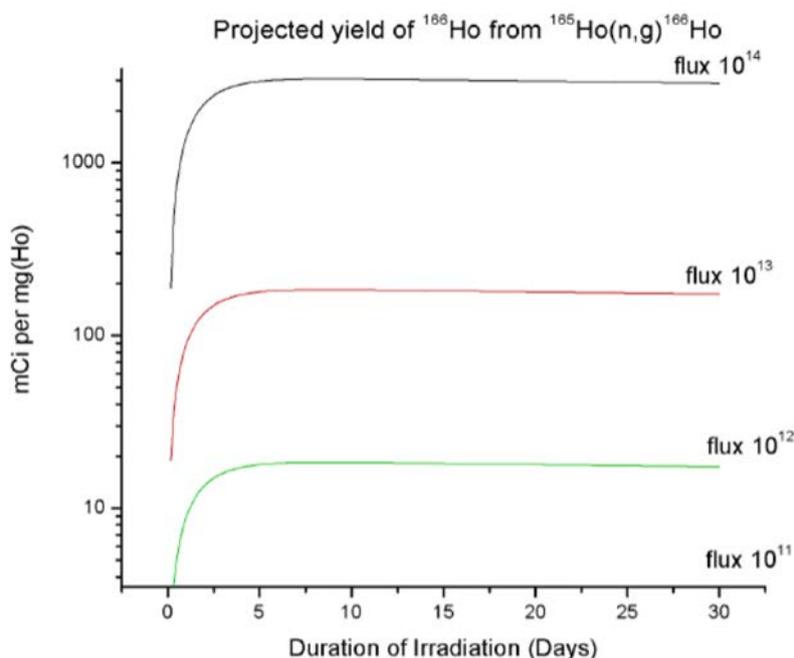


FIG. 4. *Variation of production yield of $^{166}$Ho at different neutron flux levels. Reproduced from Ref. [190].*

### 4.2.5. $^{177}$Lu

Both the 'direct' and 'indirect' reactor production routes are used to produce high-SA $^{177}$Lu [195]. The direct production route is based on neutron activation of highly enriched $^{176}$Lu targets following the $^{176}$Lu (n,γ) $^{177}$Lu reaction. The indirect production route consists of the irradiation of enriched $^{176}$Yb targets to produce $^{177}$Yb followed by β$^{-}$ decay to produce NCA $^{177}$Lu($^{176}$Yb(n,γ)$^{177}$Yb → $^{177}$Lu) [196, 197].

The radiochemical processing of neutron-irradiated targets in the direct production route is simple, comprising target dissolution where gentle warming is needed to dilute mineral acid. On the other hand, target processing in the indirect production route requires an elaborate radiochemical separation as well as a purification procedure to separate $^{177}$Lu from ytterbium [2]. The direct and indirect production routes for $^{177}$Lu are shown in Fig. 5.

The advantages of the direct production route include a simple irradiated target processing procedure, flexibility to tune the production scale without sacrificing efficiency and a cost effective route to obtain $^{177}$Lu of requisite purity. The necessity of using enriched $^{176}$Lu targets owing to the 2.6% abundance of natural $^{176}$Lu in the unenriched targets limits the concomitant production of $^{177m}$Lu. The presence of $^{77m}$Lu raised concerns about radiation protection and waste disposal problems in some countries [195]. A schematic diagram depicting the processing of a neutron irradiated $^{176}$Lu target to produce $^{177}$Lu is provided in Fig. 6.

The surge of interest in the use of $^{177}$Lu for a variety of therapeutic applications led to the widespread use of the (n,γ) method of $^{177}$Lu production [198–206].

The indirect production route offers the possibility of producing $^{177}$Lu with the highest SA that is free from long lived radioactive impurities and for which neutron flux is not a determining factor for SA [182]. The inherent limitations of the indirect production route include the fact that it has low production yields because of the reduced $^{176}$Yb reaction cross-section ($\sigma_{th}$=2.5 b) as compared with the direct production route ($\sigma_{th}$=2090 b), and it requires an elaborate radiochemical separation and purification procedure. It produces a substantial amount of radioactive waste [182] and is the most expensive method of producing $^{177}$Lu of acceptable purity. The surge of interest in obtaining NCA $^{177}$Lu led to the development of myriad radiochemical separation procedures by several groups [207–215]. Because of their chemical similarity, the separation of two neighbouring elements in the lanthanide group is not only challenging, but also demanding. In light of the perceived need to separate microscopic amounts of $^{177}$Lu from macroscopic amounts of ytterbium, every conceivable radiochemical separation strategy, including ion exchange
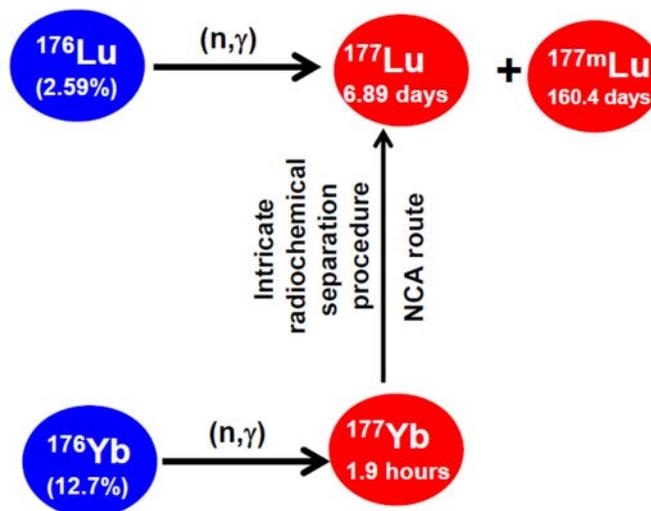


*FIG. 5. Two different production routes of $^{177}$Lu.*
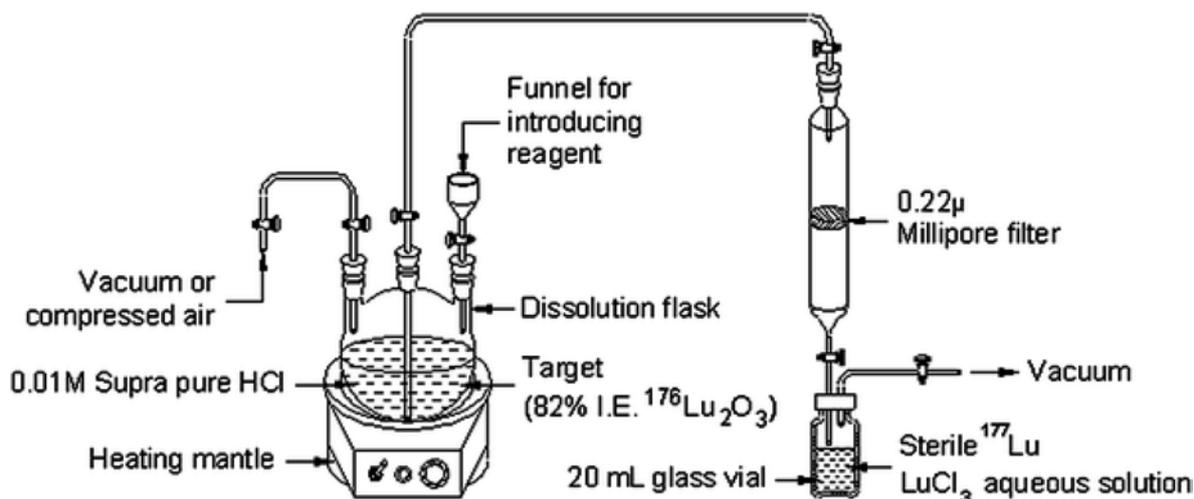
*FIG. 6. Processing of neutron irradiated target for $^{177}Lu$ production [202].*

chromatography, solvent extraction, supported liquid membrane extraction, extraction chromatography and the electrochemical method, has been exploited [192, 208–217].

### 4.2.6. $^{32}P$

$^{32}P$ can be produced in a reactor using one of three possible methods: $^{31}P(n,\gamma)^{32}P$, $^{32}S(n,p)^{32}P$ and $^{36}Cl(n,\alpha)^{32}P$. The $^{35}Cl(n,\alpha)^{32}P$ production method is not utilized in practice because of its low production yield. The remaining two options are widely used for large scale production of $^{32}P$ in a cost effective manner [218–226].

The neutron activation route of $^{32}P$ production following the $^{31}P(n,\gamma)^{32}P$ ($\sigma$=172 mb) nuclear reaction is less demanding, uses low cost natural elemental phosphorus ($^{31}P$) target material and involves a simple irradiated target processing procedure [182]. A thorough optimization of irradiation parameters and careful consideration of the target are essential to obtain $^{32}P$ with the required SA and yield [2, 195]. $^{32}P$ produced through this route is of low SA due to the low thermal neutron capture cross-section. Because of the small thermal neutron capture cross-section of $^{32}P$ for $^{32}P(n,\gamma)^{33}P$, the concomitant production of $^{33}P$ during target irradiation is insignificant. The indirect production route using the $^{32}S(n,p)^{32}P$ nuclear reaction offers the ability to produce NCA $^{32}P$. However, the low reaction cross-section (0.068b) and requirement to use fast neutron flux to produce appreciable active amounts constitute the major roadblock for its widespread use. In order to produce a few hundred MBq of $^{32}P$ using this method, several hundred grams of sulphur need to be irradiated. Even though the cross-section values for the $^{32}S(n,p)^{32}P$ nuclear reaction are much lower than for the $^{31}P(n,\gamma)^{32}P$ route, this method of production holds significant promise because of its ability to offer $^{32}P$ of higher possible SA [226]. Both the wet chemical extraction and dry distillation methods of radiochemical processing procedures can be followed to separate and purify $^{32}P$ from neutron irradiated S [221, 227–229]. The apparatus used to perform distillation generally entails a vacuum system, gas feeding apparatus and distillation assembly [223], and an appropriate strategy to control pressure and temperature [221–229].

### 4.2.7. $^{186}Re$

Both reactor and accelerator paths can produce $^{186}Re$. In a research reactor, $^{186}Re$ is produced by direct neutron activation of metallic enriched $^{185}Re$ following the $^{185}Re(n,\gamma)^{186}Re$ nuclear reaction [2]. The radiochemical processing consists of dissolving the irradiated target in 5–6 M $HNO_3$, evaporating the solution to incipient dryness and adding water to the reaction mixture. In order to ensure complete

elimination of $HNO_3$, it is recommended that the addition of water and the evaporation process be repeated four to five times with the [186]Re finally being taken up in water. This is the easiest way to obtain [186]Re of the required SA for RSV, because of the simplicity of dissolving the target in dilute mineral acid with gentle warming and of its extensive use [230, 231]. Due to the relatively large nuclear reaction cross-section (106 b), the yield of [186]Re is high and the SA is moderate. The SA and production yield of [186]Re are usually higher than those calculated because of the high epithermal neutron cross-section for [185]Re (1632 b), which usually depends on the neutron energy spectrum of the reactor.

In a typical process reported by Deutsch et al. [10], enriched (85.84%) [185]Re metal (1–2 mg) in a quartz vial was irradiated in a flux of $10^{14}$ n·cm$^{-2}$·s$^{-1}$ at the University of Missouri's research reactor for 24 hours. The rhenium metal was then dissolved in concentrated nitric acid and the resulting solution was neutralized with ammonia and then diluted to obtain an Re concentration of ~0.004 M [232]. The radioactive concentration of the resulting solution became 1.11 GBq/mL. Approximately 0.5 mL of 0.1 M tetrabutyl ammonium bromide (0.05 mmol) was added to aliquots (0.5–1.0 mL) of this solution and passed through a Sep-Pak C$_{18}$ cartridge (Waters) that had been prepared by successive washings with 3 mL of 95% ethanol and 3 mL of 0.01 M tetrabutyl ammonium bromide. The cartridge was washed with 20 mL of water to remove aqueous soluble impurities added during the dissolution of the irradiated target and [186]Re activity was eluted with a 99% yield with 2 mL of absolute ethanol [233]. The SA of [186]Re is produced by using a reactor such as MURR, with a thermal neutron flux of $4.5 \times 10^{14}$ n·cm$^{-2}$·s$^{-1}$, and is about 111 GBq/mg Re.

With a view to producing higher SA[186]Re, the Szilard–Chalmers process, which uses ReN(S$_2$CNEt$_2$)$_2$ rhenium (V) nitride complex as the target, has also been tried [234]. The chemical and/or physical changes to Re that result from a neutron capture reaction are exploited advantageously. The ~6 MeV of excitation gamma energy emitted by the rhenium nucleus after thermal neutron capture nuclear reaction (i.e. recoil energy) ruptures the organometallic bonds. In this method, neutron irradiated rhenium compound was dissolved in dichloromethane solution and the recoiled [186]Re rhenium was isolated from the irradiated rhenium compound by stripping with an aqueous solution. Using this method, it was possible to produce [186]Re with a SA of 0.72 GBq/mg Re (721.5 KBq/mg Re). On a similar theme, investigators at MURR used a target consisting of thin film and powdered [185]Re in the form of metal or oxide in which rhenium is present in a lower oxidation state [235]. Target irradiation was performed in the presence of an oxidizing medium sufficient to form [186]ReO$_4^-$. The radiochemical processing of the irradiated target consists of the dissolution of the target in a non-oxidizing solvent such as water or saline [234]. While the use of the Szilard–Chalmers process is a step forward in obtaining high-SA [186]Re, the time consuming radiochemical processing procedure, the requirement for extensive handling and processing of irradiated materials, the generation of unwanted by-products that need to be separated from the perrhenate and the low production yields limit its widescale use.

Taking into account the high-SA production of [186]Re, accelerator routes had be explored succeeding [186]W(p,n)[186]Re and [186]W(d,2n)[186]Re reactions [236–239]. Among the two nuclear reactions, the [186]W(p,n)[186]Re route is not commonly followed due to its poor reaction cross-section. In this context, the prospect of following the [186]W(d,2n)[186]Re reaction route is attractive because of the larger cross-section [236]. Post-irradiation radiochemical processing is carried out by dissolving the target in a mixture of 30% $H_2O_2$ and 1 M NaOH, followed by gentle heating. The recovery and recycling of expensive non-activated enriched [186]W target material are a necessity for cost effective production of [188]W [2, 195].

### 4.2.8.    [188]Re

Radionuclidically pure [188]Re can be prepared by irradiating highly enriched [187]Re target in research reactors. The corresponding nuclear reaction cross-section is 72 b. While the (n,γ) method of production using enriched [187]Re target leads to carrier added [88]Re, the SA is adequate for preparing radiopharmaceuticals useful for RSV; radiochemical processing of irradiated rhenium metal consisting of target dissolution with concentrated nitric acid; and neutralizing the resulting solution with ammonia followed by treating the neutralized solution, containing solubilized perrhenate, with a soluble lipophilic

counter ion, such as a solution of tetrabutyl ammonium bromide. The resulting solution is then passed through a Sep-Pak $C_{18}$ cartridge loaded with the lipophilic counter ion to retain both aqueous soluble impurities as well as $^{188}$Re. The aqueous soluble impurities from the Sep-Pak $C_{18}$ cartridge are eluted with water and subsequently the perrhenate or pertechnetate compound can be eluted from the column with a less polar solvent, such as ethanol [233]. While the (n,$\gamma$) method of production using enriched $^{187}$Re target is prolific in producing $^{188}$Re, the relatively short 16.9 hour physical half-life of $^{188}$Re emerged as a shortcoming for transport to sites away from the production site due to decay loss [195].

In view of this shortcoming, use of the $^{188}$W/$^{188}$Re generator that is prolific in producing $^{188}$Re may be viewed as a practical proposition. $^{188}$W can only be produced by double neutron capture with low neutron absorption cross-sections ($^{186}$W(n,$\gamma$)$^{187}$W ($\sigma$=37.9±0.6 b); $^{187}$W(n,$\gamma$)$^{188}$W ($\sigma$=64±10 b)) using an enriched $^{186}$W target. Since cross-sections have relatively low values (~$10^{-24}$ cm$^{-2}$), the production yields are low even when very high flux research reactors are used [240]. Similarly, the neutron flux is very important as the production yield is a function of the square of the flux ($\varphi$). Increasing the flux by only one order will make two order higher amounts of $^{188}$W activity. Hence, reactors with a flux of >5×$10^{14}$ n·cm$^{-2}$·s$^{-1}$ are only suitable for the production of $^{188}$W.

The natural abundance of $^{186}$W is 28.6% and enriched targets are essential for the production of sufficient $^{188}$W for generator use. By using enriched $^{186}$W targets, the SA of $^{188}$W is correspondingly augmented. Because of the long half-life of $^{188}$W, relatively long irradiation periods are required even for the production of $^{188}$W of modest SA using a high flux reactor [241]. An SA of up to 185 GBq (5 Ci)/g can be obtained by using enriched targets and following an irradiation cycle of ~20–24 days at $10^{15}$ n·cm$^{-2}$·s$^{-1}$. The current status of reactor production and processing of $^{188}$W is summarized in a chapter of IAEA Radioisotopes and Radiopharmaceuticals Series No. 2 [242]. As per this publication, $^{188}$W with an SA that is adequate for the production of $^{188}$W/$^{188}$Re generators can only be obtained in a limited number of research reactors: the BR2 reactor in Belgium; the SM Reactor (RIAR) in Dmitrovgrad, Russian Federation; and the High Flux Isotope Reactor (HFIR) at Oak Ridge National Laboratory (ORNL) in the USA. Enriched $^{186}$W in metal as well as oxide form is used for irradiation. At ORNL, 97% enriched $^{186}$W as the oxide sealed in quartz tubes enclosed in aluminium capsules is irradiated for one or two cycles of 23–24 days each at a neutron flux of approximately 2.5×$10^{15}$ n·cm$^{-2}$·s$^{-1}$ [243]. The production yields are substantially lower than the calculated values using reported cross-sections for different reactions taking place during irradiation. The loss of $^{188}$W due to neutron burnup, $^{188}$W(n, $\gamma$)$^{189}$W ($\sigma$=12 b), is one of the factors contributing to reduced production yields of $^{188}$W [244]. The sodium tungstate solution required for subsequent treatment for generator loading is produced by dissolving tungsten oxide in a sodium hydroxide solution with moderate heating [179].

Extensive efforts by investigators at ORNL in the mid-1980s culminated in the emergence of a $^{188}$W/$^{188}$Re generator system consisting of acidic alumina matrix analogous to the widely used $^{99}$Mo/$^{99m}$Tc generator [245–249]. Owing to the limited sorption capacity of alumina (maximum 50 mg W/g) [248], $^{188}$Re obtained from alumina based $^{188}$W/$^{188}$Re generators is of low radioactivity concentration, if low-SA $^{188}$W is used. This, in turn, would require post-elution concentration of the $^{188}$Re eluate [250–255]. The incredible prospects associated with the use of $^{188}$Re obtained from a radionuclide generator have been directed to the development of automated systems for the concentration of $^{188}$Re eluate [256, 257]. Over the years, different approaches such as those used with gel generators, electrochemical generators, thermo-chromatographic generators, chromatographic generators with high capacity adsorbents and nanomaterial based adsorbents have been explored, which in turn has opened up the prospect of using $^{188}$Re for RSV [179, 258].

## 4.2.9. $^{153}$Sm

$^{153}$Sm is produced by the nuclear reaction $^{152}$Sm(n,$\gamma$)$^{153}$Sm by irradiating either $Sm_2O_3$ or $Sm(NO_3)_3$ targets in a nuclear reactor. Both natural samarium and enriched $^{152}$Sm are used. Natural target will decay to long lived radionuclide impurities such as $^{145}$Sm ($T_{1/2}$=345 d), $^{151}$Sm ($T_{1/2}$=90 a) and $^{155}$Eu ($T_{1/2}$=4.76 a).

Chemical processing of neutron irradiated target is simple, concise and technically less challenging, as it is possible to dissolve the target in dilute hydrochloric acid with gentle warming [195]. Due to the large thermal neutron capture cross-section of $^{152}Sm(n,\gamma)^{153}Sm$ reaction (206 b), $^{153}Sm$ can be produced in large quantities and with an SA of 222 GBq/mg Re when irradiated at a flux of $1.2 \times 10^{14}$ n·cm$^{-2}$·s$^{-1}$ for approximately 155 h [110].

While the use of natural samarium as the target for the production of $^{153}Sm$ provides lower SA than an enriched $^{152}Sm$ target, it is adequate for the preparation of radiopharmaceuticals for synovectomy [195]. Neutron irradiation of natural samarium target results in concomitant production of long lived radionuclide impurities such as $^{145}Sm$ (T$_{1/2}$=345 d), $^{151}Sm$ (T$_{1/2}$=90 years) and $^{155}Eu$ (T$_{1/2}$=4.76 years) [182, 258]. $^{155}Eu$ can be separated from $^{145}Sm$, $^{151}Sm$ and $^{153}Sm$ using the ion exchange chromatography technique [259]. The radionuclide impurity burden can be effectively reduced by optimizing irradiation parameters such as irradiation time and neutron flux. Its burden ($^{145}Sm$ and $^{151}Sm$) will not be too high to preclude its use for RSV [258].

### 4.2.10. $^{117m}Sn$

$^{117m}Sn$ was prepared at optimized conditions in research reactors to achieve the maximum SA (~740 GBq/g). However, later produced $^{117m}Sn$ with an SA of ~37 TBq/g was thereby allowed for the essential step of labelling the targeting molecules used to treat a variety of life threatening diseases.

### 4.2.11. $^{90}Y$

$^{90}Y$ can be produced directly by neutron activation of $^{89}Y$ in a nuclear reactor. As $^{89}Y$ is mononuclidic, there is no need for enriched isotopes for irradiation. The radionuclide purity of this directly (n,$\gamma$) activated product is generally very high. However, depending on the epithermal flux in the reactor, detectable levels of $^{89}Sr$ could be present owing to the (n,p) reaction. Due to the poor neutron absorption cross-section ($\sigma_{th}$=0.001 b) of the $^{89}Y(n,\gamma)^{90}Y$ reaction, $^{90}Y$ obtained by following the (n,$\gamma$) production route is of low SA [260]. $^{90}Y$ of moderate SA can only be produced by irradiating the target in high flux reactors.

The reactor production route is possible for NCA $^{90}Y$ by following the $^{90}Zr(n,p)^{90}Y$ reaction, which requires 100% enriched $^{90}Zr$ target as well as fast neutron flux of $~7.5 \times 10^{13}$ n·cm$^{-2}$·s$^{-1}$ [261]. While it is possible to produce NCA $^{90}Y$ by pursuing this route, the accessibility of expensive enriched $^{90}Zr$ on a sustainable basis makes it difficult. The need for fast neutron flux, challenges associated with target design, isolation of microscopic amounts of $^{90}Y$ from macroscopic amounts of $^{90}Zr$ and the recovery of expensive $^{90}Zr$ target for recycling need to be addressed. Additionally, it is possible to produce limited quantities of NCA $^{90}Y$ by following this route.

In this context, accessing large amounts of NCA $^{90}Y$ from a $^{90}Sr/^{90}Y$ generator seemed an attractive possibility [2]. As one of the major fission products of $^{235}U$ with a fission yield of 5.93%, $^{90}Sr$ is abundantly available in high level waste (HLW) solutions and can be separated from the other constituents of HLW by using suitable radiochemical separation methods [242, 262–269]. $^{90}Sr$ that is used for making a $^{90}Sr/^{90}Y$ generator for clinical applications ought to be of adequate purity and thus warrants intensive and stringent quality control measures [2].

The separation of NCA $^{90}Y$ from $^{90}Sr$ for medical applications is not a trivial process and poses formidable challenges due to the requirement to keep the $^{90}Sr$ contamination in $^{90}Y$ within permissible levels to preclude $^{90}Sr$ localization in the skeleton. The maximum permissible body burden of $^{90}Sr$ was found to be 74 kBq (2 $\mu$Ci) over the patient lifetime [2]. With the aim of isolating $^{90}Y$ from $^{90}Sr$, a wide range of radiochemical separation strategies, including precipitation, solvent extraction, ion exchange chromatography, extraction chromatography, electrophoresis, membrane based separation and electrodeposition, among others, have been well described in the literature [270, 271]. Among the $^{90}Sr/^{90}Y$ generator technologies reported [271], the automated electrochemical $^{90}Sr/^{90}Y$ generator holds significant promise, as it offers the possibility of being adopted in centralized radiopharmacy set-ups, which can provide $^{90}Y$ of acceptable quality and the requisite quantity on a sustainable basis for a long

period (>10 a) [2]. In order to avoid the radiotoxicity risk posed by $^{90}$Sr and to ensure that it is well within the pharmacopeia established limits, the availability of a reliable quality control (QC) technique for the reliable estimation of Bq levels of $^{90}$Sr impurity in GBq quantities of $^{90}$Y is essential. In this context, using the extraction paper chromatography concept [272] based on the ability of the reagent 2-ethyl hexyl, 2-ethyl hexyl phosphonic acid to retain $^{90}$Y selectively at the point of spotting was attractive [2].

# 5. RADIOPHARMACEUTICALS FOR RADIOSYNOVECTOMY

## 5.1. PRINCIPLE

As discussed earlier in this publication, radiosynovectomy is defined as the restoration of the inflamed and damaged synovial membrane of the joints by an intra-articular injection of a beta emitting radionuclide in colloidal or particulate form into the synovial cavity. The radioactive compounds are phagocytized by the outermost cellular layer of the synovial membrane and deliver a radiation dose to the synovium without excessive irradiation of surrounding tissue.

In the articular cavity of the joint, the subintima recognizes radioactive colloids or particulates as foreign bodies. As a result, they are phagocytosed by the type A synoviocytes and deliver selective radiation doses to the synovium without causing collateral damage to surrounding tissue [3]. This subsequently leads to fibrosis and sclerosis of the synovial membrane, which results in apoptosis and ablation of the inflamed synovial membrane [273, 274].

This is followed by progressive fibrosis of the synovial stroma and the vessels and, infrequently, mild diffuse damage to the joint bones [275]. Nevertheless, there is also a reduction in the filtration and reabsorption of the synovial fluid. After a few months, the synovial membrane is fibrosed without signs of mononuclear infiltration. In this way, further destruction of the joint cavity by immunological reactions is prevented and long term remission is achieved [276]. This process results in alleviation of the pain, improvement of mobility and preservation of joint function, all contributing to a significant improvement in quality of life.

While from a design perspective, the radiopharmaceuticals used for RSV could be grouped into either colloids or larger aggregates, their selection is primarily governed by the choice of the carrier molecule and the radionuclide. The radiopharmaceuticals used for RSV ought to conform to the following standards [2, 3]:

(a) Radiopharmaceuticals used for RSV ought to contain a $\beta^-$ emitting radionuclide of optimum tissue penetration range conjugated to the microparticle, owing to its ability to deliver localized cytotoxic ionizing radiation to ablate the inflamed synovial membrane.

(b) An important necessity is a suitable method to facilitate the preparation of radiolabelled agents for RSV to preclude radiation exposure of the operating staff and minimize radioactive decay of radionuclides.

(c) It is essential to create metabolically resistant bonds between the radionuclide and carrier molecular and to ensure that the radiolabelled particle possesses both in vitro and in vivo stability.

(d) The radioactive particles ought to be minimally affected by changes in pH, temperature and other denaturing agents.

(e) Radiolabelled agents for RSV ought to be sufficiently small to be taken up by the type A synoviocytes that partly make up the surface layer of lining cells in the synovial membrane, but at the same time they ought to be large enough to preclude leakage beyond the joint prior to undergoing phagocytosis. A particle size between 2–10 $\mu$m is recommended.

(f)     Minimal lymphatic leakage of the radioactive particle from the joints is desirable. Ideally, the rate of leakage of the nuclide vehicle from the treated region ought to be negligible in comparison with the rate of decay of the nuclide.

(g)     Homogeneous distribution of the radiolabelled particles in the intra-articular space ought not to initiate an inflammatory response.

(h)     Cost effective preparation of the radiopharmaceuticals is desirable.

The development of radiolabelled agents for RSV consists of the following major steps [2]:

(a)     Choice of a radionuclide of optimal beta energy that is appropriate for the size of the joints to be treated (this is obligatory to minimize radiogenic damage to the articular cartilage and the overlying skin);

(b)     Proper identification of the size of the joints to be treated (large, medium sized and small);

(c)     Identification of a particle for conjugation of the radionuclide;

(d)     Selection of a simple radiolabelling procedure associated with minimal manipulation and the ability to provide high labelling efficiency and high SA;

(e)     Quality control of radioactive particles;

(f)     In vitro and in vivo stability evaluation of the radioactive particles.

### 5.1.1.  Radionuclide selection

The success of RSV is primarily based on the selection of a suitable radionuclide, which is governed by a number of factors [10, 277, 278]. Beta particle emitting radionuclides, and Auger electron emitting radionuclides are well suited for RSV because of their ability to deliver localized cytotoxic ionizing radiation [2]. Any accompanying radiation ought not to generate an unacceptable extraneous radiation dose to the patient [279]. The selection of $\beta^-$ emitting radionuclides for RSV stems mainly from their reasonable (high) linear energy transfer (LET) and their intermediate tissue penetration (typically several millimetres). They have the ability to deliver sculpted radiation doses to the synovium without collateral damage to critical structures such as the cartilage, bone marrow and skin [3].

On the other hand, gamma rays with lower LET have the potential to deliver doses at lower levels over much greater distances and are thus incapable of localizing the dose within a small region. Use of gamma emitting radionuclides will not only dilute the effect, but is also prone to delivering doses adjacent to non-synovial tissues, causing collateral damage to distant joint structures. While alpha particles can deliver a lethal radiation dose as a consequence of their high LET without causing significant damage to the surrounding healthy tissue and offer greater biological effectiveness than $\beta^-$ emitters, their short penetration depth necessitates intimate contact with the cells of the tissue to be treated for favourable therapeutic outcomes [3].

The choice of emission type depends on the size of the synovial membrane of the joint to be treated. The penetration depth of the radiation emitted by the radionuclide ought to correspond to the thickness of the inflamed synovium in the treated joint to ablate the proliferating layer of the inflamed synovium, but it is important to avoid the cartilage, bone marrow and skin. While inadequate penetration will lead to an inferior therapeutic effect, excessive penetration depths may constitute a radiation hazard to the cartilaginous surface. For smaller joints, radionuclide emitting shorter range beta particles ought to be used.

High energy $\beta^-$ emitters such as $^{90}$Y and $^{188}$Re are used for RSV of the knee. Medium energy $\beta^-$ emitters such as $^{186}$Re, $^{153}$Sm and $^{177}$Lu are used for RSV of medium sized joints (such as the glenohumeral joint, elbow, radiocarpal joint, hip and tibiotarsal joint). Low energy $\beta^-$ emitters ($^{169}$Er) and radionuclides that emit Auger and Coster–Kronig electrons ($^{117m}$Sn) are usually effective for smaller joints such as the metacarpophalangeal, proximal interphalangeal and metatarsophalangeal (e.g. finger and toe) joints [3]. Other joints for which $^{169}$Er could be used are the distal interphalangeal, tarsometatarsal and proximal tibiofibular joints and the thumb base joint or first carpometacarpal joint [131, 280].

The beta emitting radionuclide ought to decay to stable nuclides with no relevance to the radioactive dose. In addition to the thickness of the synovium, it is also essential to consider the amount of synovial fluid when delivering radiation [7]. The radionuclide ought to have an optimal half-life that is long enough to ensure homogenous distribution within the synovium's surface to deliver the needed radiation dose, and concurrently short enough to prevent excessive irradiation within the joint. The half-life of the radionuclide will preferably be significantly shorter than the retention time of the radiolabelled particle in the articular cavity, while it ought to be long enough to minimize decay loss during transportation and distribution from the site of manufacture to the users [3].

While it is desirable for the radionuclide and particle conjugate to show high in vivo thermodynamic stability and kinetic inertia, in reality no conjugate is 100% kinetically stable due to the substantial variation in the biological systems of different patients; as a consequence, radioactive leakage from the joint subsequent to administration cannot be avoided. Nevertheless, the stability of the complex depends to a larger extent on the half-life of the radionuclide being used and could be successfully exploited. After the radionuclide has decayed to an insignificant level, the stability of the complex is of little interest and utility [279]. The radionuclide ought to be available with high purity levels (radionuclide, radiochemical, elemental purity). Trace metal contaminants are a concern when using metallic radionuclides, as they interfere with chelate radiolabelling.

While the therapeutic potential of the radionuclide is governed by the particulate emission properties, the presence of low energy (100–200 keV) gamma emission photons of low abundance enables the imaging of low doses to evaluate the distribution of the particles in the articular cavity; the assessment of extra-articular leakage from a joint; dosimetry calculations; and the monitoring of residual activity using an Anger gamma ray camera or single photon computed tomography system [2].

The chemical characteristics of the radionuclide ought to pave the way for the conjugation of a variety of particulates with variable chemical characteristics [2]. The existence of large scale cost effective production of radionuclides of acceptable SA and requisite purity has contributed to the widespread adoption of RSV. Radionuclides that exhibit attractive characteristics but lack a cost effective production route are less likely to be used widely in RSV.


## 5.2. CHARACTERISTICS OF RADIONUCLIDES USED IN RADIOSYNOVECTOMY

The selection criteria for a radionuclide for use in RSV are based primarily on its nuclear decay characteristics, production and chemistry. The important nuclear decay characteristics to consider include the radionuclide half-life; the type, energy and branching ratio of particulate radiation; the gamma ray energy; percentage abundances; and the depth penetration of the emitted radiation into biological tissues [3]. The half-life of the radionuclide ought to be long enough to permit homogenous distribution within the synovium and adequate radiation doses, while being short enough to preclude unnecessary radiation doses and substantial leakage from the joint cavity [3].

The use of radionuclides with some gamma emission allows gamma camera imaging for dosimetry as well as leakage studies. Alternatively, they can be investigated using bremsstrahlung imaging. Unfortunately, the scintigraphic resolution from bremsstrahlung may be poor, making quantitation for dosimetry difficult. The tissue penetration depth ought to be commensurate with the thickness of the synovium in the treated joint [3]. The retention time for the nuclide within the synovial capsule is an important criterion that dictates the success of RSV. This will ideally be longer than the decay time of the nuclide. Beta emitters offer a much wider choice of candidates, with a selection of particle ranges and chemical properties.

## 5.3. PARTICLES FOR RADIONUCLIDES

The administration of unconjugated radionuclides into the synovial cavity is not recommended as it would rapidly diffuse out of the joint cavity due to its small molecular size. With the objective of avoiding radiation dose to normal organs, attachment of the radionuclides to non-diffusible microparticles is a desirable proposition [2, 3].

### 5.3.1. Particle selection

A particle required for RSV ought to meet the following requirements:

(1) It ought to be biologically inert — non-toxic, physiologically inert and not evoking an inflammatory or toxic response.
(2) It ought to be non-immunogenic — not provoking an immune response (absence of body recognition could cause rejection).
(3) It ought to have a similar density to the blood in order to achieve very slow sedimentation during therapy, if any.
(4) It ought to have good uptake by the synovial lining macrophages of the joints.
(5) It ought to be free flowing and not exhibit aggregation or adherence; it also ought to be minimally affected by changes in pH, temperature and other denaturing agents or environmental conditions.
(6) It ought to have favourable chemical characteristics to permit radiolabelling with a variety of radionuclides to form a thermodynamically stable and kinetically inert conjugate.
(7) It ought to be chemically stable, resisting in vivo degradation and being able to maintain size range in normal physiological conditions and during the process of therapy.
(8) It ought to be sufficiently strong to maintain its size and properties after it has been administered until it is taken up by the macrophages of the joints and it ought to be removable from the joint by the normal biological degradation mechanisms in the joint without intervention; it ought to be cleared from the body in standard ways in a rapid manner with little or no toxicological effect.
(9) It ought to be biocompatible (biocompatibility is one of the main prerequisites for use in RSV) and ought not to elicit any undesirable local or systemic effects in the synovial tissue of the host; the accumulation of non-biocompatible material in the synovial cavity will likely cause inflammation.
(10) It ought to show resistance to radiological degradation.
(11) It ought to be commercially available, with particles being manufactured in large quantities or having a quick, easy and reproducible preparation method.
(12) It ought to be easily sterilized.

### 5.3.2. Particle size

Particle size plays an important role in RSV. The size of the radionuclide and particle conjugate needs to be sufficient to remain intact in the synovial joint to be phagocytized by the superficial cells of the synovium administration. In order to prepare a radioactive particle possessing excellent synovectomy properties, the size and properties of the particle need to be defined and controlled before it is conjugated to the radionuclide of interest [279]. Inappropriate particle size will lead to extra-articular leakage of radionuclides to regional lymph nodes and non-target organs outside the injected joint, such as the liver and spleen [13].

Relevant considerations for particle size are as follows:

(1) The particle has to be small enough to be phagocytized by the superficial cells of the synovium, but not so small as to facilitate a fast biological clearance by diffusion from the joint.
(2) While a small diameter particle allows homogeneous distribution on the synovium to be irradiated, it seems to be associated with a high frequency of extra-articular spread. On the other hand, although

a large particle resists leakage, it results in heterogeneous distribution, which in turn may give rise to variable irradiation of the synovial membrane.

(3) Using micro-particulates with a substantially uniform size distribution with a view to offering a homogeneous radiation dose distribution around the synovium for reliable therapeutic outcomes is favoured.

(4) Micro-particulates ought to be of a size such that they will maintain their characteristics during radiolabelling, as it involves several manipulations such as aliquoting, mixing, vortexing, centrifuging and ultra-sonication. Furthermore, they ought to be able to form physiologically acceptable, injectable or infusible suspensions or dispersions when added to physiologically acceptable liquid carriers, such as isotonic saline or phosphate buffer solutions for in vivo injection and/or infusion (they cannot sediment or aggregate).

(5) Micro-particulates are of a size such that they are able to remain stable in liquid carriers for heat treatment at a temperature of at least 100°C for the purposes of sterilization. This is particularly significant as they will not be easily sterilized by filtration.

(6) The particulates may have any shape or mixture of shapes, including spheres, plates, needles, rods, etc.

(7) The most appropriate particle size to avoid leakage out of the joint cavity by lymphatic drainage is 2–10 $\mu$m [1].

### 5.3.3. Common particles used in radiosynovectomy

Particles commonly used in RSV are depicted in Table 2.

TABLE 2. PARTICLES COMMONLY USED IN RSV

| Abbreviation | Full name |
| --- | --- |
| FHMA | Ferric hydroxide macro aggregate |
| HA | Hydroxyapatite macro aggregate |
| GMS | Glass microsphere |
| COL | Colloid |
| OXP | Oxalate particle |
| SIL | Silicate |
| CIT | Citrate |
| PMS | Polymeric microsphere |
| HSA | Human serum albumin microsphere |
| PLA | Polylactic acid microsphere |
| HMA | Hydroxide macro aggregate |

## 5.4. KEY PARTICLES USED IN RADIOSYNOVECTOMY

### 5.4.1. Glass

Glass has several advantages, including excellent stability, resistance to radiation damage, being highly insoluble and non-toxic, the ability to produce different compositions and minimal leaching [281, 282]. However, its high density, irregular particle shape and non-biodegradability are major disadvantages that limit its applicability. The high density of glass makes it difficult to keep particles in suspension in the liquids used to inject them into the body. Non-biodegradability can lead to immunological reactions.

The glass mixture containing the nonradioactive precursor is melted in a platinum crucible at the formation temperature of glass, annealed, crushed and sieved [182, 283]. The sol–gel method and the flame spheroidization process are the other two methods by which glass may be prepared. Strategies to prepare glass microspheres from biodegradable glass material have been studied in detail [281, 283–286].

### 5.4.2. Chitosan

Chitosan (poly-β-(1-4)-2-amino-2-deoxy-D-glucose) is an amino-polysaccharide that is a cationic polymer produced by the N-deacetylation of chitin. Chitin (poly-β-(1-4)-N-acetyl D-glucosamine) constitutes one of the most abundant natural biopolymers, second only to cellulose. It is mostly found in the exoskeletons of crustaceans, in the cartilage of molluscs, in the cuticles of insects and in the cell walls of microorganisms. It has recently been recognized as a biosorbent owing to the existence of amino and hydroxyl groups in its molecules, leading to adsorption interactions between chitosan and radionuclides [287, 288]. The attractive characteristics of chitosan, such as its biocompatibility, non-toxicity, low allergenicity and biodegradability, allow it to be used in various applications [289]. Chitosan can be obtained easily by alkaline hydrolysis of chitin, because it is abundant (next to cellulose) in nature, and in particular is contained in the shells of shrimp, lobsters, crabs and oysters. The chemical structure of chitosan is shown in Fig. 7.

Chitosan microspheres can be produced via spray drying [289–292], emulsification [293], internal gelation [294], electrospinning and freeze-drying processes. Several studies have dealt with chitosan as a particle in RSV [295–299].

### 5.4.3. Silicate

Silica possesses remarkable attributes, including the availability of simple, controllable and scalable synthesis protocols, low cost, biocompatibility, negligible toxicity, in vitro and in vivo stability, and flexibility for surface modification to radiolabel radionuclides of interest [300]. It is possible to control silica particle size, porosity, crystallinity and shape precisely. Furthermore, it is possible to modify the surface of silica particles to allow precise control of surface chemistry to bind a wide variety of
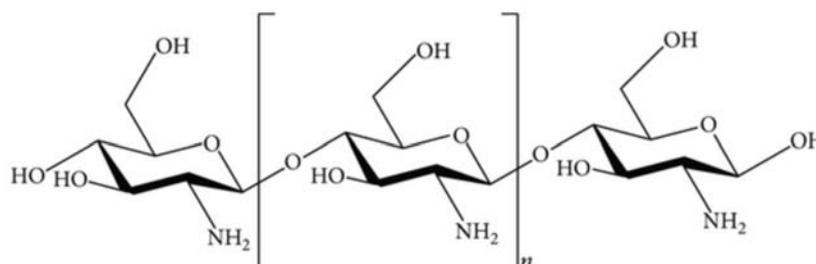


*FIG. 7. Chemical structure of chitosan. Reproduced from Ref. [290].*

radioisotopes without additional selective chelation molecules. The ability to combine these properties makes silica particles a desirable platform for RSV.

### 5.4.4. Citrate

Citric acid, historically known as an intermediate in the Krebs cycle, is a multifunctional, non-toxic, readily available and inexpensive chemical used as a citrate in the preparation of RSV agents. Due to the antimicrobial nature of citric acid, citrate based RSV agents could possess intrinsic antimicrobial properties.

### 5.4.5. Polylactic acid

Polylactic acid (PLA) is an aliphatic polyester, with extraordinary advantages over several polymers. The use of PLA and its derivatives has attracted attention due to its unique mechanical and biological properties, such as biocompatibility, biodegradability and non-toxicity. Its non-toxicity and non-carcinogenicity in the human body make PLA and its degradation products such as $H_2O$ and $CO_2$ acceptable candidates for RSV. PLA has been approved by the US Food and Drug Administration (FDA) for food and pharmaceutical applications since the 1970s. PLA is usually synthesized using a range of processes, including polycondensation, polymerization and azeotropic dehydration condensation reaction [301–305].

In vitro degradation analysis of holmium-loaded PLA microspheres (before and after neutron or gamma irradiation) over a 52 week period was performed by Zielhuis et al. [303]. Preparation of PLA microspheres by an emulsion solvent evaporation method based on solution induced phase separation has been well described by Hong et al. [306]. Polycondensation is another method of synthesis [307, 308]. The promising possibilities associated with the use of PLA in RSV have inspired a number of studies [303–310].

### 5.4.6. Hydroxyapatite

Hydroxyapatite (HA) has been receiving a great deal of attention for application as a particle in RSV. The inimitable physicochemical characteristics of HA include biocompatibility; bioresorbability; being non-allergenic, non-toxic, non-immunogenic and porous with superior mechanical properties; and chemical similarity to the carbonated apatite in human bones and teeth. It is the natural mineral constituent of the human bone matrix and has the ability to be converted by a natural metabolic process into $Ca^{2+}$ and $PO_4^{3-}$ ions, which can be eliminated over a period of six weeks. The particles have sites on the surface that permit absorption or covalent binding of the radionuclide or radionuclide complex [279].

HA is a stoichiometric apatite phase with a Ca/P molar ratio of 1.67 and is considered to be the most stable calcium phosphate salt at normal temperatures and a pH of 4–12. Thermodynamically, HA is the most stable calcium phosphate compound under physiological conditions such as temperature, pH and the composition of the body fluids. A myriad of techniques to synthesize HA have been reported in the literature; each method has advantages and disadvantages.

#### 5.4.6.1. Precipitation

Precipitation is the most common and widely researched method of HA synthesis [311–317]. It is also called 'wet precipitation', 'chemical precipitation' or 'aqueous precipitation'. Precipitation typically involves slowly adding di-ammonium hydrogen orthophosphate to a solution of calcium nitrate by maintaining the pH at ~10 with the steady dropwise addition of ammonium hydroxide under continuous stirring to ensure a constant pH. The resulting precipitate is washed to remove nitrates and the ammonium hydroxide [311, 312].

In this method, continuous stirring is essential to ensure the slow incorporation of calcium into the apatite structure to reach a stoichiometric Ca/P ratio. The reaction temperature changes the size of the HA particles, with a higher temperature generally resulting in more whisker-like particles, although $NH_4OH$ consumption goes up. Other factors, such as the reaction rate (length of time for additions) of the HA, provide the means with which to improve stoichiometric quality.

*Advantages*

The advantages of precipitation include:

(a)   Simplicity;
(b)   Low operating costs;
(c)   Relatively inexpensive raw materials;
(d)   Easily scalable production batch;
(e)   Low reaction temperatures;
(f)   Water as the only by-product;
(g)   Production of HA with high superficial area and small particle size distribution.

*Disadvantages*

The disadvantages of precipitation include:

(a)   Its dependence on several influences, such as the reactants involved in synthesis, the concentration and preliminary pH of solutions, the reaction temperature, etc.;
(b)   Difficulty in obtaining stoichiometric HA;
(c)   High pH required to prevent the formation of Ca-deficient HA;
(d)   High sintering temperature required to form crystalline HA.

### 5.4.7. Hydro- and solvothermal

The hydro- and solvothermal process of synthesis involves the use of a solvent (with precursor soluble ions) in a sealed vessel under moderate to high pressure (typically 1–10 000 atm) and temperature (typically between 100 and 1000°C) that facilitates the interaction of precursors during synthesis. In this process, calcium and phosphate solutions are subjected to reaction in a sealed vessel kept at very high pressure and temperature to produce HA particles [318–330]. A variety of starting calcium and phosphate salts have been reported, including: calcium hydroxide; calcium nitrate; calcium carbonate and calcium chloride; calcium hydrogen phosphate and dipotassium; and diammonium hydrogen phosphates. A typical hydrothermal reaction is shown in the following equation:

$$4Ca(OH)_2 + 6CaHPO_4 \times 2H_2O \rightarrow Ca_{10}(PO_4)_6(OH)_2 + 18H_2O \tag{1}$$

*5.4.7.1.   Advantages*

The advantages of hydro- and solvothermal synthesis [323] include the following:

(a)   HA can be produced in one step.
(b)   It is energy efficient, as synthesis can be performed at low temperatures.
(c)   It is an environmentally friendly process because of closed system conditions and the ability to recycle unused components.
(d)   High purity products can be synthesized.

(e)    It offers yields approaching 100%.
(f)    It uses relatively low cost reagents and involves short-time reactions.

*5.4.7.2.   Disadvantages*

The disadvantages of hydro- and solvothermal synthesis include the following:

(a)    Batch sizes are limited to the size of the reaction vessel.
(b)    High pressures are required for processing.

### 5.4.8.   Solid state reactions

The main difference between wet chemistry products and similar products of solid phase synthesis is that much smaller grains (crystallites) usually have a lower temperature and shorter duration phase formation in the latter. In this method, precursors are first milled and then calcined at a very high temperature (e.g. 1000°C), which leads to the formation of a highly crystallized structure [331–333]. While the procedure relies on the solid diffusion of ions amongst precursors, it requires relatively high temperature processing (>1250°C) to initiate the reaction. Even though the technique is comparatively simple, it is associated with a number of processes.

*5.4.8.1.   Advantages*

The advantages of solid state reaction synthesis include the following:

(a)    It is a simple procedure.
(b)    It is low cost.
(c)    It is appropriate for mass producing HA powder.
(d)    It is the preferred option for commercial production.

*5.4.8.2.   Disadvantages*

The disadvantages of solid state reaction synthesis [334] include the following:

(a)    Heterogeneity of phase composition because of the low diffusion of ions during the reaction;
(b)    Large particle size;
(c)    Lack of control of particle morphology;
(d)    Unattractiveness, both scientifically and technologically.

### 5.4.9.   Sol-gel process

The first stage of this method is to form a 'sol': a dispersion of solid particles, a liquid. Precursor materials such as metal alkoxides (e.g. tetraethoxysilane to introduce silicon) and metal salts (e.g. calcium nitrate to add calcium; ammonium phosphate to add phosphorus) are mixed mechanically in a solvent at a pH that prevents precipitation. Hydrolysis and polycondensation reactions occur to link these monomer units and form M–O–M bonds within the sol, causing the viscosity to increase; this process is termed gelation. The next step is the removal of the liquid via a drying process [335–340].

The advantages of sol-gel synthesis include the following:

(a)    Low temperature formation;
(b)    Increased control over formation of particular phases and phase purity;
(c)    Improved chemical homogeneity of the resulting powder;
(d)    Attainabilty of stoichiometric structure with a large surface area and a small cluster size.

*5.4.9.2.   Disadvantages*

The disadvantages of sol-gel synthesis include the following:

(a)    High cost of some of the starting materials, especially alkoxide based precursors; the energy saving gained from the low temperatures used is offset by the high cost of the reactants;
(b)    Generation of secondary phase (usually calcium oxide, CaO);
(c)    Very limited scalability due to the sensitivity of the process.

## 5.5.   PREPARATION OF RADIOACTIVE PARTICLES

Radiolabelled particles can be prepared either during or after their preparation. Important factors include the ease and efficiency of preparation as well as the stability of the isotope–particle conjugate without in vitro or in vivo release of the radioisotope.

### 5.5.1.   Radiolabelling during particle preparation

In this method, an inorganic compound of a radioisotope is precipitated to form relatively homogeneous particles. The method essentially consists of first transforming a radioactive substance into a precipitate and then converting the precipitate into particles. Colloids are frequently used for radiolabelling during preparation. They usually consist of the defined inorganic compounds of a radioisotope that have precipitated into relatively homogeneous particles. While a myriad of factors contributes to the successful optimization of preparation conditions, the temperature and pH of the reaction mixture are the key parameters that determine the range/size of particles.

### 5.5.2.   Radiolabelled particles after their preparation

*5.5.2.1.   Neutron activation of pre-made particles*

In this case, particles containing the non-radioactive precursor are synthesized and activated in a nuclear reactor to induce radioactivity shortly before use [3]. During neutron activation, the non-radioactive precursor captured neutron becomes radioactive.

*Advantages*

The advantages of neutron activation of pre-made particles include the following:

(a)    Avoids the handling of radioactive material for radiolabelling;
(b)    Activity content can be controlled by irradiation time as well as neutron flux;
(c)    Simple post-irradiation processing.

*Disadvantages*

The disadvantages of neutron activation of pre-made particles include the following:

(a)    Availability of a reactor;
(b)    Activation of isotopes is only possible in practice with high activation cross-sections;
(c)    Success of the technique depends on the radiation stability of the particle;
(d)    Susceptible to radiolytic degradation: leakage of radionuclide.

By far the most stable matrix for this method of radioactive particle preparation is glass [341].

### 5.5.2.2.    *Reaction of radionuclide with particles*

In this case, non-radioactive particles are radiolabelled shortly before use. Compared with radiolabelling during particle preparation, the methods for radiolabelling already-prepared particles are conceptually more straightforward [341]. The advantage of this process is that radiochemical stability problems during irradiation can be minimized, and logistical problems that are inherent in the use of radiolabelled particles can be avoided.

In this method, it is essential to consider whether the radionuclide can be incorporated into the particle, which can be assessed from knowledge of the chemical characteristics of the two partners. It is also crucial to ascertain the amount of each component to be added. An unduly high or low concentration of any component may well affect the integrity of the radiolabelled particles.

The various techniques used for radiolabelling are the following:

(a)    *Isotope exchange reactions.* In this technique, one or more of the atoms in a particle of interest are substituted for a radioactive atom of the same element. As the radiolabelled and the non-labelled particles are chemically identical, they are expected to possess the same chemical properties. For isotope exchange labelling, it is crucial that the radionuclide be NCA to ensure optimal labelling yields.

(b)    *Introduction of a foreign label.* In this type of radiolabelling, a radionuclide is incorporated into a particle of interest by adsorption processes, by the formation of covalent bonds or by chelation. While the tagging radionuclide is foreign to the particle, it is distributed throughout the entire volume, or is only attached on certain structural components of the particles, including the surface, the outer wall or the inner wall [3].

(c)    *Covalent attachment or chelation (complex formation) of the radionuclide.* Techniques resulting in covalent attachment of the radionuclide use chemical linker molecules and a number of wet chemistry steps to facilitate the attachment [341]. With a view to creating stable covalent binding sites on the surface of the particle for the attachment of radionuclides, myriad functional groups such as $-OH$, $-NH_2$, $-SH$ and $-COOH$ are conjugated to the particles either covalently or may simply adsorb very strongly to the surface of the particle. Each process requires a tailored functionalization protocol making use of chemical linker molecules and associated wet chemistry. The ligands that can be used for chelation are preferably polydentate, that is, they contain more than two coordinating atoms per ligand molecule. A coordinating atom is defined as one that has a free pair of electrons that can be bonded to the radionuclide. This atom is preferably separated by two or more atoms from any other coordinating atom. The coordinating atoms are chosen from nitrogen, oxygen, sulphur, phosphorus or carbon, with nitrogen and/or oxygen and/or sulphur being the preferred coordinating atoms. Examples of chelates include all phosphonate carboxylate and amine carboxylate ligands, MAG3 (mercapto acetyl glycyl glycine) and all polycarboxylic acid–amine ligands, especially DTPA (diethylenetriaminepentaacetic acid). For example, EDTA (ethylenediaminetetraacetic acid), DADS (N,N′-bis(mercaptoacetamido) ethylenediamine) and $CO_2$-DADS (N,N′-bis(mercaptoace tamido)-2,3-diaminopropanoic acid) and their derivatives. Further, mono- and polyphosphonates,

BATs (N,N′-bis(2-mercaptoethyl)ethylene-diamine) and thiosemicarbazones, PnAO and other amine–oxime ligands, and macrocyclic and open chain tetra-, penta-, hexa-, hepta- and octa-coordinating nitrogen-containing compounds with or without other coordinating atoms or unsaturation [279].

(d) *Adsorption.* This is a valuable way to incorporate the radionuclide from the solution into the solid particles. While both physical and chemical adsorptions are capable of retaining the radionuclide of interest in the particle, chemisorption follows the chemical reaction between the surface and the radionuclide, leading to the formation of chemical bonds at the particle surface. The physical adsorption interaction between the particle surface and the radionuclide is primarily due to weak molecular forces that embrace permanent dipole, induced dipole and quadruple attraction. Chemisorption, on the other hand, involves the rearrangement of the electrons of the interacting radionuclide, with the consequential formation and rupture of chemical bonds. The enthalpy changes in physical adsorption are small, typically in the range of $-10$ to $-40$ kJ/mol, whereas those of chemisorption are typically in the range of 80 to 400 kJ/mol [342]. Factors affecting the extent of chemisorption are the chemical characteristics of the radionuclide and particle, radionuclide concentration in the solution, adsorption temperature, the pH of the reaction media and specific surface area, and the pore volume and pore structure of the particle.

## 5.6. KEY RADIONUCLIDES EVALUATED FOR SYNOVECTOMY

### 5.6.1. $^{198}$Au

$^{198}$Au ($E_{\beta max}$ = 0.96 MeV, $E_{\gamma}$= 412 keV (95.6%), $T_{1/2}$=2.7d), with a half-life of 2.7 days, decays to $^{198}$Hg with the emission of beta and gamma radiation. Approximately 99% of the beta emission has an energy of 0–0.96 MeV, with the maximum range in soft tissue being 3–8 mm, but most of the energy is absorbed in the first millimetre. Approximately 95% of the gamma emission is at 0–412 MeV. The decay characteristics of $^{198}$Au are shown in Fig. 8.
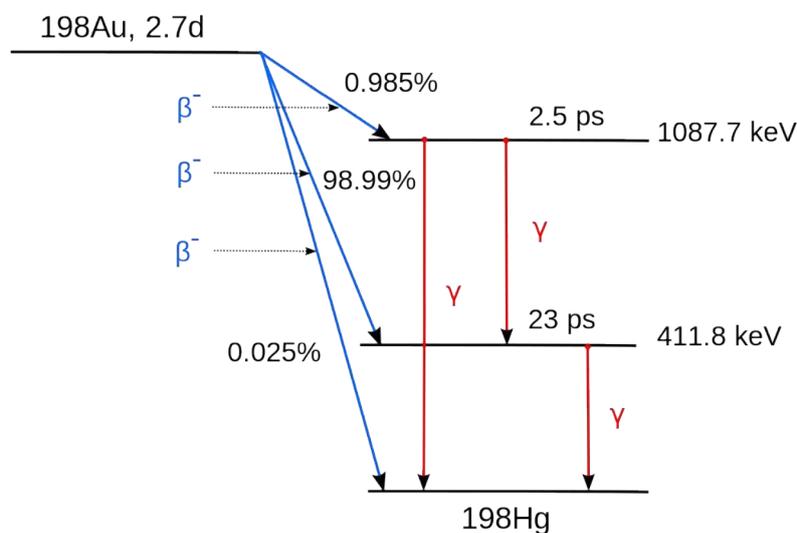


*FIG. 8. Decay characteristics of $^{198}$Au. Reproduced from Ref. [343].*

*5.6.1.1. Advantages*

The use of $^{198}$Au in RSV is associated with the following advantages:

— The energy of beta emissions, 0.96 MeV, is suitable for the treatment of inflamed joints.
— The mean range of beta energy lies between 3 and 8 mm and is suitable for use in RSV of large joints.
— High-SA $^{198}$Au can be produced by reactor irradiation of metallic gold target, and radiochemical processing of the irradiated target is easy, as simple target dissolution will suffice.
— The 2.7 day half-life of $^{198}$Au is adequate to perform radiolabelling, and for completing quality control and patient administration [195].

*5.6.1.2. Disadvantages*

The use of $^{198}$Au in RSV is associated with the following limitations:

— $^{198}$Au has a β particle with a maximum range of only 4 mm in tissue, and the synovium in these chronic knee effusions can attain a thickness of >1 cm, but a complete synovial ablation is not produced.
— The leakage (related to particle size) when combined with its relatively long half-life of approximately 2.7 days results in significant integrated radiation doses to other organs, such as the lymph nodes, liver and kidneys.
— $^{198}$Au possesses a significant gamma ray component (411 keV gamma emission), which creates an unnecessary radiation hazard while undertaking preparation of synovial agents and this gives an unwanted radiation dose to the proximal lymph nodes.
— High cost has impeded its routine application.

The first studies on the use of $^{198}$Au in RSV were produced in 1963, in which patients with chronic effusions of the knee were treated using 370 MBq of $^{198}$Au colloids [6]. Subsequently, a few more studies on the use of $^{198}$Au have been reported in the literature [344–354].

## 5.6.2. $^{165}$Dy

$^{165}$Dy emerged as the first RSV agent that motivated clinicians to treat refractory synovitis as a substitute for surgical intervention [3]. $^{165}$Dy has a 139 min half-life, a maximum beta energy of 1.3 MeV and little accompanying gamma emission. This radionuclide has a 3.6 abundance of gamma emission at 108 keV that can be used by the gamma camera to detect a possible leak. It has a tissue penetration range of 5.7 mm. The nuclear decay characteristics of $^{165}$Dy are depicted in Fig. 9.

*5.6.2.1. Advantages*

$^{165}$Dy possesses the following advantages [195]:

— A beta emission energy of 1.3 MeV is suitable for therapy.
— An extremely short half-life of 2.3 h reduces the effects of potential leakage.
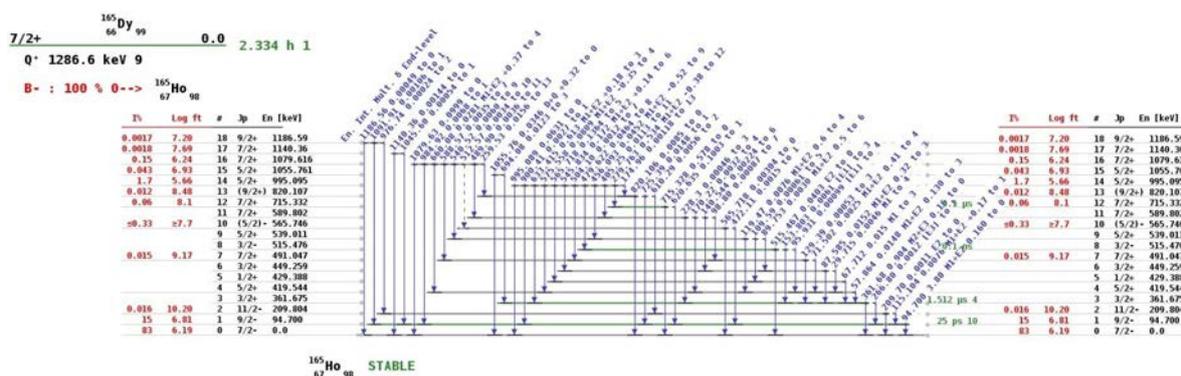
*FIG. 9. Nuclear decay characteristics of $^{165}$Dy.[2]*

— High-SA $^{165}$Dy can be produced by the irradiation of dysprosium oxide with neutrons in a nuclear reactor for 1 day; post irradiation processing of targets is simple and rapid and essentially consists of the dissolution of neutron irradiated targets in dilute mineral acid followed by gentle warming.

— Its gamma emission of 3.6% abundance at 108 keV permits gamma camera imaging for dosimetry as well as leakage studies.

— Minimal radiation dose during radiopharmaceutical preparation and patient administration owing to the emission of the moderate energy beta particles, as well as low energy gamma photons; this facilitates the handling of relatively high $^{165}$Dy activity.

— The chemical characteristics of $Dy^{+3}$ are favourable for performing radiolabelling with a broad range of particles.

— The mean penetration range of $\beta^-$ particles emitted by it in soft tissue is <10 $\mu$m, making this radionuclide ideal for delivering energy to small volumes with less damage to surrounding normal bone and tissue.

### 5.6.2.2. Disadvantages

$^{165}$Dy possesses the following disadvantages:

— Owing to its short half-life, it is necessary to have a nuclear reactor close to the hospital for regular production.

— It needs to be injected within a few hours.

$^{165}$Dy ferric hydroxide macroaggregate was the first RSV agent to motivate clinicians to increase its use because it is an alternative to surgical intervention for the treatment of refractory synovitis [355–368]. Although $^{165}$Dy has several attractive attributes, the radionuclide has not met with widespread acceptance because its extremely short half-life requires that the medical centre be located a short distance from a high flux nuclear reactor. Despite groundbreaking clinical outcomes and proven therapeutic effectiveness, the FDA has not approved the use of this radionuclide in RSV on the basis of the dosimetric implications of 'potential capsule' leakage, which would result in significant integrated radiation doses to other organs, such as the lymph nodes, liver and kidneys [3].

### 5.6.3. $^{169}$Er

$^{169}$Er ($T_{1/2}$=9.4 d, $E_{\beta(max)}$=342 keV (45%) and 351 keV (55%), $E_\gamma$=110.5 KeV (0.0014%)) decays under the emission of beta particles to stable $^{169}$Tm with a physical half-life of 9.5 days. The maximum

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[2]  Figure 9 available at the IAEA database: https://www-nds.iaea.org/relnsd/vcharthtml/VChartHTML.html

range in soft tissue is 1 mm, whereas the mean range lies between 0.2–0.3 mm. The fraction of gamma rays is negligible; therefore, a distribution study after therapeutic scintigraphy is not possible. The nuclear decay characteristics of $^{169}$Er are shown in Fig. 10.

### 5.6.3.1. Advantages

$^{169}$Er offers the following advantages when used in RSV:

— The 342 keV energy of beta emissions is suitable to treat painful inflamed small joints.
— The maximum range in soft tissue is 1 mm, whereas the mean range, lying between 0.2 and 0.3 mm, is suitable for use in RSV of digital joints.
— High-SA $^{169}$Er can be produced by reactor irradiation of $Er_2O_3$ target; radiochemical processing of irradiated targets is easy, as a simple target dissolution in dilute mineral acid on gentle warming suffices.
— The 9.4 day half-life of $^{169}$Er is suitable for radiolabelling, quality control and patient administration without significant radioactivity decay.
— The relatively long 9.4 day physical half-life of $^{169}$Er is long enough to minimize decay loss during transportation and distribution from the site of manufacture to the users.
— The chemical characteristics of $Dy^{+3}$ permit radiolabelling with a broad range of particles.

### 5.6.3.2. Disadvantage

$^{169}$Er offers the following disadvantage when used in RSV:

— The fraction of gamma rays is negligible; therefore, a distribution study after therapeutic scintigraphy is not possible.

$^{169}$Er is the most preferred option for RSV of digital joints [11, 131, 369–376]. A review of the use of $^{169}$Er for RSV of small joints was published in 2010 [280]. There is considerable variation in the administered activity as well as the injected volume according to the size of the joint to be treated [131]:

— 10–20 MBq for proximal or distal interphalangeal joints;
— 20–40 MBq for metacarpophalangeal or metatarsophalangeal joints;
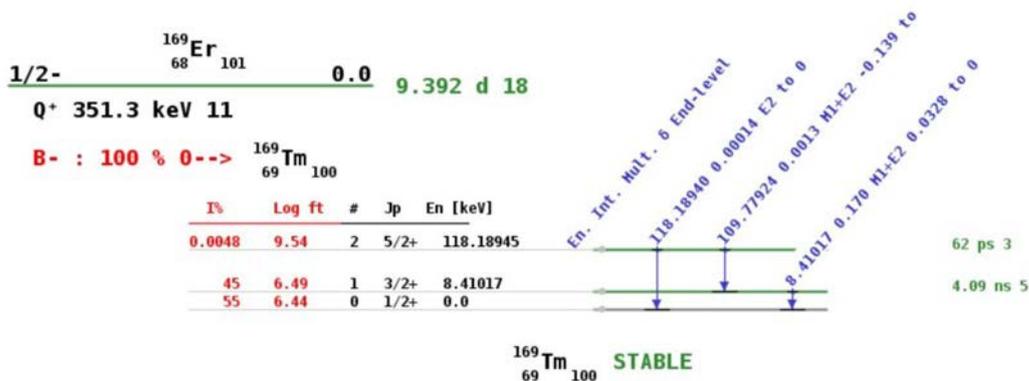


FIG. 10. Nuclear decay characteristics of $^{169}$Er.[3]

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— 20–80 MBq for trapeziometacarpal joints.

It is possible treat many joints using the same formulation at the same session, but the total activity of injected $^{169}$Er ought not to exceed 750 MBq at a single session.

### 5.6.4. $^{166}$Ho

$^{166}$Ho is predominantly a beta emitter ($E_{max}$=1.85 MeV) with $E_{\beta1}$=651.9 keV (47.7% abundance) and $E_{\beta2}$=694.6 keV (51.0% abundance) with a half-life of 26.808 hours. It has a therapeutic radius of ~2.1 mm. The soft tissue penetration range (average) is 3.2 mm, depositing 0.2 keV/mm. The total equilibrium dose constants $D_{np}$ and $D_p$ for non-penetrating and penetrating radiations of $^{166}$Ho are 0.398 g·Gy·Mbq$^{-1}$·h$^{-1}$ and 0.017 g·Gy·Mbq$^{-1}$·h$^{-1}$, respectively. A reasonably short half-life (27 h) decreases the risks associated with eventual leakage of the radioisotope, and strong beta radiation energy ($\beta_{max}$ 1.8 MeV) ensures efficient radiation of the synovium. $^{166}$Ho deposits 90% of its energy within an area 2.1 mm in diameter, while the remainder is deposited within an area measuring 2.1–8.7 mm [189]. The nuclear decay characteristics of $^{166}$Ho are shown in Fig. 11.

#### 5.6.4.1. *Advantages*

$^{166}$Ho offers the following advantages when used in RSV:

— A reasonably short half-life of ~27 hours decreases the risks associated with eventual leakage of the radioisotope.
— It decays by emission of 1.855 MeV (51%) and 1.776 MeV (48%) maximum energy beta particles, which have an adequate penetration range for synovial ablation, while avoiding damage to adjacent cartilage or bone.
— It has an average soft tissue penetration of approximately 3.3 mm and a maximum soft tissue penetration of approximately 9 mm.
— It also emits gamma photons (0.081 MeV; <1% in abundance) that can be imaged with a gamma camera for quantitative dosimetric studies, but are of low enough photon yield (5.4%) to result in limited absorbed radiation dose to surrounding tissue.
— It is cost effective; it is produced in a simple way by the nuclear reaction $^{165}$Ho(n,γ)$^{166}$Ho in a nuclear reactor; it has a natural abundance of 100%, a neutron capture cross-section of 64 b and can be produced from $^{165}$Ho, a naturally abundant element that is less expensive.

#### 5.6.4.2. *Disadvantages*

$^{166}$Ho offers the following disadvantages when used in RSV:

— The physical half-life is 26.8 hours, which causes logistical difficulties for the transportation and distribution of radioactive particles from the site of manufacture to the user [182].
— The prospects associated with the use of RSV led to a considerable amount of innovative work [174, 309, 377–383], while not many reached the clinical applications.

### 5.6.5. $^{177}$Lu

$^{177}$Lu decays to stable $^{177}$Hf with a half-life of 6.65 days. $^{177}$Lu decays to excited (9.7% $E_{\beta(max)}$=0.384 MeV and 12% $E_{\beta(max)}$= 0.176 MeV) and ground states (76% $E_{\beta(max)}$=0.497 MeV) of $^{177}$Hf by the emission of beta particles. $^{177}$Lu decays to an excited state of $^{177}$Hf, whose energy level lies at 0.24967 and 0.32132 MeV, respectively, above the ground state. It subsequently de-excites to the ground state
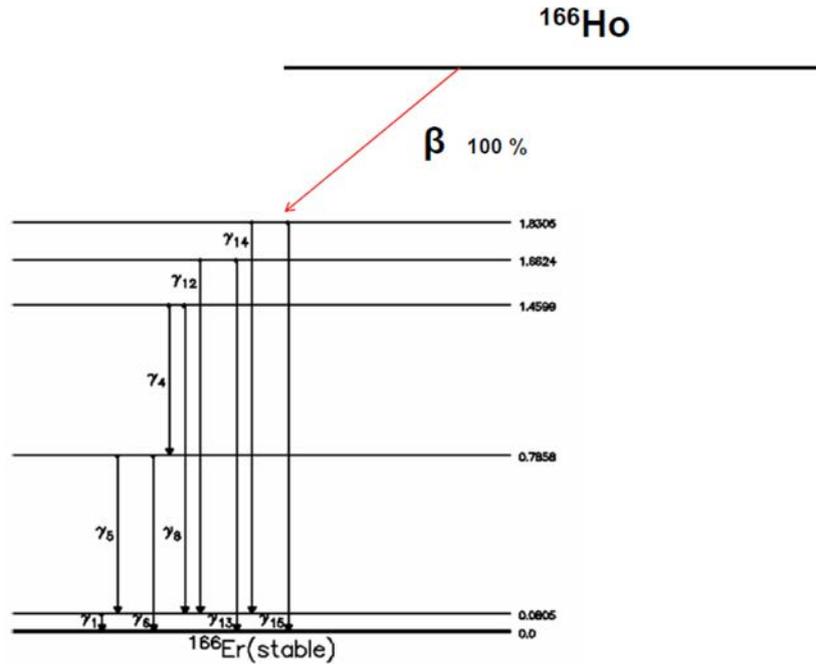
FIG. 11. Nuclear decay characteristics of $^{166}$Ho. Courtesy of A. Dash.
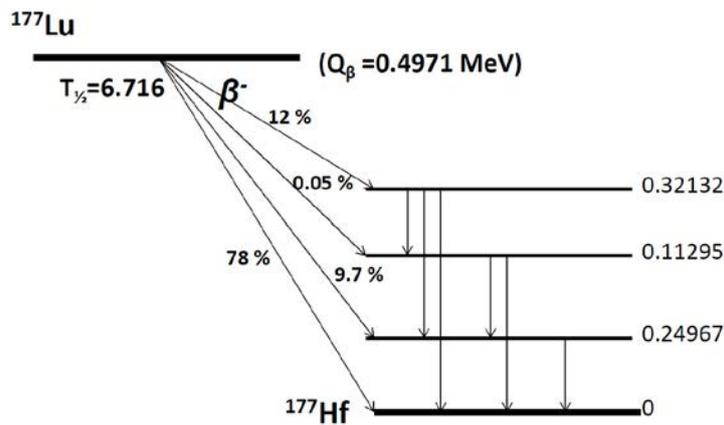


FIG. 12. Simplified decay scheme of $^{177}$Lu. Reproduced from Ref. [195].

accompanied by the emission of low energy gamma photons ($E_\gamma$=113 keV (6.6%), 208 keV (11%)) [195]. A simplified decay scheme for $^{177}$Lu is shown in Fig. 12.

### 5.6.5.1. Advantages

The use of $^{177}$Lu in RSV is associated with the following advantages [195]:

— The beta particles emitted by $^{177}$Lu have a mean range of 670 $\mu$m and thus it is considered suitable for synovectomy of median articulations.
— The low energy gamma photons ($E_\gamma$=113 keV (6.6%), 208 keV (11%)) emitted by $^{177}$Lu offer good quality scintigraphic imaging for the evaluation of the homogeneity of joint distribution, analysis of leakage to other organs and dosimetry.

— Lutetium exhibits an oxidation state of only +3, hence preventing any redox complications of its solution chemistry; the chemistry of $^{177}$Lu is amenable for conjugation with a wide range of particles by following standard radiolabelling procedures.

— $^{177}$Lu can be produced in many nuclear reactors throughout the world following $^{176}$Lu(n,γ)$^{177}$Lu using an enriched $^{176}$Lu target and this reactor method of production provides $^{177}$Lu with very high activity and high SA.

### 5.6.5.2.   Disadvantages

The use of $^{177}$Lu in RSV is associated with the following disadvantages [195]:

— The requirement for an enriched $^{176}$Lu target to produce $^{177}$Lu of acceptable SA and requisite quality makes it cost ineffective compare to $^{166}$Ho [195].

— $^{177}$Lu's half-life of 6.65 days causes logistical difficulties for the transportation and distribution of radioactive particles from the site of the manufacturer to the user.

The increasing use of $^{177}$Lu in RSV has been impressive and the last two decades have witnessed extensive activity for the development of a number of $^{177}$Lu based RSV agents [378, 384–388].

## 5.6.6.   $^{32}$P

$^{32}$P (T$_{\frac{1}{2}}$=14.3 d) decays to $^{32}$S by beta emission (E$_{\beta max}$=1.7 MeV) with a half-life of 14.3 days. It has mean and maximum tissue penetration depth of 2.2 mm and 7.9 mm, respectively. Its radioactive decay characteristics make it suitable for RSV of the knee, where applied activity for knee joints ought to be 37–54 MBq [131]. The nuclear decay characteristics of $^{32}$P are shown in Fig. 13.

A vast number of studies that use $^{32}$P for RSV of the knee are available in the literature [389–400].

### 5.6.6.1.   Advantages

$^{32}$P has the following advantages when used in RSV:

— The 1.7 MeV energy of its beta emissions is suitable for the treatment of inflamed large joints such as the knee.

— The maximum range in soft tissue is 7.9 mm, whereas the mean range is 2.2+/–0.3 mm, and thus it is suitable for use in RSV of knee joints.

— It is the most commonly available radionuclide with no carrier added form and comes at a reasonable cost, making it a cost effective treatment option.
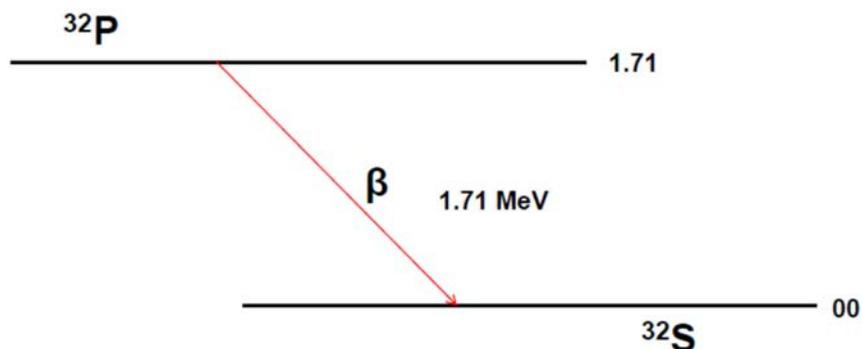


*FIG. 13.  Nuclear decay characteristics of $^{32}$P. Courtesy of A. Dash.*

— Its 14.3 day half-life allows a more gradual deposition of energy and avoids immediate inflammatory reactions.
— Its 14.3 day physical half-life is long enough to minimize decay loss during transportation and distribution from the site of manufacture to the user.
— Its chemical characteristics permit radiolabelling with a broad range of particles.

### 5.6.6.2. *Disadvantages*

$^{32}$*P has the following disadvantages when used in RSV:*

— It has no imageable gamma photon, which makes it very difficult to obtain quantitative dosimetric information on patients treated with agents based on $^{32}$P.
— Any leakage of activity will give an unacceptable extraneous bone dose.
— High energy beta radiation ($\beta_{max}$=1.7 MeV) induces injuries of both articular cartilage and the growth plate [401].

## 5.6.7. $^{186}$Re

$^{186}$Re has a half-life of 90 hours (3.68 days) and decays with a beta particle emission with a maximum energy of 1.08 MeV with a mean tissue penetration depth of 0.92 mm and 135 keV (9%) gamma, which permits imaging [182]. The 135 keV (9%) is ideal for gamma camera imaging and the very small fraction (0.05%) of higher energy gamma photons (>600 keV) results in minimal radiation exposure. It is ideal for treating medium sized joints: the hip, shoulder, elbow, wrist, ankle and subtalar joint. $^{186}$Re labelled particles are commercially available in Europe, for example, for this clinical application. The nuclear decay characteristics of $^{186}$Re are depicted in Fig. 14.

When performing RSV with $^{186}$Re sulphide colloid, the recommended activity range is as follows: for the hip, 74–185 MBq; for the shoulder, 74–185 MBq; for the elbow, 74–111 MBq; for the wrist, 37–74 MBq; for the ankle, 74 MBq; for the subtalar joint, 37–74 MBq [3]. In a situation where several joints are to be treated simultaneously in a single session, the total administered activity ought to be kept below 70 MBq [1].

### 5.6.7.1. *Advantages*

The possibility of using $^{186}$Re for the preparation of bone seeking radiopharmaceuticals is attractive because of the following advantages:

— Its physical half-life is 3.8 days, which is long enough for the preparation, quality control, shipment and distribution of the radiopharmaceutical to end users who are distant from the production facility.
— Its beta emission exhibits a mean energy of 349 keV and an average range in soft tissue of 1.1 mm (maximum range, 4.5 mm) [132] and because of its short penetration distance, radiation reaches only structures in the immediate vicinity of the joint cavity [402].
— It has a 9% abundant gamma emission (135 keV), which allows external imaging with a standard gamma camera and permits evaluation of dosimetry.
— It can be produced in many nuclear reactors throughout the world following the $^{185}$Re(n,$\gamma$)$^{186}$Re method by using an enriched $^{185}$Re target [180]; sufficient SA for RSV can be attained because of the high thermal and epithermal cross-sections for neutron capture of $^{185}$Re (106 and 1632 b, respectively).
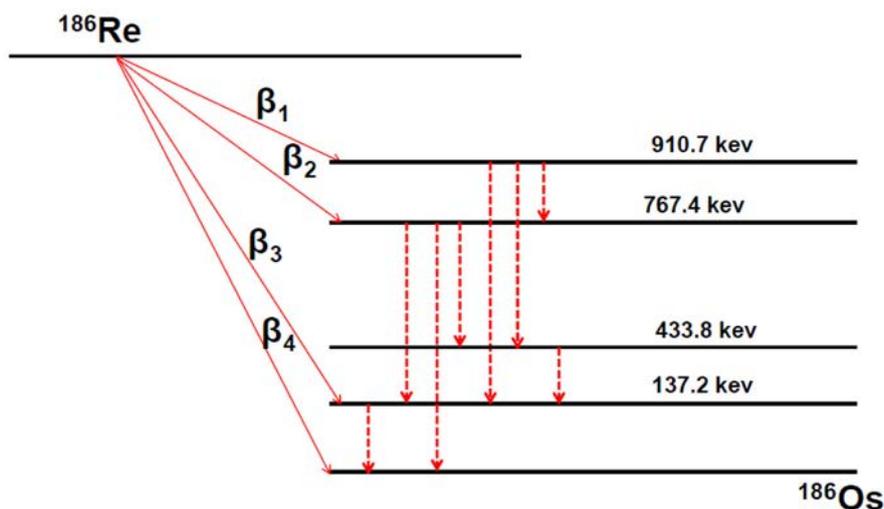
*FIG. 14. Nuclear decay characteristics of $^{186}$Re. Courtesy of A. Dash.*

### 5.6.7.2. Disadvantages

Using $^{186}$Re for the preparation of bone seeking radiopharmaceuticals is limited by the following disadvantages:

— The requirement for an enriched $^{185}$Re target for production makes it cost ineffective compared with $^{166}$Ho.
— The chemistry for radiolabelling is complicated compared with that of trivalent lanthanides.

The prospect of developing particles radiolabelled $^{186}$Re for use in RSV has attracted considerable attention and led to much fascinating research and innovative strategies being published in the literature [175, 403–412].

### 5.6.8. $^{188}$Re

$^{188}$Re has a half-life of 16.9 hours and decays to $^{188}$Os with emission of β– particles with a maximum energy of 2.11 MeV, followed by a 155 keV gamma emission (15%) with an average tissue penetration depth of 3.5 mm. Its low level gamma ray emission (155 keV) makes scintigraphic monitoring as well as dosimetry evaluation possible. The radionuclide $^{188}$Re has a beta ray emission of sufficient energy (2.11 MeV) to penetrate 5–10 mm of thickened synovial membrane. Its half-life (16.9 h) is adequate to obtain an appropriate therapeutic effect and suitable for handling and avoiding hazardous residual effects. The nuclear decay characteristics of $^{188}$Re are shown in Fig. 15.

### 5.6.8.1. Advantages

The use of $^{188}$Re in RSV is associated with the following advantages:

— $^{188}$Re is a more attractive candidate than $^{186}$Re, since it can be obtained on demand in NCA form in a highly reproducible manner from a $^{188}$W/$^{188}$Re generator at a hospital based or central radiopharmacy. The long 69.7 day half-life of the $^{188}$W generator parent ensures that the generator has an operational shelf life of some months. It is possible to use one generator for 6–12 months (depending on the generator rated activity).
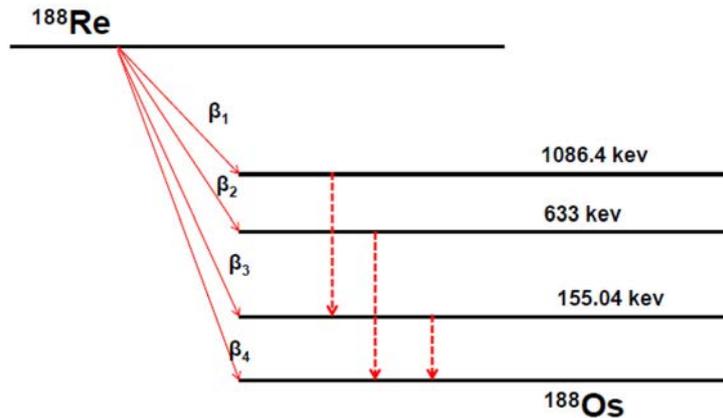
*FIG. 15. Nuclear decay characteristics of $^{188}$Re. Courtesy of A. Dash.*

— The highly energetic $\beta^-$ radiation emitted by $^{988}$Re ($E_{\beta(max)}$=2.1 MeV) is able to penetrate 5–10 mm of thickened synovial membrane and is thus suitable for treating large joints such as knees.
— $^{188}$Re decay is accompanied by a 155 keV predominant energy gamma emission, which can be detected by gamma cameras for imaging, leakage and dosimetry calculation.
— The 16.7 hour half-life of $^{188}$Re is optimal for preparing the radiolabelled particles either in a hospital radiopharmacy or centralized radiopharmacies, performing quality control and administration.
— The versatile chemistry of rhenium emerging from eight possible oxidation states allows attachment to a variety of bone targeting molecules with specific characteristics. Such a possibility provides great versatility for the development of a range of $^{188}$Re labelled bone seeking radiopharmaceuticals.
— $^{188}$Re is a non-bone seeking and non-residualizing radioisotope that does not linger in the body and lymph nodes due to extra-articular leakage, making it particularly attractive for RSV.
— $^{188}$Re has equivalent tissue penetration to $^{90}$Y but a shorter half-life, which is important for reducing the radiation dose due to leakage of radionuclides to non-target organs outside the injected joint.

### 5.6.8.2. *Disadvantage*

The use of $^{188}$Re in RSV is associated with the following disadvantage:

— Cost effective availability of the $^{188}$W/$^{188}$Re emerged generator is the main roadblock obstructing its widescale use in clinical practice.

The extensive use of $^{188}$Re in RSV is a reflection of its key clinical importance [273, 413–428].

### 5.6.9. $^{153}$Sm

$^{153}$Sm decays with a physical half-life of 46.27 hours (1.93 days) through beta emissions with maximum energies of 0.810 MeV (20%), 0.710 MeV (49%) and 0.640 MeV (30%) and has an average penetration of 0.8 mm and a maximum one of 3.1 mm in soft tissues. It is produced by neutron capture of natural or isotopically enriched $^{152}$Sm with thermal and resonance neutron cross-sections of 210 and 3020 b, respectively. The nuclear decay characteristics of $^{153}$Sm are presented in Fig. 16.

The main advantages of $^{153}$Sm are its optimal half-life, relatively high thermal neutron activation cross-section (210 b) and diagnostic gamma energy of 103 keV, which can be easily distinguished via energy windowing. Hence, images with high spatial resolution and minimal noise can be obtained following each procedure. Although its beta energy is about 2.8 times lower than that of $^{90}$Y, this can always be compensated by administering higher activity of $^{153}$Sm to deliver complementary therapeutic
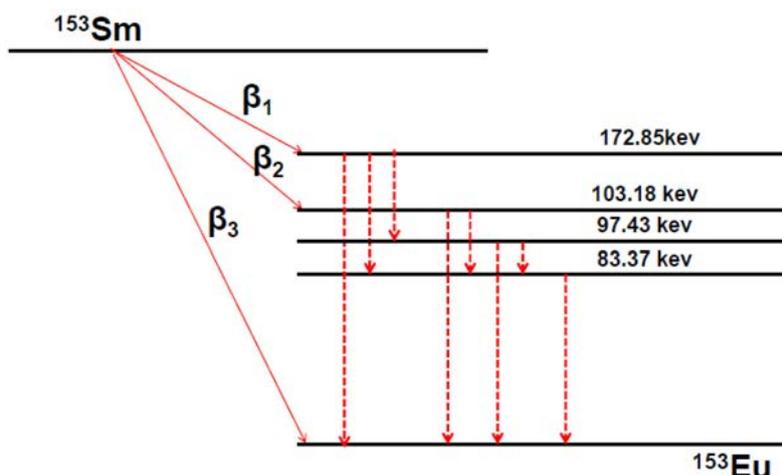
*FIG. 16. Nuclear decay characteristics of $^{153}$Sm. Courtesy of A. Dash.*

dose to the tumour, which can easily be achieved due to its high cross-section value. A number of studies using $^{153}$Sm in RSV have been reported in the literature [297, 429–434].

### 5.6.9.1. Advantages

$^{153}$Sm has the following advantages when used in RSV:

— A reasonably long half-life of ~46.27 hours is an advantageous attribute as it decreases the risks associated with eventual leakage of the radioisotope.
— The medium energy beta particles have an average range of 0.8 mm and maximum range of 3.1 mm in soft tissues. This tissue penetration depth is satisfactory for synovial membrane ablation without causing substantial damage to nearby extra-articular tissue, including cartilage or bone. The beta energy emitted by $^{153}$Sm is suitable for synoviorthesis of medium-sized joints such as the hip, shoulder, elbow, wrist, ankle and subtalar joint, and at the same time it offers the possibility of improving the radionecrosis effect using higher radioactivity levels [1].
— The medium energy beta emission offers protection to the extra-articular tissue and adjacencies from radiation dose.
— The beta decay is accompanied by 28% emission of 103.2 keV gamma rays, which can be distinguished easily via energy windowing. Hence, images with high spatial resolution and minimal noise can be obtained following each procedure and these can be used to analyse leakage to other organs.
— The chemistry of $^{153}$Sm offers enormous scope for conjugation with a wide range of particles following standard radiolabelling procedures using a post-labelling approach.
— Cost effective production of $^{153}$Sm with the required SA and quantities can be carried out via neutron capture of natural or isotopically enriched $^{153}$Sm as $Sm_2O_3$ in a nuclear reactor following the $^{152}$Sm(n,$\gamma$)$^{153}$Sm path due to the relatively high thermal neutron capture cross-section (206 b). It can be produced in many nuclear reactors throughout the world and can offer a certain degree of independence from importation of isotopes for performance of RSV.

### 5.6.9.2. Disadvantages

$^{153}$Sm has the following disadvantages when used in RSV:

— The physical half-life is 46.27 hours, which causes logistical difficulties for shipment to nuclear medicine centres that are distant from reactors.

— The requirement for an enriched $^{152}$Sm target for the production of $^{153}$Sm makes it cost ineffective compared with $^{166}$Ho.

## 5.6.10. $^{117m}$Sn

Initially, low-SA $^{117m}$Sn was employed in phase 1 and 2 clinical trials in the USA and Canada for bone pain palliation. This radioisotope emits both conversion electrons for therapy and gamma energy for imaging. The energy emitted is lower than that of traditional radiation therapy; the conversion electrons deposit their energy in an absolute 1/3 mm range in a discrete, predictable fashion with an ideal two week half-life suitable for delivering an extended low dose rate treatment.

The homogeneous $^{117m}$Sn colloid is manufactured to a consistent size range (full width 2–20 $\mu$m; mean 5–6 $\mu$m). The particle size is large enough to allow the $^{117m}$Sn colloid to remain >99% within the injected joint, and yet is small enough to be readily engulfed by the inflammatory synovial macrophages. Pre-clinical studies on animal models have been completed. A commercial $^{117m}$Sn colloid formulation was well characterized with a validated shelf life of two weeks and is being finalized in a trial of dogs with naturally occurring elbow arthritis. The production yields of 117$^{m}$Sn using an inelastic pathway in a research reeactor are shown in Fig. 17.

## 5.6.11. $^{90}$Y

$^{90}$Y has a half-life of 64.1 hours and decays to the stable $^{90}$Zr decay product by emission of high energy $\beta-$ radiation ($E_{\beta max}$=2.28 MeV and $E_{\beta mean}$=0.935 MeV). The beta radiation deposits ~80% of the energy into the first 4–5 mm, which makes it an almost ideal radionuclide for intra-articular RSV of large joints (knees). $^{90}$Y is an appropriate radionuclide for the knee joint and those with substantially thickened synovia. With a half-life of 2.7 days, the ionization is persistent enough to shrink this tissue by reducing the production of synovial fluid. A simplified decay scheme for $^{90}$Y is shown in Fig. 18.
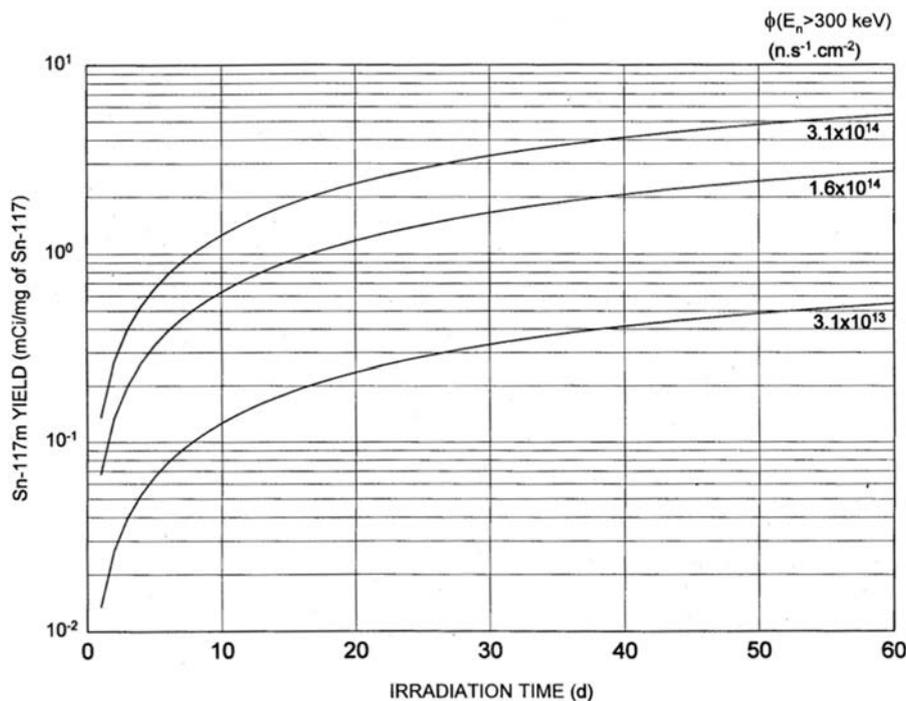


FIG. 17. Production yields of $^{117m}$Sn by the inelastic pathway. Reproduced from Ref. [187].
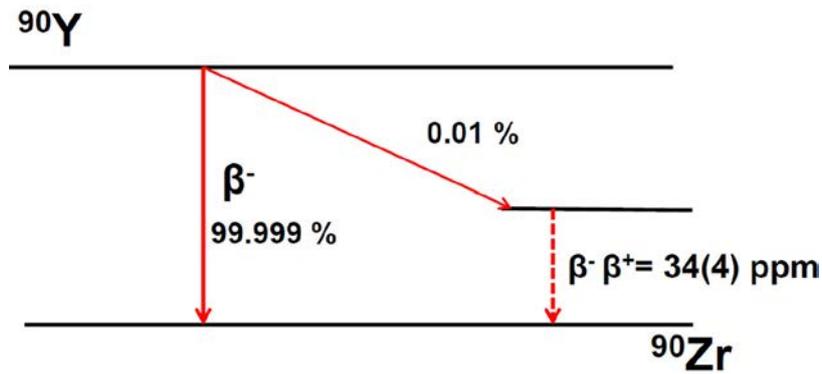
FIG. 18. Simplified decay scheme of $^{90}Y$. Courtesy of A. Dash.

### 5.6.11.1. Advantages

The striking diffusion of and exciting prospects for $^{90}Y$ in RSV are primarily attributed to the following:

— A half-life of 64.1 hours is convenient for radiolabelling and performing quality control and administration.
— As a pure beta emitter of high energy $\beta^-$ radiation ($E_{\beta max}$=2.28 MeV), it has the ability to penetrate deeply into the tissue, which makes it an appropriate radionuclide for the knee joint and those with substantially thickened synovia.
— $^{90}Y$ is available on demand in NCA form in a highly reproducible manner from a $^{90}Sr/^{90}Y$ generator at a hospital based or central radiopharmacy.
— Because of the 28.8 year half-life of $^{90}Sr$, it is possible to obtain $^{90}Y$ for long term use.
— The widespread availability of $^{90}Y$ at a reasonable cost makes it an economical choice for RSV.
— Yttrium exists almost exclusively in a tricationic state and is amenable for conjugation with a wide range of particles following standard radiolabelling procedures.

### 5.6.11.2. Disadvantages

The principal limitations of using $^{90}Y$ in RSV are as follows:

— Because of the lack of gamma photons, conventional scintigraphic imaging and assessment of the post-therapy distribution of its radioactivity are challenging.
— Safe handling requires operators with the knowledge and skill to use appropriate radiation protection techniques to minimize the risk of a potentially harmful dose to the skin as it poses a high risk to the skin of operators and patients.
— Any leakage that may occur from the joint when combined with the 2.7 day half-life is likely to result in significant integrated radiation doses to other organs, such as the lymph nodes, liver and kidneys.

By a large margin, $^{90}Y$ is the radioisotope used most extensively in hypertrophic and exudative knee synovitis in patients with rheumatic diseases: rheumatoid arthritis, osteoarthrosis and peripheral spondyloarthropathies (psoriatic arthritis and ankylosing spondylitis) [1, 17, 99, 162, 164, 387, 435–467].

# 6. METHOD USED TO PREPARE PARTICLES FOR RADIOSYNOVECTOMY

## 6.1. INTRODUCTION

Particles are defined as particulate dispersions or solid particles with diameters in the micrometre range (typically from 1–1000 $\mu$m). They are composed of a homogeneous mixture of a defined chemical composition and can be manufactured from a large variety of starting materials, both natural and synthetic, and by using many different preparation techniques. Depending upon the method of preparation and starting materials, a wide variety of particles or microspheres can be obtained, in terms of size, size distribution, composition, surface chemistry, topography and morphology. While microspheres are completely spherical and homogeneous in size, particles that are less homogeneous in size and shape are generally also termed microspheres. Depending on the preparation method and material used, microspheres show a typical size distribution that often deviates from the mono-sized ideal [181].

Achieving simple, low cost and high yield preparation of particles has been a great challenge since the very early development of RSV. Numerous methods have been developed for the preparation of particles. The properties of particles depend largely on their preparation methods. Each procedure has specific benefits and drawbacks. The selection of an appropriate method for the preparation of particles depends on the expected size of the particles and their physicochemical characteristics. In this chapter, the methods used for the preparation of particles include:

— Precipitation;
— Emulsion;
— Evaporation or extraction of solvent;
— Sol-gel;
— Spray-drying;
— Electrospraying.

The techniques, principles, advantages and disadvantages of each preparation method are also a point of discussion.

## 6.2. PRECIPITATION

Precipitation involves mixing two aqueous solutions of soluble salts to form an insoluble precipitate that is separated. In the precipitation method, the precursors used are mostly inorganic salts (nitrate, chloride, sulphate, etc.) that are dissolved in water or any other suitable medium to form a homogeneous solution. The solution is then subjected to pH adjustment and precipitated by the addition of precipitating reagents (usually hydroxides, carbonates, oxalates or citrates, etc.) to the solution. Precipitation and aggregation are influenced by the concentration of salt, temperature, the actual pH and the rate of pH change. In actual practice, the precipitate is heated to the required temperature in an appropriate atmosphere to undergo condensation. Precipitation reactions involve the simultaneous occurrence of nucleation, growth, coarsening and/or agglomeration processes.

Nucleation is the formation within a supersaturated solution of the smallest particles of a precipitate (nuclei) capable of spontaneous growth. If the precipitation is carried out in such a manner as to produce numerous nuclei, it will be rapid, the individual crystals will be small, filtration and washing will be difficult, and the purity will be low. On the other hand, if precipitation is carried out so that only a few nuclei are formed, precipitation will be slower, crystals will be larger, filtration will be easier and purity will be higher. Hence, control of nucleation processes is of considerable significance in precipitation.

Once the crystal nuclei are formed, crystal growth proceeds through diffusion of the ions to the surface of the growing crystal and deposition of those ions on the surface. This crystal growth continues until supersaturation of the precipitating material is eliminated and equilibrium solubility is attained.

The reactions tend to exhibit the following characteristics:

— The products of precipitation reactions are generally sparingly soluble species formed under conditions of high supersaturation.
— Such conditions dictate that nucleation will be a key step of the precipitation process and that a large number of small particles will be formed.
— Secondary processes, such as Ostwald ripening and aggregation, will dramatically affect the size, morphology and properties of the products.
— The supersaturation conditions necessary to induce precipitation are usually the result of a chemical reaction.

A schematic diagram of the precipitation process is presented in Fig. 19.

Precipitations are generally carried out from dilute solutions, adding the precipitant slowly with some form of agitation to a hot solution. Normally, the precipitant is then allowed to age before it is removed by filtration and washed. Due to the necessity of producing particles of desired sizes, these precipitates are subsequently calcined at appropriate temperatures, cooled and sieved to obtain the final product. Each precipitation reaction requires its own precursor and precipitating reagent and at the same time each precipitation process requires control of the concentration of the solution, the pH, the temperature and the stirring speed of the mixture in order to obtain a final product with the required properties.

A few commonly used steps that dictate the success of precipitation are:

— Taking appropriate stoichiometric amounts of the starting materials;
— Making an appropriate quantity of solution of optimum pH;
— Keeping the precipitation solution at optimum pH;
— Performing filtration to remove water, undesired ions and impurities.

A precipitation process needs to satisfy the following three main requirements:

(1) Quantitative precipitation is desirable.
(2) The precipitate formed ought to be amenable to filtration and ought not to creep.
(3) The precipitate ought to be obtained from known purity.
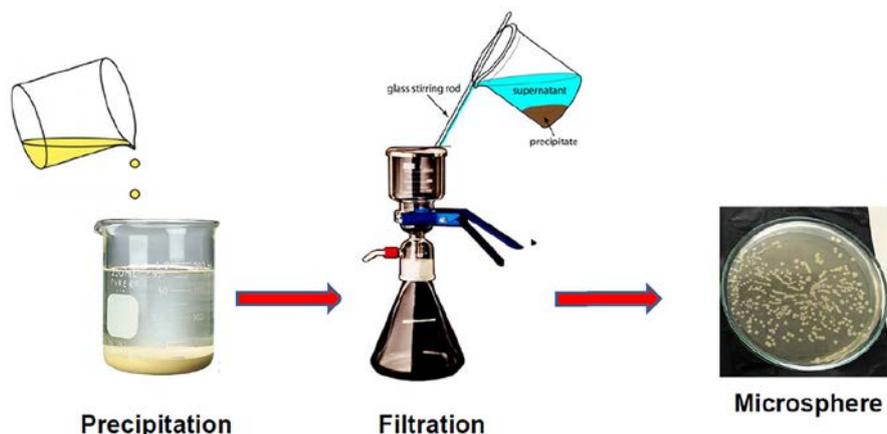


FIG. 19. Schematic illustration of the precipitation process. Courtesy of A. Jalilian.

Factors affecting precipitation include the following:

— *Rate of precipitation.* A slow rate of precipitation is desirable as it favours the growth of larger crystals. The solubility of larger crystals is lower than that of smaller crystals due to the exposure of less surface area to the solution. The gradual addition of dilute solution of the precipitant to a medium, with stirring, is desirable.
— *Concentration of ions and solubility of solids.* The rate of precipitation depends not only on the concentration of ions in solution, but also on the solubility of the solids formed during the equilibrium process. While a solution containing an optimal concentration of ions sufficient to form a precipitate will slow down the process, it is advantageous because larger crystals of lower solubility can be formed.
— *Temperature.* While precipitation at elevated temperatures is desirable to slow down the nucleation and crystal growth due to the increased thermal motion of the particles in solution, the increased solubility of the precipitate at elevated temperature is an impediment and reduces the precipitate yield. Therefore, an optimal temperature is chosen that balances these opposing factors.
— *Digestion.* Digestion is a process that involves heating the solid and parent liquor for a certain period of time. The growth of larger nuclei or crystallites can be encouraged by digestion. During digestion, the small crystals dissolve and larger crystals grow (Ostwald ripening). Digestion also reduces impurities (occluded ions) effectively, as the process reduces the surface area for adsorption of foreign ions owing to the recrystallization of the small crystals and growth of larger crystals. During the process of digestion, impurities are replaced by common ions that properly fit the crystal lattice.
— *Solvent.* The polarity of the solvent affects the solubility of an ionic solid (precipitate) in the solvent. The addition of another miscible solvent in the solution is avoided, as it would alter the polarity. The polarity of water is reduced by the addition of alcohols, thereby reducing the solubility of precipitates.
— *Common ion concentration.* The addition of a reagent, exploiting the common ion effect for the complete precipitation of a particular ion of a sparingly soluble salt with a low value of solubility product, is routine. However, in some cases, the excess presence of common ions increases the solubility of the precipitate by decreasing the activity of the ions in solution, as they become more concentrated in the solution and deviate from ideal behaviour.
— *Stirring.* Stirring the solution during precipitation is desirable as it increases the motion of particles in the solution and decreases the localized buildup of concentrations of ions. Both of these properties not only slow nucleation and crystal growth, but also promote the formation of larger and purer crystals. Stirring also promotes recrystallization because the smaller crystals, with their net larger surface area, are more soluble under these conditions.
— *Complex ion formation.* In order to prevent impurities from precipitating by producing a more soluble form of a solid, forming complex ions may be effective, if pursued diligently.
— *pH effect.* Altering the pH of aqueous solutions will alter the concentration of ions in the precipitation equilibrium by the common ion effect if the hydrogen ion ($H+$) or hydroxide ion ($OH-$) is common to the equilibrium.
— *Precipitation from homogeneous solution.* The addition of a precipitating agent to a solution of ions causes a localized excess of the reagent (higher concentrations) to form in the mixture. While the excess reagent is conducive to rapid formation of a large number of small crystals, it produces a precipitate of imperfect crystals that contains excessive impurities. The precipitate formed under these conditions is sometimes voluminous and difficult to filter. Localized excesses can also cause precipitation of more soluble solids than the expected precipitate.
— *Reprecipitation.* This approach increases the purity of precipitates. During the initial precipitation, the precipitate formed only contains a small number of foreign ions as a result of adsorption. Upon dissolution of the precipitate, the foreign ions are released into the solution, producing a much lower concentration of impurities than that in the original precipitating solution [468]. On reprecipitation, a small fraction of impurities is carried down with the precipitate, but the amount is much smaller

than in the original because their concentration in solution is lower. While the elimination of foreign ions due to adsorption is not ruled out, their concentration can be reduced to an appreciable extent.

The precipitation method offers the following advantages:

— It is a very simple and rapid technique for the synthesis of small sized particles, homogeneously and evenly distributed with a single phasic nature.
— It requires very low heating treatment; there is sometimes no need to calcinate the product and infrared or microwave drying is sufficient.
— It can achieve uniform particle size.
— It is possible to control particle size and composition.
— It is preferable when large quantities of particles are required.
— A variety of precursor selections can be chosen as the starting materials, from simple salts to complicated organic–inorganic materials.
— It offers various possibilities for modification of the particle surface state and overall homogeneity.
— It is cost effective and easy to set up and scale up.

Despite the above benefits, this method has its share of challenges, including the following:

— There is difficulty in controlling the process in terms of reaction kinetics and the solid phase nucleation and growth processes. Therefore, solids obtained by chemical precipitation have a wide particle size distribution plus uncontrolled particle morphology, along with agglomeration.
— It is very pH sensitive and this has to be carefully controlled to achieve better products.
— It is highly susceptible to the reaction conditions, and because of incomplete precipitation of the metal ions, control over the stoichiometry of the precursors is rather difficult to achieve.
— It does not work well in cases where:
    • The two reactants have different solubilities in water;
    • The reactants do not precipitate at the same rate;
    • Supersaturated solutions commonly occur.

## 6.3. EMULSION: EVAPORATION OR EXTRACTION OF SOLVENT

The emulsion technique is used to prepare microspheres of natural polymers (i.e. proteins and carbohydrates). The process essentially consists of emulsifying polymers in oil in water (o/w). Usually the organic phase is composed of a volatile solvent, which dissolves the polymer and emulsifies it in an aqueous phase.In light of the perceived need to prevent the organic droplets from coalescing after their formation, the inclusion of a surfactant in the aqueous phase is deemed worthy of consideration. During the second step, the polymer solvent is evaporated, inducing precipitation. The particles are collected by ultracentrifugation and washed with distilled water to remove impurities. A flowchart illustrating the emulsion technique is presented in Fig. 20.

The polymer–solvent solution is emulsified (with appropriate experimental conditions) by using a propeller or magnetic bar to mix the organic and aqueous phases to yield an o/w emulsion. The next step consists of crosslinking the dispersed globule either by means of heat or by using the chemical crosslinkers. Glutaraldehyde, formaldehyde and acid are the common chemical crosslinking agents used. Heat denaturation is not recommended for thermolabile substances. The nature of the surfactants used to stabilize the emulsion phases can greatly influence the size, size distribution, surface morphology and in vivo stability of the final particulate product [469, 470]. Particle preparation using the emulsion technique is depicted in Fig. 21.
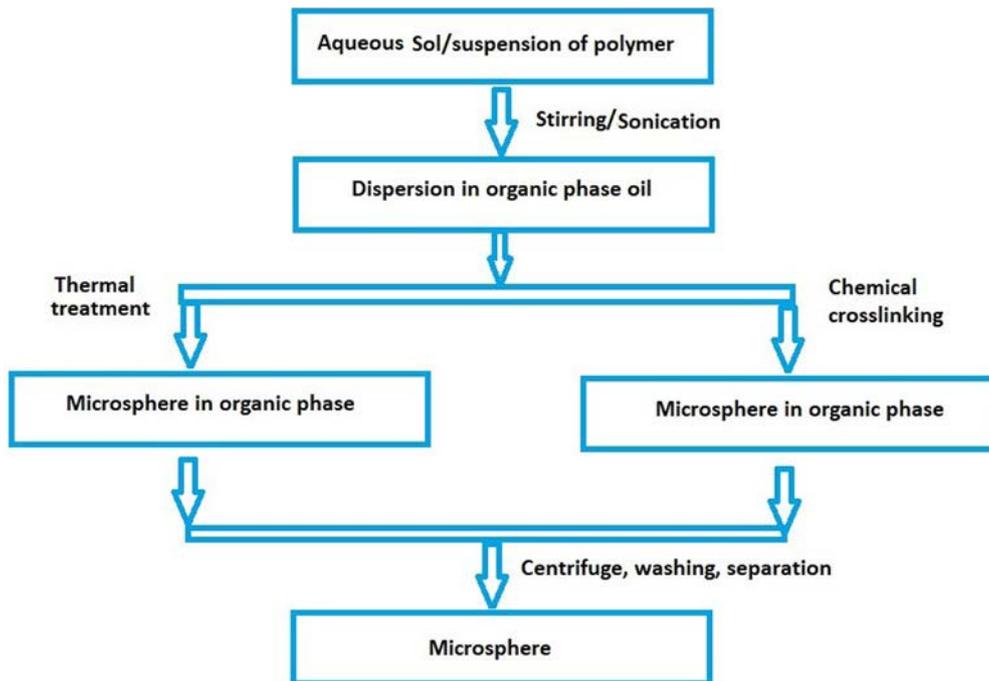
*FIG. 20. A flowchart illustrating the emulsion technique. Courtesy of A. Dash and A. Jalilian.*
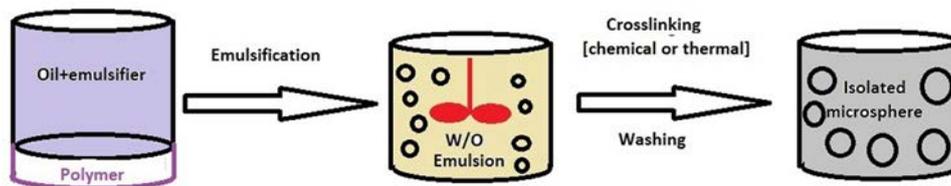


*FIG. 21. Microparticle preparation using the emulsion technique. Courtesy of A. Dash and A. Jalilian.*

The preparation method essentially consists of four major steps [471]:

(1)  Dissolving the polymer in an organic solvent containing the matrix-forming material;
(2)  Emulsiying this organic phase, called the dispersed phase, in an aqueous phase immiscible with the first one, which is called the continuous phase;
(3)  Extracting the solvent from the dispersed phase by means of the continuous phase and evaporating the solvent;
(4)  Harvesting and drying the microspheres.

Operating conditions such as the ratio of dispersed phase to continuous phase, agitation, pressure and temperature have a great influence on solvent evaporation and consequently on the structure of the particles.

Emulsion processes offer the following advantages:

— It is easy to control the particle size.
— There is the potential for rapid polymerization to yield high molecular weight polymers with low polydispersity.

— The viscosity of polymer emulsion is much lower than that of straight polymer in the melt phase; it is easier to process but also allows the production of polymers that are extremely sticky as 100% polymer.
— The final product can easily be removed from the reactor due to lower viscosity (and can be washed out with water).
— The continuous phase (water) acts as a heat sink and allows the temperature to be much better controlled, avoiding dangerous overheating.

Some disadvantages associated with this technique include the following:

— Emulsions are thermodynamically unstable and have a short shelf life.
— Polymer can easily become contaminated with traces of the emulsifier.
— Improper selection of the emulsifying agent leads to phase inversion and may sometimes lead to cracking.

## 6.4. SOL-GEL PROCESS

Sol-gel is a wet chemistry process of preparing microparticles or microspheres that encompasses preparing a solution (sol), gelating the sol to obtain gel, and removing the liquid inhering in fine interconnected channels within the gel. It basically involves the transformation of liquid precursors to a sol and finally to a network structure called a 'gel' that contains both the liquid phase and the solid phase. The morphologies of these two phases range from discrete particles to continuous polymer networks and offer the scope to control the chemical composition of the product [472].

*Sol*

A sol is a dispersion of solid particles (~0.1–1 $\mu$m) in a liquid where only Brownian motion suspends the particles . A sol is a state in which solid particles are neither dissolved nor agglomerated or sedimented. Generally, sol particles may interact by means of van der Waals forces or hydrogen bonds. The stability of sols may be maintained by using dispersing agents. Sols are commonly used in preparing sol-gel [473].

*Gel*

A gel is a state in which both liquid and solid are dispersed in each other and which presents a solid network containing liquid components [474]. A gel is a solid, jelly like material that can be defined as a substantially dilute crosslinked system that exhibits no flow in the steady state. While gels are mostly liquid by weight, they behave like solids owing to the presence of a three dimensional crosslinked network within the liquid. The interactions between gel particles are short range and the gel process is irreversible [475, 476]. The solid network within the fluid of a gel contributes its structure (hardness) and is primarily responsible for its adhesive characteristics [472].
The preparation method consists of the following steps:

(a)    Dispersion of the desired colloidal particles in a liquid to form a sol following  hydrolysis and partial condensation of alkoxides;
(b)    Formation of the gel via polycondensation to form metal–oxo–metal or metal–hydroxy–metal bonds;
(c)    Syneresis or 'ageing', in which condensation continues within the gel network, often shrinking it and resulting in expulsion of solvent;
(d)    Drying the gel either to form a dense 'xerogel' via collapse of the porous network or an aerogel, for example through supercritical drying;
(e)    Removal of surface M–OH groups through calcination at a high temperature up to $800^{\circ}$C (if required).

A schematic diagram of the various steps involved in the sol-gel process for microparticle/microsphere preparation is provided in Fig. 22.

A sol-gel synthesis involves two major steps: the first step consists of the creation of a colloidal solution from the hydrolysis and polymerization reactions of the precursors, and the second step comprises the conversion of this solution into a gel, usually by hydrolysis, by adding a gelling agent or by hydrothermal treatment. In the second step, the sol is chemically transformed into a gel [477]. Experimental factors that affect either or both of these reactions determine the properties of the gel and, in turn, the properties of the material at the subsequent processing steps. These factors include the chemical nature of the precursor, the type of solvent, water content, acid or base content, precursor concentration and temperature.

The physicochemical process involved in sol-gel consists of the following:

(a) *Mixing.* The alkoxide precursor is hydrolyzed by mixing it with water. In the sol-gel process, controlling the pH of the starting solution is very important to avoid precipitation and form a homogenous gel; this can be achieved by the addition of base or acidic solutions [478].

(b) *Gelation.* The condensation reaction can build up larger networks by processing polymerization to form a three dimensional network, which leads to formation of the gel. The gelation time will depend on the temperature, solvent, pH condition and removal of the solvent.

(c) *Ageing.* After gelation, the wet gel can be either aged in its parent liquor or in another solvent or be washed. The time between the formation of a gel and its drying is known as ageing. During the ageing period, polycondensation takes place and results in the expulsion of liquid from the pores. This increases the thickness of particle necks and decreases the porosity. Thus, with ageing, the strength of the gel increases.

(d) *Drying.* Liquid existing in the interconnected pore network is removed during the drying process. Thus, there is a decrease in the volume of the gel, which is equal to the volume of the liquid lost by evaporation. Here, after drying, the pores of the gel are substantially emptied.

(e) *Stabilization.* This involves the removal of unwanted elements such as H and R, respectively, from M–OH and M–OR bonds to obtain the chemically stable required compound.

(f) *Densification.* This is the last treatment process for the gel. By heating the porous gel at high temperatures, the pores can be eliminated and densified and a polycrystalline material can be obtained. The densification temperature depends on the dimensions of the pore network, the conductivity of pores and surface area, among other factors.

*Advantages*

The sol-gel process offers the following advantages:

(a) There is no need to reach the melting temperature, since the network structure can be achieved at relatively low temperatures.

(b) A variety of precursors can be selected as starting materials. This enables the preparation of microspheres of extended composition range, including inorganic as well as organic compositions.
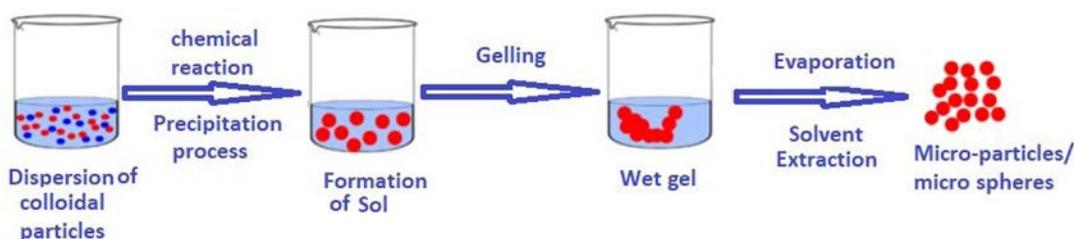


*FIG. 22. Microparticle/microsphere preparation by sol-gel. Courtesy of A. Dash and A. Jalilian.*

(c)     It is possible to control the structure of microspheres, including porosity and particle size.
(d)     It produces small, homogeneous particles (due to mixing at the molecular level) with uniform size distribution.
(e)     It yields predefined stoichiometric compounds of a monodispersive nature.
(f)     The smaller particle size offers the possibility of controlling the morphology.
(g)     It is very easy to handle and set up, avoiding the need for special or expensive equipment.
(h)     It is cost effective.

*Disadvantages*

The sol-gel process also has disadvantages:

(a)     It requires expensive raw materials (in the case of metal alkoxides) compared with mineral based metal ion sources.
(b)     The shrinkage of a wet gel upon drying may lead to fracture due to the generation of large capillary stresses. As a result, it is difficult to obtain large monolithic particles.
(c)     Particles will contain high carbon content when organic reagents are used in the preparative steps and this may inhibit densification during sintering.
(d)     As the process is multistep, close monitoring of each step is warranted.
(e)     Difficulties are encountered during the preferential precipitation of a particular oxide during sol formation due to the different reactivity of the alkoxide precursors.

## 6.5.   SPRAY DRYING

Spray drying is a technique in which a fluid is transformed from a fluid state into dried particulate form by spraying the feed into a hot drying gas medium (generally air) [479]. This process is attractive as it involves both particle formation and drying. Based on the action of drying, the transformation of liquid from a fluid state into dried particulate is divided into two main categories: spray drying and spray congealing. In spray drying the action is primarily that of evaporation, whereas in spray congealing the action consists of a phase change from a liquid to a solid. While the two processes are similar, the energy flow is different. In the case of spray drying, energy is applied to the droplet to cause evaporation of the medium, resulting in both energy and mass transfer through the droplet. In spray congealing, energy is only removed from the droplet, forcing the melt to solidify [480].

Four fundamental steps are involved in spray drying [481, 482]:

(1)     Atomization of a liquid feedstock into a spray of fine droplets. The atomization stage is designed to create optimal conditions for evaporation and to lead to a dried product with the desired characteristics. Selection of an atomizer is based primarily on the droplet sizes to be produced in order to achieve the required particle size [483].
(2)     Spray–air contact, mixing and droplet/particle flow. When the feed is atomized and sprayed through the drying chamber, the droplets come into contact with the heated drying medium, resulting in solvent evaporation.
(3)     A combination of drying and particle formation. When contact is established between the spray droplets and the drying air, evaporation of the solvent takes place immediately. In this process, diffusion of solvent from within the droplet is maintained at saturated surface conditions to result in a constant drying rate. When the solvent content in the droplet becomes too low to sustain a saturated surface, a dry layer begins to form at the droplet surface.
(4)     Particle separation from the drying air and collection of the dry product from the gas stream.

Figure 23 provides a schematic diagram of the typical spray drying process.
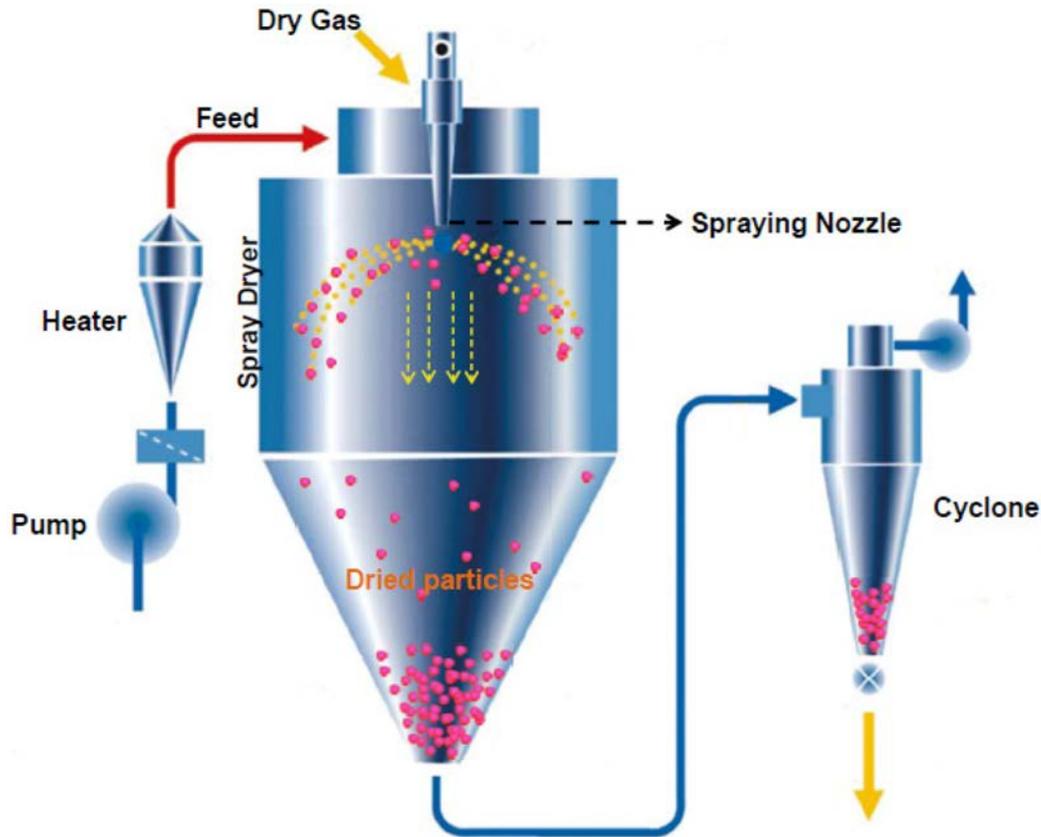
*FIG. 23. Schematic diagram of the typical spray drying process. Courtesy of A. Dash.*

At the beginning, the fluid is fed into the drying chamber through an atomizer or nozzle using a suitable pumping device [484]. The small droplets generated (micrometre scale) are brought into contact with hot gas (usually air, in a vacuum) in a spray dry chamber, resulting in fast solvent evaporation in the droplets, which leads to the formation of dry particles [485]. The way in which the spray makes contact with the air in the dryer influences the behaviour of the droplet during the drying phase and has a direct bearing on the properties of the dried product. Different products have differing evaporation and particle forming characteristics. Some expand and others contract, fracture or disintegrate.

Following completion of drying, the product particles are separated from the drying air following primary and final separation strategies. Primary separation is realized by allowing the particles to fall at the bottom of the chamber in which a small fraction of the particles remain entrained with the air and can be recovered in separation equipment. A cyclone is used for the final separation stage to depose particles in a glass collector situated at the bottom of the device.

The fluids used in the spray drying process include solutions, suspensions, emulsions, slurries, pastes or melts [486, 487]. The operating configurations in spray drying may be either open loop or closed loop. Air is used in the open loop configuration as drying gas and is not recirculated. In the closed loop configuration, by contrast, an inert gas (e.g. nitrogen) is used as a drying gas and is recycled in the drying chamber throughout the entire process. The open loop configuration is widely used, as it is more cost effective and stable.

The operating parameters that can be fine tuned to obtain products with desirable characteristics are:

(a) The process parameters;
(b) The properties of the liquid feed;
(c) Equipment design.

*Advantages*

The spray drying process has the following advantages:

(a) It is rapid, continuous, single step and scalable.
(b) It offers product reproducibility: as long as the drying conditions remain constant, the dried product characteristics remain constant.
(c) It is possible to obtain uniform and controllable particle size.
(d) It is suitable for heat sensitive and non-drying heat sensitive materials without major detrimental effects, because of the atomization of the liquid into small droplets with a high surface area to volume ratio that results in very fast solvent evaporation.
(e) Solid products obtained after the process have the advantage of higher chemical and physical stability compared with liquid formulations.
(f) A wide variety of sprays are commercially available to meet various conditions.
(g) It provides the scope for precise control of particle size, bulk density, degree of crystallinity, organic volatile impurities and residual solvents.
(h) It can produce almost spherical uniformly sized particles.

*Disadvantages*

Regardless of the numerous advantages displayed by the spray drying process, it has the following limitations:

(a) Product yield is strongly dependent on the work scale, with yields being high in larger scale set-ups (the yield is 20–70% at the laboratory scale).
(b) It involves dry convection, and the thermal efficiency is relatively low, generally 30–40%.
(c) It requires expensive and bulky equipment.

## 6.6. ELECTROSPRAYING

In a typical electrohydrodynamic process, a liquid precursor is fed into a nozzle with the aim of forming a droplet at the nozzle. When the droplet is exposed to a strong electric field, a charge is induced on the surface of the droplet. Under the influence of the electrostatic field, the droplet at the tip of nozzle forms a conical spraying mode. From the tip of this cone, a charged jet of liquid precursor is driven into the collector, which carries a charge that is opposite to the droplet or is grounded.

Processing parameter (e.g. working distance, voltage) techniques can be effectively tuned to produce micro- and nanoscale fibres and particles composed of polymers, ceramics or composites [488, 489]. There are two main techniques in electrohydrodynamic atomization processing: electrospraying and electrospinning. Electrospraying describes a technique whereby particles are created while the term electrospinning is used in situations in which fibres are created. Electrospraying is a method of producing particles by using a high voltage electric field to break up a solution.

Electrospraying is a physical process, used to form particles from a variety of materials, in which a viscous liquid is subjected to an electrical shear stress by maintaining the nozzle at a high electric potential. This process avoids the use of additional mechanical energy other than that from the electric field. In this process a liquid precursor is passed through a capillary that is held at high potential. The effect of the high electric field as the solution emerges from the capillary nozzle in the form of a fine jet is to disperse into highly charged droplets [490]. The droplets produced by electrospraying are usually close to one half of the Rayleigh limit, and can be smaller than 1 mm. The size distribution of the droplets

is usually narrow, with low standard deviation. During that transition, the droplets reduce in size by evaporation of the solvent or by 'Coulomb explosion' (droplet subdivision resulting from the high charge density). Eventually, fully desolvated ions form as a consequence of complete evaporation of the solvent or field desorption from the charged droplets. It is possible to produce small, almost monodisperse particles using a colloidal suspension or a solution of a material through this route [491]. The size of the droplets can be controlled effectively, mainly by fine tuning the liquid flow rate, and their charge by regulating the voltage applied to the nozzle. It is important to emphasize that the charged aerosol is self-dispersing, which prevents the droplets from coagulating. The standard electrospraying configuration is shown in Fig. 24.

Electrospraying consists of four major components:

(1)    A pumping system (often a syringe pump);
(2)    A metal nozzle;
(3)    A high voltage power supply;
(4)    A grounded substrate as collector.

The solution delivered to the tip of the electrospray capillary encounters the electric field because of the preservation of the tip at high potential. For a sufficiently high applied potential, the free charges at the surface of the liquid leaving the nozzle cause an electrical stress that leads to the formation of what is commonly called the Taylor cone jet mode (the meniscus at the tip of the nozzle forms a conical shape) [492]. At the apex of the cone, where the free charges are highly concentrated, the liquid accelerates away from the nozzle via a 'budding' process when the surface tension is exceeded by the applied electrostatic force and a jet with high charge density is obtained. The diameter of the droplets formed is influenced by a number of parameters, including the applied potential, the solution flow rate and the solvent properties [493]. At this point, the fate of the jet is determined by the competition between the electrostatic repulsion and the surface tension stress on the liquid–gas interface holding the droplet together. The charged liquid jet will at some point break up into droplets. Fission (Coulomb explosion) will occur at the point (the Rayleigh limit) at which the magnitude of electrostatic repulsion is sufficient to overcome the surface tension holding the droplet together. During their flight to the collector, the solvent
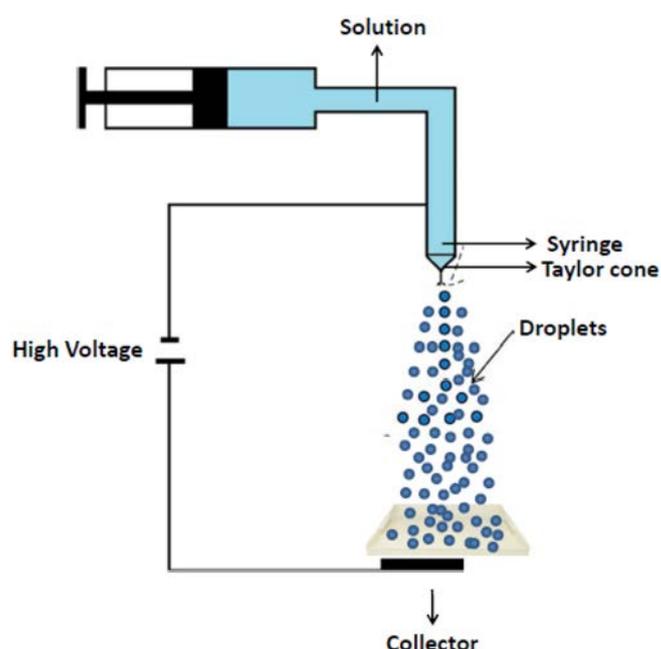


FIG. 24.  Standard electrospraying configuration. Courtesy of A. Dash.

evaporation makes the primary droplets shrink, which leads to an increase in charge concentration, so the primary droplets finally break up into smaller offspring. The various mechanisms operating in the electrospraying process are shown in Fig. 25.

*Advantages*

Electrospraying has numerous advantages for particle generation:

(a) Ease of particle synthesis due to single-step processing: The electrospray process lends itself well to efficient high throughput particle formation, as it is an easy and continuous process.
(b) Generation of particles of uniform size and shape: As charged droplets are self-dispersing in the space, droplet agglomeration and coagulation can be avoided.
(c) Scope to operate in atmospheric conditions, while the rate of particle production is easy to tune by adjusting voltage and flow rate.
(d) Flexibility: The flow rates and compositions of the sprayed liquids are controlled independently, and both are independent of the composition of the collection liquid, making the process very flexible.
(e) Long term stability of the emulsion is assured owing to the presence of residual charge on the particles.
(f) Ability to fabricate smaller particles (of $\mu$m range) by tuning the solution and process parameters.
(g) Narrow particle size distribution, with low standard deviation.

*Disadvantages*

Like any other process, electrospraying also has some limitations:

(a) The equipment is usually expensive;
(b) Low throughput;
(c) Difficulties are encountered when controlling the mode of spraying;
(d) High sensitivity to liquid, physical properties and the electric field in the vicinity of the emitter tip;
(e) Highly conductive solutions, such as salt solutions, may be too conductive to hold a charge to reach the target droplet size.
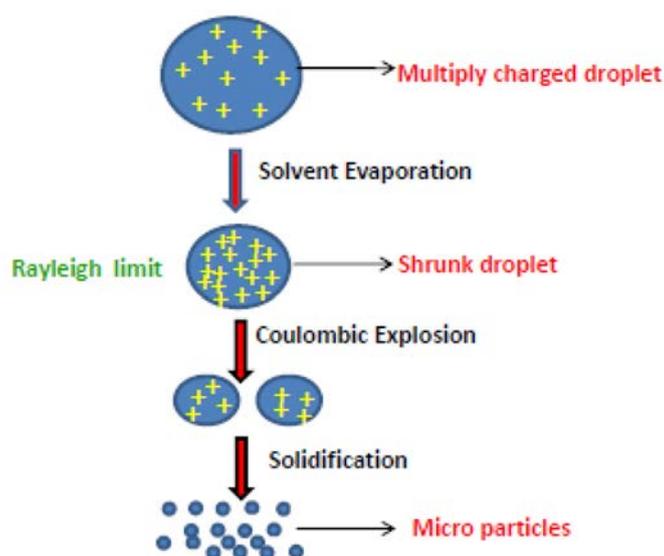


FIG. 25. Mechanism of electrospraying process for making particles/microspheres. Courtesy of A. Jalilian.

# 7. REGULATORY AND MANUFACTURING ISSUES

## 7.1. RADIOPHARMACEUTICAL MANUFACTURING ELEMENTS

In Europe and the USA, radiopharmaceuticals are considered a special group of medicines and are regulated by a number of directives, regulations and rules. One of the directives is that the manufacturing of radiopharmaceuticals for RSV ought to be undertaken in accordance with the principles of good manufacturing practice (GMP). In Europe, GMP rules have legal character, as they are issued by the European Medicines Agency and the Directorate-General for Enterprise and Industry of the European Commission. The level of precaution required depends in particular upon the radionuclide handled, taking into account factors such as types of radiation, the energy of radiation and half-lives.

The Radiopharmacy Committee of the European Association of Nuclear Medicine has prepared a guidance document [494], with the aim of providing a more sustainable alternative to the classic GMP that applies to the pharmaceutical industry, while maintaining the same quality, safety and efficacy standards. This document ought to provide a general framework for the preparation of radiopharmaceuticals on a 'small scale' basis that covers all practical aspects.

Preparation of radiopharmaceuticals for RSV ought to be carried out in strict adherence to radiation protection guidelines prescribed by the regulatory authority of the country. While preparing radiopharmaceuticals for synovectomy, care has to be taken to prevent cross contamination, and careful attention has to be paid to the retention of radionuclide contaminants and to waste disposal. Radiopharmaceutical preparation has to be carried out under aseptic working conditions to ensure sterile products.

As the radiolabelled particles for RSV are meant for parenteral administration, they need to be sterile. The frequency of testing depends on the practice followed by the institution. Usually, the samples for sterility testing are stored with the aim of decaying the radioactivity content sufficiently and then sent for sterility testing by an external validated laboratory. Internal sterility testing is only recommended subject to the availability of dedicated rooms and equipment. In cases where it is not practical to wait for results concerning the sterility of the product before release for clinical use because of the short half-life of the radionuclide, the test ought to constitute part of QC. The production process for radiolabelled particles ought to be validated by using appropriate test runs at regular intervals as per pharmacopoeias.

The aseptic work area ought to be suitable for the preparation of radiolabelled particles. The light needs to limit the presence of microorganisms and particulate matter, and the air quality in the aseptic processing area needs to be adequately controlled at regular intervals [494]. Critical activities in the preparation and testing of radiolabelled particles or the sterile surface of the container/closure system to the environment ought to be conducted within an aseptic workstation with a grade A rating [494]. The requirements include the following:

(a) The aseptic workstation where radiolabelled particle preparation is carried out needs to be sanitized at appropriate intervals.
(b) Microbiological monitoring of the workstation needs to be carried out during aseptic activities.
(c) Care needs to be taken that during that time no additional personnel enter the room.
(d) Items within the aseptic workstation ought to be kept to a minimum.
(e) Working personnel ought to wear designated laboratory coats and sterile arm protection and sterile gloves when conducting an aseptic manipulation within the aseptic workstation, and the work ought to be done in a well planned and expedient way.

The basic concepts of quality assurance (QA), GMP and QC are inter-related. This section portrays their relationships and their importance for the production and control of products [495]. The basic requirements of GMP are as follows [496]:

(a) A procedure for the preparation of radiolabelled particles for RSV needs to be clearly defined, systematically reviewed and shown to be capable of producing the required quality and complying consistently with their specifications. Procedures are to be written in clear and unambiguous language.
(b) All critical parameters of the preparation process are required to be validated.
(c) Everything necessary to ensure GMP is to be available, including: suitable equipment and services; correct materials, containers and labels; approved procedures and instructions; adequate premises and space; and qualified and trained personnel.
(d) Trained personnel are to be available to ensure product reproducibility.
(e) The defined procedures and instructions taken and the quantity and quality of the product obtained have to be recorded. Any significant deviations from the standard operating procedure (SOP) have to be fully recorded and investigated.
(f) The complete history of a batch has to be recorded and retained in a comprehensible and accessible form. Complaints about the quality of the supplied products are to be examined, the causes of quality deficiencies are to be investigated, and appropriate measures are to be taken to prevent reoccurrence.
(g) A system to recall any batch of product, from sale or supply, is to be available.

### 7.1.1. Personnel

Personnel play a major role in the production and QC/QA of radiopharmaceutical processes; the following are worth considering:

(1) Preparation ought to be carried out under the responsibility of personnel with competence in radiation protection and radiopharmaceutically specific aspects of the quality management system.
(2) All personnel involved in the preparation of radiolabelled particles ought to receive appropriate training specific to radiolabelling procedures and products analysis.
(3) Personnel have to be adequately trained in GMP regulations and the QA function.

### 7.1.2. Premises and equipment

The choice, design and installation of the site and required equipment is also critical point in obtaining optimal products; the following is worth considering:

(a) Radioactive products ought to be handled in designated controlled areas. Preparation of radiolabelled particles ought to be carried out either in a lead shielded fume hood or in a special hot cell facility.
(b) The flow of materials and personnel through the building or facilities ought to be designed to prevent mix-ups or contamination.
(c) Access to the radioactive area ought to be restricted to authorized personnel.
(d) Work ought to be monitored regularly with respect to radioactive contamination and particulate and microbiological quality and ought to adhere to established performance qualification.
(e) Regular preventive maintenance, calibration and qualification programmes ought to be in place to ensure that the facilities and equipment used in the preparation of radiolabelled particles are appropriate and qualified. Records and logs ought to be maintained.
(f) Appropriate controls ought to be in place not only to prevent radioactive contamination within the facility, but also to detect any radioactive contamination.
(g) Appropriate measures ought to be taken to protect the areas where preparation of radiolabelled particles is carried out from particulate and microbial contamination.

(h) Hot cells meant for radiolabelled particle preparation ought to feature a high degree of air cleanliness, with filtered feed air, when closed and operated under aseptic conditions.

### 7.1.3. Documentation

In light of the perceived need to achieve GMP compliance, it is essential to have a full documentation system providing traceability. This needs to include the following [495]:

(a) Records of each lot of ingredients and excipients received with an identification code number;
(b) Records of each lot of radioisotope received with an identification code number;
(c) Records of product preparation: batch numbers, activity and volume added, results of quality control and release;
(d) Specifications of ingredients, excipients and radioisotopes;
(e) Laboratory cleaning and maintenance, in addition to the date, time and signature of the persons involved in these activities;
(f) Equipment calibration and maintenance, as well as the date, time and signature of the persons involved in these activities;
(g) Operating procedure;
(h) Batch processing records;
(i) Training of personnel;
(j) Transport of radioactive materials;
(k) Radioactive contamination monitoring and radioactive waste disposal, in addition to the date, time and signature of the persons involved in these activities;
(l) Report and follow-up of product defects and events of non-conformity to SOPs, as well as documenting actions performed to correct the problem;
(m) Microbiological monitoring.

A system of documentation has to be in place to make each preparation step traceable [495]:

(a) All documents related to the radiolabelled particles preparation ought to be composed, reviewed, approved and followed as per the written procedures.
(b) The specifications of the starting materials, including radionuclides as well as the finished radiolabelled particles, ought not only to be established, but also documented.
(c) Specifications, any other critical items and those likely to impact the quality also ought to be in place.
(d) Acceptance criteria for radiolabelled particles, including criteria for their release as well as shelf life for clinical use, ought to be established and specified.
(e) The procedures used for the preparation and sterilization of radioactive particles, including batch number, date, time and signature of the persons involved in these activities, ought to be recorded.
(f) These records ought to be preserved for a duration of least three years, unless another timeframe is specified in national requirements.

### 7.1.4. Training

Even if the right staff have been employed, ongoing training in routine and new aspects of the process is required:

(a) All production and QC personnel ought to receive appropriate training in the principles of GMP, radiation protection and preparation of radiolabelled particles.
(b) Continuing training ought to be given by qualified individuals, and its practical effectiveness ought to be periodically assessed and recorded.

### 7.1.5. Quality assurance

QA covers all activities that can individually or collectively influence the quality of radiolabelled particles for RSV. The system of QA ought to ensure that:

(a) Radiolabelled particles are prepared with respect to the requirements of GMP.
(b) Preparation and control operations are clearly specified and GMPs applied.
(c) All staff responsible for ensuring quality are clearly specified.
(d) Necessary arrangements have been made to ensure the availability of sufficient starting material and active pharmaceutical ingredients of requisite quality to undertake preparation of radiolabelled particles.
(e) Preparation of radiolabelled particles is carried out according to the defined procedures.
(f) Radiolabelled particles are not used for therapy unless an authorized person has certified that each batch has been produced and controlled in accordance with the requirements of the regulatory authority of the country relevant to the production, control and release of radiopharmaceuticals for therapy.
(g) Necessary arrangements are in place to ensure that the radiolabelled particles are stored, distributed and subsequently handled so that quality is maintained throughout their shelf life.
(h) A quality audit system is in place to appraise the effectiveness and applicability of the quality assurance system regularly.

The principles of qualification and validation ought to be applied to radiolabelled particle preparation and a risk management approach ought to be in place to determine the extent of qualification/validation, focusing on a combination of GMP and radiation protection.

### 7.1.6. Quality control

QC for radiolabelled particles in terms of specifications, testing, documentation and release procedures ensures that the necessary and relevant tests are actually carried out for their safe clinical use. This is an important part of the overall QC procedures performed in the nuclear medicine department. The basic QC requirements mandated by GMPs are as follows:

(a) Adequate radiological facilities, skilled manpower and approved procedures are available for testing starting materials, intermediate materials and finished radiolabelled particles.
(b) A system to verify the quality of starting materials is in place.
(c) Testing of starting materials, active pharmaceutical ingredients, intermediate materials and finished radiolabelled particles is carried out by trained personnel following approved and validated QC methods.
(d) Records are maintained to demonstrate that all the required testings are actually carried out and meet required specifications; any deviations have to be recorded and investigated.
(e) Batch processing records encompassing production conditions and analytical testing performed are assessed by a designated person before being sent to the clinical department.
(f) A written procedure pertaining to the assessment of the quality of the radiolabelled particles is available.
(g) Radiolabelled particles complying with the qualitative and quantitative acceptance criteria required for RSV are enclosed in a proper glass container and correctly labelled.
(h) Radiolabelled particles that fail to meet acceptance criteria are rejected.
(i) Product assessment, including a review and evaluation of relevant production documentation, and an assessment of deviations from specified procedures are in place.

(j)     Batches of product released for clinical use are certified by an authorized person, ensuring that satisfactory test results have been received and assessed in accordance with the regulatory requirements of the country.

(k)     Samples of each batch of radiolabelled particles are retained for at least six months, unless otherwise justified through risk management practices.

### 7.1.7.  Responsibilities

The person responsible for the preparation of radiopharmaceuticals ought to have the following responsibilities [494]:

(a)     To establish procedures for the examination and evaluation of incoming materials required for the preparation of RSV agents and ensure that each lot of incoming material complies with specifications;

(b)     To review the preparation batch records and laboratory control records and conformance of established specifications before authorizing the final release or rejection of a batch;

(c)     To approve preparation methods, including related SOP and product specifications;

(d)     To ensure that the personnel involved in the preparation of radiolabelled particles are suitably trained and qualified;

(e)     To scrutinize errors and ensure that corrective action is taken to preclude their reappearance;

(f)     To ensure that the radiolabelled particles have the requisite strength, quality and purity for the RSV procedure.

The person responsible for QA ought to have the following responsibilities:

(a)     To manage the overall QA system;

(b)     To verify that the documentation is correctly written and followed;

(c)     To conduct periodic audits in order to ensure that established procedures and practices are in compliance with stipulated norms.

The person responsible for production ought to have the following responsibilities:

(a)     To write the SOPs related to radiolabelled particle preparation and ensure that they are implemented;

(b)     To approve the radiolabelled particle preparation;

(c)     To evaluate, sign and store the production records;

(d)     To ensure that the radiolabelled particles are produced and stored according to the appropriate documentation in order to obtain the required quality;

(e)     To verify that premises and hot cells are correctly maintained according to the prescribed maintenance programme.

The person responsible for QC ought to have the following responsibilities [494]:

(a)     To write the SOPs related to QC operations and verify that they are followed stringently;

(b)     To define specifications, test methods and other QC procedures as applicable;

(c)     To approve or reject starting materials based on their quality;

(d)     To evaluate, sign and store QC reports, records of starting materials and finished products;

(e)     To evaluate the batch records;

(f)     To verify that premises and QC equipment are correctly maintained according to the prescribed maintenance programme.

## 7.2. QUALITY EVALUATION OF RADIOSYNOVECTOMY AGENTS

Since radiolabelled particles are intended for administration to humans, it is imperative that they undergo strict QC measures. Essentially, this involves several specific tests and measurements that ensure the following aspects of radiolabelled particles:

(a) Purity;
(b) Potency;
(c) Product identity;
(d) Biological safety;
(e) Efficacy.

No discussion about RSV is complete without mentioning QC issues. It is the key factor that underpins its success, survival and strength. It is divided into three parts:

(1) QC of the particle;
(2) QC of the radionuclide;
(3) QC of the radiolabelled particle.

### 7.2.1. Quality control of the particle

#### 7.2.1.1. Determination of the particle density

The density ($\rho$) is an elementary physical property of the particle and is defined as the ratio of its mass ($m$) to its volume ($V$):

$$\rho = \frac{m}{V} \ [\text{kg·m}^{-3}] \tag{2}$$

The SI unit of density is $\text{kg·m}^{-3}$. However, $\text{g·cm}^{-3}$ is another unit commonly used in laboratories. Its conversion is: $1 \ \text{g·cm}^{-3} = 1000 \ \text{kg·m}^{-3}$.

Determining density by means of a pycnometer is a very precise method. The pycnometer (from the Greek *puknos*, meaning 'density'), also called a pyknometer or specific gravity bottle, is a flask with a close fitting ground glass stopper with a fine hole through it. This fine hole releases spare liquid after closing a top filled pycnometer and allows one to obtain a given volume of measured and/or working liquid with high accuracy. A given mass of the particle is added to the pycnometer, which is then weighed, giving the weight of the particle. A photograph of a pycnometer is shown in Fig. 26.

The pycnometer is then filled with a liquid (water) of known density where the particle is completely insoluble. The weight of the displaced liquid can then be determined, and thence the specific gravity of the particle. The weight of the pycnometer has to be measured together with the inserted solid particle $m_0 + m_S$. We add water and determine the weight $m_{water}$ (weight $m_0 + m_S + m_{water}$).

First, it is essential to determine the weight of the pycnometer together with the inserted object $m_0 + m_S$. Then water is added and its weight $m_{water}$ is determined (measured weight minus $m_0 + m_S$). The volume of added water $V_{water}$ can be obtained as:

$$V_{water} = \frac{m_{water}}{\rho_{water}} \tag{3}$$

The volume of the measured particle $V_S$ is the difference between the volume of water that fills the empty pycnometer $V$ and the volume $V_{water}$.
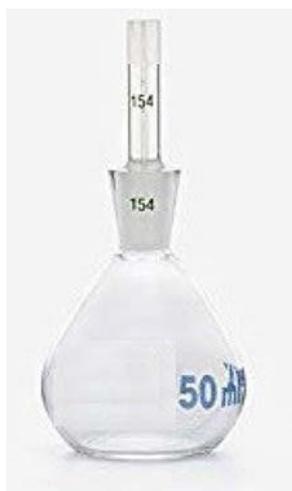
*FIG. 26.  Photograph of a pycnometer. Courtesy of A. Jalilian.*

The density of the measured object $\rho_S$ can then be calculated as:

$$\rho_S = \frac{m_s}{V_s} \tag{4}$$

It is essential that the particle used in RSV has a density of approximately 0.7–2.0 gm/mL, preferably 0.7–1.3 gm/mL. Its density ought to be such that the particulate matter of a suspension will not tend to settle in the liquid form vehicle in which it is dispersed. The particles used in RSV ought to be suspendable in pharmaceutically acceptable vehicles.

Sieve analysis is the oldest and most widely known method for characterizing particle size distributions [497]. The particle size distribution is defined via the mass or volume. The process divides the particulate material into size fractions by passing the material through a number of sieves of different mesh sizes and then determines the mass fraction of the particles within each size range.

The particles are vibrated through a series of sequentially decreasing sieves using either horizontal, vertical or rotational motion or a combination of them in accordance with the chosen method. This causes a relative movement between the particles and the sieve; depending on their size, the individual particles either pass through the sieve mesh or are retained on the sieve surface. Particles under motion will eventually orientate to present their two smallest dimensions to the sieve mesh opening and pass to the next sieve with a smaller nominal opening. The likelihood of a particle passing through the sieve mesh is determined by the ratio of the particle size to the sieve openings, the orientation of the particle and the number of encounters between the particle and the mesh openings. Upon completion of the sieving process, the weight of the sieves is measured and compared with the weight of the sieves before adding the sample. This gives the mass of the material on each sieve. Through addition of the mass fraction on each sieve, from the smallest to the largest sieve size, a cumulative mass distribution of the test sample is obtainable.

The US Pharmacopeia Convention describes the dry sieving method (Method I) as follows [498]:

"Tare each test sieve to the nearest 0.1 g. Place an accurately weighed quantity of test specimen on the top (coarsest) sieve, and replace the lid. Agitate the nest of sieves for 5 minutes. Then carefully remove each sieve from the nest without loss of material. Reweigh each sieve, and determine the weight of material on each sieve. Determine the weight of material in the collecting pan in a similar manner. Reassemble the nest of sieves, and agitate for 5 minutes. Remove and weigh each sieve as previously described. Repeat these steps until the endpoint criteria are met.…"

When the analysis is completed, the analyst reconciles the material weights. The total losses cannot exceed 5% of the weight of the original test specimen. If particles retained on any sieve are aggregates (rather than single particles), then the use of dry sieving is not likely to be an easily reproducible method. At that point, the analyst could consider the use of the wet sieving method (Method II) as an alternative technique, as described in Ref. [498]:

"Modify the lid and collecting pan of the sieve nest to permit addition of a liquid onto the surface of the top sieve and the collection of the liquid from the pan.… Select a liquid in which the test specimen is insoluble, and modify the sieving method.… Thoroughly disperse the dried test material in the liquid by gentle agitation, and pour this dispersion onto the top sieve. Rinse the dispersion equipment with fresh liquid, and add the rinsings to the top sieve. Feed the sieving liquid through a suitable pumping mechanism to the nozzle(s) in the lid, and collect the sieving liquid from the pan in a suitable container. Continue the wet sieving process until the emerging liquid appears free of particles. Remove each sieve from the sieve nest, and dry each sieve to constant weight at the same temperature as that used above. Determine the weight of dried material on each sieve."

One has to remember that the particle diameter information obtained using analytical sieving represents the minimum square aperture through which the particle can pass [498]. Details of the particulate shape influence the separation of particles in sieving because particles will pass through openings on the basis of their cross-sectional diameter.

### 7.2.1.2. Dynamic light scattering method

The dynamic light scattering (DLS) method is a preferred method for particle sizing owing to its short analytical time, robustness, high precision, reproducibility, wide measurement range and flexibility of operation using liquid, spray and dry dispersion. When a laser beam is passed through liquid suspensions containing particles in Brownian motion, it experiences fluctuations in its intensity due to light scattering. In the DLS instrument, measurements of this fluctuation of intensity at a given scatter angle are used to infer the particle size or 'hydrodynamic diameter' of the suspended particles. The DLS instruments measure the fluctuations in the intensity of the scattered light with time in order to generate an exponentially decaying autocorrelation function. This function is then analysed for characteristic decay times to determine the diffusion coefficient unique to the scattering suspensions in conjunction with the Stokes–Einstein equation, the hydrodynamic radius.

The primary advantage of the DLS method is that it provides an absolute measurement without any further information about the composition and the optical properties of the particles in suspension [472]. The lower limit of the instrument depends on the laser power and signal to noise ratio, which can be as low as 2 nm. The data obtained using the instrument are usually in two formats, depending on the type of algorithms used for the inversion of the autocorrelation function. A Gaussian distribution is typically used to represent unimodal dispersions. The algorithms used provide information about the mean particle size and the widths and peak modes of the particle size distributions. The intensity based data, collected by the instrument, can be reliably reduced to a volume weighted particle size distribution.

One of the disadvantages of the DLS method is that samples in some cases may require significant dilution for accurate size measurements, which can be problematic for measurement of the droplet sizes of emulsions. Figure 27 provides a schematic diagram of a DLS system.

### 7.2.1.3. Scanning electron microscopy

An electron microscope uses a particle beam of electrons to illuminate a specimen and create a highly magnified image, as seen in Fig. 28. Electron microscopes have much greater resolving power than optical microscopes and can obtain much higher magnifications of up to 2 million times, while the best optical microscopes are limited to magnifications of several thousand times. Both electron and
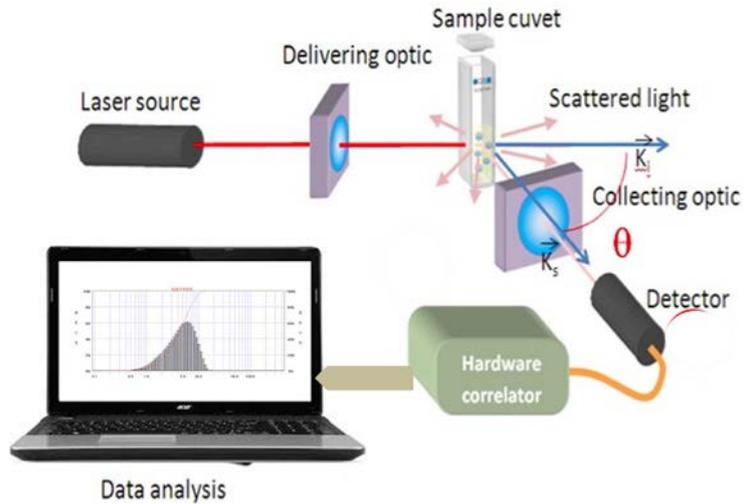
*FIG. 27. Schematic diagram of a typical dynamic light scattering system. Courtesy of A. Dash.*
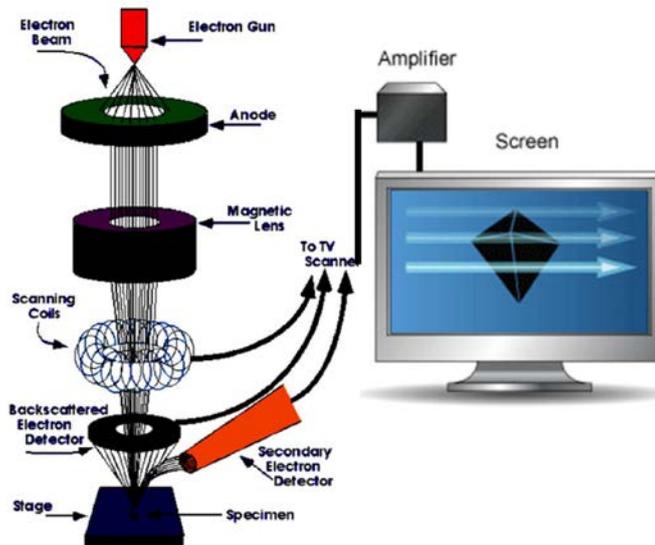


*FIG. 28. Schematic diagram of a typical scanning electron microscope. Courtesy of A. Dash.*

light microscopes have resolution limitations, imposed by the wavelength of the radiation they use. The electron microscope has greater resolution and magnification because the wavelength of an electron (i.e. the De Broglie wavelength) is much smaller than that of a photon of visible light.

Figure 28 provides a schematic diagram of a typical electron microscope. A scanning electron microscope images the sample surface by scanning it with a high energy beam of electrons in a raster scan pattern (the rectangular pattern of image capture and reconstruction on a television or computer that then highlights on the screen). The electrons interact with the atoms and hence make up the sample producing signals that contain information about the sample's surface topography, composition and other properties.

### 7.2.2. Quality control of radionuclides

*7.2.2.1. Radionuclide purity*

Radionuclide purity is defined as the percentage of radioactivity of the radionuclide of interest in terms of the total radioactivity of the radioactive preparation. The purity of the radionuclide is based upon the percentage of the radionuclide present in the desired radionuclide (free from contaminants) and determines whether other radionuclides that are not of interest are present in the solution. Such radionuclide impurities arise during radionuclide production; hence, they are dependent on the production method–route. Any radionuclide other than the one of interest is considered to be an impurity [499]. Radionuclidic purity is an important quality parameter and it is mandatory that the radionuclide impurities be within the stipulated limits.

*7.2.2.2. Determination of the nature and energy of the radiation*

The nature and energy of the radiation emitted can be determined using several procedures, including construction of an attenuation curve and use of spectrometry. The attenuation curve offers the scope for analysis of beta radiation.

*7.2.2.3. Gamma (γ) ray spectrometry*

Gamma (γ) ray spectrometry is mostly used for the identification of γ rays and detectable X rays. The measured energy of a γ ray corresponds to the type of element and its isotope, while the number of counts corresponds to the abundance of the radioactive source present in the measured sample with some little considerations. The success of the gamma ray spectrometry technique requires information on the photopeak efficiency of the detector as well as the counting geometry for each photon energy. Figure 29 depicts the gamma ray spectrum for $^{177}$Lu obtained from a high purity germanium detector.

The preferred detector for γ and X ray spectrometry is high purity germanium. High purity germanium detectors are the most sensitive and efficient devices, and they are widely used in determining the activity of radionuclides from higher order down to less than 0.1 Bq [501].

Gamma detectors need to be calibrated using standard sources owing to the fact that detection efficiency is a function of the energy of the γ and X rays as well as the form of the source and the source to detector distance. The detection efficiency is generally measured using a calibrated source of the radionuclide to be measured, or, for more general work, a graph of efficiency against γ and X ray energy may be constructed from a series of calibrated sources of various radionuclides.

The detector efficiency, *E*, at a given photopeak energy for a given geometry is determined using a known quantity or concentration (for a volume geometry) of a γ emitting radionuclide, as follows:

$$E = \frac{C}{A \times B} \tag{5}$$

where

*C*    is the net count rate (cpm) (integrated counts in the photopeak above the baseline continuum divided by the counting time in minutes);

*A*    is the activity of the radionuclide added to the given geometry container (dpm);

and *B*    is the γ ray abundance of the radionuclide being measured (gamma/disintegration).

The γ and X ray spectra of a radionuclide that emits γ and X rays are unique to that nuclide and are characterized by the energies and the number of photons of particular energies emitted per transformation
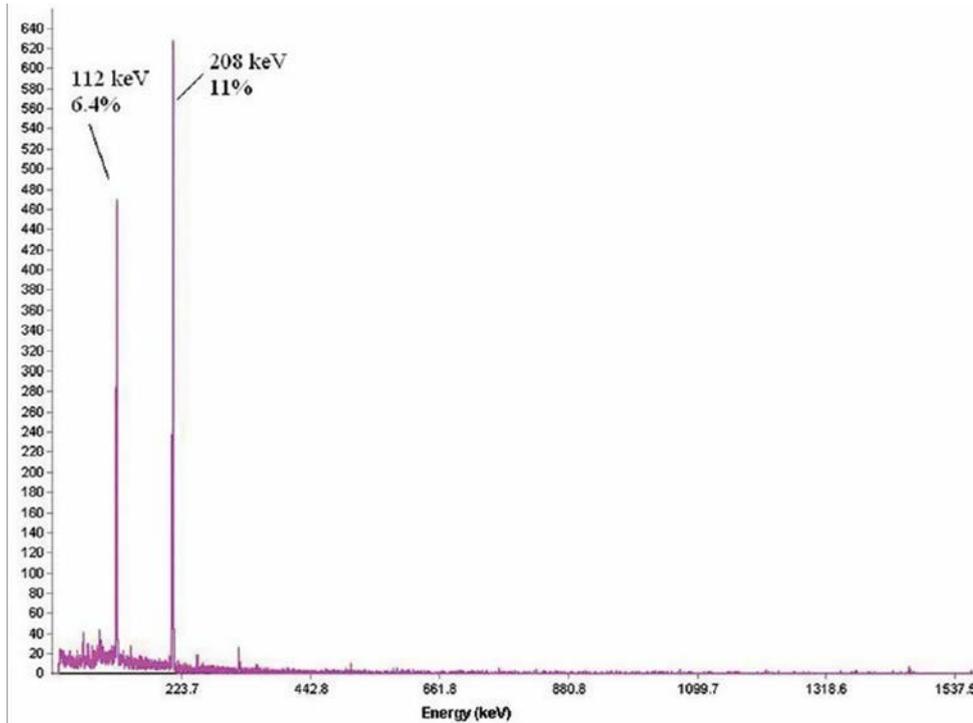
*FIG. 29. Gamma ray spectrum for $^{177}$Lu. Reproduced from Ref. [500].*

from one energy level to another energy level. This property contributes to the identification of radionuclides present in a source and to their quantification.

The isotopes indicated by the $\gamma$ spectrum are determined as follows:

(a) Identifying all photopeak energies;
(b) Integrating the photopeak regions of the spectrum and subtracting the area under the baseline continuum to determine the true photopeak area;
(c) Identifying radionuclides by their photopeaks, and ratios to each other when more than one gamma photon is emitted by an isotope in the sample;
(d) Identifying radionuclide impurities by detecting peaks other than those expected.

The radionuclide concentrations of the sample are calculated as follows:

$$A = \frac{C}{B \times E \times V} \tag{6}$$

where

$C$      is the net count rate (cpm) in the peak area above baseline continuum;
$B$      is the gamma ray abundance of the radionuclide being measured (gammas/disintegration);
E      is the detector efficiency (counts/gamma) for the particular photopeak energy being considered;
and $V$    is the volume of sample aliquot being analysed.

Gamma spectrometry offers the scope to establish the rate of decay of radioactivity using the peaks to diminish in amplitude as a function of the $T_{1/2}$. If a radioactive impurity with a different $T_{1/2}$ is present in a sample, it is possible to detect it by identifying the characteristic peak or peaks, whose amplitudes
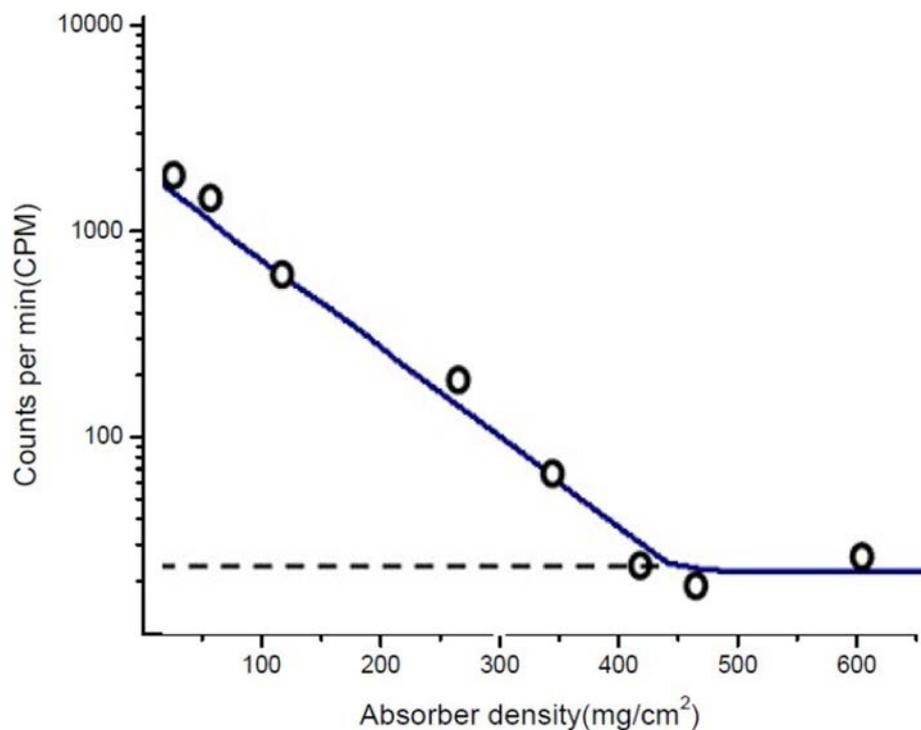
*FIG. 30. Attenuation graph for a beta emitting radionuclide. Courtesy of A. Dash.*

decrease at a different rate from that expected for the particular radionuclide. A determination of the $T_{1/2}$ of the additional peaks by repeated measurements of the sample will help to identify the impurity. Due to differences in the half-lives of the different radionuclides that can be present in a solution, the radionuclidic purity changes with time. The radionuclidic purity requirement has to be fulfilled throughout the period of validity.

### 7.2.2.4. Attenuation curve

The beta energy for pure beta emitters is determined using the attenuation curve when a spectrometer for *β* rays is not available or for *β*/*γ* emitters when a gamma spectrometer is not available.

This method essentially consists of estimating the maximum energy of *β* radiation (beta max), which only provides an approximate value. The source, suitably mounted to a fixed geometry, is placed in front of the thin window of a Geiger–Müller counter or a proportional counter. The source is protected as described above. The count rate of the source is then measured. Between the source and the counter are placed, in succession, at least six aluminium screens of increasing mass per unit area. The position and geometry of the detector, foils and the source have to be the same during this measurement. With a pure beta emitter, this count rate is not affected by the addition of further screens. The screens are inserted in such a manner that constant geometrical conditions are maintained. A typical attenuation graph for a *β* emitting radionuclide is presented in Fig. 30.

A graph is drawn in which the mass per unit is expressed in milligrams per square centimetre as the abscissa, and the logarithm of the count rate as the ordinate for each screen examined. A graph is drawn in the same manner for a standardized preparation. The mass attenuation coefficients are calculated from the median parts of the curves, which are practically rectilinear.

The mass attenuation coefficient *μ*m, expressed in square centimetres per milligram, depends on the energy spectrum of the beta radiation and the nature and the counting geometry. It therefore allows beta emitters to be identified. It is calculated using the equation:

$$\mu\mathrm{m} = 2.303\,\frac{\log A_1 - \log A_2}{m_1 - m_2} \tag{7}$$

where

$m^1$      is the mass per unit area of the lightest screen;

$m^2$      is the mass per unit area of the heaviest screen, with $m^1$ and $m^2$ being within the rectilinear part of the curve;

$A^1$      is the count rate for mass per unit area $m^1$;

and $A^2$   is the count rate for mass per unit area $m^2$.

The mass attenuation coefficient $\mu$m, thus calculated, does not differ by more than 10% from the coefficient obtained under identical conditions using a standardized preparation of the same radionuclide. The range of beta particles is an additional parameter that can be used to determine the beta energy. It is obtained from the graph described above as the mass per unit area corresponding to the intersection of the extrapolations of the descending rectilinear part of the attenuation curve and the horizontal line of background radioactivity.

Liquid scintillation counting (LSC) may be used to obtain the spectra of $\alpha$ and $\beta$ emitters. Due to the low penetrative power of beta radiation, the detection efficiency of beta emitters is quite low, and beta emitting isotopes are quantified using LSC. The best possible contact is achieved when the sample is dissolved in the scintillation solution. By counting the photons produced in the reaction of beta particles with the scintillator, the beta emitting isotopes can be easily quantified. In LSC, the radionuclide is mixed with a cocktail that consists of a solvent and scintillator (fluor). The decay energy will be transferred to the cocktail, and converted to photons, which are counted using a photomultiplier tube (PMT), and the activity of radionuclides is measured. A digital picture of the energy distribution of the isotope is obtained using a multichannel analyser, which is a form of memory that stores the electrical pulses from the PM tubes of the liquid scintillation counter. The beta spectrum of $^{90}$Sr/$^{90}$Y obtained from a liquid scintillation counter coupled to a multichannel analyser is shown in Fig. 31.
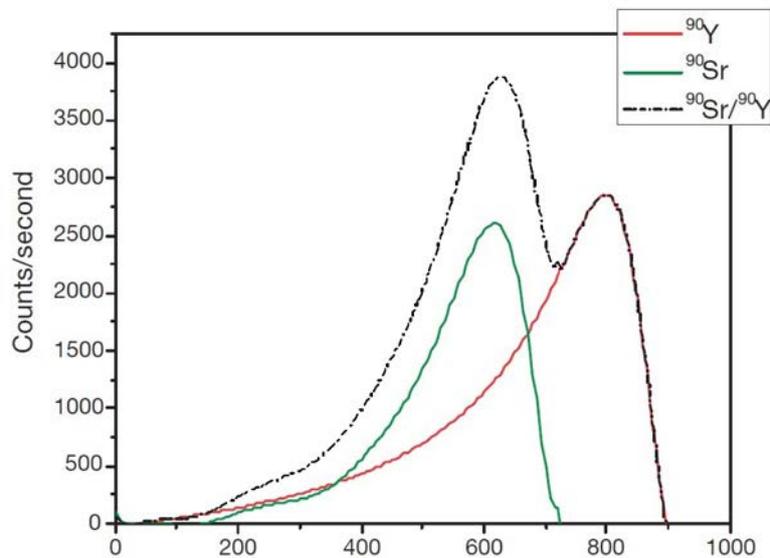


FIG. 31. Spectra after complete decay of $^{90}$Y (dashed line). Reproduced from Ref. [260].

### 7.2.2.5. Radiochemical purity

The ratio — expressed as a percentage — of the radioactivity of the radionuclide of interest in a stated chemical form to the total radioactivity of that radionuclide present in the preparation is referred to as 'radiochemical purity'. Given the perceived need to determine the radiochemical purity of a radionuclide, it is essential to separate the different chemical substances containing the radionuclide and estimate the percentage of radioactivity associated with the declared chemical substance. Radiochemical impurities may arise during the production of a radionuclide, during subsequent chemical processing, from incomplete preparative separation and from chemical changes during storage. The requirement for radiochemical purity has to be fulfilled throughout the validity period.

Radiochemical purity can be determined using analytical techniques, including paper chromatography, thin layer chromatography, instant thin layer chromatography, electrophoresis, size exclusion chromatography and liquid chromatography. Instant thin layer chromatography assays use specific cellulose backed silica gel chromatography strips as a solid phase. This method is easy to use, rapid and can be incorporated easily into a routine QC programme. Thin layer and paper chromatography are also commonly used. As very small quantities of the radioactive material are applied, a carrier may be added while undertaking the analysis. Subsequent to the development of the chromatogram, the support is dried and the positions of the radioactive areas are sensed by autoradiography or by measuring the radioactivity over the length of the chromatogram by using suitable collimated counters or by cutting the strips and counting each portion. The positions of the spots or areas permit chemical identification by comparison with solutions of the same chemical substances (non-radioactive) using a suitable detection method. The radioactivity in the strip can be detected in a number of ways.

The percentage of activity in each section can then be determined. For example, if a strip is cut into two sections, $A$ and $B$, then the percentage activity in section $A$ is given by:

$$\%A = \frac{A \times 100}{A + B} \tag{8}$$

The strip can be imaged under a gamma camera and regions of interest can be drawn around the areas of radioactivity, from which the percentage of counts in each region can be determined. Although this method offers the advantage of imaging the whole chromatography strip, enabling artefacts to be seen, it is not practicable for most hospital departments due to the cost in camera time. The strip can be imaged using a radiochromatogram scanner, which uses a sodium iodide detector to detect the radioactive emission. If the scanner is linked to an integrator, then the peaks can be quantified. One of the major limitations for the paper and thin layer chromatography methods of determining RCP is the resolving power of the methods.

### 7.2.2.6. High performance liquid chromatography

HPLC has higher sensitivity and resolving power than simple thin layer chromatography (TLC) and photon correlation (PC) methods. HPLC separation is based on the hydrophilic/lipophilic properties of the components of a sample used. The detectors used are either radioactive or UV or refractive index, which can be connected in series, allowing simultaneous identification of compounds. It is pertinent to point out that HPLC does not detect colloidal contaminants and that these ought to be estimated using TLC methods.

### 7.2.3. Quality control of radiolabelled particles

The flow properties (such as syringeability and injectability) of the radiolabelled particle suspension are the major determinants that govern its success in RSV:

(a)  Syringeability describes the ability of the suspended radiolabelled compound to pass easily through a hypodermic needle on transfer from the vial prior to injection. An increase in the viscosity, density, particle size and concentration of solids in suspension hinders the syringeability of suspension.
(b)  Injectability refers to the performance of suspension during injection and includes factors such as pressure or force needed for injection, evenness of flow, aspiration qualities and freedom from clogging.

The syringeability and injectability of suspension are closely related its viscosity and particle characteristics (as shown in Fig. 32):

(a)  Syringes may become clogged or blocked when a radioactive particle suspension is administered because a single large particle or an aggregate may block the lumen of the needle or because of a bridging effect of the particles.
(b)  Drainage refers to the ability of the suspension to break cleanly away from the inner walls of the primary container closure.

The number of particles in a preparation and whether their sizes are suitable for RSV applications can be determined using several methods, such as autoradiography or phase contrast microscopy if the sample is placed on a haemocytometer grid [502]. Alternatively, transmission electron microscopy may be used.

#### 7.2.3.1.  Stability studies

Radiolabelled particles have to remain stable until they are administered. In order to achieve this, the following procedure needs to be adhered to: radiolabelled particles have to be kept at room temperature for 2 h or at 37ºC for 24 h after radiolabelling in 2 mL each of saline solution (0.9% NaCl), ascorbic acid (pH 5), human serum and human synovial fluid diluted 1:1 with saline (to reduce viscosity). In every case the percentage of bound activity has to be measured.

Approximately 1 mg of the particles is to be placed in a 10 mL vial, and 2 mL of each medium is to be added. The vials will be stoppered and placed on a rocking platform for gentle agitation, and then



*FIG. 32.  Photograph of a radiolabelled particle suspension. Courtesy of A. Dash.*

immersed in a water bath incubator maintained at 37°C for 2 h and 24 h. At various times, the tubes are to be removed and 2 mL of saline is to be added; the tubes will then be shaken and centrifuged at 5000 rpm for 5 min. Three 1 mL aliquots are removed from each test tube with a volumetric pipette and placed in three different 10 mL vials so that the geometry is the same in all of the samples. The vials are then to be counted in a NaI(Tl) well type counter. The release of activity from the radiolabelled particle ought to be less than 5%.

The long term particle size stability of radiolabelled particles can been checked using gel filtration [503], PC spectroscopy [503, 504] and microfiltration [504]. The radiochemical stability can be checked with PC, TLC, HPLC, gel filtration or electrophoresis.

### 7.2.3.2. Size of radiolabelled particles

Since batch to batch differences in radiolabelled particle size sometimes occur, routine QC of radiolabelled colloids is essential. This QC focuses primarily on determining the particle size together with checking the radiochemical purity. In this method, either the particle size or the activity size distribution is obtained. The different methods include the following:

(a) *Electrophoresis.* It is possible to separate colloid particles carrying a charge by means of electrophoresis. Lim et al. [505] developed an elaborate technique to measure the size and charge distributions of colloid particles by combining electrophoresis and laser light scattering measurements.

(b) *Gel filtration.* Colloid preparations may be eluted through a chromatographic bed in a column in order to separate particles of different sizes following the method reported by Persson et al. [506] concerning a filtration technique for colloids in which the colloid sample is applied at the top of the column and eluted with 10 mL of isotonic saline. The column is sealed afterwards and scanned using a slit collimated NaI(Tl) detector. The scanning profile obtained provides qualitative information on the size distribution as well as the presence of radiolabelled impurities. This technique can be used for routine quality control of radiolabelled particles. The method described by Billinghurst and Jette [507] for determining the activity size distribution of colloids can also be used.

(c) *Scanning electron microscopy.* This can be used to determine the size distribution, particle shape, concentration and chemical composition of colloids. In this method, the radioactive particle sample is usually spread on a polycarbonate filter and allowed to dry [503]. Low-*Z* particles are then coated with a thin layer of gold foil not only to increase the image contrast, but also to prevent heat effects. With a freeze fracture technique it is possible to eliminate the risk of volatilization of particles [507].

(d) *Transmission electron microscopy.* This can be used to determine the size distribution, particle shape, particle concentration and chemical composition of colloids. Before it is analysed, the radioactive particle sample is spotted or nebulized onto a plastic-coated grid and allowed to dry or partially dry. This method suffers from the drawback that there is the possibility that the particles may change or sublimate due to the vacuum in the microscope and the heat of the electron beam, making analysis of preparations containing stabilizers and contaminants difficult [508]. In spite of this drawback, Warbick et al. [508] considered this method to be their preferred choice for determining the size of radioactive particles.

(e) *Photon correlation spectroscopy.* This technique involves the illumination of a particle solution with a laser in which light scattered at 90° is detected in a photomultiplier. As the particles move and diffuse in the solution due to Brownian motion, the scattered light will give rise to a diffraction pattern. The rate at which this intensity pattern changes is inversely proportional to the particle size. A computer is used to calculate the average particle size and a polydispersity index, which is an indication of the width of the size distribution [504].

(f) *Ultra filtration.* This is essentially a pressure driven process in a liquid flow through a membrane [509]. The technique is based on the separation of particles and molecules according to the molecular weight cut-off value of the membrane. In this method, the membrane retains most particles above its retention rating and permits most smaller particles, along with the solvent, to flow through it. There

is a possibility that some proportion of the particles will be adsorbed on the surface of the membrane and create a 'gel layer', which in turn may have higher retention than the membrane itself. In order to circumvent this phenomenon, it is essential to establish the gel layer by conducting a pre-filtration step before consistent results can be obtained.

(g) *Microfiltration.* This method makes use of polycarbonate membrane filters of well defined pore size for microfiltration [510]. The commercially available Nuclepore polycarbonate membranes with 17 different pore sizes, ranging from 0.01–12 μm, can be employed for this method. A sample of radioactive colloid is passed through a membrane (held in a filter holder) and then washed with 2 mL of distilled water. The fraction of activity passing the filter can then be determined by radioactivity measurements on the filter using a radioisotope calibrator or a well type NaI(Tl) detector.

(h) *Ultracentrifugation.* This technique can also be used for sizing colloids. In this method, a sample of radioactive colloid is layered on a sucrose gradient and is then spun in an ultracentrifuge to separate the gradient into fractions. Each fraction is then measured for radioactivity using a radioisotope calibrator or NaI(Tl) detector. The success of the technique depends on effective calibration of the radioactive detector.

(i) *Microscopy.* Phase contrast microscopy or light microscopy is an optical microscopy technique that converts phase shifts in light passing through a transparent specimen to brightness changes in the image. In a phase contrast microscope the phase difference between light that is diffracted by a specimen and the light that is direct and undeflected is one quarter of a wavelength or less. By placing an appropriate mask in the back focal plane of the objective to provide selective filtering of the diffracted light, this phase difference is increased by another quarter wavelength. Waves that differ in phase by half a wavelength cancel one another. In the places in the phase image where this occurs, no light is transmitted. As a result, phase differences caused by variations in the specimen appear as intensity variations in the image. This may be used for sizing radioactive particles. It is a fast and simple technique and provides a rough estimate of the particle size of these types of colloids.

(j) *Coulter counter.* The Coulter method of sizing and counting particles is based on measurable changes in electrical impedance produced by nonconductive particles suspended in an electrolyte. In a Coulter counter, radioactive particles suspended in an electrolyte are allowed to pass through a small aperture between electrodes, across which an electric current flows. In the sensing zone, each particle displaces its own volume of electrolyte. The volume displaced is measured as a voltage pulse, with the height of each pulse being proportional to the volume of the particle. As fluid containing radioactive particles is drawn through each aperture, each particle displaces electrolyte in the aperture and thus produces a pulse proportional to its displaced volume. Each pulse is counted and sized in order to obtain the size distribution. The quantity of suspension drawn through the aperture is controlled precisely to allow the system to count and size particles for an exact reproducible volume.

*7.2.3.3. Sterility*

Radiolabelled particles for parenteral administration have to be prepared with precautions designed to exclude microbial contamination and ensure sterility. In the production of sterile radiolabelled particles, the aim has to be that in a million units at most one living microorganism may be found. With a view to ensuring a low microorganism count before the sterilization procedure, the method of production and the sterilization procedure need to be regularly controlled microbiologically. Suitable sterilization methods are autoclaving (heating in saturated steam under a suitable temperature–time ratio, e.g. 120°C for 20 min) and dry sterilization (dry heating with a suitable temperature–time ratio, e.g. 160°C for 2 h, or 180°C for 30 min). When selecting the method of sterilization, care has to be taken to ensure that it has no adverse effect on the quality of the product [2].

*7.2.3.4. Apyrogenicity*

Bacterial endotoxins (pyrogens) are polysaccharides from bacterial membranes. They are water soluble, heat stable and filterable. If they are present in a preparation and administered to a patient, they can cause fever and leucopoenia in immune suppressed patients. To minimize the chances that pyrogens are present, it is important that preparations are manufactured and dispensed under aseptic conditions, and that all used consumables and equipment have been heat treated and are known to be pyrogen free [511].

The limulus amebocyte lysate (LAL) test is used to detect pyrogenic endotoxins. In the past, the LAL test was only considered an alternative to the rabbit pyrogen test [512]. In the new edition of the European Pharmacopoeia [513] and Supplement 2000 [514], the LAL test is mentioned as being of equal value to the rabbit pyrogen test. Analogously, the LAL test is classified at the same level in other national pharmacopoeias. For example, the US Pharmacopoeia XXIV [515], the British Pharmacopoeia [516] and the Czech Pharmacopoeia [517] and its supplements.

The following six methods are described in the current European Pharmacopoeia [518]:

(1)    Method A: gel clot method: limit test.
(2)    Method B: gel clot method: semi-quantitative test.
(3)    Method C: turbidimetric kinetic method.
(4)    Method D: chromogenic kinetic method.
(5)    Method E: chromogenic end point method.
(6)    Method F: turbidimetric end point method.

The gel clot technique (methods A and B) allows the detection or quantification of endotoxins and is based on clotting the lysate in the presence of endotoxins. The concentration of endotoxins required to cause the lysate to clot under standard conditions is the labelled lysate sensitivity. Both kinetic methods (methods C and D) use the linear regression of the logarithm of the response vs the logarithm of the endotoxin concentration [518]. The end point method (methods E and F) is based on the quantitative relationship between the endotoxin concentration and the quantity of chromophore (method E) released at the end of the incubation period, irrespective of the turbidity of the reaction mixture [514].

In situations where it is not possible to carry out these tests before releasing the batch for clinical use due to the short half-life of the radionuclide used in the preparation, the test is regarded as a control of the production quality [518].

The injection ought not to contain more than $175/V$ x I.U. of endotoxins per millilitre, in which $V$ is the maximum recommended administered total dose in millilitres.

Note that endotoxins are measured in endotoxin units per millilitre (EU/mL). One European unit (EU) is equal to one international unit (IU) of endotoxin.


7.3. DOCUMENTATION

The aim of documentation is to achieve traceability for each radioactive particle preparation and provide an audit to trace an individual product for suspected defects. It guarantees that all personnel involved in the manufacture of RSV agents are intimately aware of the information required to decide on the suitability of the radioactive particle release in a batch for patient use [495]. The instructions as well as SOPs of radioactive particle preparation ought to be written by the person in charge of production and approved independently. A specification ought to be available for each material/chemical/radioisotope used as well as for the final dispensed radioactive particle.

### 7.3.1. General requirements

The general requirements include the following considerations [495]:

(a) Good documentation is the backbone of the quality assurance system. A written procedure mitigates errors arising from spoken communication, and activities that have been accomplished can be traced.

(b) Documents have to be designed sedulously, prepared diligently, reviewed thoroughly and distributed.

(c) It is obligatory that the prepared document be approved, signed and dated by the appropriate authorized persons.

(d) Documents (including the title, nature and purpose) ought to be well defined and methodically written in a clear manner. Documents containing instructions ought to be defined systematically and be easy to follow. The style and language of documents ought to be commensurate with their intended use.

(e) It is crucial to review documents periodically and they need to be up to date to comply with new editions of the national pharmacopoeia or other official compendia. During the document revision process, utmost care has to be taken to preclude inadvertent use of superseded documents.

(f) Handwritten documents ought to be avoided. In a situation where documents require data entry, it is crucial to provide sufficient space to incorporate such entries.

(g) In the event of any correction being made to a document or record, it has to be signed or initialled and dated. Whenever necessary, the reason for amending the document has to be recorded.

(h) Records have to trace all activities related to radioactive particle preparation at the time that they are done.

(i) Critical records have to be stored at a secure place with access limited to authorized persons. Additionally, adequate care has to be taken to protect the records from loss, destruction or falsification, and from damage due to fire and water, among other threats, while being stored.

(j) Critical records for regulatory compliance for day to day activities have to be duplicated on paper or microfilm or electronically, and stored in a secure location in a separate building located away from the originals.

(k) The data may be recorded by either electromagnetic or photographic means, and detailed procedures pertaining to the adopted system have to be available. In cases where documentation is followed through electronic data processing methods, only authorized persons are permitted to enter or modify data via a computer in which access is controlled by passwords or other suitable methods, and entry of critical data has to be checked individually.

(l) It is equally important that during the period of custody the extracted data can be read within an appropriate period of time.

(m) If data are altered, this has to be noticeable.

### 7.3.2. Preparation procedures

In light of the need to achieve regulatory compliance, it is crucial to have a full documentation system offering traceability of radiopharmaceuticals for RSV. A list of the most common types of documents, along with a brief description of each, is provided below [495]:

(a) SOPs: documents containing step by step instructions for performing operations related to the preparation of radioactive particles.

(b) Batch records: documents prepared by production personnel for a particular product manufactured in the department containing step by step instructions for the tasks related to production activities.

(c) Test methods: documents relating to the step by step instructions for testing chemicals, materials, radionuclides and other production related tasks and activities. The test procedure contains forms that have to be filled in at the end of the procedure to ensure inspection and checking of all QC activity by document. This ensures that the product fulfils its requirements for use in RSV.

(d)   Specifications: documents that report on the mandatory requirements for the radiolabelled particles have to be completed before the particles are released for clinical use. The purpose of this documentation is to compare the test results from the QC department with the approved specifications and decide whether the particles pass the test.

(e)   Logbook: this is a bound collection of forms arranged in chronological order that is used to record the operation, maintenance and calibration of a piece of equipment, preventive maintenance and repairs, and unexpected events/deviations for manufacturing equipment.

Given the need to ensure quality standards for each radiolabelled particle, sometimes it is essential to change the product specifications and manufacturing or control procedures. Maintaining written records of such modifications/alterations is essential. Written procedures need to be in place to justify such modifications/alterations, and everything needs to be documented appropriately [495]:

(a)   Special attention ought to be given to reviewing a representative number of batches, either approved or rejected, and a summary of the records associated with the batches needs to be documented.

(b)   There ought to be established written procedures to review and update regarding complaints, recalls and returned or salvaged radiolabelled particles. Based on the related investigations, corrective and preventative actions ought to be taken to allow trend analysis.

All production, quality control and product distribution need to have mandatory records for regulatory compliance and ought to be retained for at least one year post-expiration date of each batch. This is so that the history of each manufactured batch can be traced [495]. In the case of active pharmaceutical ingredients (APIs), all records have to be retained for at least three years after the batch has been completely distributed for clinical use to cover the potential maximum shelf life of the product using this API.

Systems have to be in place to maintain records of the following [495]:

(a)   The name of the laboratory where the radioactive particles have been manufactured as well as:
   (i)    The identity and quantity of the radioisotopes and carrier particles received from each batch;
   (ii)   The name of the supplier from whom the radioisotopes and carrier particles were obtained;
   (iii)  The control number(s) or any identification number for the radioisotopes and carrier particles assigned by the supplier;
   (iv)   The number allocated and the date of receipt of the radioisotopes and carrier particles at the manufacturing site.

(b)   Test certificate on the receipt of radioisotopes, carrier particles and chemicals.

(c)   Records to identify the radioisotopes and carrier particles used for making radioactive particles.

(d)   The decision taken to reject radioisotopes, carrier particles and chemicals.

### 7.3.3.   Batch records

Batch production records constitute a written document of each production batch prepared during the production of radioactive particles. They contain the following: sequential data pertaining to each chemical and radioisotope used for production; complete information related to the production; and control of each batch of radiolabelled particles. They constitute the documentation pertaining to the step by step manufacturing process of each batch. The batch production records need to be checked before the delivery of products to ensure that they are the accurate version. If the batch production records are gathered from a discrete part of the master document, that document ought to comprise a reference to the current master production document being used [495].

Prior to the preparation of radioactive particles, a checklist of all equipment and workstations ought to be prepared to ensure that they are clear of previous products and suitable for use. The cleaning of the equipment needs to be checked and documented appropriately. Batch and date of cleaning with a

signature is also mandatory. Data entry for each batch ought to be made in chronological order to ensure traceability. The batch number, including product code, date and time of production, and batch size, either in a logbook or using an electronic data processing system, is to be recorded immediately [495].

All essential information for each significant step in the batch production process has to be recorded. This includes the following [495]:

(a)  Dates and times (when appropriate);
(b)  The characteristics of the major equipment used for formation of radiolabelled particles (e.g. reactors, synthesizers);
(c)  The precise characteristics of each batch, including the activity content of the radionuclide, SA, quantity used, quantity produced and batch numbers of carrier particles used during the preparation of radiolabelled particles;
(d)  Actual radiolabelling yield recorded under optimized experimental conditions;
(e)  The signatures of the persons performing and supervising the task;
(f)  Any deviation from the written procedure (deviations need to be properly noted and investigated by the appropriate authority to ensure that the quality of the product remains unaltered);
(g)  Test results prior to product release for clinical use;
(h)  All analysis results for each batch of the product (if required, this may permit recall of any batch);
(i)  Release or rejection of the batch (duly signed by the responsible personnel with the date);
(j)  All essential information for the production record review.

Accurate reviewing of production batch records and quality control records is mandatory as part of the approval process for batch release. Any deviation from the batch specifications needs to be thoroughly scrutinized. Investigation, including both the conclusion and follow-up action in the form of a written record, ought to be pursued. As part of the approval process for batch release, it is crucial to review the production and quality control records. Any deviation from the product specifications of a batch ought to be scrutinized scrupulously. This practice ought to be extended to other batches of the same product. The investigation performed, including the conclusion and follow-up action, ought to be in the form of a written record [495].

The following information, along with date, time and signature of the responsible person, ought to be recorded at the time of each action taken [495]:

(a)  The product name, the batch number and the activity content of the products to be packed, as well as the quantity actually attained and its reconciliation;
(b)  The date(s) and time(s) of the packaging operation;
(c)  The packaging process's date(s) and time(s);
(d)  The name of the person responsible for packaging;
(e)  The initials and signatures of the operators for different significant steps;
(f)  The checks made to ensure that packaging instructions are followed meticulously.

### 7.3.4.  Staff training

Personnel who are well qualified to perform radioactive particle preparation are an essential part of GMP [519]. As such, the requirements for qualifications, training and development of all employees involved in radioactive particle preparation have to be met to ensure that employees can aptly perform their assigned tasks according to their positions. The best way to accomplish this is through training programmes tailored to each employee's job profile. This ought not to just end with an induction programme but continue with annual training plans and periodic retraining to ensure that an employee's

knowledge and behaviour are maintained at the required level. Various types of training programmes are conducted and documented. Training is conducted for each category of employees on the following topics:

(a)  Basics of cGMP;
(b)  Glossary of cGMP;
(c)  Quality management system;
(d)  Process and documents.

Training ought to be planned, scheduled, conducted and documented using a systematic approach. Training is conducted as classroom training. The training is followed by an assessment and is documented.

(a)  *SOP training.* All employees working in a radiological laboratory have to undergo training on the procedures of the respective functions. SOP training is also given to employees from cross functions wherever applicable. Refresher training is carried out whenever there is a major procedural change to the preparation of radiolabelled particles. This training is not only assessed, but also documented.

(b)  *External training.* The concerned head of the department of a radiological laboratory usually nominates people for external training, depending on the type of and need for training. The nominee submits a copy of all the training material pertaining to technical training to the QA or training department.

(c)  *Specific training.* Specific training is conducted in accordance with identified training. Specific training may be either on the job or classroom training, and it is documented.

(d)  *On the job training.* On the job training is carried out in the radiological laboratory, wherever applicable. It is assessed by the trainer with an assessment or a demonstration of the radiological procedure by the trainee and the same is documented in the assessment record.

(e)  *Safety training.* The radiological laboratory identifies those who need to have radiological safety training, which may be given individually or to a group of employees in the same or related occupations. The topics approached will be defined according to the existing radiological risks and complexities. These ought to cover knowledge of the mechanisms of radioactive materials' exposure, including radionuclides, biohazards and process equipment. They include the appropriate use of radiological protection items and how to proceed in an emergency.

(f)  *Job change training.* Job change training may be organized and accomplished after reviewing the employee's training record and training requirements for the new job position. It ought to be based on a training plan for the employee after an analysis of the employee training record vis-à-vis the training requirements for the new job has been prepared.

(g)  *Training for contract/temporary employees.* This type of training poses a special challenge for most departments as it concerns transient personnel. Temporary employees in the production areas or quality control laboratories have to be trained appropriately as their work can impact the quality of the product. They ought to be educated and trained thoroughly to obtain desired results without any deviations.

### 7.3.5.  Validation of training

Employees have to be evaluated after training to ensure that they have learned the necessary information and are qualified for the job. Validation provides assurance that the training programme is meeting expected standards and assures that the trainees have acquired the required skills and knowledge [520]. Assessment and evaluation of training are carried out through oral examinations, written examinations (using paper or computer systems), simulations (using cold samples) and performance based analysis. Snap tests — surprise tests — are conducted in various radiological departments on several topics, including radiological safety, cGMP compliance and QA/QC, among others. With a view to checking awareness of and adherence to systems and procedures, snap tests are conducted at regular intervals. Snap tests can be recorded with a form that can be stored for further evaluation. Self-assessments

are used frequently in self-study and computer based courses to give trainees a chance to evaluate how much they have learned. Evaluation should be graded appropriately to ensure that the objectives set for training are met and form the basis for review and the next training activity.

The minimum qualifying marks for the cGMP, refresher cGMP, SOP training and snap test assessments ought to be 75%. A training certificate ought to be issued to successful employees. Only those who have passed ought to be allowed to perform their assigned duties and responsibilities independently [110].

### 7.3.6. Retraining

Retraining or additional training is necessary for those employees who have not qualified in the training course.

### 7.3.7. Periodic review of training

The top management team of the department ought to review the training programme with the human resources department periodically to ensure that the plan has been completed for satisfactory performance of the functions employees are expected to perform. Documentation of training and retention of training records ought to provide evidence that the training has been carried out. The training records ought to be archived as specified in the document management SOPs. The department heads ought to ensure that the training records are updated. All training documents ought to be retained for a period of five years.

# 8. STANDARD OPERATING PROCEDURE FOR RADIOSYNOVECTOMY

## 8.1. INFORMED CONSENT

As for any medical treatment with potential hazards, a patient's written informed consent is mandatory, and this is more pronounced in cases of invasiveness and additional use of radiation. Informed consent includes:

(a) Verbal and written information about the procedure;
(b) Knowledge of the procedure's benefits and risks and the nature of the treatment;
(c) Joint specific choice of the radionuclide;
(d) Knowledge of the radionuclide's side effects;
(e) Instructions for the 48 h after administration;
(f) An outline discussing the efficiency of the therapy and a questionnaire including specific questions on subjective symptoms, history of disease and medication with the signatures of the patients and the doctor being documented. A medical questionnaire sample is provided in Annex II.

The patient ought to be informed about the invasive nature of RSV and about the accompanying complications of joint puncture, such as infection, local haemorrhage, and the risk of iatrogenic and/or non-iatrogenic extra-articular distribution of the radiopharmaceutical [1]. In addition, patients have to be informed about the RSV mechanism, indications, contraindications, the nature of the radioactive procedure and alternative treatment modalities, such as surgical synovectomy [1]. An informed consent sample is provided in Annex I.

Patients ought to be informed about the need for immobilization for 48 hours after the treatment and the potential complications resulting from immobilization, such as thromboembolic events. They also ought to know about the delayed response to RSV (up to 1 month), with further improvements from three to six months, advancement of joint inflammation of ~60–80%, and the possibility of retreatment in case of non-response [1]. Patients also ought to be warned that they may experience a temporary increase in inflammation and pain following the treatment. Information about possible side effects, complications and precautions ought to be written in a detailed and complete written informed consent document, which may include the following [1]:

(a) The procedure, mechanism, indications, contraindications, benefits and risks.
(b) Alternative treatment options.
(c) Treatment with radioactivity and radiation exposure.
(d) Complications from puncturing a joint:
    (i) Infection;
    (ii) Local haemorrhage.
(e) Risk of radionecrosis (very rare).
(f) Risk of pyrexia or allergy (very rare).
(g) An initial increase in pain due to radiation synovitis.
(h) Delay in response of up to a month.
(i) Final improvement up to six months after RSV.
(j) Overall improvement of approximately 60–80%.
(k) Theoretical risk of future malignancy comparable to that from routine diagnostic radiological and nuclear medicine procedures.
(l) Risk of thromboembolism due to immobilization for 48 hours after RSV (if necessary, prophylactic antithromboembolic precautions may be taken).
(m) Necessity of repeating RSV in non-responders to the first RSV after a period of six months.
(n) Follow-up examination and response evaluation from three to six months after RSV.
(o) No requirement for withdrawal of biological therapy, since it is not associated with an increased risk of infection [37].

## 8.2. DIAGNOSIS

A complete history of the disease has to be evaluated, and all patient documents relating to it, including previous treatments, ought to be provided at the consultation. Important information such as clinical symptoms, duration of synoviopathy, duration and doses of medication as well as previous treatments should be shared. The joints involved need to be clinically examined with respect to swelling, hyperthermia, pain and range of motion. Most patients referred for RSV have experienced a long history of antiphlogistic medication or intra-articular injection of glucocorticoid with brief or insufficient response, and in some cases they will have undergone surgical synovectomy [1].

Recent imaging results (not older than three months), such as planar X rays, magnetic resonance imaging (MRIs) or bone scans with [$^{99m}$Tc] phosphonate of the joint, ought to be evaluated to confirm the indication of RSV. Planar X rays do not show signs of synovitis, but any morphological abnormalities can be visualized. In some cases, to clarify uncertainty, a computed tomography (CT) scan or MRI can be helpful. A bone scan with blood pool imaging is considered to be a predictor of response to RSV in patients with synovitis [130, 131]. Increased periarticular activity in the blood pool phase and the intensity of the blood pool are correlated with patient response to RSV [521]. However, the prerequisite for RSV response is an adequate intra-articular injection, and distribution and retention of the radiopharmaceutical to achieve the highest radiation dose to the synovialis [522]. The three phase bone scan is the conventional, inexpensive gold standard for the detection of metabolic abnormalities in soft tissue in and around the joint, such as synovitis, and can distinguish those from degenerative disease. A high resolution bone scan

from the affected site can localize exactly the joints that can benefit from RSV, especially in cases where a patient's subjective pain perception indicates that multiple neighbouring joints are affected. Comparison of scans in the blood pool and mineralization phases can distinguish between the inflamed and degenerative components of the joint. De novo disease with exclusively inflamed features in the perfusion and blood pool phases, and with no degeneration in the mineralization phase, are extremely rare. In general, almost all joints examined by RSV reveal mixed inflamed and degenerative features in the bone scan. This is mostly due to the selection bias for patients with a long history of disease referred for RSV treatment after multiple refractory local treatments and surgeries. Ultrasound examination of the joint can evaluate and estimate the joint fluid and synovial thickness [1].

## 8.3. FACILITIES

According to the European Association of Nuclear Medicine's guidelines and country-specific regulations [131], the application of radiopharmaceuticals with beta emitters ought to be performed in a dedicated room intended for handling open sources of ionizing radiation, suitable for sterile injection procedures and approved for the use of beta emitters as required by the national regulatory committees for atomic law and specialized nuclear medicine staff [37]. An appropriate aseptic technique is mandatory, with adequate sterilization of the treatment site and use of sterile utensils, drapes and gloves [37].

A C-arm radiographic device ought to be present. Around the application site, typically on and underneath the C-arm detector, tissue has to be laid out to absorb unintentionally spilled droplets of beta emitter. In addition, separate plastic waste bags have to be provided exclusively for contaminated waste to meet safety requirements for storage and later discharge. If inpatient treatment is required by national legislation, this should take place in an approved facility with appropriately shielded rooms and en suite bathroom facilities.

Joint puncture has to be performed by an experienced physician and all means need to be taken to ensure the exact intra-articular position of the needle tip, complete intra-articular injection and distribution of the radiopharmaceutical. Extra-articular application and/or leakage could result in extensive complications and necrosis of healthy tissue [298]. Extra-articular or par-injection of radiopharmaceuticals can be avoided by using imaging guidance [130, 131]. In cases of large and medium sized joints such as the knee or shoulder, ultrasonographic-guided joint puncture can be used. However, fluoroscopic-guided arthrography with application of contrast media can be more accurate in treating small joints of the hands and feet [298].

## 8.4. PREPARATION OF PATIENTS

The following is required during preparation of patients for RSV:

(a) Double checking the identity of the patient and medical history, medications and allergies.
(b) Defining the indication for RSV of the proposed joint clearly. Imaging of the joint can be performed with a scintigraphy, MRI, and/or ultrasound. This ought to be presented and the presence and extension of synovitis in the joint proposed for treatment ought to be clarified [280].
(c) Patients ought to empty the bladder before the procedure to avoid mobilization during and immediately after the RSV procedures.
(d) All treatments with radiopharmaceuticals in women of childbearing age, or in those who are pregnant or breastfeeding ought to be excluded.
(e) The RSV procedure ought to be explained to the patient and the family, if required.

## 8.5. INSTRUMENTATION

The following instruments are required:

(a)    Activimeter;
(b)    Fluoroscope;
(c)    Instrumentation for decontamination.

It is important to prepare and store the radiopharmaceuticals in a safe place to prevent contamination. Access to RSV rooms ought to be restricted to authorized persons. The number of attendants ought to be limited to the operating personal and their names ought to be documented in the study protocol for each session. All operating personal have to have fulfilled all approved certifications and SOPs. They need to wear convenient and advisable radiation dosimeters and trunk monitors for the trunk between the waist and the neck. When working with beta emitters, it is essential to carry an extremity monitor on the left index finger (right handed persons) or the right index finger (left handed persons) to monitor the high exposed short range radiation. Personnel should stay as far away as possible from the C-arm. Figure 33 shows simple preparation of the equipment used in the procedure.
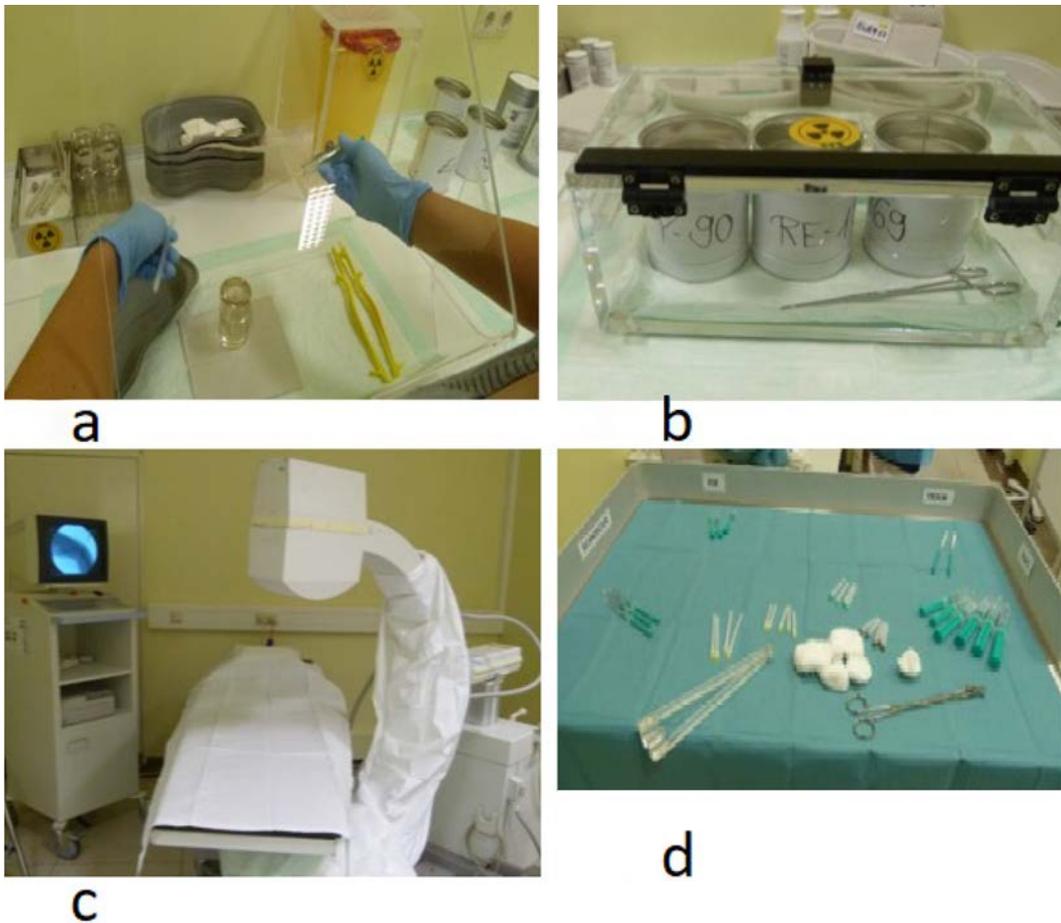


*FIG. 33.   (a) Preparation of radiopharmaceutical. (b) Small containers for radioactive waste. (c, d) Preparation of workspace. Bethesda, Duisburg, Germany. Courtesy of J. Farahati.*

## 8.6. UTENSILS

The required utensils include:

(a)    70% alcohol for cleaning with gauze or swabs;
(b)    Sterile isotonic solution for injection (e.g. 0.9% saline);
(c)    Anaesthetics (e.g. lidocaine);
(d)    Sterile gauze;
(e)    Sterile tools;
(f)    Glucosteroids;
(g)    Contrast media;
(h)    20–22 gauge needles;
(i)    1, 5 and 10 mL syringes;
(j)    Radiopharmaceuticals, preferably in a 1 mL syringe in a plexi shield.

## 8.7. CONSIDERATIONS FOR THE RECEIPT AND HANDLING OF RADIOPHARMACEUTICALS

The receipt and handling of radiopharmaceuticals is tied to strict approval by authorities, depending on the country's specific regulations. These include locality, radiation protection, handling procedures and staff. Usually, approval for handling and storage of a maximum amount of beta emitting radionuclide activity is granted, allowing for sufficient radiopharmaceutical activity to treat the expected number of patients and joints during the day of delivery. Radiation protection requires supervision regarding contamination and exposure surveillance. The first step after receipt of the ordered activity is the distribution into portions suitable for administration into the joints.

Detection and imaging of beta emitting radionuclides is difficult. In general, dose calibrators are used to measure the Bremsstrahlung of the radionuclides indirectly. For this purpose, the dose calibrators have to be configured specifically to ensure a constant geometry of the holder for the syringe with the beta emitter [1]. The activities are drawn from the delivered glass vial, preferably with an insulin syringe. The insulin syringe has the advantage of a subscale, allowing for good judgement of the activity volume drawn, which is useful for reducing the number of probe measurements and exposure to radiation. Table 3 shows the recommended dose and penetration of radiopharmaceuticals for each joint.

It is advisable to handle the syringes and vials with suitable grippers following the principle of maintaining distance between fingers and beta emitters to avoid Bremsstrahlung. Importantly, plexi shielding has to be used with syringes or vials to avoid direct contact with beta emitters. Studies were carried out by the German Bundesamt für Strahlenschutz showing dose rates of 9 mSv/s at syringe tips filled with 185 MBq $^{90}$Y, whereas the rear (empty) end showed a dose rate of 0.36 mSv/s. Therefore, holding the syringe near the tip with two fingers is to be strictly avoided. Acrylic plastic is an appropriate shielding material for beta emitting radionuclides. Fingertip doses up to 22.1 $\mu$Sv/MBq were observed by others when not using appropriate shielding, as compared to 0.4 $\mu$Sv/MBq when using a clamp and acrylic shield [1]. Hence, it is imperative to use strict aseptic procedures according to the guidelines for joint puncture, and to ensure that before the procedure all needed materials have been prepared and are available and reachable during the puncture procedure. Insulin syringes are frequently used because they are more convenient for intra-articular injections (especially for small joints) with subscale radioactivity for exact judgement of the activity volume. Syringes and vials with suitable grippers maintain distance between fingers and beta emitters to avoid bremsstrahlung, especially in the case of $^{90}$Y. Additionally, the use of plexi shielding for syringes or vials prevents directly touching beta emitters with the hand and fingers and can dramatically reduce radiation exposure. Figure 34 shows the shielding parts for the safe handling of radiopharmaceuticals for RSV procedures to maintain distance and avoid contamination by directly touching beta emitters.

TABLE 3. CHARACTERISTICS OF RADIOPHARMACEUTICALS FOR
RADIOSYNOVIORTHESIS [1, 131, 146]

| Radionuclide (particle) | Vol. (mL) | Particles (m) | Half-Life (d) | β max. energy (MeV) soft tissue/ cartilage | Penetration β radiation (mm) | γ energy (KeV) | Joints |
|---|---|---|---|---|---|---|---|
| Y-90 (citrate) | <2 | 3–6 | 2.7 | 2.2 | 3.8–11/<8.5 | — | Knee |
| Re-186 (colloid/sulphide) | <1 | 5–10 | 3.7 | 1.07 | 1.2–3.7/<3.1 | 140 | Shoulder |
| Er-169 (citrate) | <0.2 | 3–8 | 9.4 | 0.34 | 0.3–1.0/<0.7 | — | PIJ |
| Au-198 | | 2.7 | 0.96 | | 1.2–3.6 | 411 | Knee |
| P-32 (chromic) | | 10–20 | 14 | 1.7 | 2.6–7.9 | — | Knee |
| Ho-166 (FHMA) | | 5–10 | 1.2 | 1.8 | 2.2–8.7 | 81 | Knee |
| Dy-165 (FHMA) | | 3–10 | 0.09 | 1.3 | 1.4–5.6 | 95 | Knee |

**Note:** FHMA — ferric hydroxide macroaggrogate; PIJ — proximal interphalangeal joint.



*FIG. 34.  Plexi shielding for syringes and vials. Bethesda, Duisburg, Germany. Courtesy of J. Farahati.*

Technicians and doctors should use thermoluminescent finger dosimeters. Syringes and vials have to be transported in electron catching acrylic boxes. These can be put inside portable lead boxes to additionally shield gamma radiation. Use of nitryl or vinyl instead of latex gloves has to be enforced. Latex gloves do not protect skin from contamination by high local doses. By following these principles, staff should not have finger doses exceeding the sensitivity threshold of the official finger dosimeters.

The activity of radiopharmaceuticals ought to be estimated by calculating their volume. To avoid confusion, all vials and syringes need to be labelled clearly with the name of the patient, their birth date, the name of the radiopharmaceuticals, the activity and volume (e.g. "185 MBq — $^{90}$Y citrate; Meier Maria 1.1.1956"). If necessary, it can be beneficial to record the quality control, administered radioactivity, date and time of all administered medications in a permanent medical record. Periodic observation of patients is mandatory to check possible complications of the RSV procedure and medications.

8.8. PUNCTURE

The puncture procedure includes the following steps:

(a) Double checking the patient's identification, the joint and the side proposed for RSV, the indications and informed consent. Puncture of the joint ought to be performed in accordance with local guidelines for joint puncture. It ought to be performed by a nuclear medicine specialist although it can be performed by a skilled physician (e.g. orthopaedist) in the presence of a nuclear medicine physician. The nuclear medicine physician is responsible for the entire procedure and should inject the radiopharmaceutical on his or her own after securing the intra-articular position of the needle. Figure 35 shows the disinfection of the puncture site as well as coverings.

(b) Checking the joint proposed for RSV before the procedure for any injury, infection or other possible risks.

(c) Checking and palpating the possible injection site and injection target and positioning the angle of the needle to insert the tip of the needle intra-articularly at the first attempt to avoid multiple-insertion pain. Multiple insertions may also lead to more leakage of radiopharmaceuticals from the joint cavity.

(d) Shortening and removing the hair over the puncture area, but not shaving it (this may cause skin injury). Adopting comfortable positioning for the joint puncture with the best view of the patient and C-arm monitor.

(e) Covering cuts in the skin of the hands with adhesive plaster before the procedure and washing the hands.

(f) Using aseptic techniques and personal protective equipment, a laboratory coat or surgical gown, disposable sterile gloves and a surgical mask, and avoiding any contact with or touching of non-sterile areas.

(g) Covering the joint carefully with a sterile drape under sterile conditions.

(h) Puncturing the joint with a needle gauge appropriate to the joint's size by simultaneously infiltrating and anaesthetizing the skin over the puncture area with local anaesthetic (e.g. lidocaine 1%). Excess joint fluid ought to be aspirated prior to injection of the radiopharmaceutical [37].

(i) Using a 22 gauge syringe for medium and small joints. A hose is attached to the needle with a small syringe with 50% contrast media. While still on the skin's surface, the needle is targeted at the joint gap while a single X ray shot with the C-arm is performed when appropriate. The single shot mode ensures minimization of radiation exposure. X ray focus should be adopted as much as possible.

After detecting and confirming the homogenous intra-articular position of the needle by aspiration of the synovial fluid or by fluoroscopy, while still touching the skin, the necessary quantity of contrast media is injected, followed by a single X ray shot to document needle position and visualize the intra-articular distribution of the contrast media. The puncture procedure can be laborious for the physician and painful for patients, especially in cases of finger or toe joints in patients with progressive rheumatoid arthritis with close or untraceable intra-articular space. After documentation, the contrast media and excess synovial fluid ought to be aspirated as much as possible. Then, the syringe containing the radiopharmaceutical is coupled to the needle and the activity is administered. This procedure ensures a minimum of exposure time and a maximum of distance between the fingers and the beta emitter. It also ensures a determined joint puncture and safe placement of the needle without any radiation hazard.

Long acting glucocorticoids can be injected to:

(a) Bridge the lag phase of the onset of the RSV effect;
(b) Avoid/lower the risk of radiation induced synovitis;
(c) Lower the grade of hypervascularity and/or hyperpermeability, diminishing leakage;
(d) Spread in the distally located inter carpal compartments in the wrist joint;
(e) Adjust the corticosteroid dose to the joint size (2–4 mg, finger joints; 10 mg, medium sized joints; 20–40 mg, knee).
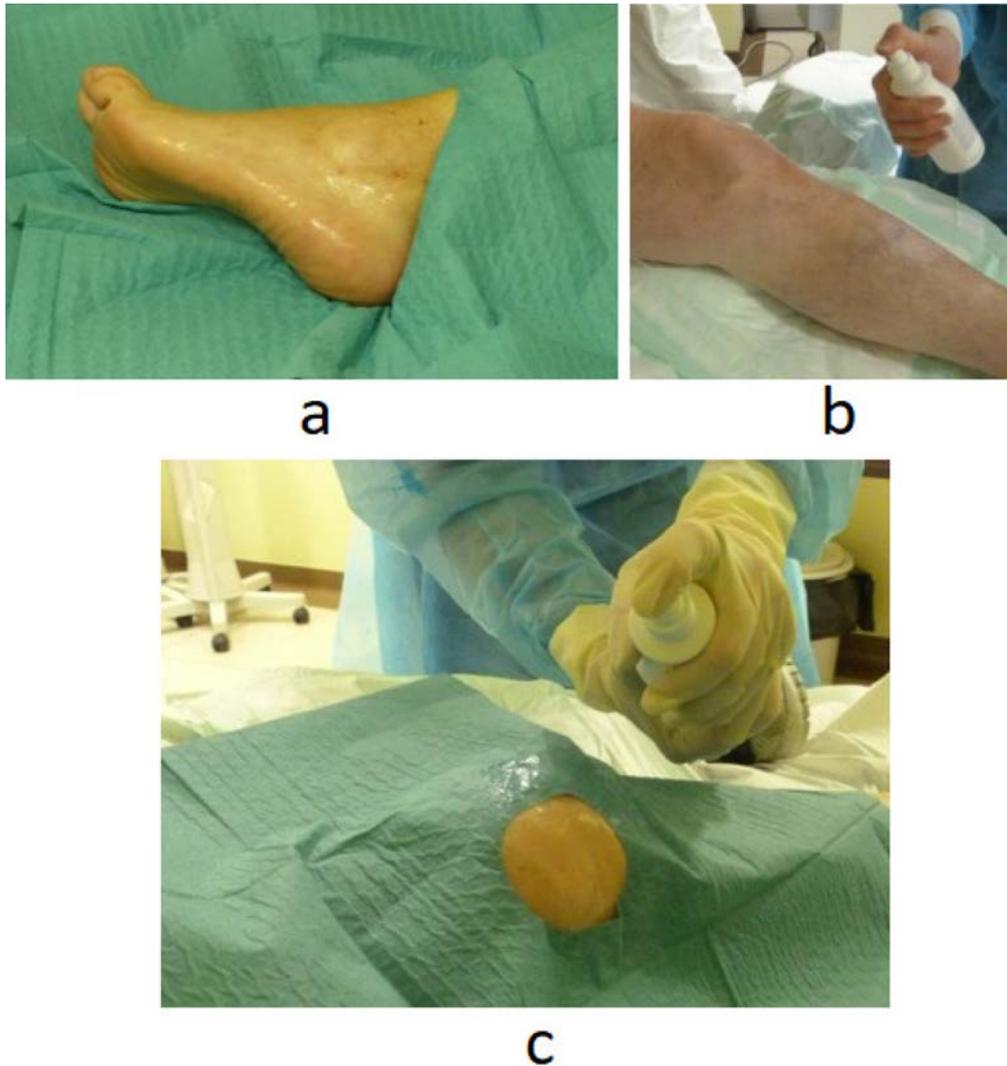
*FIG. 35. (a–c): Extensive disinfection of the puncture site. (c) Sterile drape for knee. Bethesda, Duisburg, Germany. Courtesy of J. Farahati.*

After the radiopharmaceutical is applied, the needle can be flushed with saline/corticosteroids/local anaesthetic solution during withdrawal to reduce the risk of skin necrosis. A visual overview of the procedure is provided in Figs 36 and 37. Additionally, after RSV application, is it advisable to immobilize the treated joint for at least 48 hours to reduce the risk of radioactive leakage to para-articular tissues. In the case of lower limb joint treatment (hip, knee, ankle), the patient is recommended to avoid walking, and thus requires the assistance of third parties [1]. Finally, to control the appropriate performance of the RSV, post-therapeutic imaging can be performed. Planar scintigraphy of the treated joint reveals the distribution of radioactivity inside the joint cavity clearly for up to several days following RSV [1]. For one week after RSV, the patient needs to refrain from any kind of strenuous activity, rehabilitation or physical therapy of the treated joint. For four to six months after RSV, women of reproductive age ought to avoid pregnancy [37, 130, 131].
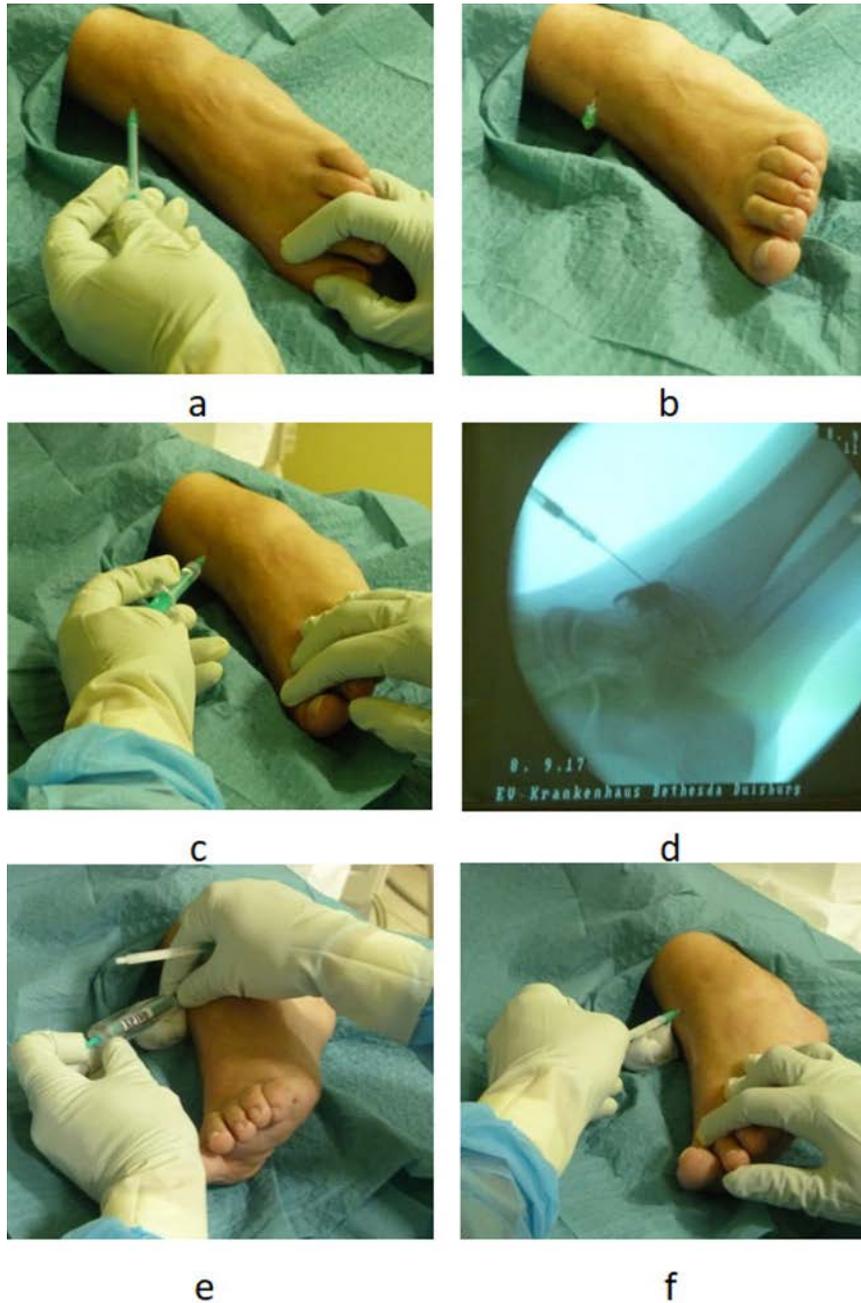
*FIG. 36. Ankle. (a) Puncture and local anaesthesia. Conforming of needle position: (b) by aspiration; (c) with contrast agent; (d) by fluoroscopy; (e) injection of radiopharmaceutical; (f) injection of corticosteroid. Courtesy of J. Farahati.*

## 8.9. POST-RADIOSYNOVECTOMY PROCEDURES

Post-RSV procedures include the following:

(a) Positioning the patient using supportive materials and immobilizers;
(b) Scanning the treated joint and adjacent lymph nodes with a scintillation camera (using Bremsstrahlung energy window and photopeak) or Geiger–Müller counter for $^{32}P$;
(c) Indicating appropriate anatomic landmarks for imaging;
(d) Reviewing images to ensure that the required information has been acquired with appropriate quality;
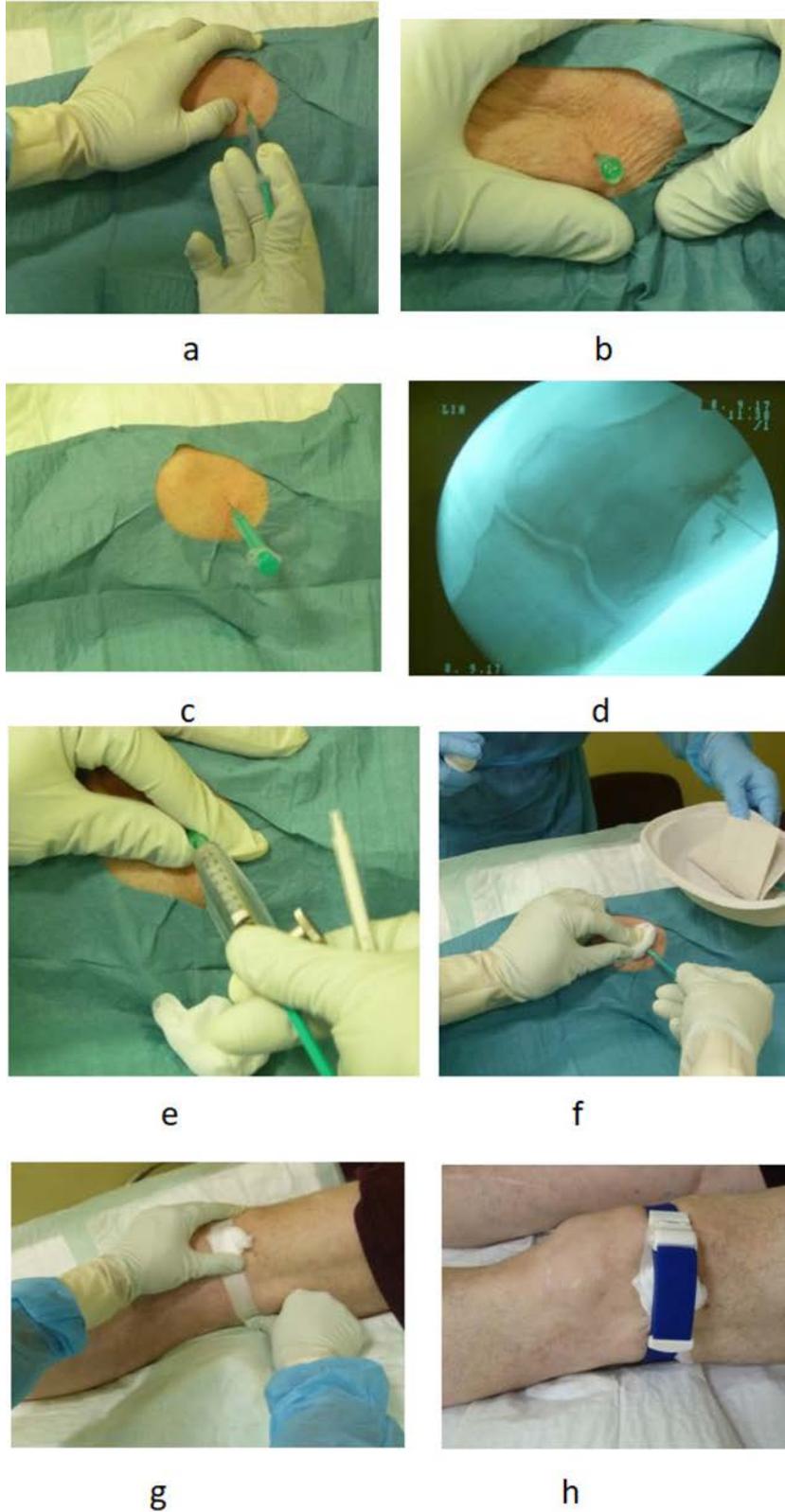
FIG. 37. Knee. (a) Puncture and local anaesthesia. Conforming of needle position: (b) by aspiration; (c) with contrast agent; (d) by fluoroscopy; (e) injection of radiopharmaceutical; (f) injection of corticosteroid; (g, h) tourniquet. Bethesda, Duisburg, German. Courtesy of J. Farahati.

(e)   Documenting the intra-articular distribution of the radiopharmaceutical in the joint and excluding any extra-articular transport of radiopharmaceuticals to the adjacent lymph nodes;

(f)   Immobilizing the treated joint for 48 hours with a splint to reduce the rate of lymphatic leakage;

(g)   Avoiding draining radiation induced synovitis with increased pain and effusion during the first 4 weeks after RSV;

(h)   Detecting any possible contamination;

(i)   Decontaminating after any radiopharmaceutical leak;

(j)   Using a prophylactic cooling pad for pain relief.

After finishing the RSV treatment, all procedures, including information on proper puncture, application of radiopharmaceuticals and applicated co-medications, ought to be documented and stored securely in an archive (in Germany for 30 years). All possible risks and hazards and risky issues or safety conditions also need to be documented, including:

(a)   Monitoring personal contamination after leaving the RSV room;

(b)   Monitoring the background contamination, disposal and equipment before and after RSV;

(c)   Monitoring and documenting the body contamination following an incident and decontamination;

(d)   Attending all proper training courses;

(e)   Identifying clearly radioactive material at any time with radioactive warning tape;

(f)   Marking the radiopharmaceutical with information about the activity and date.

## 8.10. POST-RADIOSYNOVECTOMY IMAGING

After radionuclide injection, a distribution scan ought to be acquired with a gamma camera to document successful intra-articular injection and proper distribution within the joint. Follow-ups with the referring physician in close collaboration with the nuclear medicine specialist are indicated at four weeks, three months, and six months after the procedure. An early check-up for side effects or other complications is recommended from three to seven days after treatment to assess the response to RSV. Figure 38 demonstrates imaging examples for follow-up after the injection.



*FIG. 38. Post-radiosynovectomy imaging of the knee by scintigraphy reveals periarticular distribution of Y-90 citrate in the knee joint. Bethesda, Duisburg, Germany. Courtesy of J. Farahati.*

## 8.11. FOLLOW-UP

Follow-up ought to include the following:

(a)    Patients to be reviewed four to six days after injection to evaluate, respond to, report and document the early side effects;
(b)    Clinical examination to be performed to assess the therapeutic success;
(c)    Follow-up to be performed with the collaboration of an attending rheumatologist.

The patient ought to be told to immobilize the joint for at least 48 hours after RSV treatment. Early pain after RSV can be treated with antiphlogistics. Patients ought to be given all recommendations and information clearly to avoid unnecessary radiation exposure to family members and the public. These rules vary by country. For example, women ought to avoid pregnancy after treatment for at least four to six months [1]. Nevertheless, such risks are hypothetical, since excretion of the intra-articular radionuclides via bladder or bowel is negligible. Furthermore, increased observation of hygienic measures is strongly encouraged.

Patients who receive treatment in multiple joints may be helped if they receive inpatient treatment over 48 hours and if the facility has a therapeutic ward to host these patients. The nursing personnel in nuclear medicine facilities ought to have the appropriate radiation safety knowledge. If significant medical conditions are observed, such as acute radiation lesions, contingency plans ought to be provided to treat these cases as a medical emergency. Under no circumstances are medical personnel who are unfamiliar with such measures to take planned action, although radiation exposure concerns ought not to interfere with prompt medical treatment. The follow-up for a regular RSV includes a patient evaluation six to eight weeks after treatment. In cases of positive treatment response, this can be dispensed with. A clinical examination is recommended four to six months after treatment, and in some countries, such as Germany, this is mandatory. Re-evaluation can also be interdisciplinary, involving the rheumatologist or orthopaedic surgeon as the physicians primarily taking care of these patients [1]. Depending on the response, a second treatment may be envisioned.

## 8.12. OUTCOME

Many studies have been published reporting the results of RSV in patients treated for different indications. Studies reaching evidence based medicine level 1a and featuring randomized and double blind controlled multicentre trials are rare. The reported success rates range from 40–90% for the different joints and different underlying diseases [11, 16, 370, 461, 523–526]. Deutsch et al. [10] summarize the results of 72 studies carried out between 1975 and 1992 in patients with rheumatoid arthritis. After a one year follow-up, the results of treatment for 60–80% of patients were classified as good or excellent. The efficacy of RSV in patients with osteoarthritis or other diseases not caused by rheumatoid arthritis has been studied in more detail. In these patients, similar results have been observed, with response rates of between 40 and 80% [523, 527].

One study considered the time to remission after RSV and the effect of underlying diseases, the type of joint and the duration of illness, as well as age and gender, on the success rates for RSV in 97 patients with a combined 174 treated joints [523]. After six months, the probability of pain release of more than 20% was 78% and was significantly dependent on the age of the patient ($p=0.02$) and the duration of illness ($p=0.05$) [1]. However, no influence was found for gender ($p=0.17$), underlying disease ($p=0.23$) or joint type ($p=0,69$) [523]. Hence, RSV is effective in rheumatoid arthritis and in activated osteoarthrosis with reactive synovitis and effusion.

Another study evaluated the effectiveness of RSV in relation to joint type and underlying disease by both self-assessment of patients and scintigraphic assessment to determine the conditions under which RSV might be preferable to intra-articular corticoid injection alone [522]. The group included

136 patients, 313 with RA and 111 with OA, and a combined 424 treated joints. The subjectively estimated success rates for small, medium sized, and large joints ranged from 79–89% for both RA and OA. The scintigraphically determined response rates ranged from 69–81%, and were higher in patients with RA than in patients with OA. Based on this study, earlier switching to RSV is recommended.

Several prospective double blind studies have evaluated the efficacy of RSV [11, 369, 408]. In one double blind, randomized, placebo controlled, international multicentre study, patients with rheumatoid arthritis with recent ineffective corticosteroid injections into their finger joints were treated [370]. This study reached the highest level of evidence. Eighty-five finger joints of 44 patients were treated with either $^{169}$Er citrate or saline solution. The results of an evaluation six months later in their intent to treat approach showed a significant effect of $^{169}$Er citrate compared to placebo for the principal criteria of decreased pain or swelling ($p$=0.04) and decreased pain and swelling ($p$<0.01). Mobility was also significantly increased ($p$=0.04). These results clearly confirm the clinical efficacy of $^{169}$Er citrate RSV of RA diseased finger joints after previous ineffective intra-articular corticosteroid therapy. Consequently, RSV is becoming a viable alternative for treatment of chronic synovitis in RA and a secondary treatment for inflammatory arthropathies [1]. The advantages of RSV compared with surgical synovectomy include equivalent results, lower costs, the fact that it is an ambulatory procedure and repeatability [51, 60]. In patients developing chronic effusions after arthroplasty (e.g. of the knee), RSV is able to stop effusions effectively [528].

According to a review by Deutsch et al., nine studies have reported good to excellent results in 60–80% of patients with haemophilia [10]. Concordant data from Siegel indicated significantly decreased incidence of bleeding in 70–80% of patients. This resulted in a considerable reduction in treatment costs in comparison to the conventional surgical approach, which makes intensive use of clotting factors in patients mandatory [60]. Furthermore, promising new agents are currently under preliminary biological evaluation, such as $^{177}$Lu and $^{175}$Yb hydroxyapatite particles [384]. These agents seem to be viable alternatives to $^{169}$Er based agents, coming from a feasible and cost effective production route.


## 8.13. RADIATION PROTECTION

Virkkunen et al. [529] reported the first adverse effects of RSV after intra-articular application of $^{198}$Au. Extra-articular irradiation of the lymphatic and venous system after RSV can result in leakage of the radiopharmaceutical from the joint. A wide range of leakage has been reported for different radiopharmaceuticals in the literature. In general, the rate of leakage after RSV is reported to be approximately 10%; however, some reports give a figure of as high as 48%. A wide range of leakage can cause iatrogenic or non-iatrogenic diseases. The extra-articular injection is the major iatrogenic cause of leakage and in this area success depends on the knowledge and experience of the physician. Non-compliance is the major cause of non-iatrogenic leakage and can result in 40% leakage from the joint [530]. Thus, immobilization of the treated joint after each RSV is essential to reduce leakage and optimize results.

Increased leakage can also result from the small size of a labelled particle. One week after RSV, 6% of the activity is taken up in the lymph nodes and 2% in the hepatosplenic system [172]. A higher leakage rate of 14% is reported for $^{169}$Er colloid [372], and lower leakage has been observed after RSV of knee joints with $^{165}$Dy and $^{32}$P chromic phosphate [363, 531], resulting in doses to the lymph nodes of between 0.5 and 2.4 Gy. The fact that the particle size of chromic phosphate is 10 times larger than that of colloid particles of $^{90}$Y is the likely reason for the different leakage rates [532]. Higher leakage rates can also result from instability of the radiopharmaceutical. RSV with 200 MBq $^{90}$Y is reported to result in whole body radiation: doses of between 9 and 99 mSv and a gonadal dose of 0.1–0.2 mSv [533]. Increased chromosomal aberrations after RSV of the knee joint with $^{90}$Y were reported by Daker in 1979 [534]; $^{186}$Re is reported to increase the dicentric lymphocytes. However, in other studies, no chromosomal aberration has been reported when using $^{169}$Er and $^{32}$P [399, 534] or $^{165}$Dy. Figure 39 shows an inflamed knee joint before and after treatment [535].

## 8.14. CONCLUSION

RSV has been used for decades to treat patients with haemarthropathy and rheumatoid arthritis, while more recently, it has also been used to treat those with osteoarthritis. However, there are only a few controlled studies with clear-cut evidence regarding the clinical results from using different radiopharmaceuticals and the effects of internal irradiation with respect to different pathophysiologies and stages of disease. In addition, discrepancies with regard to expertise, selected criteria, diagnostic work and the radiopharmaceuticals used in different countries make comparisons of published data on this topic difficult [1]. Studies with proper inclusion criteria and appropriate expertise are needed to justify the role of RSV as a minimally invasive therapy option for patients with synoviopathy with distinct underlying pathologies. Several clinical studies have already indicated that RSV can result in years of improved symptoms and delay of a surgical option when conservative therapy has failed [528]. In addition, recent reports suggest that RSV can do more than synovitis [31].

Ideally, RSV should be employed before progressive radiological signs of joint destruction are evident. However, it is unusual to have patients referred for RSV who have not previously been treated by a general physician, orthopaedist or rheumatologist. Most patients have already had symptoms for many months, despite prolonged conservative treatment, multiple applications of intra-articular corticosteroids and, in many cases, prosthesis surgery. In other words, RSV is unfortunately considered to be the last option by musculoskeletal disease specialists.

The major advantages of RSV include little or no need for hospitalization, no physical therapy, low cost and the possibility of repeated administration, while the results are comparable to those for surgical synovectomy. In patients with chronic synoviopathy secondary to rheumatoid arthritis or activated arthrosis, the results of RSV are reported to be positive. RSV is considered to be the initial procedure of choice for the treatment of patients with refractory haemarthrosis in haemophilia. RSV can effectively reduce joint effusions after the implantation of a prosthesis. The radiation dose to the gonads is low and the morbidity rate for tumours induced by whole body radiation is negligible. Additionally, an increased risk for cancer after RSV has not been reported [1]. However, leakage of the radionuclide along the needle track can result in serious radiation necrosis to the skin with later scarring [130, 131]; thus, irrespective of different radiopharmaceuticals and techniques used, immobilization of the treated joint after RSV is mandatory [1].

Despite modern modalities for diagnosing arthropathy, the bone scan remains the only imaging technique that assesses the bone metabolism throughout the body, offering overall an available modality with a high sensitivity at an affordable cost. Using a bone scan in a three phase mode of perfusion, blood



FIG. 39. *Immobilization of (a) left upper ankle and (b) left knee. Bethesda, Duisburg, Germany. Courtesy of J. Farahati.*

pool and mineralization enables the clinician to detect inflammation with high sensitivity, distinguish it from localization and determine the extent of the degenerative joint compartment [536].

Open and arthroscopic surgical synovectomy and radionuclide synovectomy are the options for patients with haemarthropathy and RA with hypertrophic and exudative joint disease who fail to respond to systemic therapy and local corticosteroids. The outcomes are reported to be similar for all three procedures, decreasing the frequency of effusion (as seen in Fig. 40) and joint bleeding from 70 to 100% [394, 537], with pain relief and reduction in synovitis in 60–80% of RA cases [1]. However, with respect to cost effectiveness and minimal invasiveness [538], RSV is the treatment of choice, especially in low income countries, and should be the therapy of choice for patients with multiple morbidities who are at high risk for surgery.



FIG. 40.  RSV of knee joint with 185 MBq $^{90}$Y citrate. (a) Before and (b) 6 months after treatment. Courtesy of J. Farahati.

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## Annex I

## INFORMED CONSENT

**Notice of Dr** _____ **about the informed consent discussion**

Key points to discuss with the patient: the need for this intervention, therapeutic goals, pros and cons compared with other methods, risks and possible complications, special risks and risk-increasing particularities, chances of success, aftercare treatment, radiation dose, follow-up examinations, possibility of hospitalization, contraindications (in pregnancy and in lactation), patient preparation before and after the procedure.

Comments/individual conversation points, such as rejection of certain measures, care case, any concerns raised by the patient, among others:

_____

_____

The following RSV procedure of the _____ is to be treated with

(the joint to be treated)

☐ Yttrium-90

☐ Rhenium-186

☐ Erbium-169

Scheduled appointment (date): _____

**Patient consent**

I have read and understood the information sheet. I was able to ask questions about the procedure and all my questions were clarified.

I agree to the procedure.

I confirm that I do not have enough care at home after the radiosynoviorthesis.

I agree to the administration of local anaesthesia, the required supplementary treatment and the necessary follow-up procedures by a medical professional.

I have completed the questionnaire with all relevant information, honestly and fully. I will consider the recommendations provided by the medical team.

_____       _____       _____
Location, date, time                    Patient                              Doctor

**In case of rejection:**

I do not consent to the proposed procedure. I have been advised that this may make the treatment of the condition considerably more difficult, with detrimental consequences for my health.

_____       _____       _____
Location, date, time                    Patient                              Doctor

# Annex II

# MEDICAL QUESTIONNAIRE

A standard medical questionnaire to be completed by patients prior to an RSV procedure.

Age: _____     Height: _____ cm     Weight: _____ kg

| | | | | | |
|---|---|---|---|---|---|
| Have you had radiosynoviorthesis or other treatments/examinations with radioactive materials before? If yes, when and where? | □ yes | □ no | Have you had anticoagulation therapy, warfarin (marcumar)/ASS/plavix? | □ yes | □ no |
| Has any corticosteroid been used? | □ yes | □ no | Have you ever had arthroscopy/operation? If yes, which kind, when and where? | □ yes | □ no |
| Do you have diabetes (do you require insulin)? | □ yes | □ no | Have you performed any total endoprosthesis left/right? | □ yes | □ no |
| Are you allergic to contrast media? | □ yes | □ no | Are you allergic to local anaesthesia? | □ yes | □ No |
| Do you have any other allergies (e.g. to proteins, latex medication, certain foods)? | □ yes | □ no | Have you had a radiological examination with contrast media in the past few months? If yes, when and where? | □ yes | □ No |
| Have you had X rays or radiological examinations of the joint? If yes, when and where? | □ yes | □ no | Have you had a joint or cartilage disease (e.g. osteoporosis, gout, joint infection, haemarthrosis (bleeding in the joint))? | □ yes | □ no |
| Do you have thyroid disease (hyper- or hypothyroidism, struma nodosa)? | □ yes | □ no | Do you have a coagulation disorder (do you have frequent nosebleeds or bruise easily)? Do you suffer from any accident related trauma, clotting or any blood disease? | □ yes | □ no |
| Do you have any chronic infections? (hepatitis, HIV, TBC)? | □ yes | □ no | Do you have heart disease? | □ yes | □ no |
| Have you had thrombosis or vascular disease? | □ yes | □ no | Have you had any radiotherapy? If yes, on which organ and when? | □ yes | □ no |
| Are you pregnant? | □ yes | □ no | Are you breastfeeding? | □ yes | □ no |
| Do you have anyone living at home with you to help with post-operative care? | □ yes | □ no | | | |

# ABBREVIATIONS

| | |
|---|---|
| DLS | dynamic light scattering |
| GMP | good manufacturing practice |
| HA | hydroxyapatite |
| HPLC | high performance liquid chromatography |
| LAL | limulus amebocyte lysate |
| NCA | no carrier added |
| OA | osteoarthritis |
| PLA | polylactic acid |
| QA | quality assurance |
| QC | quality control |
| RA | rheumatoid arthritis |
| RSV | radiosynovectomy |
| SA | specific activity |
| SOP | standard operating procedure |

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