REVIEW ARTICLE

Recent Advances in the Formulation of Microspheres for the Effective Treatment of Rheumatoid Arthritis

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ABSTRACT
Rheumatoid arthritis (RA) is an autoimmune disorder requiring targeted and sustained therapeutic interventions. Microspheres have emerged as a promising drug delivery system for rheumatoid management, offering improved bioavalability, reduce toxicity and enhance patient compliance. Recent advances in microspheres formulation have focused on developing biodegradable and biocompatible microspheres using natural and synthetic polymers. Novel fabrication technique such as microfluidics, electrospray and 3D printing has enabled the creation of uniform microspheres with controlled size, shape and composition. Additionally surface modification strategies have been explored to enhance microsphere targeting and cellular uptake. This abstract reviews the recent advances in microspheres formulation for RA management highlighting the potential of these systems to improve therapeutic outcomes and patient quality of life.

Keywords: microspheres, rheumatoid arthritis, drug delivery, biodegradable polymer, targeted therapy
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INTRODUCTION

Microspheres are tiny, spherical particles[1] made of biodegradable materials, such as polymers[2] or lipids. They can be engineered to encapsulated drugs[3,4] proteins or other therapeutic agents and can be designed to target specific cells, tissues or organs. Now a day microspheres are one of the significant drug delivery system used because of prolonged therapeutic effect[5,6], sustained and controlled release[5,7,8], targeted drug delivery[9,10], reduced dosage frequency[11], more reproducible drug absorption, easily injected[12–14], fewer side effects[15], low toxicity[5], enhanced environmental stability[16], greater biocompatibility[17], diagnostic purpose[18], improve patient compliance.[19] The use of microspheres in rheumatoid arthritis offers several potential advantages like targeted delivery of therapeutic agents to inflamed joints, reduce systemic side effect, improve efficacy and patient compliance, potential for sustained release of therapeutic agents.[20–22]

A chronic inflammatory autoimmune disease, rheumatoid arthritis first affects small joints before spreading to larger ones and eventually affecting the skin, eyes, heart, kidneys and lungs.[23] Typically, the joints can sustain damage to the bone and cartilage, leading to weakened tendons and ligaments. This joint damage often results in deformities and bone erosion, which can cause significant pain for individuals. Common symptoms of rheumatoid arthritis include weight loss, fatigue, fever, rheumatoid nodules under the skin, and morning stiffness of the affected joints that lasts longer than 30 minutes. Between the ages of 35 and 60, this syndrome frequently appears, with flare-ups and remissions. Juvenile rheumatoid arthritis (JRA), which is similar to RA except that there is no rheumatoid factor, can also affect young children before the age of 16.[24–26] The prevalence of RA is estimated to be 1% globally[27] and 1-2 percent[28] in the West. Figure 1 shows the Anatomical comparison of Health joint and Arthritis joint. This comprehensive exploration traces the historical roots of arthritis, with Dr. John K. Spencer coining the term "osteoarthritis" in 1886, setting the stage for understanding over 100 identified types. As we navigate this intricate landscape, the focus broadens to specific conditions like-long lasting autoimmune disease such as rheumatoid arthritis (RA) disproportionately affecting females and the elderly. This section delves into the clinical nuances of RA, emphasizing the importance of early diagnosis within the critical 12-week window. Exploring challenges on a global scale, we scrutinize the dynamics influenced by healthcare systems and patient-physician interactions.[29] Zooming in on the molecular intricacies, autoimmune diseases collectively impact 23.5 million Americans, with RA serving as a prominent example. Here, we unveil the complex interplay between immune system dysfunction, autoantibodies attacking healthy cells, and the catalytic role of PAD enzymes in citrullination, a key player in RA pathogenesis. Genetic factors further contribute to RA's complexity, accounting for a significant portion of the risk. Moreover, the exploration extends to recent research shedding light on the dynamic interplay between hormonal, nervous, and immune systems in RA.

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Table 1: Risk factors, Pathogenesis, Clinical Symptoms and Diagnosis of Rheumatoid Arthritis[21,30-36]

Risk factors	Pathogenesis	Clinical Symptoms	Diagnosis
▪ Genetic: HLA-DR4 and HLA-DR1 association ▪ Environmental: infections, smoking (strongest environmental triggers), gut microbiota changes ▪ Lifestyle: stress, obesity, diet ▪ Hormonal: commonly effected in women (estrogen influence) ▪ Age: 30-50 year age people affected	▪ Autoimmune disorder with chronic inflammation of synovial joints ▪ Activation of T-cells, B-cells and macrophases leads to the production of imflammatory cytokines (TNF-α, IL-1, IL-6) ▪ Synovial hyperplasia (pannus formation) causes causes joint erosion and destruction ▪ Attachment of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA)	▪ Swelling, warmth, pain and decreasd range of motion ▪ Symmetric polyarthritis (small joints of hands, wrists, feet) ▪ Morning stiffness (> 1 hour) ▪ Joint deformities in late-stage RA (swan- neck, boutonniere deformity) ▪ Extra-articular manifestation: vasculities, interstitial lung disease, fatigue, weight loss, rheumatoid nodules, pericarditis	▪ Clinical criteria: symptoms persisting for≥6 weeks, symmetrical joint involvement ▪ Laboratory test: Anti-CCP (ACPA), rheumatoid factor(RF), elevated ESR and CRP, anemia of chronic disease. ▪ Imaging: X- ray (joint space narrowing), MRI/ ultrasound (early synovitis detection) ▪ Exclusion of other diseases: Rule out lupus, psoriatic arthritis and osteoarthritis

Pregnancy emerges as a notable factor influencing RA, with the exchange of proteins between mother and child potentially impacting the immune system and ameliorating RA symptoms.[30] In this intricate journey through the world of arthritis, we unravel the threads connecting history, pathology, and treatment strategies. This comprehensive summary aims to provide a holistic understanding of common arthritis, touching on key aspects of different major disease types and paving the way for a deeper appreciation of the ongoing advancements in arthritis research and care. Rheumatoid Arthritis (RA) is a prevalent long-term condition in developed nations, characterized by chronic inflammation leading to joint damage and disability. The disease primarily affects individuals aged 30 to 60, with various joint symptoms. Table 1 shows the risk factors, pathogenesis, clinical symptoms and diagnosis of rheumatoid arthritis.

Symptoms[37–41]

Figure 2 shows the symptoms of rheumatoid arthritis

Diagnosis of Rheumatoid Arthritis[42–45]

Figure 3 shows the diagnosis of Rheumatoid Arthritis

Pathophysiology of Rheumatoid Arthritis[46,47]

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder primarily affecting the joints. It is characterized by information and progressive damage to

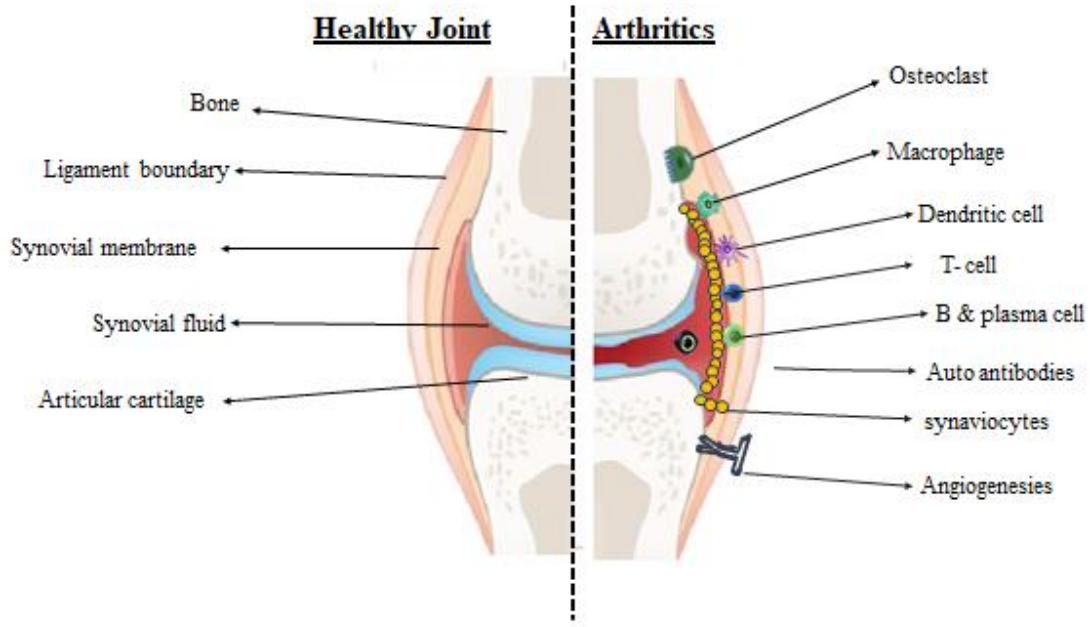

Figure 1: Anatomical comparison of Health joint and Arthritis joint

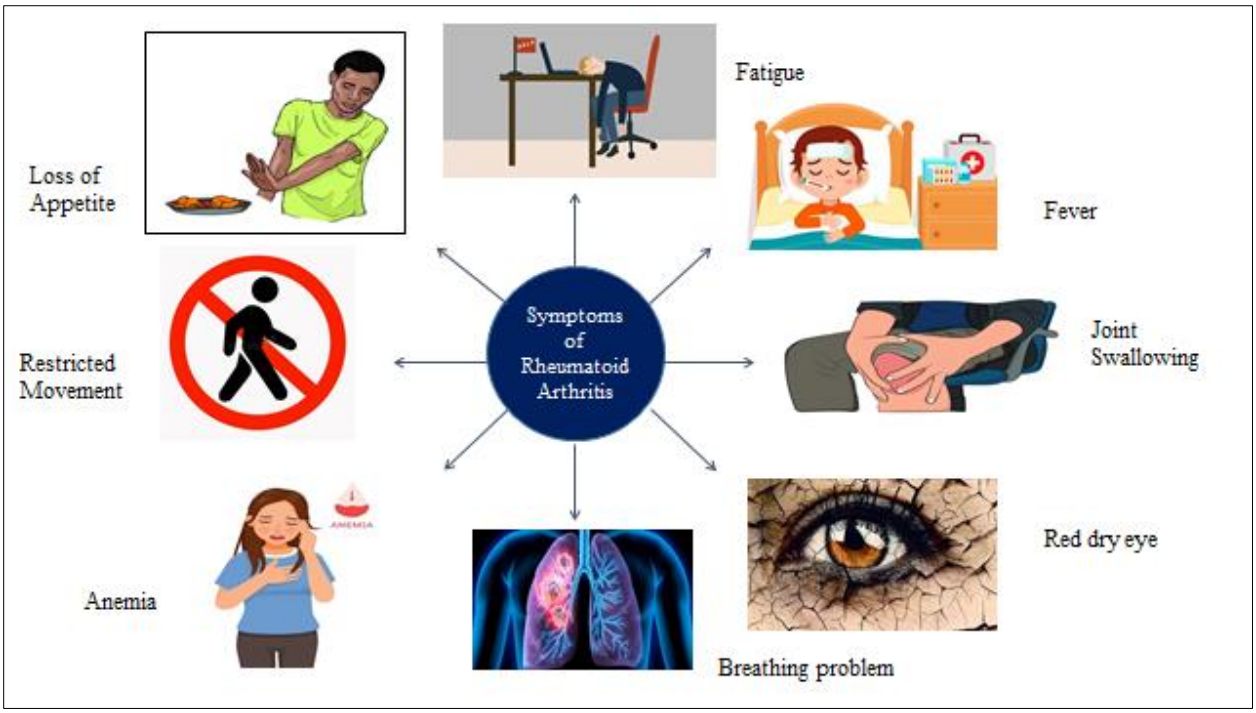

Figure 2: Symptoms of Rheumatoid arthritis

the synovial tissues, leading to pain, swelling, stiffness and also joint deformity. The pathophysiology of rheumatoid arthritis involves complex interaction between several factors like genetic, environmental and immunological factors.

Genetic Factor

Genetic Predisposition

Rheumatoid arthritis has a strong genetic component with certain human leukocyte antigen (HLA) genes being implicated, especially the HLA-DRB1 gene. This gene is involved in antigen presentation and increases the risk of RA development. This specific alleles (HLA-DRB1) cause severe form of RA. Other genes like cytokine genes such as TNF, IL-1, IL-6 also play an important role for development of RA.

Immune System Dysregulation

The immune system of the body attacks its own tissues, especially the joints, in RA. Basically the immune response in RA is primarily directed against the synovium (the lining of the joint).

Initiation of Autoimmune Response

The immune system mistakenly recognizes certain self-antigen as foreign. This triggers an immune response that activates both innate and adaptive immune cells.

Citrullination

The formation of citrullinated proteins, where arginine residues in protein are converted to citrulline. In RA condition, the immune system recognizes citrullinated proteins as foreign and produces antibodies known to inflammation and joint destruction.

T -cell Activation

CD4 + T - Heiper cell (T H CELL) are central to the initiation of RA. These cells become activated when they encounter self-antigens presented by dendritic cells or macrophages and neutrophils, to the affected joints.

Synovial Inflammation

Synovial lining hyperplasia

The inflammed synovium undergoes hyperplasia (an increase in the number of synovial cells), and the synovial fluid becomes infiltrated with inflammatory cells, including T – cells, β – cells, macrophages, neutrophils and dendritic cells.

Cytokine Release

Activated T - cells , Macrophages, and other immune cells produce a variety of inflammatory promoting cytokines, such as Interleukin - 1 (IL -1), Tumor Necrosis Factor (TNF), and interleukin-6 (IL-6). These cytokines share the persistent inflammation which is seen in RA and stimulate the release of matrix metalloproteinases (MMPs) and other enzymes enzymes that degrade cartilage and bone.

Role of β – cells - β-cells are also activated in RA and contribute to inflammation by producing a autoantibodies e.g. rheumatoid factor, ACPA), which form immune complexes that deposit in joints, promoting inflammation.

Tissue Damage and Joint Destruction

Cartilage Damage

The chronic inflammation leads to the activation of matrix metalloproteinases (MMPs), Which degreade the extracellular matrix and cartilage. This developed the destruction of the articular cartilage and subchondral bone.

Bone Erosion – In RA, the inflammation of the synovium extends to the bone, resulting in periarticular bone erosions. This occurs due activation of Osteoclasts (bone resorbing cells) stimurated by TNF - α and IL- 1. Proinflammatory cy-bkines. These cytokines inhibit bone formation by osteoblasts.

Pannus Formation

The synovium Thickens and forms a pannus, a layer of inflamed tissue that invades and destroys cartilage and bone. The pannus release pro-inflammatory Cytokines,

enzymes, and growth factors that cause inflammation" and tissue damage.

Vascular Involvement

Angiogenesis

In this, new blood vessels are formed in the synovium. This process is driven by growth factors such as vascular endothelial growth factor (VEGF) and contributes to the maintenance of the inflammatory environment by increasing the supply of immune cells and nutrients to the inflamed tissues.

Systemic Involvement

RA is not only limited to the joints but also it can affect various organs and systems.

Systemic Inflammation

Elevated levels of cytokines such as TNF, IL-6, and IL-1 contribute to systemic inflammation, leading to symptoms like fever, fatigue and weight loss.

Cardiovascular Risk

RA is associated with an increased risk of cardiovascular diseases, possibly due to chronic systemic inflammation that accelerates artherosclerosis.

Extra Articular Manifestations

RA can involve other organs such as the lung's (Interstitial lung disease), eyes (Scleritis, Uveitis), skin (rheumatoid nodules) and blood vessels (vasculitis).

Environmental Triggers

Infections

Some infections, such as Epstein-Barr Virus (EBV), may act as triggers for RA in genetically predisposed individuals. Infections could trigger an autoimmune response through molecular mimicry, where the immune system mistakes self-antigens for microbial antigens.

Smoking

Smoking is a major environmental risk factor, particularly in individuals with the HLA-DRB1 allele, it increases the development of RA.

Other Factors

Obesity and exposure to certain chemicals (such as silica) may also contribute to the development of RA.

Figure 4 shows the Pathophysiology of Rheumatoid Arthritis

Table 1 describes the Microspheres used in treatment of Rheumatoid Arthritis

Recent Advancement of Various Approaches

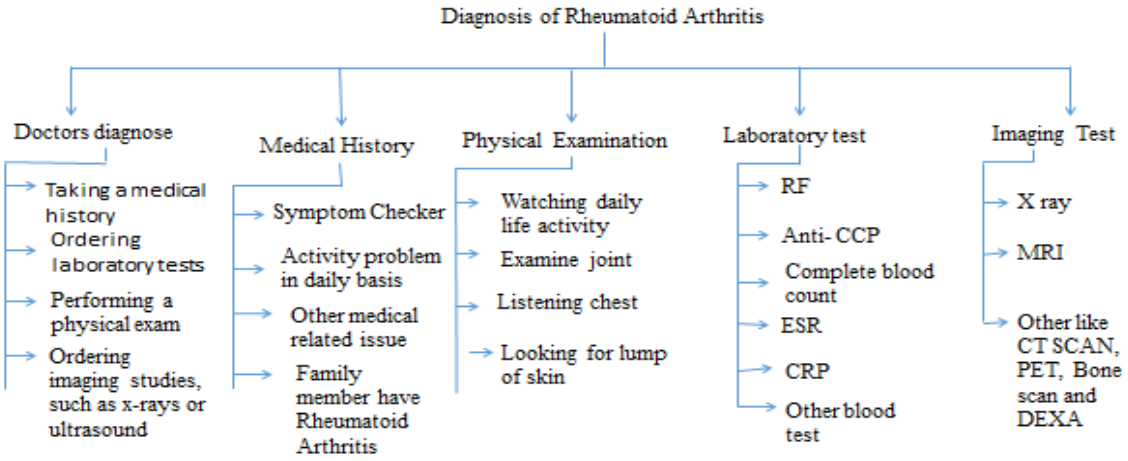

Figure 3: Diagnosis of Rheumatoid Arthritis

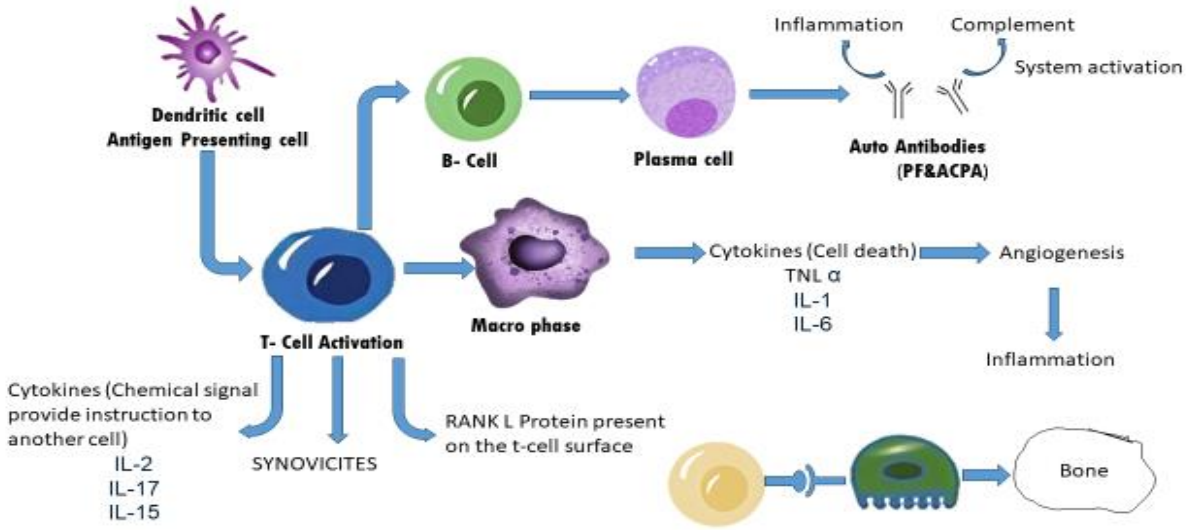

Figure 4: Pathophysiology of Rheumatoid Arthritis

By Ionic Gelation Method

For preparation of piroxicam alginate microsphere was prepared using ionic gelation method. At first 20 ml of 2% w/v sodium alginate mucilage was prepared next piroxicam was dispersed. Then the mucilage piroxicam was filled in a 22 no needle and droplets are formed in 10% w/v calcium chloride solution kept for 20 mints. By using decantation prepared microsphere were collected and washed with water and dried for 4hour at 85°c. Next the prepared microspheres were collected and proceed for evaluation test.[50] Captropril microspheres were also prepared by using ionic gelation method. Here at first polymeric solution was prepared using sodium alginate, HPMC, sodium CMC dissolved in distilled water. Then the captropril drug was added. Then prepared solution was added dropwise in calcium chloride (50 ml of 5% w/v) solution using 20 no needle for 1h. Then prepared microspheres were washed with 2-3 times with water and dried at 80°c for 2h.[51] Alginate nanoparticle medicine is the application of the ionic gelation technology that occurs most frequently. Alginate-chitosan nanoparticles were made using a two-step procedure based on polycationic crosslinking and ionotropic gelation of polyanion with calcium chloride. For upto 24 hours nanoparticle can release the drug in stomach environment.. Under intestinal pH conditions, a discharge of 75 was seen. Alginate patches have been produced using a modified emulsification/internal gelation process, as demonstrated. This system's administration of alginate nanoparticles can be done at room temperature and requires no special clothing. The process of washing the nanoparticles to remove the remaining oil painting droplets presents the biggest challenge for this technique.[54] Also, telmisarton microspheres were prepared by ionotropic gelation method. Here polymer solution was prepared using sodium alginate and chitosan, carbopol as mucoadhesive polymer with purified water. Then add telmisarton and droplets were formed using 20-22 no syringe in 10% calcium chloride solution. After 15-20 min the prepared microspheres were collected and dried at 45°c for 24 h. Then collect microsphere and store it in desiccator.[55] Saxagliptin microsphere was prepared using sodium alginate and different coating polymer like ethyl cellulose and pectin and calcium chloride used as counter ion. Here three different bathes were prepared first batches were prepared (2-4%w/v) sodium alginate polymer solution prepare and 200 mg drug was added. Then droplets were formed in 3% w/v calcium chloride solution. After 1hr the prepared microspheres was collected and washed using alcohol and dried at normal room temperature. Second batch sodium alginate with pectin (0.5-1% w/v) used as coating polymer solution. Add saxagliptin in calcium chloride solution with help of syringe and droplets were formed. Following 10 min for crosslinking and dried for 6h at 60°c. Third batches were prepared using sodium alginate and ethyl cellulose as coating polymer solution, add drug. Then droplets formed in calcium chloride solution, after 30 min of crosslinking droplets were washed with water and dried for 60°c for 6 h.[56] Enalapril maleate floating microspheres was prepared through ionotropic gelation method using different concentration of sodium alginate dissolved in distilled water and heating at 60°c and adds iota-carrageenan. Then sodium bicarbonate was added in suitable quantity with continuous stirring. After cooling this solution, drug was added. Then the solution was dropwise in $CaCl_2$ solution using 31 no needle using 200 rpm stirring speed. After 1hr for crosslinking the solution then the droplets were collected, washed with distilled water and dried for 2hr 50°c in hot air oven. After tha the prepared microspheres were collected and stored in desiccator.[57] Prochlorperazine Maleate (PCZM) floating microspheres were also prepared with ionotropic gelation method.[14] For this preparation sodium alginate polymer solution was prepared, and then adds drug and sodium bicarbonate. Using 21 no syringe needle this homogeneous solution was added dropwise in calcium chloride solution. After 30 min stirring the prepared solution was filtered and dried at 50°c in hot air oven and collected. By using in vitro dissolution method these microspheres show sustained release more than 24 h.[58] Aceclofenac microspheres also prepared using this method for sustained release drug delivery using guar gum and sodium alginate as polymer and crosslinked with different concentration of $Cacl_2$ solution.[59]

By Solvent Evaporation Method

The solvent evaporation technique is widely used for controlled drug release. It involves dissolving the drug and polymer in an organic phase, usually methylene chloride, and dispersing it in an aqueous continuous phase to form an emulsion. Different methods are used based on drug properties. The oil-in-water method is suitable for insoluble drugs, while for hydrophilic drugs, alternative methods like water in oil in water double emulsion are employed. Solvent evaporation is a straightforward method with good control and high encapsulation efficiency. However, the rate of solvent removal can impact microsphere properties, necessitating additional processing for residual solvent removal.[60] Another two method for preparation of methotrexate loaded polysarcosine microspheres. Method1. At first slurry prepared using methotrexate and polysarcosine. This slurry was dissolved in liquid paraffin using magnetic stirrer. Then sonication and stirring occurred until evaporate acetone. The solution was centrifuge at 4000 rpm and washes with petroleum ether, dry and store in 4°c desiccator. Method2. Methotrexate suspended in mannitol and magnesium hydroxide solution (contain polysarcosine in dichloromethane).Then it was allowed to sonicate for 30 sec in ice water bath for disperse primary emulsion.

Then pour the emulsion in PVA and chitosan hydrochloride solution were stirrer and formation of o/w/o emulsion. Then the solution was mixed into aqueous PVA solution and stirrer for 1 hr. The prepared solution was centrifuge wash and lyophilize and store in desiccator and maintain temperature at 4°c.[61] Ramipril microspheres were prepared using this method. At first coating polymer solution was prepared and core substance was dispersed for microencapsulation with agitation and evaporates the solution. Then the polymer constrict around the core substances and the prepared microspheres were

Table 2: Microspheres used in treatment of Rheumatoid Arthritis

Drug	MOP	POLYMER	Key finding	References
Aceclofenac	Emulsification method	Sodium alginate, Chitosan, Guar gum,	Predict lag time for the treatment of arthritis	48
Sulfasalazine	Emulsion- solvent diffusion technique	Dichloromethane, sodium lauryl sulfate solution	Prolonged gastroresistance drug using floating microspheres	49
Aceclofenac	Emulsion dehydration technique solvent evaporation method	Pectin, span 85, Eudragit S-100	Pectin-based colon-specific multiparticulate delivery system enteric polymer coating	10
S-propargyl-cysteine	Double emulsion evaporation method	Poly(lactic acid) (PLA), Poly(vinyl alcohol) (PVA)	Reduce RA symptoms by encouraging H2S release in vivo through the CSE/H2S pathway.	50
Quercetin	Solvent evaporation method	Polycaprolactone, PVA, gelatin	Using a controlled release of quercetin microspheres as an intra-articular medication delivery device, rheumatoid arthritis is managed. Because of the first burst action and subsequent controlled release, several formulations displayed a biphasic character.	51
Methotrexate	Physical encapsulation or covalent conjugation.	-	multifunctional drug delivery systems for delaying the progression of RA	52
Methotrexate	Solvent Evaporation Method	Polysarcosine, poly (n-methyl glycine), chitosan	Without a doubt, the formulation will increase bioavailability, decrease the frequency of doses, and hence increase patient compliance. This formulation seems to be a good option for treating rheumatoid arthritis based on preliminary results.	53

collected.[62] Another o/w emulsion solvent evaporation method was used for preparation of microspheres. At first emulsion was prepared using two immiscible liquid then add drug with continuous stirring until evaporation was done.[63] Microspheres were prepared using different concentration of hyaluronan polymer. At first polymer solution was prepared and added drop wise in span 85 solution with constant stirring and maintained temperature 40°c. after that the microspheres were separated from oil phase through centrifugation. Then the prepared microspheres were washed with diethyl ether for removing excess oil, filtered and stored completely in desiccator[31].

Another bovine serum albumin (BSA) loaded microspheres were prepared using water-in-oil-in-water (w/o/w) double-emulsion evaporation method. BSA solution was prepared using pH7.4 phosphate buffer saline solution (0.5% PVA and methylene chloride 12 ml which contain 400 mg PLGA). Then it was sonicated for 15 sec. Next the prepared solution was injected in phosphate buffer solution which contains PVA for formulation of o/w/o emulsion. Next the dispersed solution was kept in constant temperature for 30 min for removed methylene chloride, then 640 ml PBS solution was added with constant rate with help of pump. Then the second emulsion was kept in low temperature for solvent evaporation. Then the prepared microspheres was collected by vacuum filtration and washed with PBS solution.[64] Other porous microspheres were prepared by solvent evaporation method. At first oily phase were prepared and dispersed nanoparticles to form suspension. Then add emulsifier to form S/O/W1 emulsion and add second water phase (w2) and formation of S/O/W1/W2 with continuous stirring. Next the S/O/W1 emulsion droplets in second water phase (w2) then solidify the polymer. Then completion of organic phase diffusion, polymers gets dried and formed solid particles. Removals of w1 phase porous particles were separated with help of vacuum pump.[65] PLA based microspheres were prepared using double emulsion evaporation method (W1/O/W2) for the treatment of rheumatoid arthritis. S-propargyl-cysteine (SPRC) solution was prepared for W1 phase then oil phase (O) was prepared with PLA with DCM. Then the W1 phase dispersed in oil phase with high speed homogenizer form W1/ O emulsion. This solution dispersed in PVA solution with help of 800 rpm for 4 h agitation unless complete evaporation of organic solvent. Then the prepared microspheres were washed with distilled water and lyophilized overnight.[50]

By Emulsion Solvent Diffusion Method

In this method a drug and polymer solution was prepared using dichloromethane and ethanol. This mixture is added to a surfactant-containing agitated aqueous solution. The quick partitioning of ethanol into the external phase results in the precipitation of polymers around dichloromethane

droplets. The subsequent evaporation of entrapped DCM results in the formation of microspheres with internal cavities.[66] Other chitosan alginate microspheres were prepared using membrane emulsification technique with addition of crosslinking agent. Chitosan solution was prepared using acetic acid and sodium chloride. This solution was poured into tank which contain aquous phase then it was eject through membrane pore with help of nitrogen pressure and form w/o emulsion. Then crosslinking solution was added to this preparation with continuous stirring (300 rpm) for 1 hr. then the prepared microspheres washed with petroleum ether and then it was again washed with distilled water next lyophillisation occurred.[67]

By Spray Dying

Spray drying is a widely utilized industrial process for efficient particle formation and drying, enabling the attainment of desired particle characteristics in a single step. In this method, a polymer is dissolved in a volatile organic solvent to create slurry, which is then sprayed into a drying chamber. The drying process forms microspheres with a solid shell due to a concentration gradient of the solute within small droplets. Solid product separation from gases is typically done using a cyclone separator, and residual solvent traces are removed through vacuum drying. The spray drying method offers advantages of easy control, scalability, and the ability to achieve a narrow particle size distribution with desired size range. However, limitations include the influence of various processing variables on product morphology and the associated high cost of the process.[68] Amoxicillin microspheres were prepared using this method. At first different formulation was prepared using different concentration of drug and polymer (chitosan) ratio along with different concentration of acetic acid solution under mechanical stirrer (800 rpm for 2 hour). Then the solution was dried using spray drier (LU-222 ADVANCED) with specific condition like inlet, outlet temperature, feed rate, atomized air pressure.[69] Another chitosan based microspheres were prepared using this method. At first chitosan solution was prepared dissolving acetic acid solution. Next the drug solution was added slowly to the chitosan solution with continuous stirring and ultra-sounded for 5 min 120 W. Then the prepared microspheres were collected.[70] Spray drying method also used for preparation of microspheres using various concentrations of chitosan solution and glutaraldehyde as a crosslinking agent. SD-40 dryer and 0.5 mm nozzle was used for this formulation. At first liquid was introduced into the nozzle, atomization occurred using compressed air then the liquid disintegrate into small droplets. Then the solvent was removed through exhaust pump using hot air. After that microspheres were collected.[71]

CONCLUSION

In conclusion, recent advances in microsphere formulation have significantly improved the potential of these systems for the effective treatment of rheumatoid arthritis. The development of biodegradable and biocompatible microspheres, novel fabrication techniques, and surface modification strategies has enhanced the efficacy, safety, and patient compliance of microsphere-based therapies. These advances have opened up new avenues for targeted and sustained delivery of therapeutic agents, enabling improved management of rheumatoid arthritis. Further research and clinical translations of these technologies are expected to revolutionize the treatment paradigm for this debilitating disease.

Future directions for microsphere research in rheumatoid arthritis management may include

Investigating combination therapies and multi-drug delivery systems. Exploring the potential of microspheres for early diagnosis and prevention of rheumatoid arthritis - Developing personalized microsphere-based therapies tailored to individual patient needs

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