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Microspheres for local drug delivery in bone joints

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ABSTRACT

Bone joints are the junctions between bones in the body which link the skeletal system into a functional whole. A joint may be the connecting point between two or more bones. Overtime, as people age or due to lifestyle or genetic factors, they may experience diseases and pains in the joints. Conventional treatment options for bone and joint diseases, pain and inflammation have a number of drawbacks that obstruct optimal treatment of the disease. Various other treatment methods and formulations have been investigated to remove these drawbacks. Microspheres are one of the most interesting and attractive approaches to eliminate these limitations. In recent years, prolonged release microspheres have been developed and explored as a viable method for delivery of drugs to the bones and joints. Local delivery of drugs to the affected bone or joint offers many advantages over traditional treatment methods including- better therapeutic response, lesser required dose of drug, lesser chances of wastage of drug, better absorption of drug in the diseased site, lesser chances of side effects etc. The objective of this review is to explore the field of drug delivery to bone joints, various methods of development of drug-loaded microspheres, factors that influence the release of drug from the microspheres as well as the types of hurdles faced in their preparation.

Keywords: bone and joint diseases, drug delivery, microspheres, local drug delivery,

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INTRODUCTION

Joint pain and inflammation affects a major portion of society and has been recognized by medical organizations as one of the leading causes of disabilities in elderly patients. Though it is difficult to completely treat the causative diseases such as arthritis and no foolproof cure has been found yet[1], it is possible to relieve the painful symptoms using certain medications. Intra-articular (IA) injections of these drugs offers advantages that are not possible through conventional methods of drug administration.[2] However, the therapeutic potential of IA injections is severely restricted due to the rapid clearance of the drugs from the injected site.[3] Current treatment strategies are focused on short-term relief from symptoms but ultimately cannot replace surgical procedures. Nonetheless, treatment and suppression of pain and inflammation related symptoms are a major component of the overall therapy process. In this study, we look into the extents of joint pain and inflammation and the current medical procedures adopted to treat them. The possibility of the use of microspheres as a drug delivery device for the treatment of symptoms has also been discussed along with the research and advances done in the field and the challenges faced in the use of microspheres for treatment of joint pain and inflammation.

Joint pain and inflammation-

Joints in the skeletal system are junctions or connecting links between two or more bones. A joint consists of different parts namely- Cartilage (tissue that covers the surface of a bone at a joint. Cartilage helps reduce the friction of movement within a joint.); Synovial membrane (this tissue lines the joints and seals it into a joint capsule. It secretes a clear, sticky fluid around the joint to lubricate it); Bursas (fluid-filled sacs between bones, ligaments that help cushion the friction between joints), Tendons, Femur, Tibia, Patella etc.[4] Inflammation and pain-related diseases of the bone joints are a common disease plaguing the society today. Joint pain and inflammation can occur due to swelling in the synovial membrane or increase in the volume of synovial fluid which leads to accumulation of inflammatory material in and around the joint.[5] This adds to the swelling. As the disease progresses, structural changes within the joint amplify the sensation of pain as well as inflammation. Unless treated, these can quickly develop into more serious underlying complications such as osteoarthritis, rheumatoid arthritis, bursitis etc. and cause physical disability. According to arthritis.org, osteoarthritis affects 31 million people in the U.S. alone and by the year 2040, 78 million people would be diagnosed with arthritis.[6] Several diseases

are associated with joint pain and inflammation including osteophytes and bone cysts formation, degeneration of cartilage on the surface of a bone at a joint, synovial membrane inflammation, peri-articular bone reaction etc.[7]

Drug therapy-

Commonly, joint pain and inflammation are treated and managed by oral or topical administration of an NSAID, acetaminophen or Hyaluronic acid injection.[8] Opioids, anti-depressants and neuromodulators have also been investigated for their efficacy in treating these conditions but no strong evidence is available.[9] In severe cases, when the disease has not responded to conventional methods of treatment, surgery may be the only option left which may involve total joint replacement.

For the purpose of temporary pain and inflammation management, oral NSAIDs are preferred and frequently used.[10] Diclofenac is one of the few selective non-steroidal anti-inflammatory drugs used for suppression of pain and inflammation in the joints. Its efficacy in treatment of pain associated with joint disorders has already been established.[11] Diclofenac is a non-selective NSAID i.e. it inhibits the functioning of both COX-1 and COX-2 which are responsible for the expression of prostaglandins (pro-inflammatory mediators).[12] Several other NSAIDs are also used for the management of joint pain and inflammation including- celecoxib, ibuprofen, naproxen, piroxicam etc. which have their own upsides and limitations. Previous studies have also indicated the relatively better performance of diclofenac as well as its safety and tolerability when compared to other NSAIDs.[13,14,15] Diclofenac, however, has its own set of side effects which include- blood dyscrasias, anaphylaxis, gastrointestinal bleeding, gastric ulcers etc.[16] These might prove to be life-threatening which limits the long term use of NSAIDs in chronic conditions such as Osteoarthritis. This necessitates localized delivery of the drug and in a sustained/prolonged manner so that the corresponding side effects are prevented as well as the therapeutic effect of drug is secured for a longer period of time than conventional methods of drug delivery.

Local drug delivery and microspheres-

It is well understood that conventional methods of drug delivery have certain disadvantages which can be improved upon. A local drug delivery system (DDS) is, therefore, necessary which can deliver the drug at or to the diseased site, overcome the side effects related to systemic and conventional delivery methods and also facilitate prolonged release of drug in small but required quantities at the diseased site. Other desirable features in the DDS include its biocompatibility and biodegradability at the administration site without causing any toxicity, irritation or side effects and its ability to enhance the residence time of drug at the diseased site.

A diverse set of formulations and DDS have been investigated for this purpose. One of the most suitable and appealing candidates has been found to be microspheres. Besides satisfying the aforementioned requirements, microspheres offer other added advantages including a controlled or pulsatile release of drug, protection of drug from degradative enzymes and chemicals within the body, increased patient compliance due to reduced frequency of drug intake.[17]

Polymeric microspheres are one of the ideal carriers for the purpose of several controlled delivery implementations as they are capable of microencapsulating various types of drugs (including small molecules, proteins and nucleic acids), are biocompatible, provide high bioavailability and promote slow release of drug over a lengthy period of time. These are also easily administrable through a syringe needle.

The use of polymeric microspheres for diagnostic, therapeutic and other medical applications has grown manifold in recent years. These have been investigated for controlled release and stability of vaccines[18], stabilization of protein therapeutics[19], safe and efficient DNA delivery for gene therapy[20], tumor targeting and embolization of tumors[21] etc. Microspheres have also been developed and assessed for localized delivery of drugs to the bones and joints for diagnosis as well as treatment of various diseases and infections.[22,23,24]

Microspheres for clinical applications are strictly regulated for their shape and size as well as their release pattern within the body along with their degradation behavior so as to avoid any chances of critical complications after their administration. However, this drug delivery system suffers from its own set of limitations including- difficulty in large-scale manufacturing, difficulty in controlling the release rate of drug, potential inactivation/degradation of drug during formulation, differences in release rate from one dose to another (which may depend upon other uncontrollable factors), burst release of drug or release of whole dose of drug inside the body due to a defective formulation can cause toxicity and prove to be fatal.[25,26,27]

SOME RELEVANT METHODS/TECHNIQUES FOR PREPARATION OF MICROSPHERES FOR PURPOSE OF DELIVERY TO THE BONE JOINTS

Solvent Evaporation technique:

This method of preparation of microspheres involves the dissolution of polymer in a water-immiscible organic solvent following which the drug is dispersed or dissolved into the polymer-solvent solution. This solution is then emulsified in an excess amount of aqueous or continuous phase. Microspheres are formed by the diffusion of the organic solvent into the continuous phase and its subsequent evaporation from the air/water interface.[28,29]

Emulsion cross-linking method:

In this method, weighed quantities of polymer and drug are dissolved in a suitable organic solvent. This drug-polymer solution is then added to an adequate quantity of oleaginous vehicle (eg-liquid paraffin) containing a surfactant. The resulting mixture is stirred continuously for 2 hours, after addition of an aqueous solution of cross-linking agent, to obtain a dispersion of microspheres in paraffin oil. The microspheres are allowed to settle due to gravity and the supernatant is decanted. The residual microspheres are filtered and washed with n-hexane to remove the oil.[30,31]

Spray-drying technique:

A polymer solution is first prepared by dissolution of the polymer in a suitable organic solvent such as acetone, ethanol, dichloromethane etc. The selected drug is then uniformly dispersed in the polymer solution with the help of a homogenizer. Consecutively, spray drying of the above solution is performed using a spray drier with a standard nozzle. When the solution is supplied to the nozzle with a peristaltic pump, atomization takes place and small droplets are produced. The droplets along with hot air are blown into a chamber where the droplets are evaporated and the dry product (microspheres) are obtained.[32,33]

Solid-in-oil-in-water (S/O/W) multi-emulsion process:

A suspension of drug is dispersed in the polymer solution dissolved in a volatile organic solvent. The resulting solution is stirred at high speed for 1 minute and then added to gelatin solution to form an emulsion. A high speed homogenizer is used to prepare multi-emulsion. The resulting emulsion is continuously stirred at room temperature until the solvent is evaporated which results in the formation of solidified microspheres. These are recovered by centrifugation and washed with distilled water.[34,35]

Ionotropic gelation technique:

This technique is based on the principle of coalescence of colloidal particles of polymer. The ionotropic gelation of calcium chloride ions with the oppositely charged (anionic) polysaccharide sodium alginate results in the formation of microspheres. Subsequently, the colloidal polymer particles are fused into a homogenous matrix. The polymer particles coalesce during the drying process and form a homogenous film.[36,37,38]

Coacervation method:

This process involves the distinction of a macro-molecular solution into two immiscible phases- a dense coacervate phase (concentrated with macromolecules) and a dilute equilibrium phase. Simple coacervation is actuated by several factors such as temperature change, addition of micro-ions which cause dehydration of macromolecules because they favor polymer-polymer interactions over polymer-solvent interactions. Microspheres with specific properties can be prepared by manipulation of such parameters.[39,40] Complex coacervation method has also been utilized for the formulation of microspheres intended for intra-articular delivery.

Interfacial polymerization methods:

i. Suspension polymerization- A solution of monomer and an initiator is prepared in a suitable solvent. This solvent is added to a suspension in which the monomer and initiator are insoluble. The mixture is then subjected to agitation, in presence of low molecular weight polymers or surfactants, which results in the formation of solvent droplets. Polymerization occurs in the solvent droplets and the polymer takes the shape and size of the droplets resulting in the formation of microspheres.[41,42]

ii. Emulsion polymerization- In this method, an initiator is dissolved in a solution containing emulsifiers and stabilizing molecules. The use of dispersing agents results in the formation of micelles with monomers. This method can be used for encapsulating drug within the microspheres or their adsorption on the surface of the microspheres.[43,44]

iii. Dispersion polymerization- This technique is also referred to as phase-separation polymerization.[45] A solution mixture of monomer, initiator and polymeric stabilizer is prepared where polymerization takes place. Thereafter, the polymer chain grows until it precipitates forming nano-sized particles which can be induced to aggregate and form larger particles in the size range 1-20µm.[46,47]

Double emulsion technique: This process of microsphere preparation is suitable for water soluble drugs, proteins, peptides and vaccines and involves the formation of double emulsion (w/o/w). In this method, a continuous phase containing the polymer solution is prepared. After homogenization or sonication of this primary emulsion, an aqueous solution of polyvinyl alcohol (PVA) is added which forms a double emulsion. The emulsion is then treated with solvent removal by evaporation or extraction.[48,49]

Table 1: Drugs encapsulated microspheres for treatment of skeletal disorders

Method of preparation	Material/ Polymer	Drug	Administration site	Application	Ref.
Solvent evaporation	PLGA	Simvastatin	Rabbit calvaria critical-size defect	Bone formation	50
w/o/w double emulsion technique	PLGA/ hydroxyapatite	Simvastatin	Middle shaft of the tibia	Bone regeneration	51
Single emulsion solvent evaporation	PLGA	Melatonin	In-vitro study	Bone healing	52
Solvent evaporation	PLGA	Sodium alendronate	In-vitro study	Bone repair	53
w/o/w double emulsion technique	PLLA-PEG-PLLA tri-block copolymer	Nanosilver	Rat cranium critical-size defect	Bone regeneration	54
Emulsion cross-linking	Paselli (II)	Meclofenamic Sodium	In-vitro study	Bone tissue engineering	55
Emulsion cross-linking	Chitosan	Celecoxib	In-vitro study	Bone healing	56
Spray-drying	Chitosan/ Pectin	Ciprofloxacin hydrochloride	Anteromedial incision on proximal tibia	Treatment of Osteomyelitis	32
Spray-drying	Bovine serum albumin	Dexamethasone	In-vitro study	Treatment of ankylosing spondylitits, osteo/ rheumatoid arthritis	57
s/o/w multi-emulsion technique	PLGA	Lornoxicam	Left knee joint of New Zealand white rabbits	Treatment of Osteoarthritis	35

Ionotropic gelation	Chitosan, Gelatin B	Tramadol hydrochloride	In-vitro study	Treatment of arthritis, arthralgia	58
Ionotropic gelation	Eudragit S100, Sodium Alginate	Diclofenac Sodium	In-vitro study	Treatment of arthritis	37
Complex coacervation	Gelatin	Chondroitin-6-Sulfate	Mouse knee joints	Treatment of Rheumatoid/ Osteoarthritis	59
Suspension polymerization	PMMA	Hydrogel collagen	In-vitro study	Bone tissue engineering	60
Emulsion polymerization	Polystyrene/PMMA	Doxorubicin	In-vitro study	Bone repair	61
Dispersion polymerization	Coralline hydroxyapatite/ Gelatin	Gentamicin	In-vitro study	Bone healing	62

Yoshihito *et. al.* prepared poly(lactic-co-glycolic acid) (PLGA) microspheres incorporated with simvastatin (SIM) by solvent evaporation method. SIM-loaded PLGA microspheres (20-30µm) showed drug content loading of 91±3.78% and presented a slow drug release over a period of ~1month *in-vitro. In-vivo* tests in critical size defect of rabbit calvaria confirmed that the microspheres containing SIM were capable of enhancing bone formation.[50] In another study, starch-based microspheres were formulated by emulsion cross-linking technique and were loaded with meclofenamate sodium. With minor alterations in certain parameters, this technique allowed for controlled formation of microspheres ranging from 3-540µm. The release pattern from these microspheres was checked *in-vitro* in two different pH mediums. It was concluded that drug release from the microspheres was very fast in the initial 2 hours irrespective of the pH medium used and ionic concentration of the medium strongly influenced drug release.[55] Lornoxicam (Lnxc) encapsulated PLGA microspheres (7.47µm) were prepared by a process involving s/o/w emulsion and showed controlled release of ~80% of drug over a period of 1 month. Drug retention was examined in the synovial fluid in rats and it was determined that intra-articular administration of Lnxc-loaded PLGA microspheres enhanced drug targeting in the joint cavity due to prolonged residence time of drug in the joint.[35] Microspheres containing diclofenac sodium were prepared by ionotropic gelation technique using Eudragit S100 and Sodium alginate as the encapsulating agents. The microspheres exhibited sustained release of drug over a period of 12 hours *in-vitro*.[37]

FACTORS INFLUENCING RELEASE OF DRUG FROM MICROSPHERES:

The **method or technique employed for preparation of microspheres** plays an important role in drug encapsulation and its release kinetics. Thakkar *et.al.*, in their study, observed that heat cross-linked microspheres released drug at a much faster rate than chemically cross-linked microspheres.[56] Furthermore, a variety of other factors including- the type of polymer used, molecular weight of the polymer, amount of polymer, copolymer composition, excipients used, size of the microspheres produced, nature of the dissolution medium etc. also influence the release rate of drug from the microsphere formulation.[17]

The **choice of polymer and its degradation mechanism** affects release rates of the drug. On the basis of hydrolysis rates of the polymers, they can be classified as- surface-eroding and bulk-eroding.[63] Bulk-eroding polymers (eg-PLG) generally degrade at a much faster rate and cause a burst release of the drug initially. Subsequently, release rate of the drug is sustained.[28] However, it is difficult to control drug release in case of bulk-eroding polymers. On the other hand, polymers that are surface-eroding (eg-Polyanhydrides) exhibit uniform degradation at the surface, usually at a constant rate and as such drug is also released in a controlled manner.[64,65]

Molecular weight of the polymer also influences drug release pattern. It has been observed that higher molecular weight polymers have decreased permeability and slower drug release rates.[19,66,67] As the **amount of polymer** for encapsulation is increased, a thicker membrane/barrier/coating is formed around the drug core which decreases release rate of the drug.[68]

Copolymers consist of co-monomers in varying ratios which also affect drug release rates. Copolymers composed of rapidly degrading monomers in higher ratios tend to release drug at a faster rate than copolymers with higher concentration of slowly degrading monomers.[69,70] Nonetheless, it has been observed that the effect of copolymer composition on drug release can be influenced by phase behavior of the copolymer and thermal properties of the drug.[71]

Exipients used in the formulation of microspheres can also impact release rates of the drug. For example, Park *et.al.* used α-tricalcium phosphate based calcium phosphate cement to improve the rigidity of the protein-encapsulated microspheres. It was observed that incorporation of calcium phosphate in the formulation further sustained the release of the protein.[22] To enhance the stability of myoglobin-encapsulated PLGA micropsheres, Rhodes *et.al.* prepared the formulation using mannitol as a stabilizer. Mannitol was reported to increase the release rate by increasing the porosity of the microspheres.[72]

It has also been found that parameters related to **dissolution medium** such as its pH, temperature, buffer composition etc. also influence drug release rates.[73] **Size of the microspheres** has also been investigated and found to affect drug release.[74]

CHALLENGES/CONSIDERATIONS IN FABRICATION OF MICROSPHERES FOR DRUG DELIVERY TO BONE JOINTS

Although a suitable and interesting approach in the treatment of joint diseases, certain challenges come to the forefront which much be first taken care of. Some have been explained below.

Difficulty arises in maintaining uniform particle size of microspheres during/after formulation process. Size varies considerably ranging from a few nanometers to over 100 micrometers. Variance in size causes difference in release kinetics and statistics. This would result in infrequent and uncontrolled drug release. Butoescu *et.al.* reported that ideal

size of microspheres for intra-articular delivery should range between 5-10µm.[75] Smaller-sized microspheres can be easily uptaken by synoviocytes[76] whereas larger-sized microspheres release drug at a slower rate and may elicit a giant cell response. Liggins *et.al.* discovered that along with size, shape of the particles also influenced their efficacy in the treatment of joint diseases and disorders. Spherical particles are better suited for intra-articular delivery.[77]

Biocompatibility of the drug and polymer in the joint is of paramount importance. Polymers such as Poly (lactic acid) (PLA), Poly (glycolic acid) (PGA), Poly (lactic co-glycolic acid) (PLGA) are generally accounted as safe and biocompatible but upon breakdown, lower the pH in the surrounding tissues which can adversely affect the effect of the drug and further worsen inflammation symptoms.[78]

CONCLUSION

Joint diseases and disorders are troublesome conditions that torment a significant percentage of population today. Normal movement for patients becomes a tiresome and painful task. Conventional drug therapies were developed but these suffer from limitations which in some cases even outweigh the benefits. As such, novel drug delivery systems have been investigated and developed and are still being optimized to this day in the quest of an ideal drug delivery system which hopefully undermines all the limitations related to drug delivery to the bone joints. Microspheres are one of the most sought-after and researched formulations for this purpose. These are being investigated for not only drug delivery to the bones and joints but also tumours, brains and other vital organs and tissues of the body. Although these have numerous benefits over traditional systems, there still are some challenges which have to be considered in their formulation. New techniques and methods of microsphere preparation are emerging with newer features and the field is continually evolving and growing at a fast pace.

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