

Review Article

ALBUMIN MICROSPHERES: AN UNIQUE SYSTEM AS DRUG DELIVERY CARRIERS FOR NON STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

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Received on: 21-09-2010; Finalized on: 20-11-2010.

ABSTRACT

Non steroidal anti inflammatory drugs are the most commonly used and widely prescribed drugs all over the world. With the wide advantages they are also associated with severe Gastro-Intestinal side effects. Developments of novel drug delivery systems have always been a challenge to formulation scientists because of their high instability and economic factor compared to the conventional dosage forms. Thus the main objective of this review was to present an alternative way of developing NSAIDs as microspheres specifically using albumin polymers, which are playing an increasing role as drug carriers in the clinical setting. Hence there is a prolonged release of the drug along with minimized side effects. A brief overview of the methods developed for the preparation of albumin microspheres and the most suitable techniques for optimum entrapment of drug is emphasized. The in-vitro evaluations are also explained. In order to appreciate the medical application possibilities of albumin microspheres in novel drug delivery, some fundamental aspects are also briefly discussed.

Keywords: Albumin microspheres, NSAIDs, bovine serum albumin microspheres, egg albumin microspheres.

INTRODUCTION

Non steroidal anti-inflammatory drugs (NSAIDs) (including aspirin and ibuprofen) are widely prescribed and sometimes called non-narcotic or non-opioid analgesics. They work by reducing inflammatory responses in tissues. Many of these drugs irritate the stomach and for that reason are usually taken with food.¹

Non steroidal anti-inflammatory drugs, usually abbreviated to NSAIDs or NAIDs, are drugs with analgesic and antipyretic (fever-reducing) effects and which have, in higher doses, anti-inflammatory effects (reducing inflammation). The term "non steroidal" is used to distinguish these drugs from steroids, which (among a broad range of other effects) have a similar eicosanoid-depressing, anti-inflammatory action. As analgesics, NSAIDs are unusual in that they are non-narcotic. The most prominent members of this group of drugs are aspirin, ibuprofen, and naproxen partly because they are available over-the-counter in many areas.²

NSAIDs are usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present. Research continues into their potential for prevention of colorectal cancer, and treatment of other conditions, such as cancer and cardiovascular disease.

NSAIDs are generally indicated for the symptomatic relief of the following conditions:

- Rheumatoid arthritis
- Osteoarthritis
- Inflammatory arthropathies (e.g. ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome)
- Acute gout

- Dysmenorrhoea (menstrual pain)
- Metastatic bone pain
- Headache and migraine
- Postoperative pain
- Mild-to-moderate pain due to inflammation and tissue injury
- Pyrexia (fever)
- Ileus
- Renal colic
- They are also given to neonate infants whose ductus arteriosus is not closed within 24 hours of birth

Aspirin, the only NSAID able to irreversibly inhibit COX-1, is also indicated for inhibition of platelet aggregation. This is useful in the management of arterial thrombosis and prevention of adverse cardiovascular events. Aspirin inhibits platelet aggregation by inhibiting the action of thromboxane -A.

In 2001 NSAIDs accounted for 70,000,000 prescriptions and 30 billion over-the-counter doses sold annually in the United States.³

The widespread use of NSAIDs has meant that the adverse effects of these drugs have become increasingly prevalent. The two main adverse drug reactions (ADRs) associated with NSAIDs relate to gastrointestinal (GI) effects and renal effects of the agents.

These effects are dose-dependent, and in many cases severe enough to pose the risk of ulcer perforation, upper gastrointestinal bleeding, and death, limiting the use of NSAID therapy. An estimated 10-20% of NSAID patients experience dyspepsia, and NSAID-associated upper



gastrointestinal adverse events are estimated to result in 103,000 hospitalizations and 16,500 deaths per year in the United States, and represent 43% of drug-related emergency visits. Many of these events are avoidable; a review of physician visits and prescriptions estimated that unnecessary prescriptions for NSAIDs were written in 42% of visits.

NSAIDs, like all drugs, may interact with other medications. For example, concurrent use of NSAIDs and quinolones may increase the risk of quinolones' adverse central nervous system effects, including seizure.⁴

Formulations can affect the safety of preparations by controlling the rate of release of the drug at sensitive sites, by delivering drug to specific sites to minimise systemic exposure, or delivering drug in such a way as to change the rate or extent of the formation of toxic metabolite. Alexander et al had thoroughly reviewed the safety concerns of novel drug delivery systems of NSAIDs.⁵

Converting NSAIDs into controlled release dosage form

During the past decades, there has been an increasing interest in optimizing the efficiency of existing drugs through the use of better-designed drug delivery systems. Intensive interdisciplinary research efforts have led to a variety of advanced dosage forms. The majority of these systems are based on polymers that differ in their

permeability, rate of dissolution, degree of swelling and erodibility. An important class of polymer mediated drug delivery systems that are applied for controlled drug delivery is the albumin microspheres which controls release characteristics. The recent research has been heavily involved particularly on how the distribution of release controlling parameters among the individual microspheres of the batch alters the release profile.⁶

Microsphere is a term used for small spherical particles, with diameters in the micrometer range (typically 1 μ m to 1000 μ m (1mm)). Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. And one such natural polymer of our interest is Albumin which will be discussed in this review article.⁷

What is albumin and why albumin microspheres?

Albumin is a major plasma protein constituent, accounting for 35% of the total protein in human plasma. Since they were first described by Kramer, albumin microspheres have been extensively investigated in controlled release systems as vehicles for the delivery of therapeutic agents to local sites. The exploitable features of albumin include its reported biodegradation into natural products, its lack of toxicity, and its non antigenicity.

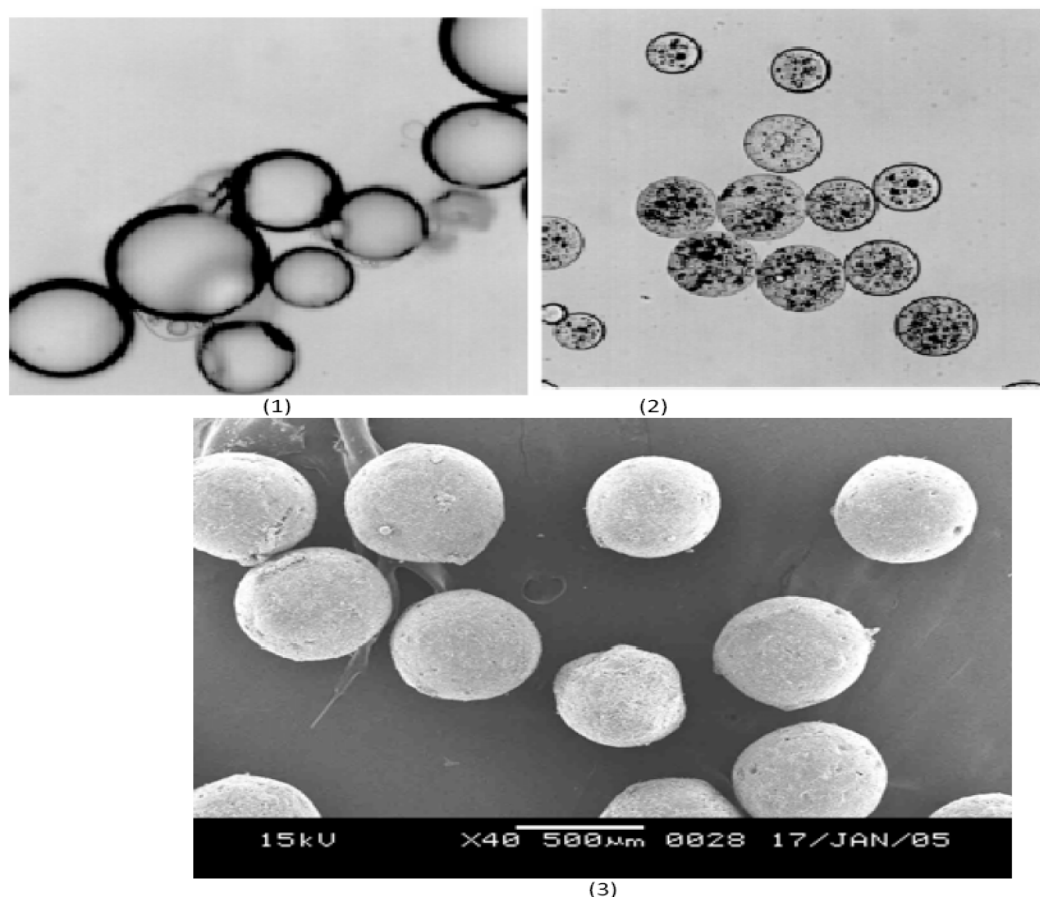


Figure 1: Scanning electron micrographs ($\times 100$) of (1) mononuclear, (2) multinuclear microspheres, and (3) surface of the microspheres

The first biodegradable and biocompatible uniformly sized albumin microspheres were formulated in the 1970s (Kramer 1974). Albumin microspheres are metabolized in the body, and the size of particles, degree of stabilization, and site of metabolism are the main factors influencing the extent of metabolism. Drug release from the microspheres can be widely modulated by the extent and nature of cross-linking, size, the position of the drug, and its incorporation level in the microspheres. Colloidal forms of albumin have been considered as potential carriers of drugs for their site-specific localization or their local application to anatomically discrete sites.

The accumulation of albumin in solid tumours forms the rationale for developing albumin-based drug delivery systems for tumour targeting. Thus it has been used as a carrier for targeting drugs to tumours, and since the synovium of the rheumatoid arthritis patients shares various features observed in tumours, albumin-based delivery systems can be used to target drugs to the inflamed joint. Intravenous administration of the drugs coupled with albumin has been reported to improve the targeting efficiency of the drug to arthritic regions. The circulation half-lives of the drugs have been reported to dramatically increase when the drug is conjugated with albumin. Increasing the circulation half-life of the formulation by reducing its uptake by the reticulo endothelial system has been shown to improve the targeting efficiency of the formulation to the arthritic paws of rats. Achieving higher concentrations of the drug at the arthritic joint and minimizing its distribution to the other tissues would minimize the side effects associated with the drug. Targeting drugs to the inflamed joints, in the treatment of rheumatoid arthritis, would reduce the amount of drug required to control the disease, with possible additional reduction or even elimination of adverse side effects.^{8,9,10}

Advantages and disadvantages of NSAID loaded albumin microspheres

The following advantages make them a promising means for the delivery of NSAIDs.

- ✓ Albumin Microspheres provide constant and prolonged therapeutic effect.
- ✓ Reduces the dosing frequency and thereby improve the patient compliance.
- ✓ They could be injected into the body due to the spherical shape and smaller size.
- ✓ Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
- ✓ Albumin microsphere morphology allows a controllable variability in degradation and drug release.
- ✓ Reduces GI toxic effects.

- ✓ Albumin has non-antigenic property and ability to control the physicochemical characteristics of the microspheres produced, depending on the cross-linking methods and characteristics of cross-linking agent.

Some of the disadvantages were found to be as follows

- ✓ The modified release from the formulations.
- ✓ The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit though gut.
- ✓ Differences in the release rate from one dose to another.
- ✓ Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
- ✓ Dosage forms of this kind should not be crushed or chewed.
- ✓ Larger size of extended release products may cause difficulties in ingestion or transit through the gut.
- ✓ Possibility of distal intestinal toxicological manifestations because of sustained release and enteric coated NSAID formulations.

Hetal Thakkar *et al.*, carried out the preparation of Celecoxib-loaded albumin microspheres by using natural polymer bovine serum albumin by emulsification chemical cross-linking method. *In vitro* release studies indicated that the microspheres sustained the release of the drug for ~6days. The blood kinetic studies revealed that Celecoxib loaded albumin microspheres exhibited prolonged circulation than the Celecoxib solution.¹⁰

Jeevana HB *et al.*, carried out the development of gelatin microspheres of Tramadol Hydrochloride for controlled delivery. The microspheres were prepared using Single emulsion technique. The microspheres were in the suitable size range of 20-160µm. The drug was released continuously for a period of 12 hours with a maximum release of 99.79%.¹¹

Hakan eroglu *et al.*, carried out the preparation of bovine serum albumin microspheres containing Dexamethasone Sodium Phosphate and the *in vitro* evaluation of the same. The microspheres were prepared by emulsion polymerization. An aqueous solution of glutaraldehyde (25% w/v) was used as the cross linking agent in two different amounts. The release time is increased as the amount of glutaraldehyde is increased.¹²

Sam T. Mathew *et al.*, carried out the formulation and evaluation of Ketorolac Tromethamine-loaded albumin microspheres for potential intramuscular administration. Albumin microspheres were prepared by emulsion cross-linking method. From the experimental results obtained,



it may be concluded that the developed albumin microspheres could be useful for once-a-day IM administration of Ketorolac Tromethamine.¹³

Sayed abolghassem sajadi tabassi et al., carried out the preparation and characterization of albumin microspheres encapsulated with propranolol HCl. The Bovine Serum Albumin (BSA) based microspheres bearing propranolol hydrochloride were prepared by an emulsion-internal phase stabilization technique. The microspheres had mean diameters between 1-25 μm . The total amount of drug released from microspheres after 12h was 70%.¹⁴

Jayaprakash et al., carried out the preparation and evaluation of biodegradable microspheres of methotrexate. The objective of this study was to prepare a sustained release methotrexate microspheres of bovine serum albumin in different ratios by the emulsion cross-linking method. An extensive attempt was made to incorporate maximum amount of drug in the microspheres.¹⁵

Yong-Liang Zhao et al., carried out the Preparation and Evaluation of Poly(3-hydroxybutyrate) Microspheres Containing Bovine Serum Albumin for Controlled Release. The utility of the Poly(3-hydroxybutyrate) to encapsulate and control the release of Bovine Serum albumin(BSA), via microspheres, were investigated. The effects of changes on the morphological characteristics of the microspheres like the size of the microspheres, drug loading, encapsulation efficiency, and drug release rates were examined. The diameter of the microspheres ranged from 6.9 to 20.3 μm and showed different degrees of porous structure depending on the different preparation parameters. The maximum and minimum BSA encapsulation efficiency within the polymeric microspheres were 69.8 and 7.5%, respectively, varying with preparation conditions.¹⁶

Brunete SJA et al., carried out the Treatment of Experimental Visceral Leishmaniasis with Amphotericin B in Stable Albumin Microspheres. Hydrophilic albumin microspheres were proposed as a new delivery system for amphotericin B (AMB microspheres). The acute toxicity of AMB microspheres was lower than that of the AMB-deoxycholate (AMBDoc). The efficacy of this new formulation was tested against *Leishmania infantum*-infected hamsters. With the 2-mg/kg dose, the activity of AMB, reductions in parasite levels of more than 99% were achieved in the liver and spleen after the administration of AMB microspheres. Significant accumulation of AMB in the spleen and liver was observed after AMB microsphere administration. The results suggested that this new formulation was a promising alternative to the conventional AMB-Doc formulation for the treatment of visceral leishmaniasis.¹⁷

Technologies used to prepare albumin microspheres

Novel drug delivery systems are the most solicitous branch of science, which involves multidisciplinary

scientific approach, contributing to advanced drug delivery and human health care. The techniques utilized for the preparation should meet certain criteria. It should have the ability to incorporate high concentration of the drug. The particle size should be controlled by altering certain parameters like (1) type of albumin; (2) albumin concentration; (3) speed of agitation; (4) chemical cross-linking or heat denaturation; (5) Crosslinking agent concentration or temperature; (6) addition or absence of surfactant; (7) type of oil; and (8) mixing-cell with or without baffles. Further Particle size may be determined by laser diffraction technique. The selection of procedure depends upon the particle size required, route of administration, duration of drug action etc., such that it releases the active ingredient over a prolonged period of time. For parenteral products the size of the particle should be minimized utmost such that they do not cause irritant action at the site if injection. The Albumin microspheres thus prepared should be stable and have a considerable shelf life.¹⁸

Preparation of albumin microspheres of NSAIDs can be done by suitable methods like:

- i. Protein gelation technique.
- ii. Single Emulsion polymerization technique.
- iii. Double Emulsion polymerization technique.
- iv. Multiple emulsion polymerization technique.
- v. Solvent evaporation technique.
- vi. Sonication technique.
- vii. Spray and freeze drying technique.
- viii. Emulsification-heat stabilization technique.
- ix. Quasi-emulsion solvent diffusion method of the spherical crystallization technique.

Protein gelation technique

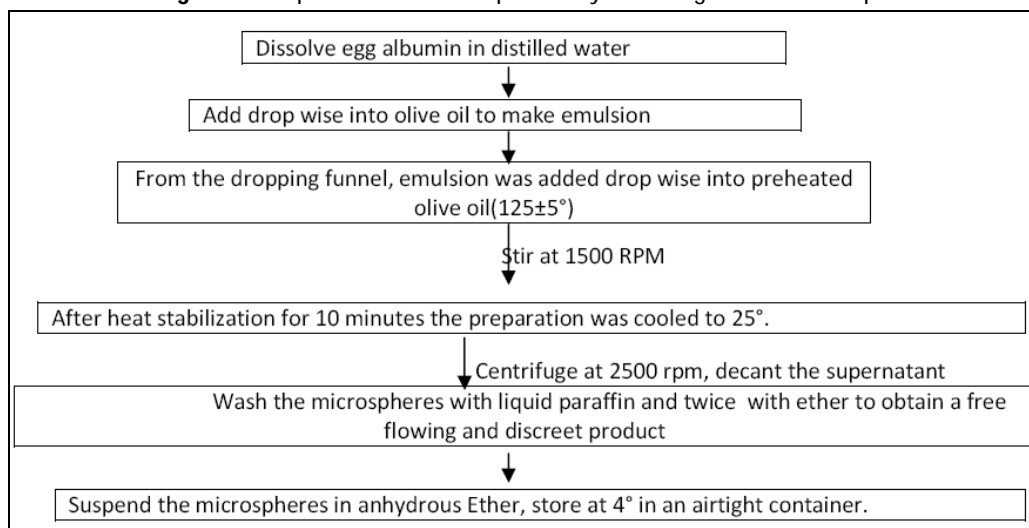
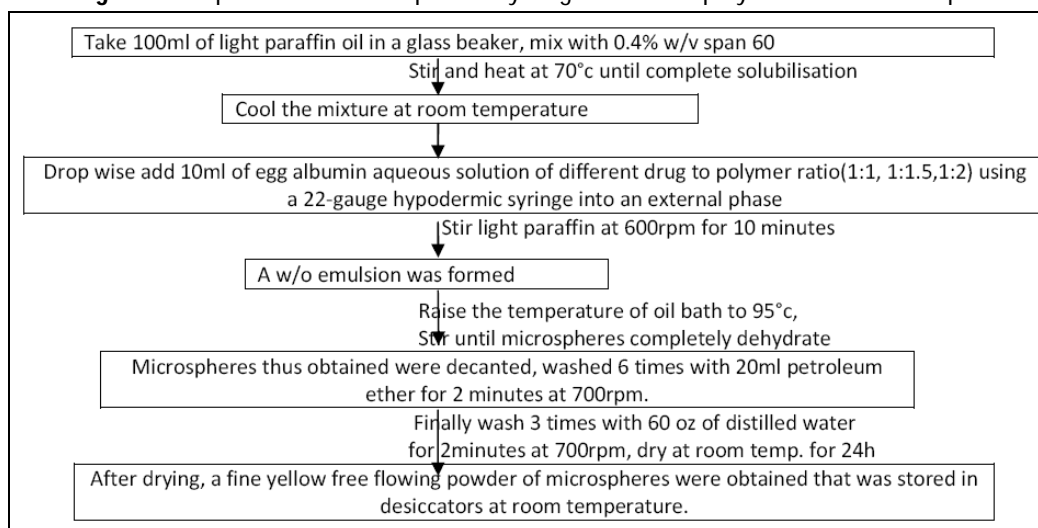
Rathod et al., carried out the preparation of Pilocarpine nitrate loaded egg albumin microspheres by thermal denaturation process and obtained albumin microspheres in the size range of 1-12 μm .

Drug loaded microspheres so obtained were evaluated for their size, entrapment efficiency, release rate and biological response. The entrapment and encapsulation of pilocarpine after process optimization was found to be 82.63% and 62.5% respectively.¹⁹

Single Emulsion polymerization technique

Shailesh TP et al., developed sustained release ethylcellulose-coated egg albumin microspheres of Diltiazem Hydrochloride to improve patient compliance. The microsphere were prepared by the w/o emulsion thermal cross-linking method using different proportion of the polymer to drug ratio.



Figure 2: Preparation of microspheres by Protein gelation technique**Figure 3:** Preparation of microspheres by Single emulsion polymerization technique.

The polymer to drug ratio was optimized to 1:1 at which high drug entrapment efficiency $79.20\% \pm 0.7\%$ and the geometric mean diameter $47.30 \pm 1.5\text{mm}$ were found.²⁰

Double Emulsion polymerization technique

A double emulsion is usually prepared in two main modes:

Mode 1 : One-step emulsification

Mode 2 : Two-step emulsification

In one step emulsification mode a strong mechanical agitation is used for the water phase containing a hydrophilic surfactant and an oil phase containing large amounts of hydrophobic surfactant. Due to this a W/O emulsion is formed which quickly inverts to form a W/O/W double emulsion.

A two-step procedure is reported where the primary emulsion can be formed as a simple W/O emulsion which is prepared using water and oil solution with a low HLB (hydrophilic-lipophilic balance) surfactant. In the second step, the primary emulsion (W/O) is re-emulsified by

aqueous solution with a high HLB surfactant to produce a W/O/W double emulsion.²¹

Multiple emulsion polymerization technique

Multiple emulsion method involves formation of (o/w) Primary emulsion (non-aqueous drug solution in polymer solution) and then addition of primary emulsion to external oily phase to form o/w/o emulsion followed by either addition of crosslinking agent (glutaraldehyde) and evaporation of organic solvent. This method of preparation is ideal for incorporating poorly aqueous soluble drug, thus enhancing its bioavailability.

Sam T et al., carried out the formulation and evaluation of Ketorolac Tromethamine-loaded Albumin Microspheres for Potential Intramuscular Administration. The microspheres were prepared by multiple emulsion technique to make the poorly aqueous soluble drug ketorolac tromethamine more bioavailable.²²

Solvent evaporation technique

This process is carried out in a liquid manufacturing vehicle. The albumin microspheres are dispersed in a

volatile solvent, which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation the core material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microsphere. The mixture is then heated if necessary to evaporate the solvent. The solvent Evaporation technique (Figure 4) to produce microspheres is applicable to wide variety of core materials. The core materials may be either water soluble or water insoluble materials. Solvent evaporation involves the formation of an emulsion between polymer solution and an immiscible continuous phase whether aqueous (o/w) or non-aqueous.

Chinna Gangadhar B et al., performed the formulation and evaluation of Indomethacin Microspheres using natural and synthetic polymers as Controlled Release Dosage Forms. And the microspheres were prepared by solvent evaporation method. The prepared microspheres were pale yellow, free flowing and spherical in shape. The mean particle size of the microspheres was found in the range of 150 to 400 μ m. The drug-loaded microspheres showed 70-86% of entrapment and release was extended up to 6 to 8 h releasing 86% of the total drug from the microspheres.²³

Sonication technique

As the technique name itself is self explanatory, it just involves a simple sonication for certain period of time till a desired size of albumin microspheres are obtained. The albumin solution of desired concentration is taken which is sonicated. To this add the drug which will then form intrachain cross-link with cysteine residues of albumin chains.²⁴

Hilpert L.P et al., prepared a stable preparation of air filled human albumin microspheres (Albunex) by sonication technique. The microspheres ranged in size from 1-10 μ m with 99% of particles smaller than 10 μ m. The mean size was 5 μ m, which is small enough to pass freely through the pulmonary capillary circulation.²⁵

Spray drying technique

In Spray Drying the polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, Acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporate instantaneously leading the formation of the microspheres in a size range 1-100 μ m. Micro particles are separated from the hot air by means of the cyclone separator while the trace of solvent is removed by vacuum drying. One of the major advantages of process is feasibility of operation under aseptic conditions. This process is rapid and leads to the formation of porous micro particles shown in (Figure3)

Lohade AA et al., Developed albumin microspheres of Fluticasone propionate inclusion complexes for pulmonary delivery by using spray and freeze drying technique. 2-hydroxypropyl- β -cyclodextrin inclusion complex of Fluticasone propionate was prepared by the spray drying and freeze drying technique in the molar ratio 1:1.²⁶

Emulsification-heat stabilization technique

Sayed bolghassem Sajadi Tabassi et al., carried out the preparation and characterization of albumin microspheres encapsulated with propranolol HCl by emulsion-heat stabilization technique. Bovine serum albumin microspheres (BSA) containing propranolol HCl were prepared by emulsification-heat stabilization technique. Briefly, a 5% solution of BSA containing 0.1% Tween80 was made, to which 4% propranolol HCl was added and used as the aqueous phase. The oil phase composed of 30 ml maize oil and 10 ml petroleum ether with 1% Span 80 as emulsifier were mixed together and allowed to stir for 10 min at 1000 rpm. The aqueous phase was added drop wise to the oil phase and stirred on a magnet stirrer at 1000 rpm for 30 min to form the initial emulsion. This emulsion was then added to 40 ml of maize oil preheated to 120° C and stirred at 1000 rpm for 15 min to allow the formation and solidification of microspheres. The microsphere suspension was centrifuged at 3500 rpm for 30 min and the settled microspheres were washed three times with ether to remove traces of oil on microsphere surfaces. The microspheres were vacuum dried in a desiccator overnight and stored at 4°C in dark.

The microspheres had mean diameters between 1-25 μ m of which more than 50 percent were below 5 μ m. The encapsulated drug was found to be about 9% w/w of that initially added to microspheres and the superficial drug was 25% of the total amount of the encapsulated drug. Also albumin microspheres were noted to possess good bioadhesion in such a way that about 70% of microspheres remained adherent on the surface mucosa of rat jejunum. The total amount of drug released from microspheres after 12h was 70%.²⁷

Quasi-emulsion solvent diffusion method of the spherical crystallization technique

Deore B.V et al., carried out Development and characterization of sustained release microspheres by quasi emulsion solvent diffusion method. The microspheres were prepared using the quasiemulsion solvent diffusion method of the spherical crystallization technique. Ketoprofen and Eu RS weredissolved completely in the acetone-dichloromethane mixture. Then Aerosil was suspended uniformly in the drug-polymer solution under vigorous agitation. The resultant drug-polymer-Aerosil suspension was poured into the distilled water (150 ml) containing 0.08% of SDS (i.e. poor solvent) under a moderate agitation (450–750rpm) and thermally controlled at 0–38°C. The suspension was finely dispersed into quasi-emulsion droplets immediately



under agitation, and the drug and polymers coprecipitated in the emulsion droplets. After agitating the system for 20 min, 150 ml of poor solvent was added slowly to promote the diffusion of the good solvent from emulsion droplets into poor solvent resulting in enhancement of the solidification of quasiemulsion droplets. Agitation was extended for another 40 min until the translucent quasi-emulsion droplets turned into opaque microspheres. The solidified microspheres were recovered by filtration and washed with water, and the resultant products were dried in an oven at 50°C for 6h. The average diameters were about 104-108µm and the drug contents in the microspheres were 62-96%.²⁸

Evaluation

Some of the evaluation characteristics considered for albumin microspheres are as follows:

1. Interaction study by TLC/ FTIR.

IR spectroscopic studies

The IR spectra of the free drug and the microspheres were recorded. The identical peaks corresponding to the functional groups and albumin (BSA, Egg albumin, Human serum albumin) features confirm that neither the polymer nor the method of preparation has affected the drug stability.

Thin layer chromatographic studies

The drug stability in the prepared microspheres can also be tested by the TLC method. The R_f values of the prepared microspheres can be compared with the R_f value of the pure drug. The values indicate the drug stability.

2. Surface topography by Scanning Electron Microscopy(SEM)

SEM of the microspheres shows the surface morphology of the microspheres like their shape and size.

3. Particle size distribution of prepared microspheres.

The size of the prepared microspheres can be measured by the optical microscopy method using a calibrated stage micrometer for randomly selected samples of all the formulations.

4. Drug entrapment capacity.

Efficiency of drug entrapment for each batch can be calculated in terms of percentage drug entrapment (PDE) as per the following formula:

$$PDE = \frac{\text{Practical Drug Content}}{\text{Theoretical drug content}} \times 100$$

Theoretical drug content can be determined by calculation assuming that the entire drug present in the polymer solution used gets entrapped in microspheres and no loss occurs at any stage of preparation of microspheres.

5. *In vitro* release studies.

In-vitro release studies can be performed according to USP XXII type I dissolution apparatus at suitable pH conditions. The temperature should be maintained at 37±0.5°C and the rotation speed of 100 rpm. Then 5 ml of sample should be withdrawn at various time intervals and replenished with an equal volume of fresh dissolution media. The drug content in the sample can be analyzed spectrophotometrically at specific wavelength (nm).

6. Solid state by DSC/XRD.

This test is done by a X-Ray diffractometer to find out the solid state of the drug, polymer and drug-polymer mixture and also to find out the solid state of the drug in the prepared albumin microspheres.²⁹

CONCLUSION

Being one of the most widely prescribed drugs, NSAIDs are found to be good candidates for controlled release formulations because of the severe GI and renal side effects which they otherwise exhibit. Due to the wider manufacturing techniques albumin microspheres are preferred over other colloidal drug delivery systems. They are biocompatible which can be used for both parenteral and subcutaneous administration. The route of administration, physicochemical properties of drug, toxicity and the site of action are the other major factors that determine the method of preparation and drug carrier for NSAID microspheres. Albumin is the most widely studied polymer for the preparation of NSAID microsphere for parenteral and subcutaneous use. Various studies indicated that the NSAID albumin microspheres were superior to the conventional formulations with respect to bioavailability and pharmacodynamic properties. Because albumin is a naturally occurring polymer and it's protein in human serum also accounts for more percentage compared to the other human proteins, thus providing greater binding and controlled release. The fluctuations in the drug plasma level between dosing intervals are relatively lower, but the safety profile of these drug delivery systems for NSAIDs is not encouraging or not reported extensively so as to conclude that they are the best for this class of drug. But most of *in vitro/in vivo* studies shows that they are the most promising drug delivery systems for NSAIDs.

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