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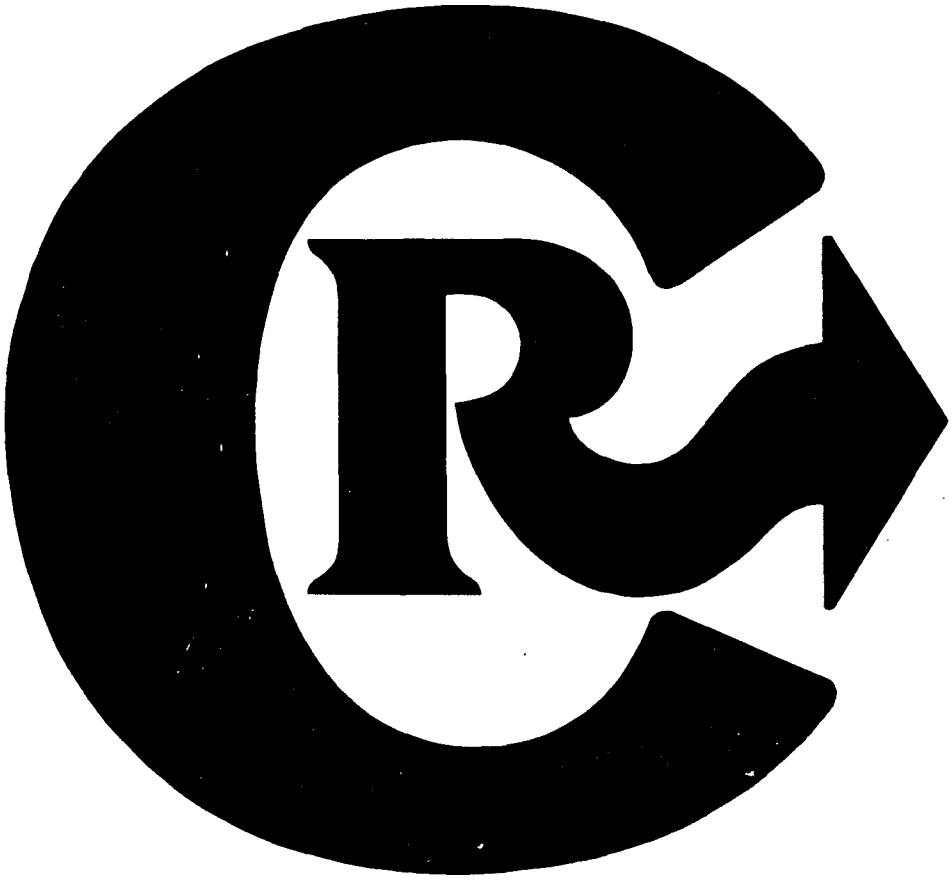

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Solvent choice and drying temperature affects the microsphere structure through their influence on solvent evaporation rate. which, in turn, affects mainx deposition rate. In general terms, highly volatile ACT rapidly evaporates to yield microspheres wilh a highly porous structure which also explains the low solvent residue measurements and the rapid release from these formulations irrespective of storage time. In contrast, reduced microsphere formation rate with CFM or DCM, particularly at lower inlet temperatures, results in a more coherent matrix. High matrix tortuousity thus formed explains their tenacious retention of organic solvent and the correspondingly slower release of RIF there from. The high solvent residue does however facilitate molecular mobility within the matrix allowing greater order to be achieved during solvent removal. This feature further attributes to the slower release rate from microspheres with high original residual solvent, which accelerates release initially, before dessication. through a matrix plasticizing action. Progressive elevation of the softening temperature is paralleled by an increase in the induction period. This feature is consistent with the mechanism of drug release described above.

Variation in yield of production can be attributed to microsphere architecture, solvent residue and the T_2. of the microsphere matrix. Rapid solvent evaporation of ACT produces low density porous particles with low solvent loud which are readily exhausted from the apparatus. High solvent residue lowers the T_2 which would promote product adherence to the glassware were it below that of the drying air. In contrast, high solvent residue is associated with formation of a more coherent matrix with a greater density which reduces the proportion of particles exhausted from the glassware. whilst promoting panicle deposition in the apparatus collector. Considerable residue of relatively dense solvents such as CFM and DCM. further contributes to individual particle density and promotes high microsphere yields.

The results in Table 1 annd the release protiles. noted in Fig. 2 support this pattern of product formation and yield which collectively indicate high product yields arc promoted at the expense of considerable solvent loads. However, prolonged drying can effectively lower these to acceptable levels [3].

Conclusion

Moderate evaporation rates provided by DCM appear to promote the formation of coherent microspheres with relatively slow release rate whilst providing high product yield. The effect of high solvent residue on microsphere release character might however result in erroneous conclusions being drawn where adequate dessication has not been perfomed. Overall, solvent choice for spray-drying has a considerable influence on final microsphere characteristics and should be carefully considered from both a technological in addition to a traditional toxicological view point.

Acknowledgements

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FORMULATION AND CHARACTERIZATION OF AL.. BUMIN MICROSPHERES CONTAINING NAPROXEN SODIUM

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Introduction

Biodegradable polymers have been mostly preferred for microparticles as sustained release drug carrier systems [1]. Bovine serum albumin (BSA) has been a favoured carrier for drugs as it is suitable for producing non-antigenic microparticles whose physicochemical characteristics can be modulated by the crosslinking methods and the nature of the crosslinking agent [2].

Naproxen sodium (NS) is one of the widely used NSAIDs which has analgesic, anti-inflammatory and antipyretic properties. The drug is used in rheumatic disorders such a.s ankylosing spondylititis. osleoarthritis and rheumatoid arthritis. Although oral administration is known to be the most convenient route, NSAIDs are reported to cause gastric irritation and gastric mucosal damagi. In the light of this information the purpose of this study was to prepare and in-vitro evaluate microsphere formulations of NS using BSA as matrix material. The formulation was designed to be administered intra-articularly to sustain release ot the active ingredient and prolong the duration period of dosage form in the knee Joint and thereby increase patient compliance.

Experimental

Materials

The drug was NS (Syntex Pharmaceuticals International). The matrix materiai was BSA (Armour Pharmaceutical), the crose linking agent used was glutaraldehyde (25% aqueous sulution Merck). All materials were used without further purification.

Methods

Microsphere preparation

NS albumin microspheres were prepared according to the emul sion polymerization procedure, in which 0.5 ml of the aqueous

solution. conlaining 25% BSA (w/v) and NS were mixed with 100 ml cottonseed oil and homogenized. The resulting homogenate was added into continuously stirring 100 ml cotton-seed oil at 1400 rpm and 25°C. Afterwards. BSA microspheres were washed with diethyl ether (anhydrous) to remove the oil phase and microspheres were stabilized by a 0.1 ml glutaraldehyde solution (25%) and a crosslinking duration of either 15 min (A), or 60 min (B). The microspheres obtained were dried in a vacuum oven overnight and stored at 4°C.

Encapsulation efficiency

For each batch. 10 mg of NS microspheres were weighed accurately. They were washed four times by keeping in an ultrasonic bath for 5 min with 1 ml or 0.9% NaCl solution (containing 0.01% Tween 80). After this procedure, they were centrifuged at 3000 rpm Ibr 10 min and the supernatant was assayed at 271 nm spectrophotometrically to determine the amount of drug at the surface of the microspheres.

Afterwards, for calculating the entrapped amount. 5 ml of glacial acetic acid were added to the remaining microspheres and stored at 24 h (4°C) followed by centrifugation (5000 rpm) to completely separate the precipitated matrix material. The amount ot NS in ihe clear supernatant of each sample was determined by measuring the absorbance in a sp*ectrophotometer at 272 nm.*

Particle size analysis

The particle size distribution of BSA microspheres of NS were measured by a Coulter Counter Multisizer II (Coulter-Limited. England). Size analysis was performed after suspending the rnicrospheres in an isotonic solution containing 0.01% (w/v) Tween *80.*

Surface morphology of albumin microspheres

SEM (Scanning Electron Microscopy) evaluation of the microspheres was carried out to study their surface morphology. Microspheres were mounted on metal stubs with conductive silver paint and then sputtered with a 15 nm thick laver of gold in a BIO-RAD apparatus. A scanning electron microscope (Jeol-SEM AS1D-10 Device in 80 KV) was used to evaluate the surface characteristics of the microspheres.

In-vivo drug release

The dissolution test in phosphate buffer (pH 7.4) was used in order to obtain NS release profiles. Weighed amount of microspheres (100 mg) were suspended in (25 ml) of buffer solution at 37±0.5ºC in horizontally shaken (50 rpm) flasks. One-ml samples were withdrawn and appropriate volumes of fresh medium were added at regular time intervals. The amount of drug released was calculated from the UV absorption measurements of samples at 271 nm.

Results and discussion

NS microspheres in which BSA was used as matrix material were determined to have a narrow size distribution (< 1μm) and to be homogeneous. As a result of morphological evaluation by SEM, they appeared to have smooth surfaces and were spherical in shape. The preparation process gave a yield of nearly 70%. The drug loading was determined to be 2% both for formulation A and B (target load was 5%). In the release experiments, formulation A for which the crosslinking duration was 15 min appeared to have a higher release rate in the release medium than formulation B in which the crosslinkins duration was 60 min. For formulation A drug release is complete in less than 30 min. while 80% was released in an hour for formulation B with a 60-min crosslinking time (Fig. 1). These results were in a good agreement with our previous study [3]. Further studies are in progress to evaluate the effect of crosslinking agent on release kinetics and to select the appropriate formulations for in-vivo studies.

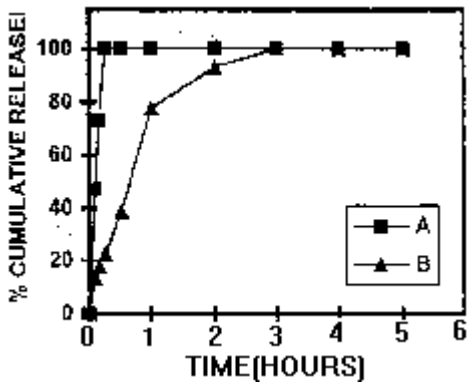

Fig. I. In-vitro release profiles of NS microspheres (in pH 7.4 phosphate buffer). (A) Formulation with a crosslinking duration of 15 min. (B) formulation with a crosslinking duration of 60 min.

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MODIFICATION OF THE BIOLOGICAL UPTAKE OF COLLOIDAL SYSTEMS BY ALTERATION OF THEIR SURFACE COVERAGE WITH PEO BLOCK COPOLYMER

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