A Reliable Predictive Factorial Model for Entrapment Optimization of a Sodium Bisphosphonate into Biodegradable Microspheres

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ABSTRACT: The aim of this work was to optimize the encapsulation of a third generation bisphosphonate (risedronate sodium RS) into polylactide-co-glycolide (PLGA) microspheres using a double emulsion technique for implant purposes. Microspheres were prepared by w/o/w double emulsion technique using PLGA in the ratio of 50:50 and 75:25. Critical process parameters namely: polymer type and amount, drug amount and internal aqueous phase volume ratio were evaluated for their effect on entrapment efficiency (EE%) of RS. Microspheres were characterized for their entrapment efficiency, morphology and particle size by UV spectrophotometry, scanning electron microscopy, and laser diffraction respectively. A 2^4 full factorial design was used for model production. High EE% exceeding 80% were obtained through the manipulation of the previously mentioned factors. Microparticles showed smooth surface with few pores and a size ranging from 1-6 μm. The factorial mathematical model was validated by check point analysis revealing good agreement between actual and predicted values. PLGA microspheres successfully encapsulated RS at high levels with suitable size and morphology suggesting their potential use in the treatment of bone diseases as injectable implants. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:612–621, 2011

Keywords: biodegradable polymers; encapsulation; factorial design; formulation; mathematical model; microencapsulation; polymeric drug delivery systems; microspheres

INTRODUCTION

The majority of hydrophilic moieties are difficult to encapsulate into hydrophobic poly(lactide-*co*-glycolic) acid (PLGA). Most methods of preparation gave low entrapment efficiency percent (EE%), since drugs are expelled out from the hydrophobic polymer into the dispersing aqueous phase during mixing.[1] In such cases, water in oil in water (w/o/w) double emulsion technique might be useful. However, the entrapment efficiency of drugs in microspheres prepared by the double emulsion methods depends on the physicochemical properties of the polymer and the drug, particularly the relative solubility of the drug in the internal and external phases, emulsification conditions, and the dynamics of microsphere formation.[2]

While the conditions for encapsulating hydrophilic macromolecular drug candidates as proteins and peptides have been explored in great detail, the conditions for proper encapsulation of hydrophilic low molecular weight chemical drug candidates did not receive a similar attention. Till now the scientific literature has not reported in details the effect of the experimental conditions of the double emulsion technique on the final properties of the microparticles. In addition, major discrepancies have been observed among the results of different authors regarding the effect of several experimental parameters on a certain microspheres property.[3–5] Furthermore, a study conducted on alendronate sodium to maximize its loading efficiency for dental applications utilized several double emulsion techniques and the authors claimed the w/o/w double emulsion method to possess the poorest

Additional Supporting Information may be found in the online version of this article. Supporting Information.

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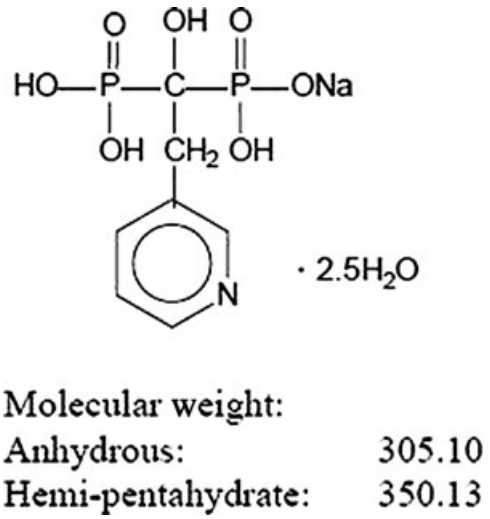

Figure 1. Structure of risedronate sodium.

entrapment efficiency among other emulsion methods like water in oil in oil (w/o/o) and solid in oil in oil (s/o/o).[2]

In light of the previously mentioned considerations, a model sodium bisphosphonate (BP) [risedronate sodium (RS)] was chosen in this study (Fig. 1). RS is a third generation BP possessing higher antiresorptive activity than other BPs[6] and is characterized by its high hydrophilicity. So far, no attempt has been made to encapsulate RS in PLGA microspheres. In addition, the delivery of BPs has always presented a challenge for pharmaceutical scientists. When administered orally, they suffer poor and highly variable absorption (less than 1% of the dose is absorbed from the GIT). Furthermore, they develop serious GIT effects such as ulcers, oesophagitis, and gastritis. Upon I.V. administration, caution must be taken especially when administering large amounts of BPs where rapid injection can lead to renal failure.[7] It has also been reported that the injection of sodium salts causes serious pain and tissue necrosis at the injection site.[8]

On the basis of the previously mentioned facts, a recommendation for the administration of BPs via implants has been encouraged.[9] Implants are generally administered by being injected subcutaneously through minor surgery. To avoid the inconvenient surgical insertion of large implants, injectable biodegradable, and biocompatible polymeric particles (microspheres, microcapsules, nanocapsules, and nanospheres) could be employed for controlled release dosage forms.[10] In addition to the conventional methods of administration of BPs, other delivery systems such as nanocrystals and microspheres made of hydroxyapatite, chitosan and PLGA have been developed.[9,11–13] In therapeutic use, implantation of PLGA microspheres may improve the treatment by possible localization of the drug at the site of action and through the prolonged release nature of the micropsheres.[11] Furthermore, PLGA and PLA (polylactide) polymers have shown positive effects on new bone formation for treating bone related problems.[14]

In this regard, our research group has centered its attention on the development of a suitable set of processing conditions to optimize the entrapment efficiency of RS into PLGA microspheres while preserving acceptable size and morphology. A factorial design approach was applied and a validated model for the prediction of encapsulation behavior of such microspheres has been developed. Check point analysis in the central region as reported from contour plots was used for the purpose. Four variables have been chosen (namely, polymer type, amount of polymer, internal aqueous phase ratio, and drug amount) for consideration in this model.

MATERIALS AND METHODS

Materials

Risedronate sodium was kindly provided by SPIC Pharma company, Chennai, India. Poly(lactide-*co*-glycolide) PLGA [Purasorb® PDLG 7507 (75:25) of inherent viscosity midpoint 0.7 dl/g, Purasorb® PDLG 5010 (50:50) of inherent viscosity midpoint 1 dl/g] were kindly supplied by PURAC company (Gorinchem, the Netherlands). Polyvinyl alcohol (PVA) M.wt. = 31,000 (Mowiol® 4-88) was purchased from Aldrich Chemical Co., St. Louis, Missouri). Dichloromethane (DCM), sodium chloride, and sodium hydroxide were purchased from Adwic, El Nasr Pharmaceutical Co., Cairo, Egypt according to the methods of Prolabo, Paris, France.

Preliminary Screening for Proper Conditions of Microspheres Preparation

A preliminary assessment was performed prior optimization of microspheres entrapment efficiency in order to choose the proper surfactant for the primary w/o emulsion. Surfactants chosen were (Tween 80, Tween 20, Span 85, Span 80, and PVA. PVA concentration in the external aqueous phase was also examined ranging from 0.5% to 2%. Finally, the temperature of the PVA external medium at the instant of primary emulsion addition was also assessed to obtain optimum microparticles size and morphology.

Microspheres Preparation

Poly(lactide-*co*-glycolic) acid microspheres were prepared by w/o/w double emulsion technique in which PLGA polymer was dissolved in 8 mL DCM. A specified amount of RS (50 or 100 mg) was dissolved in either 1600 μL or 4 mL) of 1% PVA solution which was then added to the organic polymer solution