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FORMULATION AND EVALUATION OF MICROSPHERES OF AN ANTIHYPERTENSIVE DRUG USING NATURAL POLYMERS

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ABSTRACT

In the present study formulation and characterization of microspheres of Losartan potassium using chitosan and sodium alginate (prescribed extensively in solid dosage forms) in a controlled release form to overcome drug resistance, and dosing non-compliance in patients. Losartan potassium is used as an antihypertensive belonging to angiotensin antagonist and it was successfully encapsulated into chitosan and sodium alginate. So, the purpose of this research was to formulate controlled release microspheres of Losartan potassium using chitosan and sodium alginate as a carrier polymer. Drug entrapment efficiency for Losartan potassium reached to highest level of 97.50% and percentage yield to 95.0%. Formulated microspheres gave drug release for the initial dosing and maintenance dosing in a controlled manner for 8 hours. This gave a hope to the possibility of single dose treatment for patients. The formulated microspheres show pharmacotechnical properties in the acceptable range.

KEY WORDS

Losartan potassium, chitosan, sodium alginate, microspheres.

INTRODUCTION

The efficiency of any drug therapy can be described by achieving desired concentration of the drug in blood or tissue, which is therapeutically effective and non toxic for a prolonged period. This goal can be achieved on the basis of proper design of the dosage regimen. Microspheres have potential to deliver drug in a controlled fashion. Losartan potassium is an effective antihypertensive drug but is extensively bound to plasma proteins and also causes gastrointestinal disorders, neutropenia, acute hepatotoxicity, migraine and pancreatitis. It may therefore be more desirable to deliver this drug in a sustained release dosage form. The present study was focused on development of controlled release Losartan microspheres using emulsification method and w/o emulsification solvent evaporation method. Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 µm. They are made of polymeric, waxy or other protective materials, that is, biodegradable synthetic polymer and modified natural products. Such as starches, gums, proteins, fats and waxes [1]. The development of new delivery systems for the controlled release of drugs is one of the most interesting fields of research in pharmaceutical sciences. Microparticles can be used for the controlled release of drugs, vaccines, antibiotics, and hormones. For example, by taking advantage of the characteristics of microspheres, beyond

the basic benefits, the microspheres could provide a larger surface area and possess an easier estimation of diffusion and mass transfer behaviour also the encapsulated small molecules could diffuse out of the barrier with precise kinetics modelling and control-release of drugs to the body fluid [2-3]. Among the polymer systems employed, chitosan, a natural cationic polymer, has many advantages for developing micro-particles in drug release applications. Chitosan is a derivative of chitin, the second most abundant polymer in nature, which is a supporting material of crustaceans, insects, and fungal mycelia [4-5]. Among the different species of crustaceans, shrimp and crab shells have been widely used for the isolation of chitin. Alginate, a naturally occurring biopolymer extracted from brown algae (kelp), has several unique properties that have enabled it to be used as a matrix for the entrapment and/or delivery of a variety of biological agents [6]. Alginate is a nontoxic, biodegradable, naturally occurring polysaccharide obtained from marine brown algae [7]. Alginates can be ionically cross-linked by the addition of divalent cations in aqueous solution. Alginate microspheres have been used for the encapsulation of a wide variety of biologically active agents (proteins, enzymes, DNA), and the relatively mild gelation process has enabled not only proteins, but cells and DNA to be incorporated into alginate matrices with retention of full biological activity. The use of controlled release systems has certain advantages compared with conventional dosage forms, as they can minimize side effects, and prolong the efficacy of the drug. These release forms regulate the drug release rate and can reduce the frequency of administration of the drug, thus assuring better patient compliance. The potential of chitosan as a novel excipient which might yet receive extensive application in pharmaceutical products has been highlighted in several reports [8]. The present research work was carried out with the aim to try to reduce Losartan potassium dosing frequency, as it is an antihypertensive producing a resistance if given in high frequency. So, if we can reduce the dosage frequency it will be more beneficial to all patients and treat then up to older age. At the same time a single dosing for a treatment would lead to patient compliance, and complete treatment with appropriate dosing.

MATERIALS AND METHODS

Losartan potassium was collected as gift sample from Astron research PVT. LTD., Ahmebabad, Gujarat, India. Chitosan was collected as a gift sample from shreeji chemical PVT. LTD., Mumbai. Sodium alginate was collected as a gift from Loba chemicals PVT. LTD., Kolkata. Acetic acid (Glacial 100%GR) was purchased from S d Fine chemical PVT. LTD., Mumbai. All other reagents used were of analytical grade.

Preparation of Losartan potassium microspheres by using chitosan polymer by emulsification method

The Chitosan microspheres were prepared by emulsification technique reported by Thanoo *et al* [9] with some modifications. A 4% w/v solution of chitosan was prepared in 5% aqueous acetic acid. Losartan potassium is dispersed in above solution. This solution was dispersed in 200 ml of liquid paraffin (1:1 mixture of light and heavy) containing 0.15 g of span 80 in a 250 ml beaker. The dispersion was stirred using a mechanical stirrer at 1000 rpm for 2 min, glutaraldehyde saturated toluene solution 1 ml was added, stirring was continued for 3 h, the microspheres were centrifuged, washed several times with hexane and finally with acetone. The microspheres were then dried at 50°C and stored in desiccator at room temperature. Three different formulations with drug: polymer ratios

(1:1, 1:2, 1:3) are prepared and coded as X1, X2, and X3.

Preparation of Losartan potassium microspheres by using Na alginate Polymer by water-in-oil (w/o) emulsification solvent evaporation method [10]

Microspheres were prepared by the water-in-oil (w/o) emulsification solvent evaporation technique. Losartan potassium was dissolved in sodium alginate polymer aqueous solutions. The solutions were poured in to 200 ml of sunflower oil containing 0.5% span – 80 as an emulsifying agent. The aqueous phase was emulsified into the oily phase by stirring the system in a 500 ml beaker. Constant stirring at 2000 rpm was carried out using mechanical stirrer. The beaker and its content were heated on the hot plate at 80°C. Stirring and heating were maintained for 2.5 h until the aqueous phase was completely removed by evaporation. The light mineral oil was decanted and collected microspheres were washed three times with 100 ml aliquots of n-hexane, filtered through Whatman filter paper, dried in an oven at 50^0C for 2 h and stored in desiccator at room temperature. Three different formulations with drug: polymer ratios (1:1, 1:2, 1:3) are prepared and coded as Y1, Y2, and Y3.

Scanning Electron Microscopy (SEM)

Scanning electron microscopy has been used to determine particle size distribution, surface topography, texture, and to examine the morphology of fractured or sectioned surface.

Drug Entrapment Efficiency[11]

The entrapment efficiency was calculated from the ratio of actual to theoretical drug content and expressed as percentage. The formula applied is

$$\text{Drug Encapsulation efficiency} = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

***In-Vitro* drug release**

In vitro drug release study was carried out in USP XXIII basket type dissolution test apparatus using Phosphate buffer pH7.0 as dissolution medium, Volume of dissolution medium Was 900 ml and bath temperature was maintained at (37±1)°C throughout study. Stirring speed was adjusted to 100 rpm [12]. An interval of 1 hour, five ml of sample was withdrawn with replacement of five ml fresh medium and analyzed for Losartan potassium content by UV-Visible spectrophotometer at 224 nm.

RESULT AND DISCUSSION

Scanning electron microscopy (SEM)

The surface morphology of the Losartan potassium microspheres was studied by SEM. SEM photograph of Losartan potassium microspheres by using chitosan and SEM photograph of Losartan potassium microspheres by using sodium alginate were shown in the Fig 1 and Fig 2 Surface smoothness of the Losartan potassium microspheres was increased by increasing the polymer conc., which was confirmed by SEM. At lower polymer conc. (1:1) rough surface of Losartan potassium microspheres was obtained and at higher polymer conc. (1:3) the Losartan potassium microspheres with smooth surface was obtained.

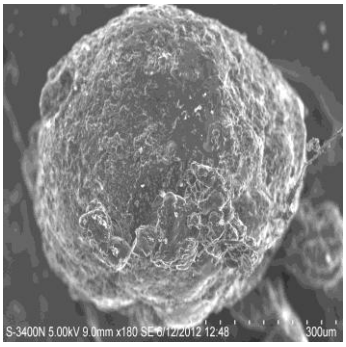


Figure 1
SEM batch X3

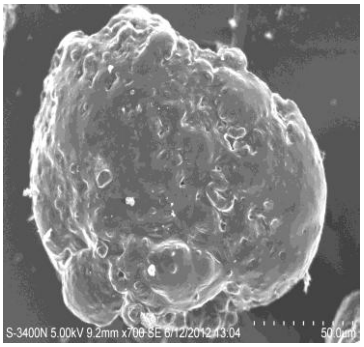


Figure 2
SEM batch Y3

Percentage Drug entrapment efficiency

Entrapment efficiency increase with increase in the polymer concentration from the results it can be inferred that there is a proper distribution of Losartan potassium in the microspheres and the deviation is within the acceptable limits. The percent of drug content in the formulations was found to be in the range of 21.35% to 13.45%. The percentage entrapment efficiency was found to be 25.00% to 97.50%. The results obtained are given in Table 1 and Fig 3. A maximum of 68.00% and 97.50% drug entrapment efficiency was obtained in the Losartan potassium microspheres which were prepared by using chitosan and sodium alginate respectively. It was further observed that the drug entrapment was proportional to the Losartan potassium: polymer ratio and size of the Losartan potassium microspheres. By increasing the polymer conc., the encapsulation efficiency was increased. The study helped in the ease to know the requirement of raw material and effect of the formulation parameters. The percentage drug entrapment efficiency of all batches varied. The idea of percentage of loading and dosage calculation is obtained from the percentage drug entrapment efficiency data. As the drug entrapment efficiency is nearer to 100% for any batch it shows best drug loading and required less amount of formulation dosage to be administered, compared to the less percentage drug entrapmented batch. Here batch X3 & Y3 gave highest drug entrapment efficiency and batch X1 & Y1 gave lowest.

Table 1 Drug entrapment efficiency of Losartan potassium microspheres

S.No	Formulatio code	Percentage yield %	Drug content %	Entrapment efficiency %
1	X1	52.5	21.35	25.00
2	X2	76.0	20.84	45.60
3	X3	77.5	18.31	68.00
4	Y1	83.0	16.00	73.00
5	Y2	92.6	14.05	85.20
6	Y3	95.0	13.45	97.50

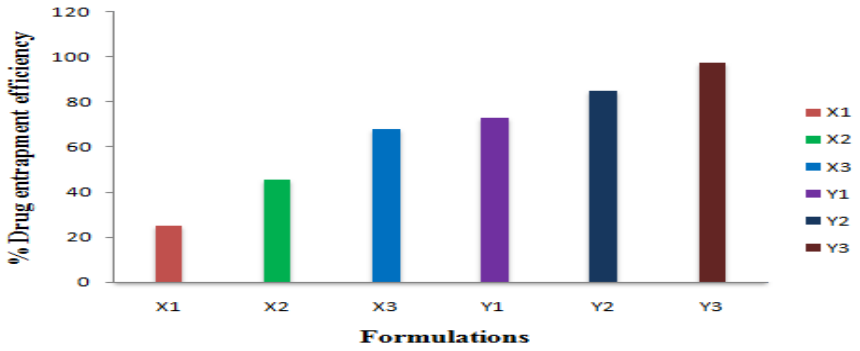
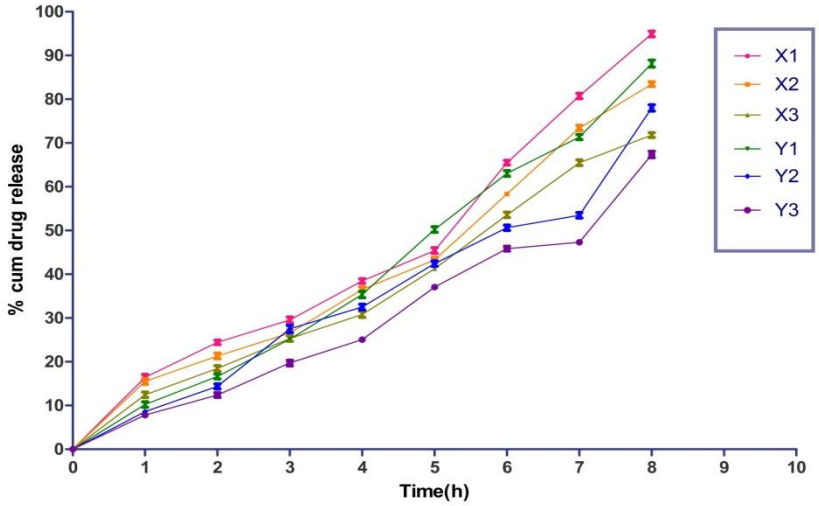


Figure 3 Drug entrapment efficiency of Losartan potassium microspheres

Drug release study

The *in vitro* performance of Losartan potassium microspheres showed prolonged and controlled release of Losartan potassium. The results of the *in vitro* dissolution studies of formulations X1 to Y3 are shown in **graph 1**.



Graph 1

***In vitro* release**

CONCLUSION

Formulated Losartan potassium microspheres gave drug release for the initial dosing and maintenance dosing in a controlled manner for 8 hours. This gave a hope to the possibility of single dose treatment for patients. The formulated Losartan potassium microspheres show pharmacotechnical properties in the acceptable range. This study clearly demonstrated that one could develop a controlled dosage form of a drug having a long biological half-life as a single dose treatment and thus reduce the drug resistance in patients.

REFERENCES

1. Harsh Mohan. Essential phathology for dental student. 3rd Ed, New Delhi, 393-400, (2005)
2. Gandhi TP, Goyal RK. Elements of Pharmacology. 11th Edn. B.S. Shah Prakashan: 243-247, (2001)

3. Satoskar, R.S., Bhandarkar, S.D., Ainapure, S.S.,. (17th Eds.), Pharmacotherapeutics, popular prakashan, Mumbai 2008, pp. 883-913.
4. Vipin B, Pramod Kumar S, Nitin S, Om Prakash P and Rishabha M. Applications of Chitosan and Chitosan Derivatives in Drug Delivery, Adv Biol Res, 5(1): 28-37(2011)
5. Kirtikar KR, Basu BD. Indian medicinal plants. B.L.M. 3rd Edn, Allahabad: Basu Publications: 65-73,(1991)
6. Meltem C, Vural M, Imaz C Y, Atilla A H. Preparation and Characterization of BSA-Loaded Alginate Microspheres, FABAD J Pharm Sci, 32:103-107,(2007)
7. Bregni C, Degrossi J, Garcia R, Lamas M C, Firenstein R Y. Alginate microspheres of Bacillus subtilis: Ars Pharm, 41(3): 245-248, (2000)
8. Hirano S, Seino H, Akiyama Y, Nonaka I. Chitosan: a biocompatible biomaterial for oral and intravenous administration, Gebelin CG, Dunn RL (eds.), Progress in Biomedical Polymers, Plenum Press, New York 1990, pp. 283-290.
9. Thanoo BC, Sunny MC, Jayakrishnan A. cross linked chitosan microspheres preparation and evaluation as a matrix for the controlled release of pharmaceutics. J Pharm Pharmcol, 44: 283, (1992)
10. Rajeshwar K K A, Ripudam Singh, vijay J. Mucoadhesive microspheres of Famotidne; preparation characterization and *in vitro* evaluation. Int J of Eng Sci Tech, 2(6): 1575-1580,(2010)
11. Sahoo SK, Mallick AA, Barik BB, Senapati PC. Formulation and *in vitro* evaluation of eudragit microspheres of stavudine. Trop J Pharm Res, 4(1): 369-375, (2005)
12. Halder A, Sa B. Preparation and *in vitro* evaluation of polystyrene-coated Diltiazem-resin complex by oil- in-water emulsion solvent evaporation method. AAPS Pharm Sci Tech, 7(2):1-8,(2006)

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