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FORMULATION AND EVALUATION OF MICROSPHERES OF AN ANTIHYPERTENSIVE DRUG USING NATURAL POLYMERS (SODIUM CARBOXY METHYL CELLULOSE)

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Abstract: In the present study formulation and characterization of microspheres of Prazosin hydrochloride using sodium carboxy methyl cellulose in a controlled release form to overcome drug resistance, and dosing non-compliance in patients. The oral administration of pharmaceutical dosage forms is the more usual, convenient and comfortable route for active drug delivery to the body. Oral controlled release systems continue to be the most popular ones among all the drug delivery systems as it offers several advantages over the conventional systems like: Improve patient's compliance and convenience due to less frequent dosing of drug.

Reduction in fluctuation of steady state plasma level and therefore helps in better control of disease condition. Prazosin belongs to a family of selective antagonists of α1-adrenergic receptors and it was successfully encapsulated into sodium carboxy methyl cellulose. So, the purpose of this research was to formulate controlled release microspheres of Prazosin hydrochloride using sodium alginate as a carrier polymer. Drug entrapment efficiency for Prazosin hydrochloride 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 pharmaco technical properties in the acceptable range.

Key words: Prazosine hydrochloride, sodium alginate, antihypertensive, microspheres.

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INTRODUCTION

Sodium alginate, a hydrophilic biopolymer obtained from brown seaweeds has been found to be highly promising with respect to drug delivery because of its high biological safety[1]. Chemically, it is a polysaccharide composed of varying proportions of D-mannuronic acid (M) and L-guluronic acid (G) residues which are arranged in MM or GG blocks interspersed with MG blocks[2]. In addition to its use as a thickening, gel forming and colloidal stabilizing agent in the food and beverage industries, it is also used as a binder in tablet formulation[3]. Drop wise addition of aqueous alginate solution to the aqueous solution containing calcium ions and/or other di and polyvalent cations causess spherical gel formation termed as alginate bead. Alginate is known to be nontoxic when taken orally and also have a protective effect on the mucous membranes of the upper gastrointestinal tract[4]. The dried alginate beads have the property of reswelling and thus they can act as controlled release system. Their re swelling property is susceptible to pH, which protects the acid-sensitive drug from gastric juice[5]. The current uses of alginate-based devices are mainly related to encapsulation of various classes of therapeutic agents[6,7,8].

Prazosin Hydrochloride [1-(4-amino - 6, 7 - dimethoxy - 2 - quinazolinyl) - 4 - (2 - fur-anylcarbonyl)-monohydrochloride] is indicated in the treatment of mild to moderate hypertension. It is slightly soluble in water, very slightly soluble in alcohol, and has an apparent pKa of 6.5 in 1:1 water and ethanol solution. It is readily absorbed after oral administration. Peak serum levels are attained in 2-3 h and it has a half-life of 4-5 h (Parker, 1980). Its average dosing is 1-2 mg three times a day. Thus, its short half-life and increased dosing frequency suggest the need for a controlled delivery of Prazosin Hydrochloride for better patient compliance. Prazosin belongs to a family of selective antagonists of α1-adrenergic receptors[9]. It was the first α1-blocker introduced for the treatment of hypertension, acting in the expansion of the smooth muscle of small blood vessels and thereby lowering blood pressure[10]. Prazosin action involves vasodilation by the selective blocking of α1-adrenergic receptors located in the walls of blood vessels, direct inhibition of phosphodiesterase, as well as increasing cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) amounts. The blocking of adrenergic receptor α1 inhibits vasoconstriction induced by endogenous catecholamines. Prazosin also reduces cardiac preload and thus leads to a small increase in cardiac output and heart rate. It is also believed that prazosin works within the central nervous system, where it inhibits the sympathetic system and modulates the activity of baroreceptors[10]. The effect of prazosin on lipid metabolism is also important, manifested by a decrease in total cholesterol levels, a decrease in low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL) and triglyceride fractions, as well as an increase in high-density lipoprotein (HDL) fraction. It has also been shown that chronic use of α1-blockers has no effect on the carbohydrate metabolism and increases insulin sensitivity[11]. The objective of this study is to develop a simple uncomplicated and easy to manufacture floating microspheres that is capable of delivering Prazosin Hydrochloride at a prolong release rate of delivery.

Sodium Carboxy methylcellulose (Na CMC) is an important industrial polymer with a wide range of applications in flocculation, drag reduction, detergents, textiles, paper, foods, drugs, and oil well

drilling operation. CMC is a derivative of cellulose and formed by its reaction with sodium hydroxide and chloroaceticacid, it has a number of sodium carboxymethyl groups (CH2COONa). Present in the cellulose molecule which promotes water solubility. The various properties of Na CMC depend upon three factors: molecular weight of polymer, average number of carboxyl content per anhydroglucose unit, and the distribution of carboxyl substituents along the polymer chains. The most important properties of Na CMC are viscosity building and flocculation. Among all the polysaccharides, Na CMC is easily available and it is also very cheap and will be useful material for drug delivery application.

MATERIALS AND METHODS

Prazosin Hydrochloride was collected as gift sample from Taj pharmaceuticals LTD., Gujarat, India. Chitosan was collected as a gift sample from Sherrji chemicals PVT. LTD.,Mumbai. Gelatin was collected as a gift from S DD chemicals limited, Mumbai., All other reagents used were of analytical grade.

PREPARATION OF PRAZOSIN HYDROCHLORIDE MICROSPHERES BY USING CHITOSAN POLYMER BY EMULSIFICATION METHOD

The Chitosan microspheres were prepared by emulsification technique reported by Thanoo et al72 with some modifications. A 4% w/v solution of Chitosan was prepared in 5% aqueous acetic acid. prazosin hcl is dispersed in above solution. This solution was dispersed in 50 ml of liquid paraffin (1:1 mixture of light and heavy) containing 0.15 g of span 80 in a 100 ml beaker. The dispersion was stirred using a stainless steel half-moon paddle stirred at 1000 rpm for 2 min, glutaraldehyde saturated toluene solution 1 ml was added and stirring was continued. After the stipulated stirring time, the microspheres were centrifuged, washed several times with hexane, methanol and finally with acetone. The microspheres were then dried at 50˚C. Three different formulations with drug: polymer ratios (1:1, 1:2, 1:3) are prepared and coded as A1, A2, and A3.

PREPARATION OF PRAZOSIN HYDROCHLORIDE MICROSPHERES BY USING NA ALGINATE POLYMER BY WATER-IN-OIL (W/O) EMULSIFICATION SOLVENT EVAPORATION METHOD

Microspheres were prepared by the water-in-oil (w/o) emulsification solvent evaporation technique. Prazosin hcl- was dissolved in chitosan 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 nhexane, filtered through Whatman filter paper, dried in an oven at 500 C 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. The entrapment efficiency was calculated from the ratio of actual to theoretical drug content and expressed as percentage. Three different formulations with drug:

polymer ratios (1:1, 1:2, 1:3) are prepared and coded as C1, C2, and C3.

***In-Vitro* drug release In vitro drug release**

Dissolution studies were carried out by using USPXXIII dissolution test apparatus by rotating basket method in stimulated gastric fluid pH 1.2 for 2 h and in phosphate buffer pH 7.4 for remaining 10 h. The dissolution media were maintained at a temperature of 37 ± 50 C. The speed of rotation of basket maintained was 50 rpm. The samples were withdrawn at 30 min intervals.

Procedure: prazosin hcl microspheres were placed in basket in each dissolution vessel to prevent floating. 5 ml of dissolution media was withdrawn at predetermined time intervals and fresh dissolution media was replaced. The withdrawn samples were analyzed and the amount of prazosin hcl released was determined by UV absorption spectroscopy at 269 nm.

Surface morphology (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. SEM is probably the most commonly used method for characterizing drug delivery systems, owing in large to simplicity of sample preparation and ease of operation. SEM studies were carried out by using JEOL JSM T-330A scanning microscope (Japan). Dry prazosin hcl microspheres were placed on an electron microscope brass stub and coated with in an ion sputter. Picture of prazosin hcl microspheres were taken byrandom scanning of the stub [Felder ChB, 2003].

Percentage yield

Percentage practical yield is calculated to know about percentage yield or efficiency of any method, thus it helps in selection of appropriate method of production.

Practical yield was calculated as the weight of prazosin hcl microspheres recovered from each batch in relation to the sum of starting material [Sinha VR, 2003].

The percentage yield of prepared prazosin hcl microspheres was determined by using the formula:

$$\text{Percentage Yield} = \frac{\text{Practical Yield}}{\text{Theoretical Yield}} \times 100$$

Determination of percentage drug entrapment efficiency (PDE) [Wang J, 2004]

Efficiency of drug entrapment for each batch was calculated in terms of percentage drug entrapment as per the following formula:

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

Theoretical drug content was determined by calculation assuming that the entire prazosin hcl present in the polymer solution used gets entrapped in prazosin hcl microspheres, and no loss occurs at any stage of preparation of prazosin hcl microspheres [Carmen RL, 1996].

Practical drug content was analyzed by using the following procedure,Weighed amount of prazosin hcl microspheres equivalent to 100 mg of prazosin hcl was dissolved in 100 ml of distilled water. This solution was kept overnight for the complete dissolution of the prazosin hcl in water. this solution was filtered and further diluted to make aconc. of 10 µg/mlsolution. The absorbance of the solutions was measured at 269 nm using double beam UV-Visible spectrophotometer against distilled water as blank and calculated for the percentage of drug present in the sample.

RESULT AND DISCUSSION

Scanning electron microscopy (SEM)

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

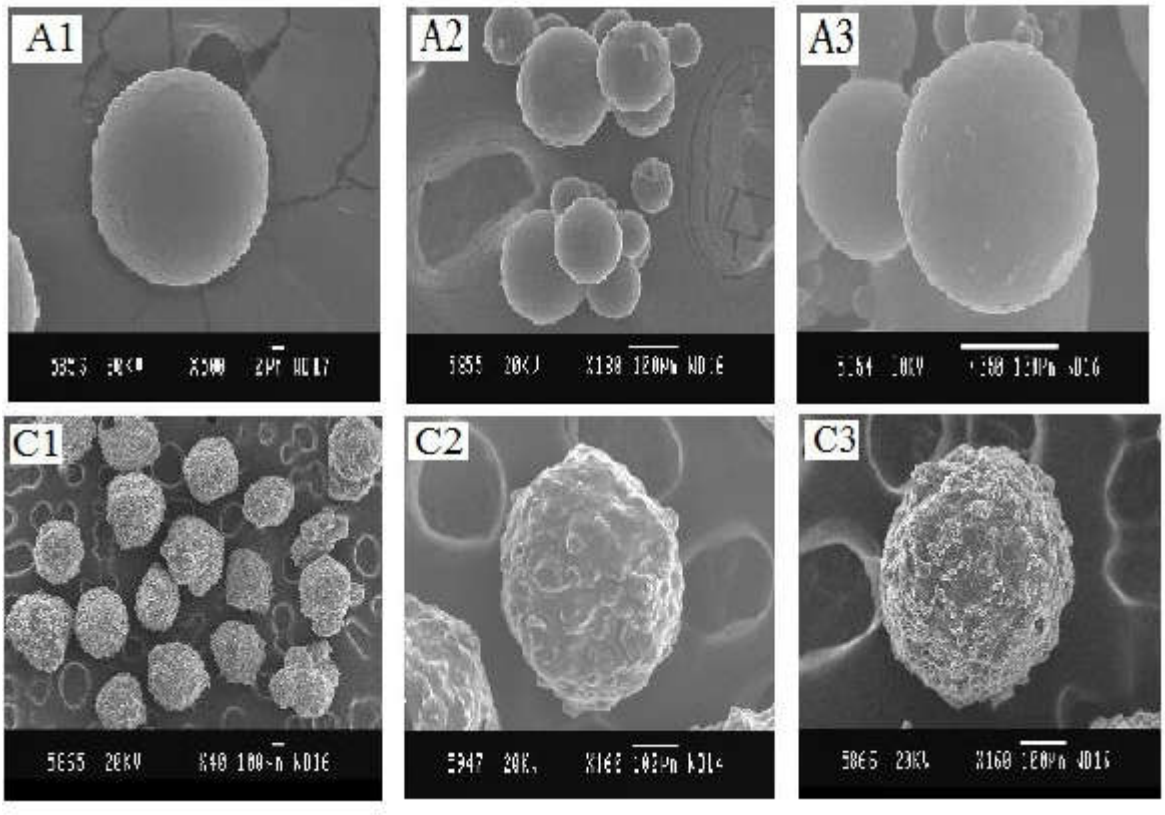

Figure 1 SEM batch A

Figure 2 SEM batch C

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 prazosin hcl 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 prazosin hcl microspheres which were prepared by using chitosan and sodium alginate respectively. It was further observed that the drug entrapment was proportional to the prazosin hcl: polymer ratio and size of the prazosin hcl 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 A3 & C3 gave highest drug entrapment efficiency and batch A1 & C1 gave lowest.

Drug entrapment efficacy

Table I: Drug entrapment efficiency of prazosin hcl microspheres

Sl.no	Formulation code	Average size(µm)±SEM	Percentage yield %	Drug content %	Entrapment efficiency %
1	A1	100±6.73	52.5	21.35	25.00
2	A2	121±5.43	76.0	20.84	45.60
3	A3	214±7.62	77.5	18.31	68.00
4	C1	291±8.26	83.0	16.00	73.00
5	C2	333±7.34	92.6	14.05	85.20
6	C3	424±8.17	95.0	13.45	97.50

Drug release study : The in vitro performance of prazosin hcl microspheres showed prolonged and controlled release of prazosin hcl. The results of the in vitro dissolution studies of formulations A1 to C3 are shown in graph 1.

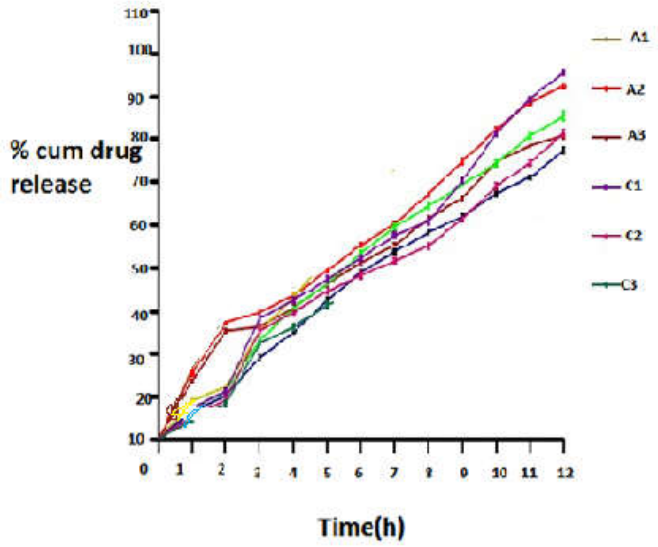

Figure 3: In-vitro dissolution studies of formulations A1 to C3

CONCLUSION

Formulated prazosin hcl 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 prazosin hcl microspheres show pharmaco technical 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.

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