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Fabrication and evaluation of propranolol hydrochloride loaded microspheres by ionic-gelation technique

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ABSTRACT

The aim of present research work was to formulate and evaluate microspheres of Propranolol Hydrochloride to achieve sustained release system using combination of algino- eudragit RS100 system by ionic-gelation technique. The prepared microspheres were evaluated for various parameters like percentage yield, particle size, flow property, entrapment efficiency, surface study, in-vitro drug release, X-Ray diffraction analysis, etc. It was found that all formulations showed improved flow behavior as compared to pure drug, it was observed that on increasing the polymer concentration of formulations the entrapment efficiency and particle size were increased. The surface morphology study by SEM indicated that microspheres were spherical with rough outer surface. There was no interaction between the drug and the polymers, as studied by FTIR study. In-vitro drug release study showed that on microsphere formulation its release was sustained and its release was affected by polymer concentration and it followed Higuchi model. Therefore, it can be concluded that Propranolol Hydrochloride loaded algino-eudragit RS100 microspheres can be formulated for sustained drug delivery of Propranolol Hydrochloride.

Keywords: Propranolol Hydrochloride, Sustained release, Sodium alginate-Eudragit RS100 system, Ionic- gelation method.

INTRODUCTION

For the treatment of chronic diseases it is important to take medication several times, this may lead to fluctuating drug level in body. In order to avoid frequent drug administration and maintenance of therapeutic drug level in body it is essential to administer drug by a sustained release system. Drug delivery by sustained release dosage form is mainly designed for maintaining therapeutic levels of the drug in body for longer period of time with minimum side effects. Drugs with short elimination half life[1],are most suitable for sustained release formulations. Sustained delivery of drugs can be achieved by microspheres formulation. Propranolol Hydrochloride (PHCl), is a nonselective beta-adrenergic blocking agent, which is commonly used in the treatment of hypertension, angina pectoris, cardiac arrhythmias [2] and other cardiovascular disorders. PHCl has a half-life of 3 to 5 hours, so it is important to take drug several times a day in order to maintain optimum drug level in body. Such frequent drug administration may reduce patient's compliance and therapeutic efficacy. Due to short elimination half-life, PHCl is a suitable candidate for sustained delivery of drug. Most of the microsphere carrier systems are prepared from various combinations of natural and synthetic polymers, so by such combinations we can achieve sustained release of drug [3]. Alginate [4], which is a naturally occurring biocompatible and biodegradable linear polysaccharide, is

commonly used for microsphere formulation. Sodium alginate is the commercially available salt form of alginate. The unique property of sodium alginate is the transformation from sol to hydro gel with more than 95% of water molecules physically held inside [5] which is important for the maintenance of bioavailability by providing an aqueous environment to the entrapped substances. When alginate reacts with calcium ions, it undergoes gelation in aqueous solution due to binding of calcium ions with G-blocks of adjacent alginate chains creating ionic inter-chain bridges. In this present work ionic gelation [6] method was selected to prepare microspheres due to its simplicity, low cost and its high entrapment efficiency. In present research work sodium alginate is used in combination with Eudragit RS 100 for sustained drug delivery of Propranolol Hydrochloride. Sodium alginate on exposure to dissolution fluids gets swelled & forms a viscous gel layer that sustained the drug release, where as Eudragit RS 100 being water insoluble polymer retards drug release. So the objective of the present study was to develop a sustained release system of PHCl and evaluate the effect of polymer concentration on drug release kinetics.

MATERIALS AND METHODS

Materials

Propranolol Hydrochloride was obtained as a gift sample from Zydus Cadila, Ahmedabad, India. Sodium alginate was a gift sample from Signet Chemical Co, India. Eudragit RS 100 was purchased from Loba Chem, Pvt. Ltd., India. Calcium chloride was purchased from Loba Chem, Pvt. Ltd., India. All other chemicals used were of analytical reagent grade.

Preparation of Propranolol Hydrochloride Loaded Microspheres

Microspheres containing PHCl were prepared by ionic gelation method using sodium alginate. First of all specified amount of sodium alginate was dissolved in sufficient quantity of distilled water to form a homogeneous polymer solution, and then specified quantity of Eudragit RS 100 was added to it and uniformly mixed with the help of magnetic stirrer. Lastly, drug i.e PHCl was added to the polymers solution and mixed to form a smooth viscous dispersion, this resulting dispersion was then added drop wise by using 24 G needle in 500 ml of 5% calcium chloride solution under continuous stirring at 200 rpm. The stirring was continued for 30 minutes to make the dispersion as fine as possible to produce spherical microspheres. Then the mixture was filtered and product was dried at 40°C for 12 hour. The prepared microspheres along with coat composition are listed in Table-1.

Percentage Yield [7]

The percentage yield of all prepared microspheres was determined on weight basis with respect to the initial weight of material; the data are described in Table-2.

Table -1 Composition of Propranolol Hydrochloride loaded microspheres

Formulation Code	Drug(g)	Sodium alginate(g)	Eudragit RS100(g)
F1	1	0.5	0.5
F2	1	0.5	1.0
F3	1	0.5	1.5
F4	1	0.5	2.0
F5	1	0.5	2.5
F6	1	0.5	3.0
F7	1	0.5	3.5
F8	1	0.5	4.0

Particle Size Analysis

Particle size of prepared microspheres was determined by optical microscopic method, [8] all readings were taken in triplicate.

Entrapment Efficiency of Drug

The drug entrapment of prepared microspheres was tested by taking 100 mg of the formulation in 50 ml of phosphate buffer of pH 7.4 in a volumetric flask and then it was stirred for 30 minutes in sonicator at 125W(Imeco Sonifier, Imeco Ultrasonics, India.). Finally, the volume was made up to 100 ml with phosphate buffer(pH 7.4) and again stirred for 1 hour and kept overnight for 24 hours to extract the drug from microspheres. Then it was filtered and the filtrate was collected by passing through 0.45µ filter and required dilutions were made and the absorbance of resulting solution was measured at 290nm [9] using UV-Visible spectrophotometer (UV- 2450 Shimadzu, Japan)

against blank. This study was conducted in triplicate and values are depicted in table-2. The drug entrapment was calculated by using the formula: % Drug entrapment = (Calculated drug content/Theoretical drug content) x 100

Micromeritic Study

The flow properties of prepared microspheres were determined by calculating angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio [10].Bulk density and tapped density [11] were determined by Bulk density apparatus (Electrolab India) and angle of repose was calculated by fixed base cone method.

In-Vitro Drug Release Study

Release of Propranolol Hydrochloride from the prepared microspheres was studied in 0.1N HCl and in phosphate buffer pH 7.4(900ml) using an USP six station dissolution (LAB DISSO 2000) rate testing apparatus with a rotating paddle at 50 rpm and 25cm depth. A sample of 5 ml was withdrawn at different time intervals and diluted using pH 7.4phosphate buffer. After suitable dilutions the absorbance was measured at 290nm using UV- visible spectrophotometer (2450 Shimadzu, Japan) against a blank. The dissolution study was conducted in triplicate [12].

Scanning Electron Microscopy

The surface morphology especially with respect to surface topography and photomicrography was done with Scanning Electron Microscopy (SEM) [13], by using the instrument JSM 5610LV SEM, JEOL, Japan. The figures of microsphere after SEM analysis are depicted in Figure-1.

FTIR

The FTIR study was carried out using Perkin-Elmer FT-IR. The sample of pure drug, pure polymers (sodium-alginate and Eudragit rs 100) and formulation containing both the drug and polymers were scanned to study the possible interaction between drug and polymers.

X-Ray diffraction (XRD) analysis

The crystalline nature of Propranolol Hydrochloride and the prepared formulations was determined by XRD patterns obtained by X-Ray Diffractometer (Miniflex Goniometer, Japan).

RESULTS AND DISCUSSION

The Propranolol Hydrochloride loaded microspheres were prepared using algino-eudragit RS 100 system by ionic gelation method with calcium chloride as cross linking agent [14]. This method was selected due to its ease of formulation, quick and cost effectiveness. The composition of prepared formulations is represented in Table. 1

Percentage yield

The yield obtained from all the batches was good. The range for % yield was 93.5±0.05% to 98.68±0.06% for the prepared microspheres, the result showed a moderate increase in yield. Table-2 depicts the detail data of percentage yield.

Particle size analysis

The mean particle size of eight formulations ranged between 46.0±3.02µm to78.88±5.52 µm. It was found that mean particle size of the formulations was increased with polymer concentration for the formulations F1, F2, F3, F4, F5, F6, F7 and F8. This may be due to the increase in relative viscosity at higher concentrations of polymer and formation of large droplets during addition of the polymer solution to the cross-linking agents.

Table- 2 Comparative percentage yield, particle size and entrapment efficiency of Propranolol Hydrochloride loaded microspheres

Parameters	Pure Drug	F1	F2	F3	F4	F5	F6	F7	F8
% Yield	-	90.8±0.52	92.02±0.05	95.16±1.02	93.89±0.07	96.14±0.87	97.04±0.06	97.88±1.08	98.68±0.06
Average particle size	18.43±2.75	46.0±3.02	53.8± 6.75	67.09± 7.0	64.76± 6.9	69.54± 7.5	77.02±5.42	78.05±4.25	78.88±5.52
Entrapment efficiency	-	68.48±0.86	73.08±0.37	75.54±0.02	76.05±0.41	78.01±0.04	78.69±2.93	77.64±6.48	78.99±0.06

Drug Entrapment

The drug entrapment efficiency for various formulations was found to vary between68.48±0.86% to78.99±0.06 %. It was observed from the obtained data that with increase in polymer concentration larger microspheres were formed

with greater amount of drug entrapped. This may be due to the greater availability of active calcium binding sites in the polymeric chains.

In-vitro drug release study

The drug release behavior from the prepared microspheres formulation was studied by in-vitro method. Form the obtained data it was observed that with increase in Eudragit RS100 concentration, sustained release pattern was obtained for Propranolol Hydrochloride. The prepared PHCl formulations F1, F2, F3, F4, F5, F6, F7 and F8 were able to sustain the drug release for around 4,5,6,7, 9, 10, 12 hours respectively. For F1formulation 97.02 % of drug was released after 4hours, for F2, 96.83 % after 5 hours, for F3 94.037% after 6 hours, for F4 92.67 % after7 hours, F5 91.92% after 9 hours, F6 91.07% after 10 hours drug was released, for F7 92.05%of the drug was released after 12 hours, and for F8 80.16% of drug was released after 12 hours. For F7 92.05 % of the drug was released after 12hours. PHCl formulations containing algino-eudragit RS100 microspheres (F1 to F8) were more efficient in sustaining the drug release because Eudragit being water insoluble polymer forms a rigid hydrophobic coat around the microspheres. From all the formulations F7 showed better dissolution profile because more than 90% drug was released in 12 hours, therefore, it was selected to be the optimized formulation. From table 3 it was seen that the highest correlation coefficient (r^2) was obtained for Higuchi model, this indicates that release of drug from prepared microspheres formulation followed diffusion mechanism [16, 17]. Another plot of log percent drug release against log time revealed higher correlation coefficient (r^2) this confirms that mechanism of drug release was diffusion controlled.

Table-3: Drug release profile for prepared microsphere formulations

Formulation Code	Zero order(r2)	First order(r2)	Higuchi model(r2)	Peppas model(r2)
F1	0.839	0.953	0.938	0.965
F2	0.899	0.957	0.992	0.990
F3	0.948	0.960	0.980	0.984
F4	0.954	0.949	0.976	0.981
F5	0.960	0.968	0.984	0.979
F6	0.968	0.978	0.981	0.985
F7	0.971	0.982	0.987	0.989
F8	0.974	0.986	0.982	0.987

Scanning electron microscopy

The scanning electron micrographs (SEM) of the microspheres are shown in Figure 1A and 1B. The SEM results revealed that Propranolol Hydrochloride loaded microspheres were discrete and spherical in shape with rough outer surface. The surface of the microspheres was rough due to the density of the polymer matrix which in turn justifies its sustained release.

Figure 1- SEM Photographs of prepared microspheres at different magnifications.

Figure 1(A) at 90 X and Figure 1(B) at 500X

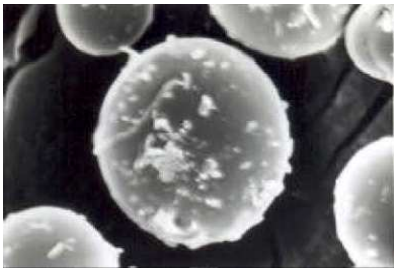

Figure 1(A)

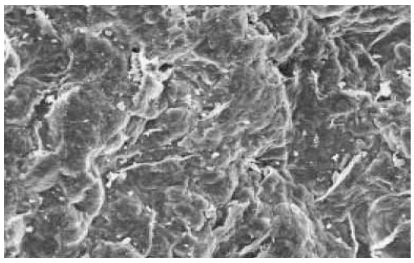

Figure 1(B)

FTIR

Infrared spectrum was taken in the Perkin-Elmer FT-IR (spectrum RX) by scanning the formulations in potassium bromide discs. Different samples of pure drug, pure polymers and formulations containing both the drug and

polymers were scanned. It was found that no interaction was observed between the drug and polymers which indicates the stable nature of Propranolol Hydrochloride in the prepared formulations.

X-ray diffraction (XRD) analysis

From XRD analysis characteristic peaks of pure PHCL was observed which indicated high crystalline nature of pure PHCL(Figure 2A), whereas for prepared PHCL loaded microspheres (Figure 2B)formulations all characteristic peaks of PHCL were found to disappear, which indicated formation of a new structure.

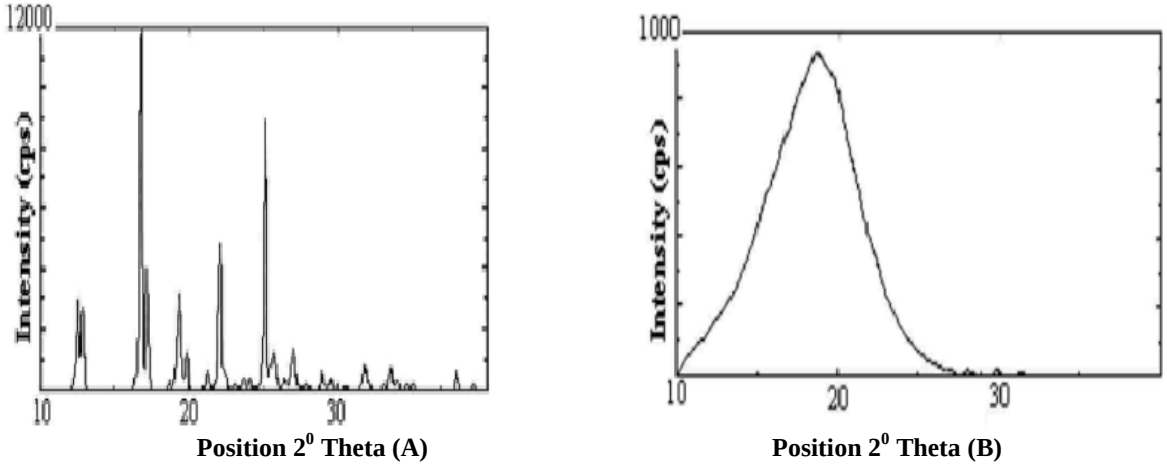

Figure 2-X ray Diffractogram of (A) Propranolol Hydrochloride (B) Propranolol Hydrochloride loaded microspheres

CONCLUSION

The Propranolol Hydrochloride loaded microspheres using algino-eudragit RS100 system showed good sustained release behavior. The physical characterization of the microsphere suggests that on formulating pure drug to microsphere the flow behavior of the drug was improved and its release can be easily sustained up to 12 hours. So, by this system we can formulate Propranolol Hydrochloride loaded microspheres for safe and sustained drug delivery.

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