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Preparation and Evaluation of Microspheres of Propranolol Hydrochloride Using Eudragit® RL as the Matrix Material

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Abstract: The aim of the work was to prepare propranolol HCl-loaded Eudragit RL 100 microspheres to achieve sustained release. Propranolol HCl-loaded Eudragit RL 100 microspheres were prepared by an emulsion-solvent evaporation method. The resultant microspheres were evaluated for morphology, average particle size, flow properties, drug content, *in vitro* drug release study and release kinetics. The mean particle size of the microspheres was influenced by varying drug: polymer ratio while drug loading was dependent on drug: polymer ratio. The drug release profiles of the microspheres were extended over a period of 8 hrs; release was influenced by polymer concentration. Drug release followed the Higuchi model. The propranolol HCl-loaded Eudragit RL 100 microspheres prepared under optimized conditions showed good sustained release characteristics and were stable under the conditions studied.

Key words: Propranolol HCl · Micromeritic studies · Eudragit RL 100 · Microspheres · Sustained release

INTRODUCTION

There is a great deal of enthusiasm in the field of micro encapsulation and controlled release of drug and proteins. Microspheres represent a very promising drug delivery system for controlled and targeted drug release, also known as microparticles. They fall under the category of monolithic matrix throughout which the drug is dissolved or distributed. Polymeric microspheres are used as carrier for controlled release of drugs to target area. Microspheres based drug delivery systems have received considerable attention in recent years [1]. Microspheres are one of the particulate delivery systems used to achieve sustained or controlled drug delivery, improve bioavailability and stability and target drug to specific sites. Microspheres also offer advantages such as limiting fluctuation within a therapeutic range, reduction in side effects, decreased dose frequency and hence improved patient compliance [2, 3].

Microspheres are made from natural and synthetic polymers. Different materials have been used for microsphere systems like albumin, gelatin, starch, ethylcellulose, chitosan, pectin, sodium alginate and synthetic polymers such as polylactic acid, polycyano-acrylates and polyhydroxybutyrate. The term microcapsules and microspheres are often used synonymously. Due to attractive properties and wider applications of microcapsules and microspheres, a survey of the applications in controlled drug formulations is appropriate [4]. Recently, it has been reported that microspheres of less than 10μm in size are taken up by the Payer's patches and may increase the retention time, in the stomach [5]. Eldridge [6] found that oral administration of polylacide-co-glycolide microspheres containing staphylococcal enterotoxin B is effective in inducing disseminated mucosal IgA Antitoxin antibody response. The popular method for the encapsulation of drugs within water-insoluble polymers is the emulsion solvent evaporation method. This technique offers several advantages and is preferable to other preparation methods such as spray drying, sonication and homogenization because it requires only mild conditions

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such as ambient temperature and constant stirring. Thus, a stable emulsion can be formed without compromising the activity of the drugs. The Eudragits are biocompatible copolymers synthesized from acrylic and methacrylic acid esters. These polymers are well tolerated by the skin and have been used in the formulation of dosage forms especially matrix tablets for oral sustained release [7-9] and in tablet coating [10]. They have also been used in the microencapsulation of drugs [11, 12, 13].

Propranolol hydrochloride [1-(isopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride] is a nonselective beta-adrenergic receptor blocking agent with a biological half life of about 3-5 hours. It is indicated in the management of hypertension. It is also indicated in the long term management of patients with angina pectoris. Propranolol hydrochloride is commercially available in the form of conventional formulation with dose 10-40 mg in 3-4 times daily. However, Propranolol hydrochloride usefulness is limited due to its short half-life that ranges from 3 to 5 hrs. Hence, it requires three-four times a day dosing which produce the patient's un-compliance. To reduce the frequency of dose administration and to improve patient compliance, a controlled/sustained release formulation is desirable. The objectives of the this study is to prepare and evaluate the microspheres containing propranolol hydrochloride using Eudragit® RL as the matrix material in order to achieve slow *in vitro* release in order to overcome the rapid elimination of drug and increase the biological half-life of the drug or maintain drug plasma concentration in the therapeutic range for desired period of time. This management generates a number of favorable outcomes in drug therapy including reduced undesirable side effects, improved patient compliance and reduced overall cost of the therapy.

MATERIAL AND METHODS

Chemicals: Propranolol hydrochloride was a obtained as a gift sample from Mann Pharmaceutical Ltd, Mehsana, India. All other chemicals were purchased from commercial sources and were used of analytical grade. All-glass double distilled water was used throughout the studies.

Preparation of Propranolol HCl Loaded Eudragit RL 100 Microspheres: The propranolol HCl loaded Eudragit RL100 microspheres were prepared by the emulsion solvent evaporation method [14]. In this procedure, required amount of propranolol HCl and Eudragit RL100 dissolved in ethanol, was emulsified using light liquid paraffin (80 mL) containing the emulsifier, Span 80 (2% v/v). The system was stirred continuously using a propeller stirrer at 2000 rpm and 38 ± 0.5°c for 5 hrs to allow the complete evaporation of the solvent. Petroleum ether (40-60°c), 100 ml, was then added dropwise to the liquid paraffin to harden the microspheres. The paraffin was decanted off. The microspheres were washed repeatedly 4 times with petroleum ether (10 mL), collected by filtration and finally dried in a hot air oven at 40°c for 1 h. The propranolol HCl loaded Eudragit RL100 microspheres were prepared using varying polymer concentrations (1, 2 and 3% w/v) in the dispersed medium (ethanol, 20 ml) and varying drug to polymer ratios (i.e., 1:1, 1:2, 1:3 and 1:4) given in table 1.

Table 1: Formulation Parameters of Propranolol HCl Loaded Eudragit RL 100 Microspheres

Formulation Code	Polymer Concentration (% w/v)	Drug: Polymer Ratio
F_1	1	1:1
F_2	2	1:1
F_3	3	1:1
F_4	3	1:2
F_5	3	1:3
F_6	3	1:4

Evaluation of Propranolol HCl Loaded Eudragit RL 100 Microspheres

Morphology of Microspheres: The external and internal morphology of microspheres were studied by scanning electron microscope (SEM). The microspheres were coated with gold palladium under an argon atmosphere using a gold sputter module in a high vacuum evaporator. The coated samples were then observed with a scanning electron microscope.

Micromeritic Properties of Microspheres: Average particle size of pure drug and prepared microspheres was determined by optical microscopic method. Flowability of pure drug and microspheres was determined by angle of repose, % compressibility index and hausner ratio. The samples were subjected to bulk density determination using tap density tester (HICON, India) [15].

Determination of Drug Content and Entrapment Efficiency: 100 mg of microspheres were crushed in glass mortar and triplicate samples of 10 mg of the crushed microspheres were dissolved in 10 ml of distilled water, vortexed for 5 min and filtered through whatman filter paper. The filtered samples were suitably diluted with

distilled water, the drug content was assayed by UV spectrophotometer at 216 nm. Percentage entrapment efficiency was also calculated according to the relationship:

$$\% \text{ Entrapment efficiency} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

***In vitro* Drug Release Study:** *In vitro* drug release studies were carried out for pure drug and prepared microspheres by using USP dissolution rate test apparatus 1 (basket type, rotating speed 100 rpm at 37±0.5°c). An accurately weighed amount of pure drug (40 mg) and microspheres equivalent to 40 mg of drug were filled in to hard gelatin capsules and placed in basket separately. The dissolution medium was 0.1 N HCl as simulated gastric fluid (SGF) (900 ml, pH 1.2) for the first 2 hrs, followed by phosphate buffer as simulated intestinal fluid (SIF) (900 ml, pH 7.4) for the rest of 6 hrs. 5 ml samples were withdrawn at specified time intervals (0, 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 h) and equal volume of fresh medium was replaced immediately. After a suitable dilution, samples were analyzed by UVspectrophotometry. All the studies were carried out in triplicate.

Kinetic of Drug Release: To find out the mechanism of drug release from microspheres, the dissolution data of each batch was fitted to various kinetic equation, namely Zero order, First order, Higuchi square root of time and Peppas-korsmeyer [16, 17]. The following plots were made: Qt Vs time (zero order kinetic model), log (Q_0 - Qt) Vs time (First order kinetic model), Qt Vs square root of time (Higuchi model), log Qt Vs log time (Peppas-korsmeyer). Where Qt is the amount of drug released at time t and Q_0 is the initial amount of drug present in microspheres. The correlation coefficient were calculated and used to find the fitness of the data.

RESULTS AND DISCUSSION

The propranolol HCl loaded Eudragit RL100 microspheres were successfully prepared by using emulsion solvent evaporation method [14]. The microspheres were satisfactory considering their size and shape. The scanning electron microscopy (SEM) analysis was shown that the microspheres formulations were appeared to be spherical and the rough surface, as well as presence of little porous and fissures were found. Further, Few drug crystals appeared on the surface of the microspheres were also observed as shown in figure 1. This may be attributed to high drug concentrations and slow solvent removal as the drug formed a particulate (crystal) dispersion resulting. The tapped density and percentage compressibility value of pure drug were found that 0.73 g/cm^3 and 49.31 % respectively which indicating that pure drug exhibited extremely poor flow properties. The tapped density value of all microspheres formulations ranged between 0.79 g/cm3 to 0.96 g/cm3. These results are further authenticated by the value of percentage compressibility index, which was found in the range of 11.45 % to 17.72 %, suggesting excellent flow properties of all microspheres formulations. Furthermore, the value of angle of repose of all microsphere formulations was found within the range of 20° to 30° which authenticate the above statement. Hausner's ratio is another mean of defining the flow properties. The numerical values of pure drug was found to be 1.98 which was greater than 1.6, this indicates that pure drug having more cohesive and less

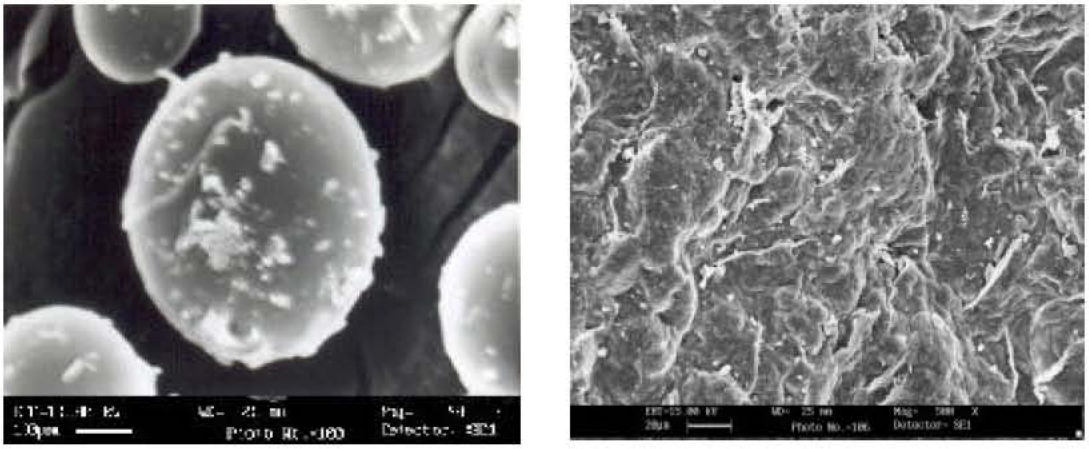

Fig. 1: SEM photographs of Propranolol HCl loaded Eudragit RL 100 Microspheres: (a): at 90 X Magnification (b): at 500 X magnification

Table 2: Comparative micromeritic studies of pure drug and Propranolol HCl loaded Eudragit RL 100 Microspheres

Parameters	Pure Drug	F_1	F_2	F_3	F_4	F_5	F_6
Poured density (g/cm^3)	0.37	0.65	0.71	0.74	0.77	0.81	0.85
Tapped density (g/cm^3)	0.73	0.79	0.84	0.86	0.89	0.93	0.96
Compressibility Index (%)	49.31	17.72	15.47	13.95	13.48	12.90	11.45
Hausner ratio	1.98	1.21	1.18	1.16	1.15	1.14	1.12
Angle of repose (degree)	78°	25°	23°	24°	22°	20°	18°
Average particle size (µm) ± SD	11.31 ± 3.25	34.46 ± 6.45	68.26 ± 8.34	65.82 ± 7.50	67.45 ± 8.48	69.98 ± 5.95	72.26 ± 9.65

Table 3: Comparative drug content and percentage entrapment efficiency of Propranolol HCl loaded Eudragit RL 100 Microspheres

Formulation Code	Theoretical Drug Content (%)	Practical Drug Content (%)(M±SD)	Entrapment Efficiency (%) (M±SD)
F_1	50	32.24 ± 0.80	64.48 ± 0.96
F_2	50	36.38 ± 0.56	72.76 ± 0.42
F_3	50	38.94 ± 0.20	77.88 ± 0.26
F_4	33.3	25.64 ± 0.72	76.99 ± 0.70
F_5	25	19.26 ± 0.48	77.04 ± 0.56
F_6	20	15.48 ± 0.62	77.40 ± 0.96

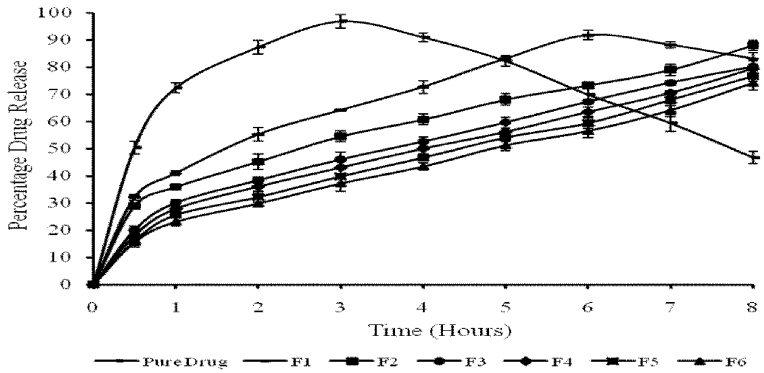

Fig. 2: Comparative percentage drug release profile of pure drug and Propranolol HCl loaded Eudragit RL 100 Microspheres

free flowing powder, whereas, mostly microspheres formulations were clearly representing the Hausner's ratio less than 1.2 (Table 2), this indicates that microspheres exhibited low interparticle friction such as: spheres and good flow property [15, 18]. The average particle size of pure drug was found be 11.31 ± 3.25 µm whereas average particle size of prepared microspheres formulations were ranged between 34.46 ± 6.45 to 72.26 ± 9.65 µm as shown as table 2. This result indicate that the particle size of the microspheres increased from 34.46 ± 6.45 µm (F_1) to 72.26 ± 9.65 µm (F_6) with increasing polymer concentration and drug-polymer ratio. These results occur due to higher concentration of polymer produced a more viscous dispersion which formed larger microspheres as reported by Pongpaibul *et al.* [19].

The practical drug content and percentage entrapment efficiency of drug loaded microsphere were also estimated and results shown in table 3. F_3 microspheres exhibited highest practical drug loading and % entrapment efficiency value of 38.94 ± 0.20 % and 77.88 ± 0.26 % respectively. As seen in table 3, the drug loading and % entrapment efficiency was also influenced by the concentration of polymer in organic solvent used: an increase in the concentration of polymer in the organic solvent from 1.0 % w/v to 3.0 % w/v led to an increase in the drug loading and % entrapment efficiency of the microspheres. The results indicate that the highest practical drug loading and % entrapment efficiency value of 38.94 ± 0.20 % and 77.88 ± 0.26 % respectively was observed when the polymer concentration was 3% at a drug: polymer ratio of 1:1. Variation in drug polymer ratio are also studied, practical drug loading decreases as the polymer ratio increases, but no significant change in entrapment efficiency were observed.

In vitro drug release studies for pure drug and prepared microspheres were carried out by using buffer change method to mimic the GIT environment conditions.

Table 4: Different drug release models as applied to percentage drug release profile of microspheres formulations

Formulations Code	Zero order model (r^2)	First order model (r^2)	Higuchi model (r^2)	Peppas model (r^2)
F_1	0.8966	0.9621	0.9347	0.9748
F_2	0.8995	0.9638	0.9935	0.9925
F_3	0.9616	0.9640	0.9805	0.9869
F_4	0.9536	0.9481	0.9733	0.9839
F_5	0.9584	0.9778	0.9837	0.9892
F_6	0.9582	0.9866	0.9872	0.9919

The dissolution medium was used as 0.1 N HCl as simulated gastric fluid (SGF) (900 ml, pH 1.2) for the first 2 h, followed by phosphate buffer as simulated intestinal fluid (SIF) (900 ml, pH 7.4) for the rest of 6 hrs. It is seen in figure 2, the pure drug was completely dissolved (96.86 ± 2.52 %) within 3 hrs, while that the maximum drug release from propranolol loaded Eudragit RL 100 Microspheres (F_1) was about 91.76 ± 1.79 % within 6 h, but could not sustain the release up to 8 h. This study clearly show that drug release (for microspheres prepared at a drug polymer ratio of 1:1) decreased with increase in the polymer concentration as follows: 1 (F_1), 2 (F_2) and 3 (F_3) % polymer concentrations showed 91.76 ± 1.79 %, 88.03 ± 1.87 % and 80.08 ± 2.34 % drug release, respectively. At other drug: polymer ratios i.e., 1:2 (F_4), 1:3 (F_5) and 1:4 (F_6) there was only a small retardation of drug release from the microspheres ranging from 79.43 ± 1.78 % to 74.13 ± 2.47 %. The microspheres prepared at a polymer concentration 3% showed considerable sustained release characteristics, especially microspheres prepared at a 1:3 drug: polymer ratio which released 74.13 ± 2.47 % of drug over a period of 8 h and showed better sustained release characteristics when compared with other microsphere types (Figure 2). This may be attributed to the higher polymer content which resulted in a larger particle size and a tightened polymer network and thus retarding drug release. From the table 4, it was observed that the highest correlation coefficient (r^2) found for higuchi square root of time profile, which indicates the drug release from the microspheres formulations, occurred via diffusion mechanism [20, 21]. Furthermore, plot of log percentage drug release against log time (peppas model) revealed a high correlation coefficient, which conform that drug release from microspheres, was diffusion controlled.

CONCLUSION

The propranolol HCl loaded Eudragit RL 100 Microspheres prepared at 3% polymer concentration showed a certain level of sustained release characteristics, especially microspheres prepared with 1:3 drug to polymer ratio which released 74.13 ± 2.47 % of drug over 8 h. From the foregoing investigations it was concluded that the propranolol HCl loaded Eudragit RL 100 microspheres under optimized conditions showed some degree sustained release and were stable under the conditions studied. The release kinetics followed the Higuchi model. Furthermore, since these microspheres posses excellent flow properties, In future, they can be readily formulated into suitable oral dosage forms such as tablets, capsules.

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