RESEARCH ARTICLE

Formulation and evaluation of intragastric floating drug delivery system of diltiazem hydrochloride

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The present study is aimed towards formulation and evaluation of floating multiparticulate oral drug delivery system of diltiazem hydrochloride, which can provide sustained release. The work also aims to study various parameters affecting the behavior of floating multiparticulate in oral dosage form. Floating microspheres were prepared by non-aqueous emulsification solvent evaporation technique, using ethyl cellulose and Eudragit RS-100 as the rate controlling polymer. The *in vitro* performance was evaluated by the usual pharmacopoeial and other tests such as drug-polymer compatibility, (%) yield, particle size analysis, drug entrapment efficiency, surface topography, *in vitro* floatability and release studies. Results show that the mixing ratio of components in the organic phase affected the size, size distribution (199-320 μm), drug content (59-84%), %yield (57-77%) and drug release of microsphere (45-99% after 12 h) and floating time >12 h. The best results were obtained at the ratio of drug: polymer Eudragit RS-100 (1:3). In most cases, good *in vitro* floating behavior was observed and broad variety of drug release pattern could be achieved by variation of the polymer ratio, which was optimized to match target release profile. Stability studies showed no significant change in the drug content in the formulation even after 3 months. The data obtained in this study thus suggest that a micro particulate floating dosage form of diltiazem hydrochloride can be successfully designed to give controlled delivery and improved oral bioavailability.

Key words: *Floating drug delivery system, diltiazem hydrochloride, in vitro drug release, microsphere*

INTRODUCTION

For oral solid delivery systems, drug absorption is unsatisfactory and highly variable between individuals despite excellent *in vitro* release patterns. The major problem is the physiological variability such as gastrointestinal (GI) transits in addition to gastric retention time, as the latter plays a dominating role in the overall transit of the dosage form. Even though the slow release can be achieved in the oral controlled release system, the drug released after passing the absorption site is less than 12 h. Therefore, it is not possible to deliver the drug for more than 12 h through the oral route. This has prompted researchers to retain the drug delivery system in the stomach for prolonged and predictable time. Such a prolonged gastric retention not only controls the time but also the space in the stomach by maintaining the delivery system positioned at a steady site and there by properly delivering the drug. Floating drug delivery system are basically prepared to increase the gastric retention time, which in turn enhance the bioavailability of drugs, which are highly absorbed in the stomach and poorly absorbed in lower part of GI tract.[1-3]

Diltiazem hydrochloride is calcium channel blocker used as anti-hypertensive, anti-anginal, etc. It has poor bioavailability (30-50%) and has absorption window in upper part of the GI tract, therefore, it was proposed to develop a gastro retentive drug delivery system to enhance the absorption of the drug intended to increase the bioavailability of the drug.[4,5]

MATERIALS AND METHODS

Materials

Diltiazem hydrochloride was obtained as a gift sample from Modi-Mundipharma, (Modipuram). Ethyl cellulose was procured from S. D. Fine Chem Labs. (Mumbai) and Eudragit RS-100 were obtained as gift samples from Deggusa India Ltd. (Mumbai). All the chemicals used in the study were of analytical grade.

Methods

Preparation of floating microspheres:[6-8]

The microspheres were prepared by non-aqueous emulsification solvent evaporation method. Briefly,

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Table 1: Drug and polymer combination in solvent mixture of acetone and isopropyl alcohol

Batches → Ingredients ↓	A1	A2	A3	A4	B1	B2	B3	B4
Ethyl cellulose (mg)	500	1000	1500	2000	--	--	--	--
Eudragit RS 100 (mg)	--	--	--	--	500	1000	1500	2000
Diltiazem HCL (mg)	500	500	500	500	500	500	500	500

Table 2: Micromeritic study

Parameters → Batches ↓	Average particle size (μm)	Tapped density (g/cm³)	Bulk density (g/cm³)	% compressibility index	Hausner's ratio	Angle of repose (θ)
A1	240.2 ± 16.3	0.814	0.783	15.2	1.03	41°29'
A2	248.0 ± 11.7	0.802	0.771	12.5	1.04	39°16'
A3	280.0 ± 9.6	0.794	0.770	13.1	1.03	39°21
A4	319.5 ±12.9	0.788	0.746	15.8	1.05	32°78'
B1	199.7 ± 15.9	0.834	0.818	10.2	1.01	45°12'
B2	208.0 ± 19.8	0.832	0.817	9.6	1.01	41°41'
B3	219.0 ± 13.7	0.802	0.795	12.6	1.01	40°18'
B4	232.0 ± 3.6	0.798	0.788	13.7	1.01	36°49'

Table 3: Percentage yield and percent buoyancy

Batch no.	Percentage yield	Percentage buoyancy	% drug entrapment
A1	70.86	52.12	62.26
A2	69.56	48.34	72.87
A3	64.45	39.56	74.56
A4	66.45	41.65	75.26
B1	74.42	57.20	60.43
B2	63.65	61.48	77.03
B3	76.29	72.05	84.93
B4	57.17	62.18	59.07

drug and polymer i.e., diltiazem HCl and Eudragit RS 100, ethyl cellulose were mixed in acetone at various ratio by using blending solvent i.e., isopropyl alcohol. The slurry was introduced in to 200 ml of liquid paraffin while being stirred at 1200 rpm by mechanical stirrer for 2 h to allow the solvent to evaporate completely and the microsphers were collected by filtration. The microspheres were washed repeatedly with petroleum ether 40-60°C until free from oil. The collected microspheres were dried for 1 h at room temperature and subsequently stored in desiccator [Table 1].

Evaluation of floating microspheres

Micromeritics studies of floating microspheres:[9]

The microspheres are characterized by their micromeritic properties, such as particle size, tapped density, Carr's compressibility index, and flow property.

Percentage yield (i.e., recovery) of microspheres formed:[10]

The measured weight of prepared microspheres was divided by the total amount of all the non-volatile components used for the preparation of the microspheres, which give the total percentage yield of floating microspheres.

Study of floatation behavior (or buoyancy) of microspheres:[11]

The floatation studies were carried out to ascertain the floating behavior of various polymer combinations. Beaker method was initially used to have an idea of the floatation behavior of the proposed dosage form.[12] 50 mg of floating microparticles were placed in each of four 50 ml beakers containing 20 ml of 0.1N HCl containing 0.02% Tween 80. The beakers were shaken in a biological shaker at 37°C ± 0.5°C at 40 rpm. Floating microspheres were collected at 3, 6, 9, and 12 h and dried till constant weight. The percentage of floating microspheres was calculated by the following equation:

$$\% \text{ Floating microsphere} = \frac{\text{Weight of floating microspheres after time } t}{\text{Initial weight of floating microspheres}} \times 100$$

% Drug entrapment determination:[13]

Accurately wt 50 mg of floating microspheres were mechanically busted. These powders were dissolved in 50 ml 0.1N HCl and filtered through filter paper. Then 5 ml of this solution was diluted to 50 ml and the absorbance was noted at 203.2 nm against 0.1 N HCl as a blank. The percentage drug retained was calculated by the formula:

$$\% \text{ Drug entrapment} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

Dissolution test (*in-vitro* drug release) of microspheres:[14,15]

Dissolution test was performed by using six-station USP XXVII type I (Electrolab Tablet dissolution tester USP, TDT-06P). The dissolution medium used was 900 ml of 0.1 N HCl (pH 1.2) for diltiazem HCl was filled in a dissolution vessel and the temperature of the medium was set at 37±0.5°C and rotational speed of paddle was set at 100 rpm. The 5 ml of sample was withdrawn at predetermined time interval for 12 h and same volume of fresh medium was replaced. The withdrawn sample was diluted and analyzed by UV-spectrophotometer (Shimadzu UV-1700) at the respective λ_{max} values for diltiazem HCl (203.2 nm). The content of drug was calculated using the equation generated from standard curve.

Morphological study using scanning electron microscopy:
Scanning Electron Microscopy (SEM): The surface topography of the uncoated and coated (optimized) microsphere and cross section of optimized microsphere were examined under a FEI-Philips XL-30 Analytical Electron microscope (IICT, Hyderabad). The sample was loaded on copper sample holder and sputter coated with carbon followed by gold.

Drug polymer interaction:
Drug-polymers interaction was studied by taking FTIR (Shimadzu, Japan.Model-8400S).

Stability studies:
Stability studies were carried out at 40±2°C and 75±5% relative humidity for 90 days.

RESULTS AND DISCUSSION

The various batches have the average particle size in the range of 200 μm to 350 μm. Where as Carr's index in between 9 and 16% and Hausner's ratio with in 0.5 and angle of repose was found within the range of 30° to 45°, which is a appreciable limit for microspheres to show flow property while formulating in the dosage form [Table 2].

The maximum percentage yield was found in B3 batch and was noted to be 76.29% among all the batches. It was found that average percentage yield was greater than 55% for all [Table 3].

Buoyancy of Batch B3 microspheres was found to be 72.05%, which indicates that most of the microspheres were still floatable after 12 h because of their low density and internal voids [Table 3].

The microspheres of batch B3 formulation showed an entrapment of 84.93% while formulation A1, B1, and B4 showed lesser entrapment than the optimized formulation. This can be attributed to the permeation characteristics of each polymer used that could facilitate the diffusion of a part of entrapped drug to the surrounding medium during preparation of floating microspheres [Table 3].

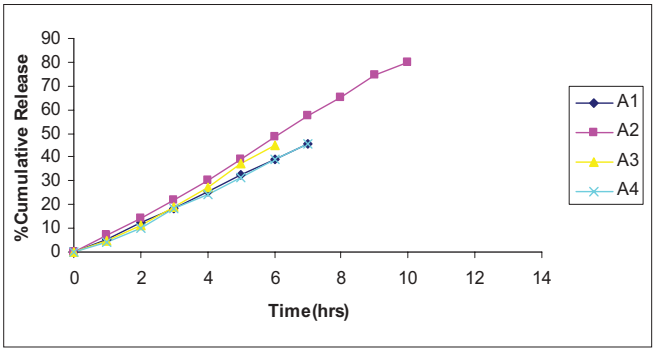

Figure 1: *In-vitro* drug release of batches A1-A4

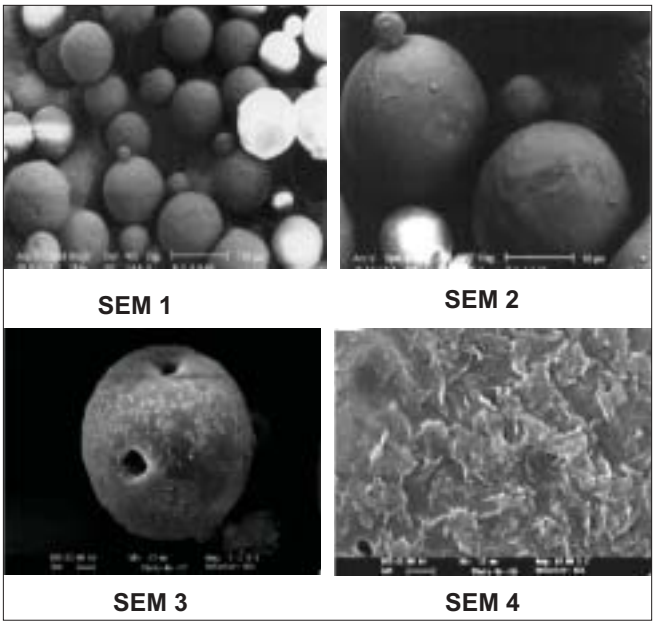

Figure 3: SEM photomicrographs of floating microspheres
SEM 1 shows size range of floating microspheres. SEM 2 shows smooth texture of floating microspheres. SEM 3 shows dents on the surface. SEM 4 shows surface morphology of floating microspheres.

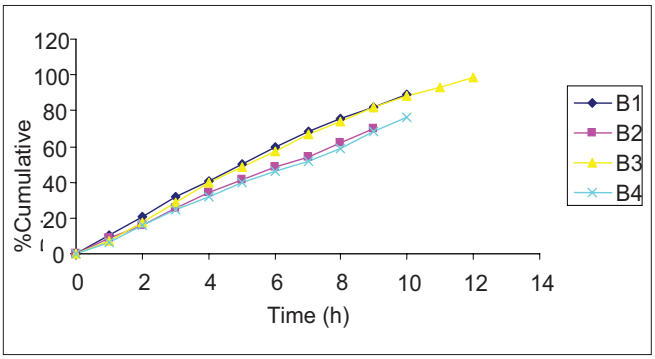

Figure 2: *In-vitro* drug release of batches B1-B4

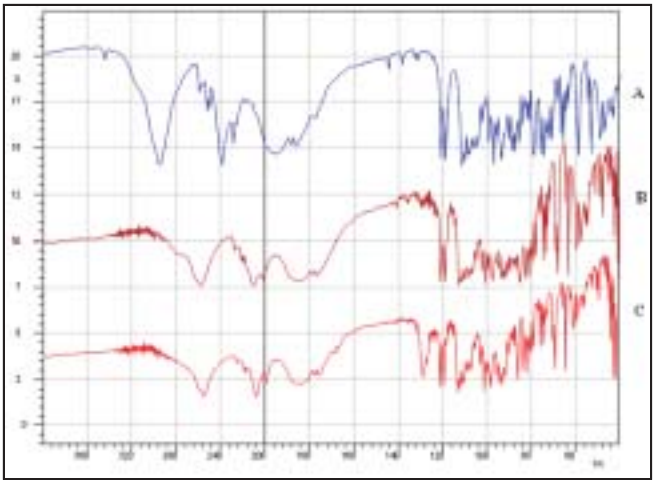

Figure 4: IR interpretation of drug and polymers A: IR spectra of diltiazem HCL, B: IR spectra of diltiazem HCL and Eudragit RS 100 physical mixture, C: IR spectra of diltiazem HCL and ethyl cellulose physical mixture

Release of the drug from floating microspheres was evaluated at pH 1.2 using diltiazem HCl as model drug. The drug release rate of diltiazem HCl was almost linear with time for the first 10 h and gradually decreased afterwards [Figures 1 and 2].

Different kinetics was applied to interpret the release rate of diltiazem HCl from the sustained release floating microspheres of formulations. From the coefficient determination ($R^2 = 0.9573$), it shows that the release of Batch B3 is best fit to Korsmeyer model.

The surface topography revealed a spherical surface for all the formulations and a round cavity enclosed by an outer shell composed of the drug and polymer. They appeared to be hollow presumably because of the rapid escape of volatile solvent from the polymer matrix. This hollow nature was also responsible for the microspheres floating capability in simulated gastric fluids [Figure 3]. Infrared interpretation showed that there was no interaction between drug and polymers [Figure 4]. The stability study showed that drug degradation was less than 5%, means the formulation was stable one and exhibit minimal degradation for period of 3 months.

CONCLUSION

Micromeritics study shows good results for floating microspheres. Floating microspheres of B3 batch was found to be satisfactory in terms of drug release, floatability, and drug entrapment and could be used as an alternative to conventional dosage forms. A maximum *in vitro* drug release of 98.89% in 12 h for floating microspheres of B3 batch was obtained. Floatation was achieved for the entire study period.

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