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RESEARCH ARTICLE

PREPARATION AND CHARACTERIZATION OF INTRAGASTRIC GASTRORETENTIVE DRUG DELIVERY SYSTEM OF DILTIAZEM HYDROCHLORIDE

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ABSTRACT

The present study is aimed towards preparation and characterization of gastroretentive floating multiparticulate oral drug delivery system of diltiazem hydrochloride, which can provide sustained release delivery of the drug. These gastroretentive floating microspheres release the drug in the stomach and upper gastrointestinal tract and thereby improve the bioavailability. In the present study, six formulations of diltiazem hydrochloride were prepared as gastroretentive floating microspheres by solvent diffusion technique using polymers such as ethyl cellulose, polyvinyl pyrrolidone K-90 and poly vinyl alcohol in different ratios. The prepared floating microspheres were evaluated for different physicochemical tests such as particle size, percent drug entrapment, drug content uniformity, SEM, buoyancy test, and *in vitro* drug release studies. The results of all the physicochemical tests of all formulations were found to be satisfactory. *In vitro* floatability studies revealed that most of the microspheres (53.21% to 96.12%) were floatable. The *in vitro* drug release was found to be in the range of 40.36 to 94.11 % at the end of 6 hours. It is concluded that these floating microspheres can be selected for the development of gastroretentive drug delivery system of diltiazem hydrochloride for potential therapeutic uses.

Keywords: Gastroretentive microspheres, diltiazem hydrochloride**,** ethyl cellulose, polyvinyl pyrrolidone K-90, poly vinyl alcohol.

INTRODUCTION

Oral drug delivery is the most used and preferred route of administration with the obvious advantage of ease of administration and patient acceptance. To develop a drug delivery system for oral administration, it is necessary to optimize not only the release rate of an active ingredient from the system but also the residence time of the system in the gastrointestinal tract [1]. Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in upper gastrointestinal (GI) tract.

A gastroretentive dosage form (GRDF) releases medications in a controlled manner for extending the absorption phase of drugs which show a limited and narrow absorption window at the upper part of the gastrointestinal tract or drugs intended to treat local ailments in the gastroduodenum. This mode of administration may prolong the time period in which the blood drug concentrations are within the "therapeutic levels" and improve

therapy. Besides being locally active in the stomach, these extended-release dosage forms with prolonged residence time in the stomach are also highly desirable for drugs that are unstable in the intestinal or colonic environment, and/or have low solubility at higher pH values [2]. Therefore, development of GRDFs has been a major pharmaceutical challenge during the past few decades.

The gastroretentive dosage forms (GRDFs) has been designed in large part based on the following approaches [3]: (a) low density form of the DF that causes buoyancy above gastric fluid; (b) high density DF that is retained in the bottom of the stomach; (c) bioadhesion to the stomach mucosa; (d) slowed motility of the gastrointestinal tract by concomitant administration of drugs or pharmaceutical excipients; (e) expansion by swelling or unfolding to a large size which limits emptying of the DF through the pyloric sphincter.

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluid and therefore remain floating in the stomach without affecting gastric emptying rate for prolonged period. The drug is slowly released at the desired rate from the floating system. After release of drug, the residual system is expelled from the stomach. These floating dosage forms may have a number of advantages in oral drug delivery because they prolong retention in the gastrointestinal tract, particularly in the stomach. Gastroretentive delivery system facilitates sustained drug release and maintains high concentrations of drug within the gastric mucosa. This property may also be performed for treatment of *Helicobacter pylori* infection. [4].

Floating delivery systems administered in a single-unit form [such as hydrodynamically balanced system (HBS)] are unreliable in prolonging the GRT owing to their 'all-or- nothing' emptying process and, thus, they may cause high variability in bioavailability and local irritation due to large amount of drug delivered at a particular site of the gastrointestinal tract (GIT). In contrast, multiple unit dosage forms (e.g. microspheres) enjoy the advantage since they pass uniformly through the GIT to avoid the vagaries of gastric emptying and provide an adjustable release, thereby, reducing the intersubject variability in absorption and risk of local irritation [5].

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 gastroretentive floating drug delivery system to enhance the absorption of the drug intended to increase the bioavailability of the drug.

MATERIALS AND METHODS

Materials

Diltiazem hydrochloride was obtained as a gift sample from Ranbaxy Laboratory Ltd. Dewas. Ethyl cellulose (EC), polyvinyl pyrrolidone K-90 (PVP K-90) and poly vinyl alcohol (PVA) were procured from Central Drug House, Mumbai. Other chemicals used were of analytical grade.

Methods

Floating microspheres containing diltiazem hydrochloride were prepared by an emulsification solvent evaporation technique [6] using EC, PVP K-90 and

PVA polymers (Table 1). Diltiazem hydrochloride (500 mg) and polymer (500 mg) were weighed accurately and dissolved in 8 ml ethanol, followed by the addition of 2 ml isopropanol and 5 ml dichloromethane. The polymer solution was slowly introduced into 100 ml of 1% poly (vinyl alcohol) aqueous solution while stirring at 250 rpm using a mechanical stirrer equipped with a 3 blade propeller. The solution was stirred for 10 min and the microspheres were collected by filtration. The floating microspheres were collected by decantation, while the non-floating microspheres were discarded along with any polymer precipitates. The microspheres were dried in an oven at 50^0C for 2h, weighed and then stored in a desiccator at room temperature till further use.

Table 1. Composition of floating microspheres of diltiazem hydrochloride

Ingredient	D1	D2	D3	D4	D5	D6
Drug	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
Ethyl cellulose (EC)	0.5%	1.0%	1.5%	0.5%	1.0%	1.0%
Poly vinyl pyrrolidone (PVP)	--	--	--	1.0%	0.5%	1.5%
Poly vinyl alcohol (PVA)	1.0%	1.0%	1.0%	1.0%	1.0%	1.0%

EVALUATION OF FLOATING MICROSPHERES

Scanning electron microscopy

To detect the surface morphology of the microspheres, SEM of the floating microspheres was performed at IIT, Delhi by Scanning electron Microscope (Jeol of Japan Model No. 5600).

True Density

The microspheres were immersed in 0.02% tween 80 solutions for three days in a metal mesh basket. The submerged microspheres were used for density measurements. True density of floating microspheres was determined by liquid displacement method using relative density bottle.

Particle size

Particle Size of floating microspheres was performed with the help of optical microscope for randomly selected samples of all the formulation [7].

Percent Drug Loading

Diltiazem hydrochloride content in the microspheres was estimated by a UV Spectrophotometric (Shimadzu 1800, Japan) method based on the measurement of absorbance in distilled water [8]. Microspheres equivalent to 100 mg were weighed and added in 100 ml of distilled water. The volumetric flask was stirred continuously for 24 hour on a magnetic stirrer. At the end of 24 hour sample was withdrawn, diluted suitable and measured spectrophotometrically for the drug content. Quantitative estimation of diltiazem hydrochloride was calculated by using equation obtained by linear regression analysis of the calibration curve of the drug in distilled water. The

drug loading in microspheres was estimated using the formula:

Percent Drug Loading (L) = (Qm/Wm) × 100

Where, Wm is the weight of microspheres and the Qm is the quantity of drug present in Wm of microspheres (Semalty and Semalty, 2008). Percent Drug Loading of various formulations is shown in Table 2.

***In vitro* floatability studies**

In vitro floatability studies on floating microspheres were carried out using USP apparatus II. To assess the floating properties, the microspheres were placed in 0.1 N hydrochloric acid containing 0.02 % v/v Tween 80 surfactant to gastric conditions. Tween (0.02% v/v) was used to impart wetting effect of the natural surfactants such as phospholipids in the GIT. The buoyancy was calculated by:

Buoyancy (%) = Wf / (Wf + Ws) 100

Where, Wf and Ws are weights of the floating and the settled microspheres, respectively (Kale et al., 2001).

***In vitro* drug release study**

The release study was carried out in a USP 24 dissolution apparatus type 1 (six-station dissolution apparatus, Veego 6DR, India), slightly modified in order to overcome the small volume of the dissolution medium. The dissolution medium was 100 mL IPB, pH 1.2 maintained at 37±0.5^{0}C and kept in a glass beaker fixed inside the USP dissolution flask. Microspheres equivalents to 100 mg of diltiazem were filled in empty capsule shells. One capsule was used in each test and placed in the basket, which was rotated at 50 rpm. Filtered samples (5 mL) were manually collected at different intervals. The samples were compensated with an equal volume. The concentration of drug released in the medium was assayed spectrophotometrically after suitable dilution with the dissolution medium when necessary. The experiment was carried out in triplicate.

RESULTS AND DISCUSSION

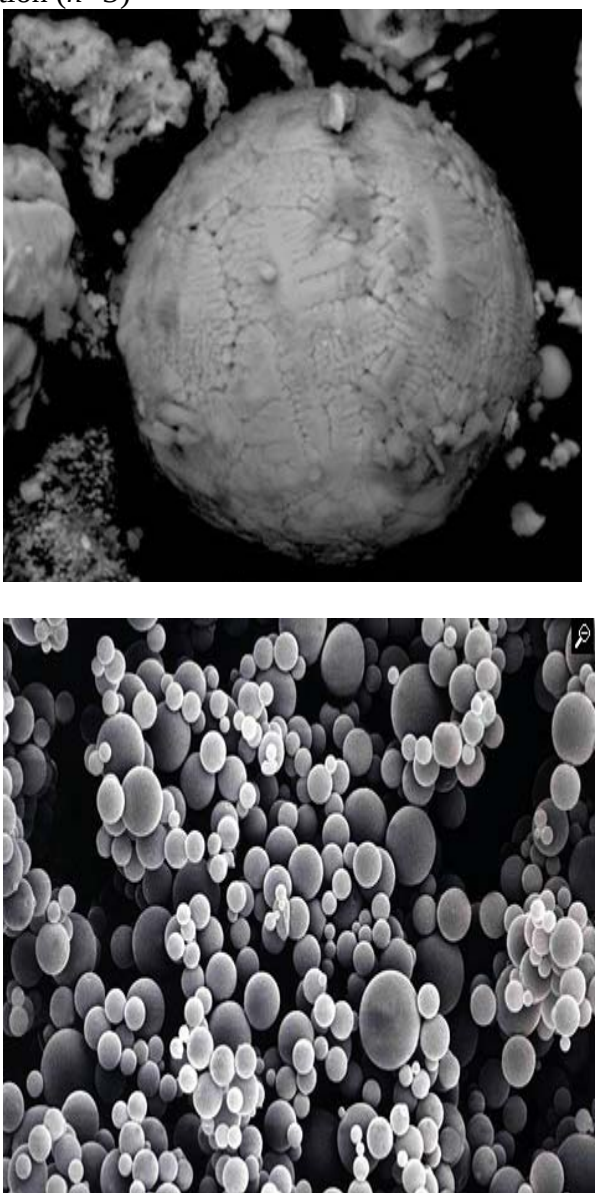
The floating microspheres of diltiazem hydrochloride were prepared by Emulsion solvent evaporation method using Ethyl cellulose, Poly vinyl pyrrolidone, and Poly (vinyl alcohol). The prepared floating microspheres were evaluated for different physicochemical tests such as particle size, true density, flow properties, drug content, *in vitro* floatability and *in vitro* drug release studies.

Scanning Electron Microscopy showed that D1, D2, D4, D5, D6 formulation produced spherical microspheres compared to D3 (Fig. 1). The scanning electron microscopy confirmed the hollow nature of microspheres with pores on the surface of floating microspheres, which imparted floating properties to the prepared floating microspheres.

Table 2. Physical evaluation of floating microspheres of diltiazem hydrochloride

Formulation code	Average particle size (µm)	True Density	Percent Buoyancy	Percent drug loading	Drug release after 6 hours
D1	342.48±2.801	0.791±0.004	96.12±1.53	87.32±1.52	71.54±1.65
D2	369.32±4.101	0.781±0.003	92.32±1.87	52.58±2.78	94.11±3.22
D3	392.64±4.234	0.808±0.012	93.21±1.12	54.73±2.99	80.13±1.97
D4	253.76±0.451	0.814±0.021	60.32±1.63	94.65±2.87	68.23±1.33
D5	256.22±2.134	0.778±0.008	53.21±1.65	40.64±3.74	40.36±1.11
D6	282.34±2.732	0.807±0.002	62.32±2.75	76.60±3.89	59.45±1.22

*Results are presented as mean ± standard deviation (*n=3*)



(a) **(b)**

Fig. 1 SEM photograph of floating microspheres of formulation F1 (a) at 50 X (b) at 100 X

To assess flow properties of prepared floating microspheres micromeritic properties like particle size and true density were determined (Table 2).The densities of floating microspheres were found to be less than the density of gastric fluid, therefore tended to float over gastric fluid [9]. So the prepared microspheres combine the advantages of multiple unit systems and good floating properties. However, like all floating systems, their efficacy is dependent on the presence of enough liquid in the stomach, requiring frequent drinking of water [10]. Particle size analysis of different formulation was done by

optical microscopy. The average particle size for ethyl cellulose microspheres was in the range between 342.48 µm and 392.64 µm, while the average particle size for ethyl cellulose and Poly vinyl pyrrolidone microspheres was in the range between 253.76 µm and 282.34 µm. The average particle size of microspheres was found to be increasing with the increase in concentration of the polymer.

Drug content in D1, D2, D3, D4, D5 and D6 formulation were estimated by UV Spectrophotometric method. Percent loading efficiency were found in the range of 40.64 to 94.65 %. Formulation D4 containing ethyl cellulose (0.5%) and Poly vinyl pyrrolidone (1%) showed maximum percent loading of drug up to 94.65 %. Formulation D3 containing ethyl cellulose (1.5%) showed least percent loading (40.64 %) of drug. The rank order of Percent loading was found to be as followed D4 > D1> D6> D3>D2>D5. *In vitro* floatability studied revealed that most of the microspheres (53.21% to 96.12%) were floatable. Rank order of *in vitro* floatability was found to be as followed: D1> D3> D2> D6> D4> D5.

In vitro drug release studies of all the formulations were performed in pH 1.2 acidic buffer. Significant difference was observed in the release pattern of diltiazem floating microspheres EC, PVP, PVA (Fig. 2). It was found that the drug release from the formulations were distinguishably different for the different polymers used in the formulations. The rank order of drug release after 6hr was found to be 71.54, 94.11, 80.13, 68.23, 40.36 and 59.45 percent of formulation D1, D2, D3, D4, D5 and D6 respectively. Formulation D2 containing ethyl cellulose (1%) showed the maximum release after the 6 hour.

CONCLUSION

The results of all the physicochemical tests of all formulations were found to be satisfactory. *In vitro* floatability studies revealed that most of the microspheres (53.21% to 96.12%) were floatable. The *in vitro* drug release was found to be in the range of 40.36 to 94.11 % at the end of 6 hour. It is concluded that these floating microspheres can be selected for the development of gastroretentive drug delivery system of diltiazem hydrochloride for potential therapeutic uses.

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