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Original Research Article

Floating Microparticulate Oral Diltiazem Hydrochloride Delivery System for Improved Delivery to Heart

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Abstract

Purpose: *To formulate and evaluate floating microparticulate oral diltiazem delivery system for possible delivery to the heart.*
Method: *Floating microspheres were prepared using cellulose acetate and Eudragit RS100 polymers by emulsion solvent evaporation technique. The dried floating microspheres were evaluated for micromeritic properties (flow properties, density, particle size determination) scanning as well as by electron microscopy, and in vitro floatability and drug release studies.*
Results: *The microspheres showed good buoyancy, good flow properties (angle of repose ranging from 24.29 to 29.02 °), particle size (262.09 to 409.60 µm) and good drug loading (74.29 to 92.09 %). The microspheres were porous, hollow and spherical. All the formulations showed good in vitro controlled drug release in the range of 77.62 ± 2.12 to 97.50 ± 1.04 % at the end of 12 h. Drug release was diffusion-controlled and followed zero order kinetics.*
Conclusion: *Microparticulate floating (gastroretentive) oral drug delivery system of diltiazem prepared using cellulose acetate and Eudragit R5100 may be an effective alternative to conventional oral tablets for cardiac drug delivery.*

Keywords: *Cardiac, Microparticulate, Drug release, Gastroretentive, Floating microspheres, Diltiazem hydrochloride*

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INTRODUCTION

Most drugs are given by oral route as this is the most acceptable, convenient and least invasive approach for getting systemic delivery of significant therapeutic levels of drug. Drugs used in the management of cardiac diseases are to be taken for longer periods of time for maintaining blood pressure, heart beat or overall cardiac health. Unlike other routes the oral route is the most preferred route of drug administration. It is also the preferred route to deliver sustained and controlled delivery of drugs [1].

However, there are many constraints in designing oral controlled-release drug delivery systems. These include varying pH changes and gastric emptying time, variation in pH across the regions of the gastrointestinal tract (GIT) and varying absorption windows available for different drugs. Various approaches have been investigated for localizing the drug to the upper part of the GIT. These include development of gastroretentive drug delivery systems through utilizing the approaches based on buoyancy, mucoadhesion, low density, etc [2,3].

An ideal gastroretentive drug delivery system (GRDDS) localizes the drug in the upper segments of the GIT so that the drug gets maximum chance to get absorbed from the site where it is optimally absorbed [4-7].

Diltiazem hydrochloride, an L type calcium channel blocker, is a widely used cardiovascular drug, for the treatment of angina, essential hypertension and atrial flutter. When administered orally, frequent dosing is needed due to its short biological half-life ($t_{1/2}$, 4 h) [11,12]. Diltiazem undergoes high hepatic first pass metabolism, and thus, bioavailability is reduced to only 40 %. Moreover, diltiazem shows absorption window phenomenon because it is preferentially absorbed from the upper GIT.

Therefore the present investigation aimed to formulate and evaluate gastroretentive buoyant microspheres of diltiazem hydrochloride that would localize the delivery system to the upper GIT from where it would be expected to slowly and continuously release the drug in a controlled manner leading to improved bioavailability [13-15].

EXPERIMENTAL

Diltiazem hydrochloride (DTH), Polyvinyl alcohol (PVA), Tween 80 and Cellulose Acetate were procured from Sigma Aldrich USA. All other reagents used were of analytical grade.

Preparation of diltiazem hydrochloride micro particles

Microparticles loaded with DTH were prepared using an oil-in-water (O/W) emulsification solvent evaporation method [16]. Six formulations were prepared using different polymers- Cellulose acetate and Eudragit RS100 (Table 1).

Drug and polymer in different proportions 1:1, 1:2, 1:4, were dissolved in the mixture of solvent system (dichloromethane, ethanol and isopropyl alcohol) or (ethyl acetate and acetone). The solution obtained was poured slowly into the aqueous phase consisting of 150 mL of 0.1 M hydrochloric acid solution containing polyvinyl alcohol. The emulsion was continuously stirred at a speed of 800 rpm using mechanical stirrer at room temperature for 2 h. The 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 ^{o}C for 2 h, weighed and then stored in a desiccator at room temperature till further use.

Scanning electron microscopy

To detect the surface morphology of the microspheres, SEM of the floating microspheres was performed using Scanning Electron Microscope (Jeol of Japan Model No. 5600).

Evaluation of micromeritic properties of floating microspheres

The microspheres were characterized for their micromeritic properties, such as particle size (by optical microscopy), true density (by liquid displacement method) and flow properties (angle of repose) as reported in various previous studies [17-19].

Drug loading

Drug loading (L) was determined by the method reported by Semalty et al as in Eq 1 [17-19].

$$L = (Qm/Wm)100 \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

where Wm is the weight of microspheres and Qm is the quantity of drug present in Wm of microspheres.

Table 1: Composition of the formulations

Ingredient	Formulation*					
	F1	***F2***	***F3***	***F4***	***F5***	***F6***
Diltiazem hydrochloride	1	1	1	1	1	1
Cellulose acetate	1	2	4	-	-	-
Eudragit RS100	-	-	-	1	2	4
Polyvinyl alcohol (% w/v)	0.05	0.05	0.05	0.5	0.5	0.5

**For formulations F1, F2 and F3, the solvent system was ethyl acetate: Acetone (1:1) while for formulations F4, F5 and F6, the solvent system was dichloromethane: ethanol: isopropyl alcohol (1:2:1); ratio are % w/w of polymers; batch size was 15 gm*

In vitro floatability studies

In vitro floatability studies on floating microspheres were carried out using USP apparatus II as reported earlier [17,20]. The buoyancy was calculated as in Eq 2.

Buoyancy (%) = Wf /(Wf + Ws)100 ……..(2)

where Wf and Ws are weights of the floating and the settled microspheres, respectively.

In vitro drug release studies

The release of DTH from the microspheres was studied in 900 ml of 0.1 N hydrochloric acid using USP XXIII method with six station dissolution test apparatus type 1 at 37 ± 0.5 ^{o} with a rotation speed of 100 rpm. For each formulation, a quantity of microspheres equivalent to 100 mg of diltiazem was filled in empty capsule shells (size 00). One capsule was used in each test and placed in the basket. Samples of dissolution fluid were withdrawn at different intervals, filtered and diluted suitably and then analyzed spectrophotometrically (Double beam UV-Visible Spectrophotometer, Shimadzu, 1800, Japan) at 236 nm.

Statistical analysis

The results were expressed as mean ± standard deviation (SD). Statistical analysis was carried out using analysis of variance (ANOVA) on GraphPad Prism© 4.0 (Graphpad Software Inc. San Diego, CA, USA). $P < 0.05$ was considered to be significant.

RESULTS

Microsphere morphology

Scanning electron microscopy showed that the microspheres prepared using cellulose acetate and Eudragit RS100 had smooth spherical microspheres (Fig 1). Cellulose acetate microspheres exhibited a more uniform surface than those of Eudragit RS100 microspheres.

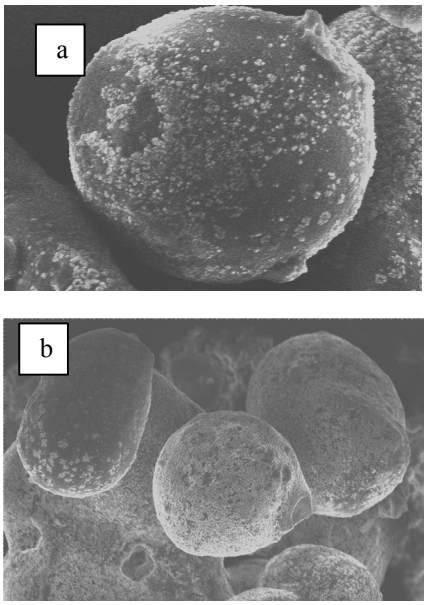

Fig. 1: SEM photographs of floating microspheres of (a) Cellulose Acetate (b) Eudragit RS100

Micromeritic properties

Table 2 reports the results of flow properties of prepared floating microspheres like angle of repose, particle size and true density.

The flow properties for the microparticles were good with angle of repose ranging from 24.29 º to 29.02 º. Density was in the range of 0.729 to 0.820 g/cc3. Particle size was in the range of 262.09 to 409.60 µm. Microspheres prepared with cellulose acetate (F1 - F3) were larger than those prepared with Eudragit R5100 microspheres (F4 - F6).

Drug loading

The formulations showed excellent drug loading ranging from 74.29 to 92.09 % with higher loading found with cellulose acetate containing

Table 2: Characteristics of floating microspheres

Formulation	Mean particle size (µm)	True density (gm/cc^3)	Angle of repose	Buoyancy 12th h (%)	Drug Loading (%)
F1	341.30 ± 1.082	0.780 ± 0.035	24.29º ± 0.846	62.8 ± 0.940	81.42 ± 1.26
F2	391.52 ± 2.136	0.729 ± 0.012	24.98º ± 0.009	79.8 ± 1.252	88.90 ± 1.49
F3	409.60 ± 3.543	0.809 ± 0.020	23.80º ± 0.921	84.4 ± 1.486	92.09 ± 1.45
F4	262.09 ± 0.446	0.820 ± 0.027	26.72º ± 0.072	60.9 ± 1.280	74.29 ± 1.69
F5	274.80 ± 2.227	0.744 ± 0.042	29.02º± 0.508	61.2 ± 2.422	86.34 ± 1.80
F6	282.04 ± 1.294	0.799 ± 0.066	26.05º ± 1.080	68.6 ± 2.005	84.90 ± 1.89

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

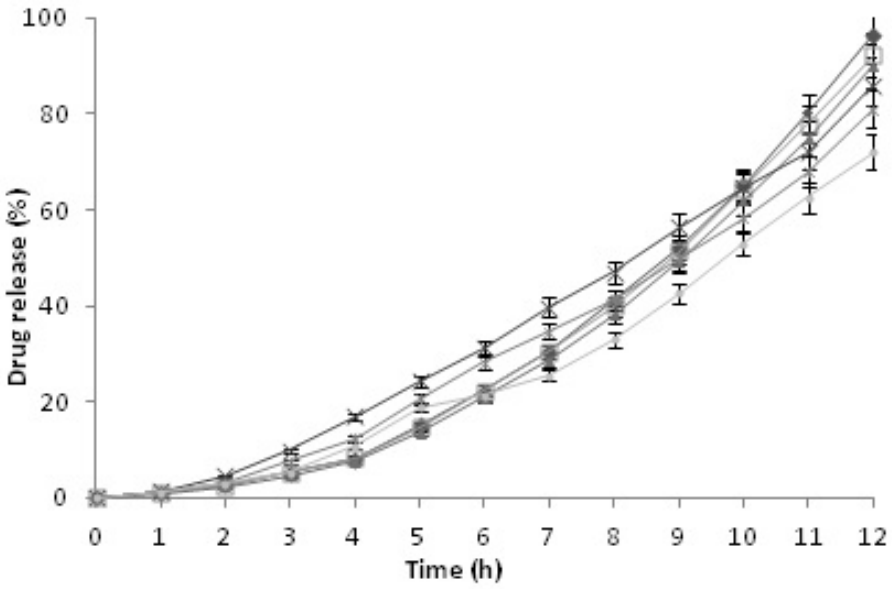

Fig 2: *In vitro* drug release of gastroretentive microspheres of diltiazem hydrochloride in 0.1 M hydrochloric acid (pH 1.2). ***Key:*** (♦) F1, (□) F2, (▲) F3, (×) F4, (*) F5 and (●) F6

microspheres (Table 2). Formulation F3 containing cellulose acetate (with drug to polymer ratio of 1:4) showed maximum percent loading of drug (92.09 %). The rank order of Percent loading was found to be as follows - F3 > F2 > F5 > F6 > F1 > F4.

***In vitro* floatability**

The microspheres showed buoyancy ranging from 60.9 to 84.4 % at the end of 12 h (Table 2). Rank order of *in vitro* floatability was found to be as follows - F3 > F2 > F6 > F1 > F5 > F4.

***In-vitro* release**

In vitro release studies of all the formulations were found to be good for a 12 h dissolution study (Fig 2).

Change in polymer and drug to polymer ratio showed the change in drug release. At the end of 12 h, release was 97.50, 94.44, 91.52 , 88.24, 84.84 and 77.62 % for formulations F1, F2, F3, F4, F5 and F6 respectively (Fig 2). Higuchi correlation coefficient values were 0.979, 0.985, 0.992, 0.912, 0.990 and 0.990, respectively.

DISCUSSION

Gastroretentive floating microparticles have been investigated for improving the drug release of the drugs such as DTH which are well absorbed from upper GIT. Being the drug showing absorption window phenomenon, DTH is the most suitable candidate for developing the floating drug delivery systems. In the present study, gastroretentive floating microparticles of DTH were prepared using a simple and reproducible method.

Scanning electron microscopy confirmed the hollow nature of microspheres with pores on the surface of floating microspheres, which might have imparted floating properties to the prepared floating microspheres [16,17]. Density was less than that of the gastrointestinal fluid, causing the microparticles to float over the gastric fluid. The presence of porous surface, internal voids and low densities of the prepared microspheres contributed to good buoyancy [17]. The average particle size of microspheres was found to be increasing with the increase in concentration of the polymer [21,22]. Drug to polymer ratio influenced almost all the physicochemical properties of the microspheres [23]. The % drug loading was found to be increasing with drug to polymer ratio in the present study.

Drug release showed an inverse relation with concentration of polymer [24,25]. The linearity of the plot of cumulative percent of drug release versus time confirmed the zero order kinetics being followed by the formulations. The linearity of Higuchi plots indicated that the drug release from the microspheres followed the matrix diffusion process [22,26]. The prepared floating

microparticles are expected to reside for longer period of time in the upper gastric region and thereby leading to better bioavailability.

CONCLUSION

Findings from the present study show that the prepared microspheres exhibited good flow, floating and drug release properties. In this regard, microsphere formulations of cellulose acetate are superior to those prepared with Eudragit RS100. Thus, gastroretentive microspheres provide a potential alternative delivery system for the delivery of diltiazem in the treatment of cardiac disease.

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