Research Article

Design, characterization, and evaluation of gastroretentive microspheres of cimetidine an antiulcer agent

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ABSTRACT

Cimetidine (CM) is a H_2 – antihistaminic agent widely used in treatment of gastric and duodenal ulcers and also in Zollinger-Ellison syndrome. In this work, we made an attempt to prepare and evaluate gastro retentive microspheres of CM using hydroxypropyl methylcellulose (HPMC) and Eudragit RL-100 by solvent evaporation method. The prepared CM microspheres were spherical in shape and free flowing. The diameter of microspheres increased with increasing the polymer concentration. The CM microspheres have shown good buoyancy and entrapment efficiency. Percent buoyancy was found to be in the range of 63.86-81.39%. The drug entrapment efficiency of the prepared microspheres was found to be in the range of 66.19-94.20%. The differential scanning colorimetry and X-ray diffraction analysis indicated that the drug was uniformly distributed in an amorphous state in microspheres. The Fourier transfer infrared spectra of the formulations confirmed the stability of CM in the polymer matrix. The results of *in-vitro* drug release study were suggested that the microspheres were capable of releasing drug up to 12 h depending on the formulation variables. The drug release was slow from the microspheres which contain higher concentration of Eudragit RL-100 as compared to those prepared with HPMC. As the polymer concentration was increased in microspheres, the drug release rate was decreased.

Keywords: Buoyancy, cimetidine, gastroretentive microspheres, polymer matrix, solvent evaporation

Introduction

Among the different drug administration routes, the oral route of drug administration has attained the most consideration and is quite successful as well as convenient. This can be due to the ease of administration as well as the fact gastrointestinal physiology offers more elasticity in dosage form than most other routes.[1] Few drugs are absorbed easily from gastrointestinal tract and due to their short half-lives, eliminated rapidly from systemic circulation. This necessitates frequent dosing of such drugs to achieve successful therapeutic response. An approach of developing oral sustained/controlled release dosage forms is an attempt to avoid such boundaries. In these dosage forms, drug is slowly released and sufficient concentration of drug is maintained in the systemic circulation for extended period.[2]

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Oral gastroretentive floating drug delivery system found to be much helpful for the drugs which are intended release in stomach, have narrow absorption window in stomach, and poorly soluble and unstable in the intestinal or colonic environment.[3-5] Gastroretentive floating drug delivery is an excellent approach to extend gastric residence time drug for its local and/or systemic effects by retaining the dosage for on gastric fluid for a longer time. Over the last few decades, different gastroretentive drug delivery systems are being designed and developed including low density (floating) systems that can float on the gastric fluid and high density (sinking) systems that is retained in the bottom of the stomach.[6-8]

Cimetidine (CM) is H_2-antihistaminic drug that has been widely used in treatment of gastric and duodenal ulceration and also in Zollinger-Ellison syndrome and reflux esophagitis. It is a model drug for H_2 antihistaminics. This drug has short elimination half-life (2 h) and reported to be poorly absorbed from the lower gastrointestinal tract. The objective of this study was to develop floating microspheres of CM to achieve an extended retention in the upper gastrointestinal tract, which may result in enhanced absorption and thereby improved bioavailability.

Materials and Methods

Materials

CM is received as gift sample from Skant Health Care, Vapi, Gujarat. Hydroxypropyl methylcellulose (HPMC) and ethyl cellulose were purchased from Loba Chemicals Pvt. Ltd., Mumbai, India. Tween 80, dichloromethane (DCM), and methanol were purchased from Central Drug House, New Delhi. All other solvents and reagents were used as analytical grade.

Method

The microspheres were prepared by solvent evaporation technique using Eudragit RL-100 and HPMC as polymers. Nine formulations (CM1 to CM9) were prepared using different ratios of these two polymers as shown in Table 1. To the mixture of DCM and ethanol (1:1), the polymers in various ratios were added. The drug was dispersed in above solution of polymers. This dispersion was added slowly with stirring into the distilled water containing 1.0% Tween 80 and maintained at the temperature between 30 and 40°C. Stirring was continued for 3 h, which allowed the evaporation of DCM and ethanol completely. After evaporation of solvents, the microspheres formed were collected by filtration, washed 3-4 times with distilled water and dried at room temperature for 24 h.[9]

Evaluation

Drug content

About 100 mg of prepared CM microspheres were crushed in a glass mortar with pestle and added to pH 1.2 buffer solutions at 37°C, kept for 12 h. The solution was filtered and remaining buffer solution was added. The clear solution was analyzed for drug content using ultraviolet (UV) spectrophotometer at 218 nm.[10]

Measurement of microsphere size

The microsphere size was measured using a digital micrometer (MDC-25S Mitutoyo, Tokyo, Japan) having an accuracy of 0.001 mm. The average diameter of the 50 particles per batch was calculated.[11]

Scanning electron microscopy (SEM)

SEM studies are used to determine the external and internal morphology of the microspheres. The samples for SEM were prepared by lightly sprinkling on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with platinum to a thickness of about 10 Å under an argon atmosphere using a gold sputter module in a high-vacuum evaporator. The stub containing the coated samples was placed in the SEM (JSM- 6360A; JEOL, Tokyo, Japan) chamber. The samples were then randomly scanned, and photomicrographs were taken.[12]

Fourier transforms infrared spectroscopy (FTIR)

The pellets were made by crushing samples with KBr to make pellets under hydraulic pressure of 600 kg, and then the FTIR spectra were recorded between 400 and 4000/cm.[13]

Differential scanning calorimetric analysis (DSC)

The sample was heated from 0 to 3000°C at heating rate of 100°C/min under ARGON atmosphere using a micrometer (DSC Q20V24.4 Build 116, TA Instruments, USA) and then thermograms were obtained.[14]

X-ray diffraction studies (XRD)

A Philips, PW-171, XRD with Cu-NF filtered CuKα radiation was used to record the spectra. Quartz was used as an internal standard for calibration. The powder XRD was attached to a digital graphical assembly and computer with Cu-NF 25 KV/20 mA tube as a CuKα radiation source in the 2θ range 0-50° 76.[15]

In-vitro drug release study

In-vitro drug release study was carried out using a USP-23 rotating basket dissolution tester. The dissolution was measured at 37.0 ± 0.5°C and 100 rpm speed. Drug release from the CM microspheres was studied in 900 ml acidic medium (pH 1.2) for 24 h. At predetermined time intervals, 5 ml aliquots were withdrawn and replaced with the same volume of fresh solution. The amount of drug released was analyzed using UV-visible spectrophotometer at a λ max of 218 nm. The release data were fitted to various mathematical models as under to know which model is best fitting the obtained release profile. Zero-order release kinetics, Higuchi model, and Korsmeyer-Peppas model.[16]

Buoyancy percentage

The buoyancy percentage of prepared microspheres was calculated by spreading weighed amount of microspheres (100 mg over the surface of a USP dissolution apparatus [Type II]) filled with 900 ml 0.01 N HCl containing 0.02% Tween 80. The medium was agitated continuously with a paddle rotating at 100 rpm for 12 h. The floating and the settled portion of microspheres were collected separately. The microspheres were dried and weighed. Buoyancy percentage was calculated by dividing mass of the microspheres that remained floating by the total mass of the microspheres.[17]

$$\% \text{ Buoyancy} = \frac{\text{Microspheres remained floating}}{\text{Total mass of microspheres}} \times 100$$

Result and Discussion

The floating microspheres of CM were prepared by solvent evaporation method using HPMC and Eudragit RL 100 to improve the gastric

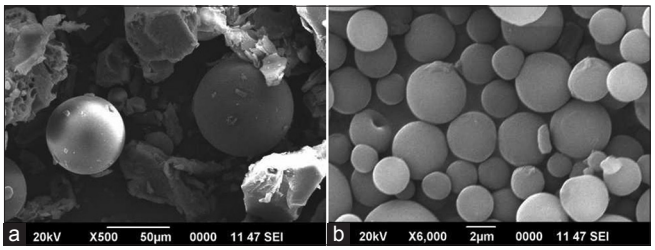

Figure 1: Scanning electron microscopic photographs of cimetidine 3 (CM3) (a) and CM4 (b)

retention time. The surface morphology of CM microspheres as examined by SEM studies showed the spherical shape and smooth surface (Figure 1).

The stability of CM was studied by FTIR analysis and shown in Figure 2. The FTIR spectrum of pure CM (A) showed some characteristics peaks, i.e., an absorption band at 3227/cm due to –NH stretching. The bands at 3145 and 3043/cm are because of C-H stretching both asymmetric and symmetric, the band at 2366/cm is ascribed to C ≡ N stretchings for amine group, band at 731/cm due to C = S stretching and the band at 1629/cm is due to –C=N groups. While in the spectra of CM1 microspheres, the same bands pertaining to CM were seen with little deviation. Thus, the FTIR study confirms the stability of CM within the prepared microspheres.

The size of the microspheres was determined using optical microscopy and mentioned in Table 2. The average size of the microspheres was found in the range of 83.22-102.42 µm. The microspheres containing higher concentration of HPMC are larger than microspheres containing higher concentration of Eudragit RL 100. The results of drug entrapment efficiency (DEE) are summarized in Table 2. The DEE was found in the range of 83.52-94.20%.

The DSC analysis of CM, drug loaded CM1 and drug free CM1 microspheres were carried out and the results are expressed in Figure 3. The plain CM has given a sharp peak at 143°C as a result of its melting point. However, the drug free and drug loaded CM1 microspheres have shown peaks at 77 and 76, respectively, but there

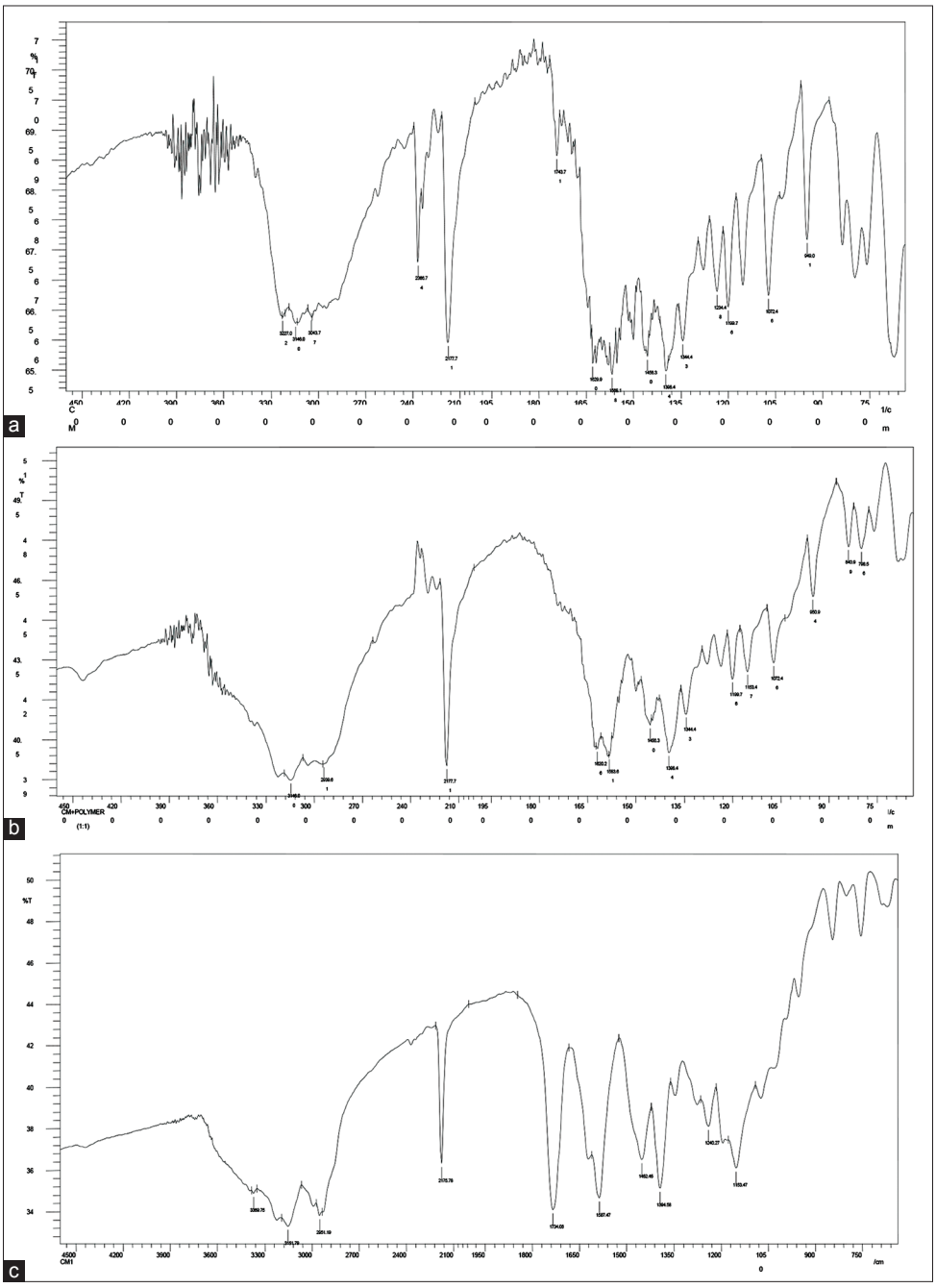

Figure 2: Fourier transform infrared spectra of cimetidine (CM) (a), CM and polymers (b), CM1 (c)

no endothermic peak at 143°C. This indicates that the CM is uniformly distributed in an amorphous state in the microspheres.

The XRD study of CM drug loaded microspheres, CM1 drug free microspheres and CM was carried out and shown in Figure 4. CM has shown peak between the 2q of 15° and 25° due to crystallinity. While in the case of drug free and drug loaded CM1 microspheres, these peaks were not observed. This suggests the amorphous dispersion of drug after entrapment into spray dried microspheres.

The *in-vitro* drug release study was performed using dissolution test apparatus in 0.1 N HCl (pH 1.2) for 12 h. The release profiles of CM are shown in Figures 5 and 6. The results reveal that the microspheres were able to release the drug up to for 12 h as per the formulation design. The drug release was decreased as the concentration of eudragit RL 100 was increased. On the other hand, the increase in initial drug loading shown increased drug release. A 84.64%, 83.81%, 80.57%, 76.97% 71.56%, 89.73%, 90.33%, 91.26%, and 93.57% of CM was released from CM1, CM2, CM3, CM4, CM5, CM6, CM7, CM8, and CM9 microspheres, respectively. The CM9 microspheres prepared with 62.5% w/w of Eudragit RL 100 have shown only 71.56% drug release at the end of 12 h.

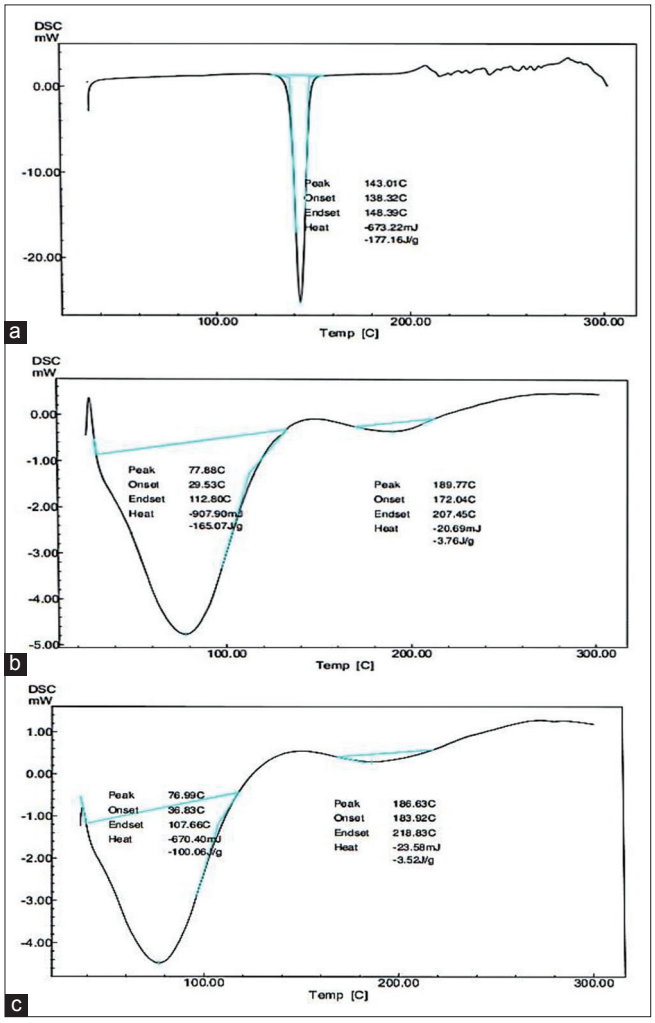

Figure 3: Differential scanning calorimetric thermograms of cimetidine (CM) (a), CM1 (b) and dummy (c)

The release data were fitted according to zero order, Higuchi's equation and Korsemeyer's equation and the mechanism of drug release was calculated using Peppas equation. The estimated *n* values along with the correlation coefficients have been given in Table 3. As the concentration of HPMC was increased, the *n* values also increased transforming form non-fickian type to Case II type.

Table 1: Composition of CM microspheres

Formulation code	Drug	HPMC	Eudragit RL-100	Solvent DCM/ ethanol	Surfactant Tween 80 (%)
CM1	200	300	300	10	1.0
CM2	200	200	400	10	1.0
CM3	200	150	450	10	1.0
CM4	200	120	480	10	1.0
CM5	200	100	500	10	1.0
CM6	200	400	200	10	1.0
CM7	200	450	150	10	1.0
CM8	200	480	120	10	1.0
CM9	200	500	100	10	1.0

CM: Cimetidine, HPMC: Hydroxy propyl methyl cellulose, DCM: Dichloromethane

Table 2: Average size and DEE of CM microspheres

Microspheres	Average size (μm)	DEE (%)
CM1	83.22	83.52
CM2	85.90	74.59
CM3	88.37	68.40
CM4	94.03	67.15
CM5	86.79	66.19
CM6	93.37	86.34
CM7	96.05	89.13
CM8	98.91	93.06
CM9	102.42	94.20

All the values are average of three determinations. CM: Cimetidine, DEE: Drug entrapment efficiency

Table 3: Kinetic values of CM loaded microspheres

Formul-ation	Zero order equation		Higuchi equation		Korsemeyer's equation	
	n	*r*	*n*	*r*	*n*	*r*
CM1	7.106	0.973	30.89	0.994	0.843	0.951
CM2	7.026	0.950	30.50	0.992	0.873	0978
CM3	7.071	0.974	27.07	0.960	1.056	0.968
CM4	7.962	0.972	26.59	0.954	1.084	0.812
CM5	7.790	0.974	25.72	0.939	1.112	0.983
CM6	7.914	0.951	30.08	0.968	0.876	0.978
CM7	7.733	0.916	30.62	0.966	0.775	0.976
CM8	7.502	0.886	30.15	0.965	0.644	0.975
CM9	7.752	0.878	30.62	0.966	0.618	0.975

CM: Cimetidine

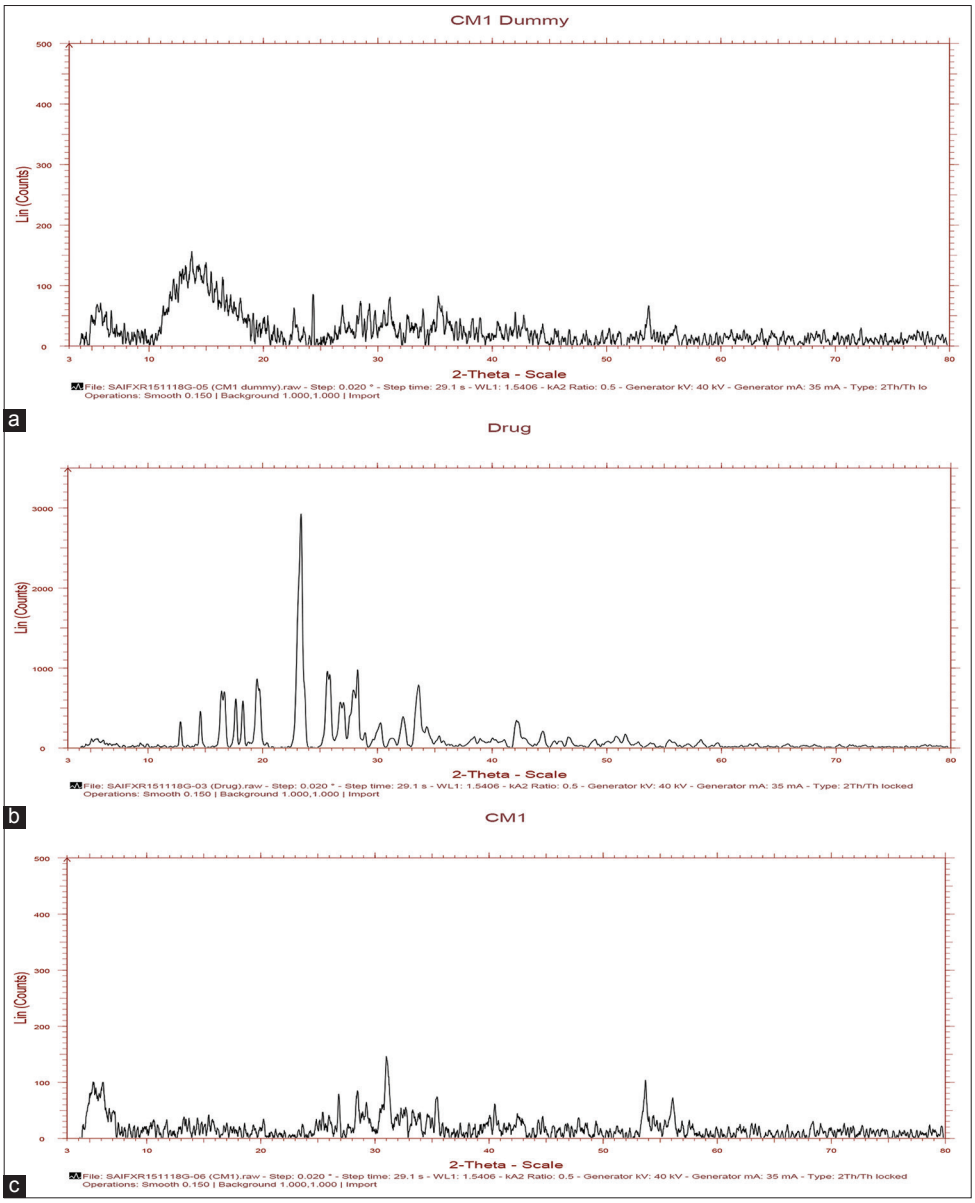

Figure 4: X-ray diffractograms of cimetidine 1 (CM1) dummy (a), CM (b), and (c) CM1

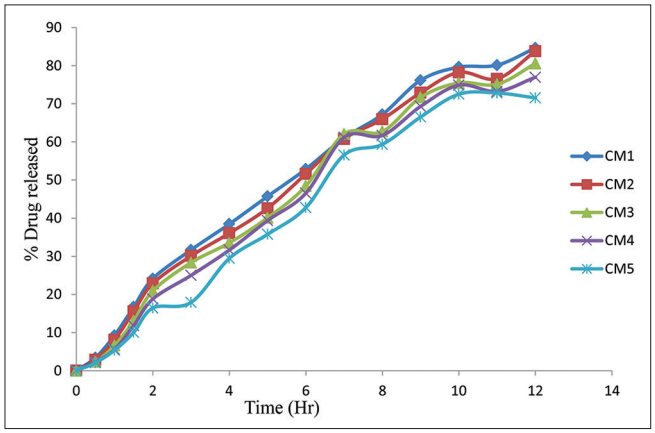

Figure 5: *In vitro* release profile of cimetidine loaded microspheres of formulations CM 1 to CM 5 (graph)

The floating efficiency of the CM microspheres was assessed by placing them in 0.1 N HCl dissolution media, to stimulate the gastric fluid. The microspheres floated over the surface of dissolution media for prolonged period of time without any apparent gelation. The hollow core of the microspheres surface also helps in the floating. So as the concentration of HPMC increased from CM5 to CM9 buoyancy percentage increased. Buoyancy percentage of the microspheres for formulations CM1 to CM9 is 71.23%, 68.01%, 67.92%, 66.61%, 63.86%, 72.89%, 77.91%, 80.74% and 81.39%, respectively, for 12 h as shown in the Table 4.

Conclusion

In this work, we made an attempt to prepare and evaluate gastroretentive microspheres of CM by solvent evaporation (emulsification) method to extend the retention of microspheres in GIT. The microspheres were

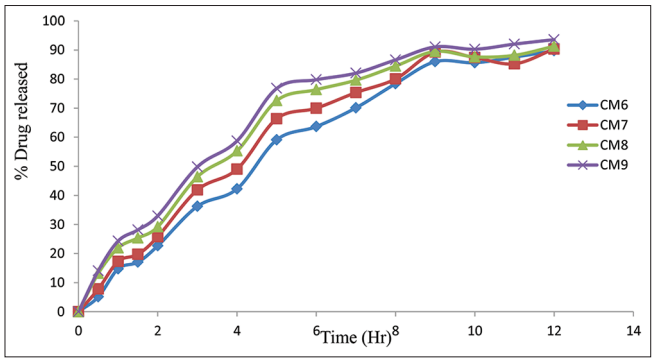

Figure 6: *In vitro* release profile of cimetidine loaded microspheres of formulations CM 6 to CM 9 (graph)

Table 4:% Buoyancy of CM microspheres

Formulation code	% Buoyancy
CM1	71.23
CM2	68.01
CM3	67.92
CM4	66.61
CM5	63.86
CM6	72.89
CM7	77.91
CM8	80.74
CM9	81.39

CM: Cimetidine

spherical in shape. It is observed that the size of microspheres decreases with increase in HPMC concentration. The DEE of CM microspheres was in rage of 83-94%. The DSC and XRD study suggest that the drug is uniformly dispersed in an amorphous form. The FTIR study confirmed the stability of CM in polymer matrix. The *in vitro* release indicated that the drug release rate increases with decrease in concentration of Eudragit RL 100. Drug release mechanism indicated that the increase in concentration of HPMC results into increased *n* values, transforming the release mechanism form non-Fickian type to Case II type. The CM microspheres showed good buoyancy; percent buoyancy was in the range of 71.23-81.39%.

The concept of formulating gastroretentive microspheres of CM offers a suitable, practical approach to achieve a prolonged therapeutic effect by continuously releasing the medication over an extended period of time by prolonging the gastric residence time, thus improving the oral bioavailability of the drug, this study has shown the promising results.

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