RESEARCH ARTICLE

Development and evaluation of bromhexine hydrochloride floating microparticulates

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The main objective of the present study is to prepare floating microsphere of the bromhexine hydrochloride in order to achieve gastro-retention which may result in the improvement of bioavailability and solubility as the bromhexine is soluble up to the pH range of 1–4. The microsphere is prepared by the non-aqueous solvent evaporation method using hydroxyl propyl methyl cellulose and ethyl cellulose in different drug polymer ratios. The *in vitro* release is studied in the USP dissolution apparatus type I. The percentage yield is more than 60% for the all the batches. The entrapment efficiency increased by increasing the polymer concentration and found to be maximum at 1:4 drug polymer ratios. The drug loading was found to be in the range of the 19.30–33.70%. All the batches show *in vitro* buoyancy percentage in the range of the 53.3% to 70.13% after 12 h. The *in vitro* dissolution and permeation studies revealed that the formulations followed zero order release pattern and 'n' values derived from the PEPPAs equation confirmed that the drug release from the floating system was the non-Fickian transport mechanism. The SEM studies revealed that the drug adsorbed on the surface of the microspheres can able to provide the burst effect in order to provide the immediate therapeutic effect. Therefore, the floating microspheres were able to be buoyant up to 12 h, having excellent flow properties, and met the required drug release kinetics for gastro-retentive systems.

Key words: *Bromhexine HCl, floating, gastro-retention, microspheres, mucolytic*

INTRODUCTION

The gastro-retentive floating drug delivery system is found to be a sophisticated mean for enhancing the bioavailability and controlling the delivery of the many drugs. The increased sophistication leads to incorporate number of the drugs in the gastro-retentive drug delivery system in order to optimize the drug molecule, which exhibit low bioavailability and high first pass metabolism. Floating dosage systems form important technological drug delivery systems with gastric retentive behavior and offer several advantages in drug delivery. Treatment of gastrointestinal disorders (such as gastro-esophageal reflux) with gastro-retentive drug delivery system, improved drug absorption, because of increased gastric residence time (GRT) and more time spent by the dosage form at its absorption site. This also helps by minimizing the mucosal irritation due to drugs, releasing drug at controlled rate and offers ease of administration and better patient compliance.[1]

Bromhexine hydrochloride is commonly used mucolytic agent. The need for its gastro retention is that it is dissolved in the pH range of 1–4 and after that its dissolution almost ceases because of the low solubility in lower region of the gastrointestinal tract.[2] The oral bioavailability of bromhexine hydrochloride is 20%. Thus, the floating drug delivery system may help bromhexine hydrochloride to stay in the acidic pH for long time and improve its oral bioavailability.

MATERIALS AND METHODS

Bromhexine hydrochloride was provided by Ross Robbinz Biotech Solan, India, hydroxypropyl methyl cellulose (HPMC) from HI media, ethyl cellulose (EC) from SD Fine laboratory. All other chemicals used are of analytical grade.

Experimental

Preparation of floating microspheres

Microspheres containing Bromhexine hydrochloride as a core material were prepared using the non-aqueous

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solvent evaporation method by taking drug and polymers in different proportions and dissolving at room temperature into a mixture of methanol–dichloromethane (DCM) (1:1 v/v) with vigorous agitation. This was slowly introduced into the dispersion medium consisting of light liquid paraffin (200 ml) containing 0.01% Tween 80. The system was stirred at 1200 rpm using a propeller type agitator at room temperature over a period of 2 h and the solvent was allowed to evaporate completely.[3]

The light liquid paraffin was then decanted and the microspheres were separated by filtration, washed three times with n-hexane and air dried for 24 h and stored in desiccator for further use.

Evaluation of floating microsphere

Micromeritics studies

The floating microsphere was characterized by their micromeritics properties as follows:

Bulk density

Bulk density denotes the total density of the material. It includes the true volume of interparticle spaces and intraparticle pores. The packing of particles is mainly responsible for bulk. Bulk density is defined as:

$$\text{Bulk Density} = \frac{\text{weight of the powder}}{\text{Bulk volume of the powder}} \quad (1)$$

Tapped density

A weighed quantity of powder blend was introduced in to 10 mL measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted.

Tapped Density = Mass of the microsphere/ Volume of the microsphere after tapping

Carr's compressibility index

The simplest way for measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow.[4]

$$\text{Compressibility index} = \frac{\text{Tapped density-Bulk density}}{\text{Tapped density}} \quad (2)$$

Hausner's ratio

This parameter was calculated from the values of tapped density and bulk density by using equation:

$$\text{Hausner ratio} = \frac{\text{Tapped dnensity}}{\text{Bulk density}} \quad (3)$$

Values less than 1.25 indicate good flow (20% Carr), whereas greater than 1.25 indicate poor flow (33% Carr).

Particle size analysis

Microsphere size was determined by using optical microscopy with the help of ocular and stage micrometer. The sizes of around 100 particles were measured and their average particle size was determined.

Scanning electron microscopy (SEM)

Scanning electron microscopy (SEM) studies were performed to determine the porous/hollow nature of the microspheres. Surface morphology of microspheres was also noted.

Percentage yield

The prepared microspheres were collected and accurately weighed. The measured weight of prepared microspheres was divided by the total amount of all excipients and drug used in preparation of the microspheres, which gives the total percentage yield of floating microspheres.[5]

$$\% \text{ Yield} = \frac{\text{Actual weight of the product}}{\text{Total weight of the excipient and the drug}} \times 100 \quad (4)$$

Estimation of drug loading/encapsulation efficiency

A weighed quantity 50 mg of the microspheres was taken. The amount of drug entrapped was estimated by dissolving the microsphere in methanol and then extracting the drug in 0.1N HCL of pH 1.2. The volume was made up to 100 mL using 0.1N HCL. The solution was filtered and from the filtrate 1 mL of the sample was taken and further diluted to 10 mL and the absorbance was measured at 245 nm.[6]

$$\% \text{ Drug entrapment} = \frac{\text{Amount of drug actually present}}{\text{theoretical drug load expected}} \times 100 \quad (5)$$

$$\% \text{ Drug loading} = \frac{\text{weight of the drug present in the microsphere}}{\text{total weight of the microsphere}} \times 100 \quad (6)$$

In vitro buoyancy studies

The microsphere weighing (300 mg) were spread over the surface of the USP XXIV dissolution apparatus type II filled with 900 mL of 0.1 N HCL. The medium was agitated with a paddle rotating at 100 rpm for 12 h. The floating and the settled portions of microspheres were recovered separately. The microspheres were dried and weighed. Buoyancy percentage was calculated using the equation.[7]

$$\% \text{ Buoyancy} = \frac{Qf}{Qf+Qs} \times 100 \quad (7)$$

where Qf and Qs are the weight of the floating and the settled microsphere, respectively.

In vitro drug release analysis

Drug release studies were carried out USP XXIII dissolution apparatus type I rotating at 100 rpm in 0.1N HCL as dissolution medium (900 ml) maintained at 37 ± 0.5°C. At specific time intervals, up to 12 h, aliquots were withdrawn and analyzed at 245 nm spectrophotometrically (Shimadzu 1700) against 0.1N HCL as blank. The withdrawn volume was replaced with an equal volume of fresh 0.1N HCL to maintain sink conditions. All experiments were performed in triplicate.

The drug release data were fitted to zero order (cumulative % drug release versus time), first order (log cumulative % drug retained versus time), Higuchi models (cumulative % drug released versus square root of time) and Korsmeyer–Pepaas to assess the kinetics of drug release and determine the release mechanism of the drug from the floating microspheres.[8-10]

Ex vivo release studies

Formulations which showed maximum *in vitro* release were selected for ex vivo permeation studies of bromhexine hydrochloride microspheres. The formulations were studied through a fabricated Franz diffusion cell. Freshly excised goat stomach tissue was fixed between clamped donor and receptor compartments of an all-glass modified "Franz diffusion cell" The receptor compartment was filled with 40 mL freshly prepared 0.1 N HCL of pH 1.2 and all air bubbles were expelled from the compartment. A known quantity of microspheres (100 mg) was spread over the surface of stomach tissue. The microspheres were wetted w ith the release medium and the opening of the donor cell was sealed with a glass cover slip. Receptor fluid was kept at 37°C with constant stirring using a Teflon-coated magnetic stir bead. The permeation study was continued for 12 h, and samples were withdrawn from receptor and analyzed for bromhexine hydrochloride content by measuring absorbance at 245 nm in a spectrophotometer (Shimadzu, Kyoto, Japan). Results were expressed as amount permeated and percentage permeation.[11]

RESULTS AND DISCUSSION

Physical properties of the microspheres

The floating microspheres of bromhexine hydrochloride was prepared by using two polymers HPMC and EC. The concentration of the drug was kept constant and polymer concentration was varied. The polymers were used alone and in combination in different proportion in order to optimize the effect of polymers on different properties of the microspheres. The formulation plan is given in Table 1.

The results of all 11 formulations are shown in Table 2, which were evaluated for various parameters such as bulk density, tapped density, Carr's compressibility index, and Hausner's Ratio.

The bulk densities of floating microspheres were found to in the range of 0.496 to 0.556 for formulation F1 to F4. For HPMC microspheres the range was 0.496 to 0.561 for formulation F5 to F7 and for formulation F8 to F11 the range was 0.492 to 0.601. The density was found to be less than the density of gastric fluid, which suggests microspheres can float over gastric fluid.[12,13] 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.[14]

The Carr's compressibility index for formulations F4, F8, F10, and F1 was found in the range of 12–16 which indicates the good flow properties, for formulations F1, F2, F3, F7, F8 and F9 was found in the range of 18–21 which indicates fair flow property to passable and only for formulation F5 was in the range of 23–25 which indicates poor flow characteristics.

Table 2: Micromeritic properties of the floating microspheres

Formulation	Bulk density (g/cm³)	Tapped density (g/cm³)	Carr's compressibility index	Hausner's ratio
F1	0.556	0.632	16.7	0.83
F2	0.511	0.632	19	1.23
F3	0.510	0.616	17.20	1.20
F4	0.496	0.589	15.78	1.18
F5	0.54	0.702	23.07	1.3
F6	0.591	0.736	21.05	1.24
F7	0.601	0.747	20.88	1.24
F8	0.509	0.601	15.30	1.18
F9	0.502	0.591	15.05	1.17
F10	0.492	0.575	11.65	1.16
F11	0.508	0.593	14.33	1.16

Table 1: Formulation plan for the floating microspheres

Materials	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Bromhexine hydrochloride (mg)	500	500	500	500	500	500	500	500	500	500	500
HPMC (mg)	-	-	-	-	500	1000	1500	250	250	250	250
EC (mg)	500	1000	1500	2000	-	-	-	250	750	1250	1750
Solvent ratio (DCM: Methanol v/v)	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1	1:1

HPMC: Hydroxypropyl Methyl Cellulose, EC: Ethyl Cellulose, DCM: Dichloromethane

The value of Hausner's ratio for all the formulations was below 1.25 which indicates good flow properties.

The mean particle size of the microspheres containing EC, i.e. for formulations F1–F4 was found to be 113.4 ± 2.1, 138.3 ± 1.9, 151.4 ± 2.6, and 158.7 ± 2.8 μm and for microspheres containing HPMC (formulations F5 to F7) was 115.5 ± 4.5, 141.3 ± 4.0, and 171.2. ± 6.3 μm, respectively, and mean particle size of the microspheres containing HPMC and EC combination was found to be 124.8 ± 7.9, 149.7 ± 5.6, 173.9 ± 5.4, and 191.1 ± 5.9 μm for F8 to F11 batches, respectively, as shown in Table 3.

Results revealed that with an increase in polymer concentration, the particle size of microspheres increased.[15] This may be because of viscosity of the polymer solution which increases as the polymer concentration increases which in turn decreases the stirring efficiency. As the stirring rate is kept constant for all batches, it was found to be insufficient to break the particles into smaller size at higher polymer concentration. The results also showed that when combination of HPMC and EC was used, the mean particle size was found to be larger due to greater viscosity of polymers than when used separately.

The SEM was used to determine the shape and surface morphology of microspheres. SEM photographs of selected formulation (F1 and F5) revealed that the floating microspheres were spherical in shape.

Figures 1 and 2 showed the size variability and spherical structure of the bromhexine hydrochloride microspheres. They had rough surface that may be due to the presence of drug crystals on the surface of the microspheres. The surface topography revealed that the microspheres were porous which may be due to rapid escape of the volatile solvents during formulation as shown in Figure 3.

The drug loading was found to be in the range of 18.14–33.70% for formulations F1 to F11. The microspheres of batch F1 showed highest drug loading of 38.24%, while lowest drug loading was observed in batch F10, i.e. 18.14%. Drug loading decreased as the concentration of polymer increased in the formulation F1 to F3, but in the case of F4, it increased. When the drug loading was compared statistically, the difference between drug loading of F3 and F4 was insignificant.

The percentage encapsulation efficiency of bromhexine microspheres in all the formulations was found to be in the range of 61.49 ± 0.75% to 78 ± 2.25%. The microspheres of batch F4 showed maximum drug encapsulation of 78 ± 2.25%. The F5 batch microspheres, i.e. HPMC microspheres showed lowest drug encapsulation of 61.49 ± 0.75% [Table 3].

From the results it was seen that as the polymer concentration increased, viscosity of the dispersed phase also increased, and therefore, encapsulation efficiency.[7]

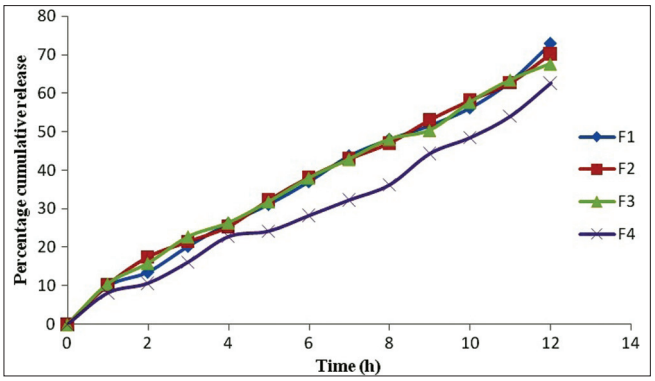

Figure 1: SEM results showing size variability of the microspheres

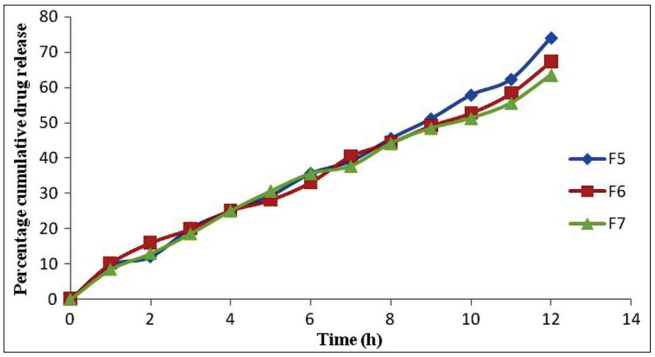

Figure 2: SEM results showing spherical structure of the microsphere

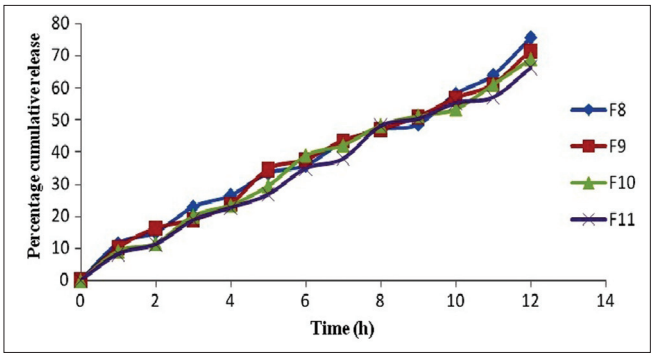

Figure 3: SEM results showing porous structure of the microspheres

In vitro buoyancy studies of the prepared microspheres were evaluated in 0.1 N HCL of pH 1.2. All the formulations remained buoyant for a period greater than 10 h. The formulations containing EC (F1 to F4) gave the floating ability in the range of 62.76 ± 1.38% to 68.46 ± 0.61%, and formulations containing HPMC (F5 to F7) gave the floating ability in the range of 53.33 ± 1.0% to 55.56 ± 0.86%, and for formulation F8 to F11 the floating range was 63.86 ± 1.12% to 70.13 ± 1.22%.

Thus, in all the formulations, the percentage buoyancy increased with an increase in the polymer concentration. The increase in buoyancy percentage may be attributed to air which caused swelling because of increased amount of the polymers present.[16]

Dissolution studies on all the formulations of bromhexine

Table 3: Characterization of bromhexine microspheres

Formulation code	Mean particle size (μm)	% Yield	% entrapment efficiency	% drug loading	% buoyancy
F1	113.4 ± 2.1	63.2	67.90 ± 1.44	33.70 ± 0.83	62.76 ± 1.38
F2	138.3 ± 1.9	71.6	70.95 ± 1.42	22.53 ± 0.97	64.56 ± 0.73
F3	151.4 ± 6	74	75.8 ± 2.02	19.30 ± 0.41	68.46 ± 0.61
F4	158.7 ± 2.8	75.4	78.00 ± 2.25	20.14 ± 0.99	63.03 ± 0.85
F5	115.5 ± 4.5	70.2	68.99 ± 1.49	32.18 ± 2.08	55.56 ± 0.87
F6	171.3 ± 4.0	73.66	61.87 ± 1.55	19.84 ± 1.04	53.60 ± 0.65
F7	195.2 ± 6.3	71	61.49 ± 0.75	24.36 ± 0.92	53.33 ± 1.00
F8	124.8 ± 7.9	66.2	64.82 ± 1.08	31.37 ± 1.45	63.8 ± 1.12
F9	149.7 ± 5.6	67	67.11 ± 1.49	31.73 ± 1.49	69 ± 1.11
F10	173.9 ± 5.4	69	71.99 ± 1.04	18.14 ± 1.33	70.13 ± 1.22
F11	191.1 ± 5.9	71.2	77.49 ± 1.45	32.02 ± 2.27	69.63 ± 0.86

hydrochloride floating microspheres were carried out using a basket-type dissolution apparatus. Table 4 shows the *in vitro* drug-release studies for formulation F1 to F4, the highest percentage cumulative drug released by the ethyl cellulose microspheres after 12 h was 73.34 ± 2.3% from F1, i.e. the formulation with the lowest content of ethyl cellulose. Maximum drug released for F2, F3, and F4 was 70.63 ± 1.8%, 67.79 ± 1.9%, and 63.69 ± 0.914%, respectively [Figures 4–6].

The *in vitro* drug release for formulation F5 to F7, the percentage cumulative drug release was found to be 74.66 ± 1.9%, 68.44 ± 1.38%, 64.12 ± 1.55% for F5, F6, and F7, respectively [Figure 7].

The percentage cumulative drug release for formulation F8 to F11 and for the combination formulation maximum percentage cumulative drug was 75.13 ± 1.55%, 72.02 ± 1.35%, 68.90 ± 1.90%, 66.96 ± 1.68% for formulation F8, F9, F10, F11, respectively, Table 4.

It was observed that with an increase in the polymer concentration, the cumulative % drug release of bromhexine hydrochloride decreases. The increase in EC concentration leads to the increased density of the polymer matrix into the microspheres which result in an increased diffusional path length. This may decrease the overall drug release from polymer matrix.[17] Further microspheres prepared at lower polymer concentration have large surface area exposed to dissolution medium and hence showed maximum drug release.[18]

For the *ex vivo* release studies, three formulations F1, F5, and F8 were taken which showed the maximum *in vitro* drug release. Cumulative percentage drug permeated from these formulations was in the range of 70.71 ± 1.23% for F1, 71.16 ± 2.1% for F4, and 72.10 ± 0.98% for F8 after 12 ho [Table 5].

The release kinetics of all floating microsphere formulations were analyzed for zero order, first order, and Higuchi kinetics and all the formulations showed zero-order kinetics as the regression values were highest among other kinetic data. The microspheres with zero-order drug release were a prerequisite especially for oral controlled release and

Table 4: *In vitro* percentage cumulative release and release kinetics from bromhexine HCl

Formulation code	cumulative release (%)	Zero order	First order	Higuchi	Korsmeyer
		R^2	R^2	R^2	*N*
F1	73.34 ± 2.30	0.994	0.957	0.984	0.834
F2	70.63 ± 1.82	0.994	0.976	0.979	0.755
F3	67.79 ± 1.95	0.993	0.983	0.979	0.753
F4	63.69 ± 0.91	0.988	0.951	0.953	0.811
F5	74.66 ± 1.91	0.992	0.936	0.968	0.823
F6	68.44 ± 1.38	0.992	0.965	0.973	0.734
F7	64.12 ± 1.55	0.991	0.985	0.989	0.814
F8	75.13 ± 1.58	0.984	0.923	0.969	0.733
F9	72.02 ± 1.35	0.989	0.960	0.977	0.773
F10	68.90 ± 1.90	0.993	0.977	0.977	0.853
F11	66.96 ± 1.68	0.992	0.976	0.970	0.871

Table 5: *Ex vivo* Percentage cumulative drug release and release kinetics from bromhexine HCl microspheres

Formulation code	Cumulative release (%)	Zero order	First order	Higuchi	Korsmeyer
		R^2	R^2	R^2	*N*
F1	70.71 ± 1.23	0.989	0.934	0.944	0.862
F5	71.16 ± 2.1	0.994	0.950	0.949	0.826
F8	72.10 ± 0.98	0.984	0.976	0.982	0.692

may lead to better therapeutic efficacy of bromhexine HCl formulations. The release kinetics were confirmed by PPAPs equation as the "n" values were between 0.5 and 1.0 indicating the non-Fickian transport mechanism. The values of "n" is the slope of log mt/m∞ vs. log time curve where mt/m∞ is the fraction of drug released. The permeation kinetics from the floating microsphere followed the same pattern as that of *in vitro* release, i.e. zero-order release and the non-Fickian transport mechanism for the selected formulations.

CONCLUSION

The floating microspheres of bromhexine hydrochloride were prepared by the non-aqueous solvent evaporation

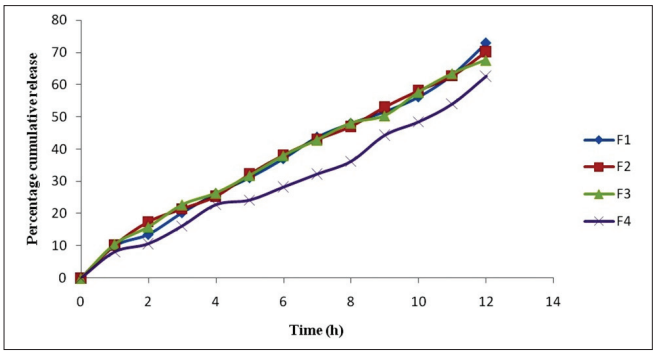

Figure 4: *In vitro* release profile of formulation F1-F4

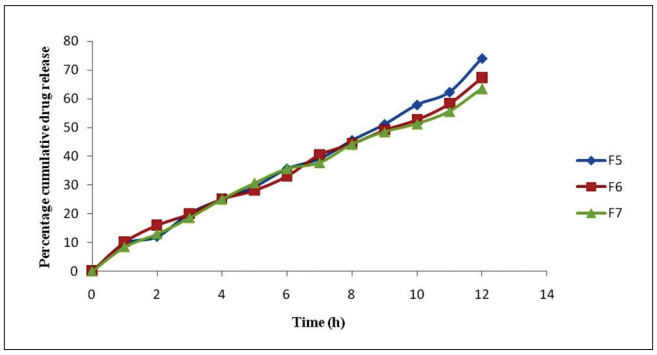

Figure 5: *In vitro* release profile of formulation F5-F7

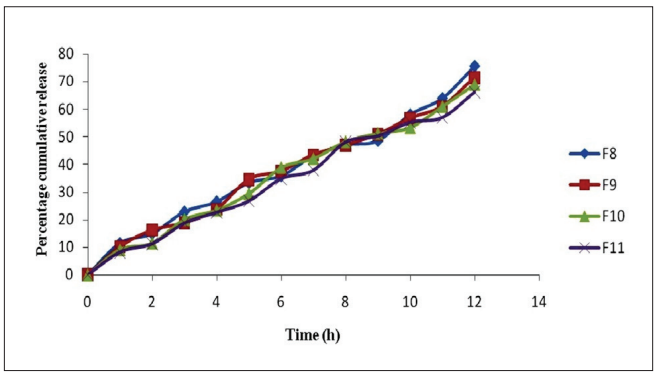

Figure 6: *In vitro* release profile of formulation F8-F11

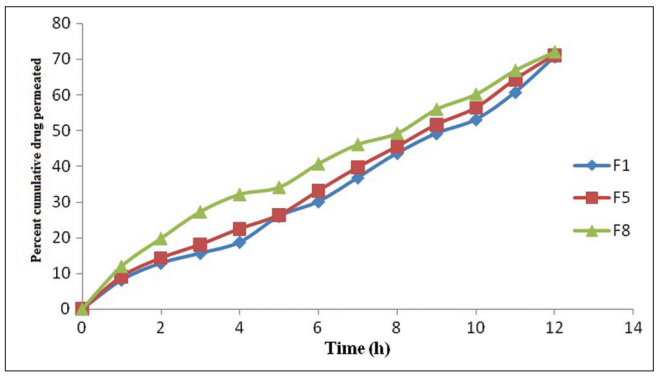

Figure 7: *Ex-vivo* permeation studies

method. The nature and amount of the polymers influenced the physical characteristics, floating behavior as well as the release of the drug from the system. *In vitro* buoyancy studies confirmed the excellent floating properties of the microspheres. The drug release was sufficiently sustained and diffusion and erosion was the dominant release mechanism. Hence, the floating microspheres prepared with the HPMC and EC may provide convenient dosage form for achieving best performance regarding flow, release, and floating properties.

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