ORIGINAL ARTICLE

Development and characterization of sustain release gastro retentive floating microsphere of diltiazem hydrochloride for the treatment of hypertension

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Gastroretentive drug delivery systems are the systems, which are retained in the stomach for a longer period and thereby improve the bio-availability of drugs. Diltiazem hydrochloride (DTZ HCl), is a calcium channel blocker, an antihypertension and antianginal drug, DTZ HCl undergoes an extensive biotransformation, mainly through cytochrome P-450 CYP3A, which results in <4% of its oral dose being excreted unchanged in urine. Suffers from poor bio-availability (~30–40%) owing to an important first pass metabolism. It has an elimination half-life of 3.5 h and an absorption zone from the upper intestinal tract. Thus, the present work is aimed to formulate sustain release floating microsphere of DTZ HCl for gastroretentive drug delivery system. Floating microsphere were prepared using nonaqueous solvent evaporation method using polycarbonate, chitosan, ethyl cellulose, hydroxypropyl methycellulose and acrycoat as materials in various quantities, in varying ratio to formulate 20 formulations of the floating microsphere. Observations of all formulations for physical characterization had shown that, all of them comply with the specification of official pharmacopoeias and/or standard reference. It was observed that microsphere of batch F3 followed the results obtained, it was concluded that the formulation 98.72% F3 is the best formulations as the extent of drug release was found to be around 99.81% at the desired time 12 h.

Key words: *Diltiazem hydrochloride, floating microsphere, in vitro buoyancy studies, swelling index*

INTRODUCTION

The oral drug delivery is by far the most preferable route of drug delivery system, due to ease of administration, patient compliance and flexibility in formulation, etc., From immediate release to site specific delivery, oral dosage form has really progressed. It is evident from the recent scientific and patient literature that an increased interest in novel dosage form that are retained in the stomach for a prolonged and period exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the gastrointestinal (GI) tract is to control the gastric residence time, that is, gastro retentive dosage form.[1,2] Effective oral drug delivery may depend upon the factor such as gastric emptying process, GI transit time of dosage form, drug release from the dosage form and site of absorption of the drug. Most of the oral dosage forms possess several physiological limitations such as variable GI transit, because of variable gastric emptying leading to nonuniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. The gastric emptying of dosage forms in humans are affected by several factors because of which wide inter- and intra-subject variations are observed.[3] Since many drugs are well absorbed in the upper part of the GI tract, such high variability may lead to nonuniform absorption and makes the bio-availability unpredictable. Among the various gastro retentive systems, gastric floating drug delivery systems offer numerous advantages over the gastric retentive systems. These systems have a density lower than the gastric fluids and thus remain buoyant in the stomach

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without affecting the gastric emptying rate for a prolonged period. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the stomach. Cardiovascular diseases are one of the life-threatening diseases of the world. Angina pectoris, hypertension and cardiac failure are the most common diseases and require constant monitoring.[4] Calcium channel blockers are emerging as very important group of the management of angina pectoris and hypertension. Diltiazem hydrochloride (DTZ HCl) is a calcium channel blocker belonging to the benzothiazepine family. It is widely prescribed for the treatment of hypertension and angina. DTZ HCl undergoes an extensive biotransformation mainly through cytochrome P-450 CYP3A, which results in <4% of its oral dose being excreted unchanged in the urine. Bio-availability of DTZ HCl is ~30–40% owing to an important first pass metabolism.[5,6] It has an elimination half-life of 3–4.5 h and has an absorption zone from the upper intestinal tract. Efficacy of the administered dose may get reduced due to incomplete drug release from the device above the absorption zone. The dosage is 30 mg, 4 times a day and increased as necessary up to 360 mg/day in divided doses. DTZ HCl requires multiple daily drug dosage in order to maintain adequate plasma concentrations. Due to a short half-life of DTZ HCl required frequent administration. These two drawbacks can be overcome by developing a floating dosage form to be remained buoyant in the stomach. Therefore, it is a suitable model candidate for gastroretentive formulation.[7,8] The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GI tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bio-availability.[9,10]

MATERIALS AND METHODS

Diltiazem hydrochloride was obtained as a gift sample from Cipla Ltd., (Mumbai India) and hydroxypropyl methycellulose (HPMC) K4M, polycarbonate, chitosan, acrycoat, ethyl cellulose were kindly supplied by S.D. Fine Chemicals Ltd. (Mumbai, India). All other ingredients were of analytical grade. An ultraviolet (UV)/visible spectrophotometer (Shimadzu-1800) was used for drug analysis.

Preparation of the standard curve of diltiazem hydrochloride

A total of 100 mg of DTZ HCl was accurately weighed and transferred to a 100 ml volumetric flask containing 100 ml of 0.1 N HCl solution and shaked to dissolve. The solution resulted is ≈1000 μg/ml. Then 10 ml of this solution is transfer red to another volumetric flask to obtain a solution of 100 μg/ml served as the stock. Then again 10 ml of this solution is transferred to another volumetric flask to obtain a solution of 10 μ g/ml and the absorbance was taken on double beam UV spectrophotometer using λ_{max} at 236.80 nm. The absorbance values were plotted against concentration (μg/ml) to obtain the standard calibration curve [Figure 1]. Preparation of 0.1 N HCl: Dilute 8.5 ml of concentrated HCl in 1000 ml of distilled water to get 0.1 N HCl.[11]

Preparation of floating diltiazem hydrochloride loaded microspheres

Microspheres are containing DTZ HCl as a core material were prepared by a nonaqueous solvent evaporation method. Briefly, drug (DTZ HCl) and polymers polycarbonate, chitosan, ethyl cellulose, HPMC and acrycoat were mixed individuals in acetone at various ratios. The slurry was slowly introduced into 40 ml of liquid paraffin while being stirred at 1300 rpm by a mechanical stirrer equipped with a three bladed propeller at room temperature (27°C ± 0.5°C). The solution was stirred for 2 h to allow the solvent to evaporate completely, and the microspheres were collected by filtration. The microspheres were repeatedly washed with petroleum ether (40°C–60°C) until free from oil. The collected microspheres were dried for 1 h at 30°C–40°C temperature and subsequently stored in desiccators over fused calcium chloride [Table 1].[11-13]

Evaluation of floating microspheres

Micromeritics studies of floating microspheres

The microspheres are characterized by their micromeritic properties, such as particle size, tapped density, Carr's compressibility index, and flow property, bulk density, Hausner's ratio.[14]

Percentage yield (i.e., recovery) of microspheres formed

The measured weight of prepared microspheres was divided by the total amount of all the nonvolatile components used for the preparation of the microspheres, which give the total percentage yield of floating microspheres.[15]

Study of floatation behavior (or buoyancy) of microspheres

The floatation studies were carried out to ascertain the floating behavior of various polymers. Beaker method was initially used to have an idea of the floatation behavior of the proposed dosage form.[16] A total of 50 mg of floating microparticles were placed in each of four 50 ml beakers

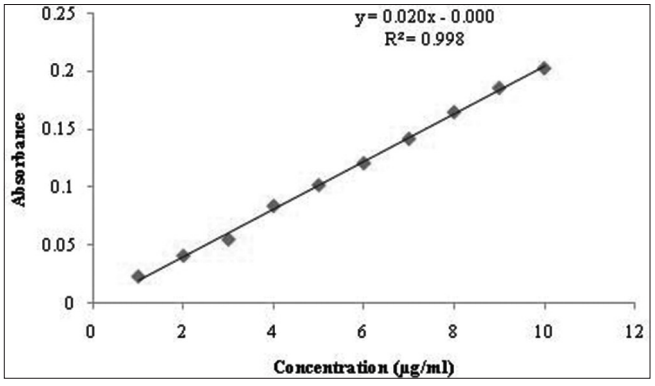

Figure 1: Standard curve of diltiazem hydrochloride in 0.1N HCL solution (pH 1.2) at λ_{max} 236.80 nm

Table 1: Drug and polymer combinations in acetone

Formulations	Drug (DLZ) (mg)	Polycarbonate (mg)	Acrycoat (mg)	Ethyl cellulose (mg)	HPMC K4M (mg)	Chitosan (mg)	Stirring rate	Temperature (°C)
F1	100	50	-	-	-	-	1300	30°C-40°C
F2	100	100	-	-	-	-	1300	30°C-40°C
F3	100	150	-	-	-	-	1300	30°C-40°C
F4	100	200	-	-	-	-	1300	30°C-40°C
F5	100	-	50	-	-	-	1300	30°C-40°C
F6	100	-	100	-	-	-	1300	30°C-40°C
F7	100	-	150	-	-	-	1300	30°C-40°C
F8	100	-	200	-	-	-	1300	30°C-40°C
F9	100	-	-	50	-	-	1300	30°C-40°C
F10	100	-	-	100	-	-	1300	30°C-40°C
F11	100	-	-	150	-	-	1300	30°C-40°C
F12	100	-	-	200	-	-	1300	30°C-40°C
F13	100	-	-	-	50	-	1300	30°C-40°C
F14	100	-	-	-	100	-	1300	30°C-40°C
F15	100	-	-	-	150	-	1300	30°C-40°C
F16	100	-	-	-	200	-	1300	30°C-40°C
F17	100	-	-	-	-	50	1300	30°C-40°C
F18	100	-	-	-	-	100	1300	30°C-40°C
F19	100	-	-	-	-	150	1300	30°C-40°C
F20	100	-	-	-	-	200	1300	30°C-40°C

containing 20 ml of 0.1 N 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:[17]

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

% Drug entrapment determination

Accurately weight 50 mg of floating microspheres were mechanically busted. These powders were dissolved in 50 ml 0.1 N 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:[18]

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

Dissolution test (in vitro drug release) of microspheres

The dissolution medium used was 900 ml of 0.1 N HCl (pH 1.2) for DTZ HCl was filled in a dissolution vessel and the temperature of the medium was set at 370°C ± 0.50°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 the same volume of fresh medium was replaced. The withdrawn sample was diluted and analyzed by UV-1700 spectrophotometer at the respective λ_{max} values for DTZ HCl (203.2 nm). The content of the drug was calculated using the equation generated from the standard curve.[19,20]

Morphological study using scanning electron microscopy

Scanning electron microscopy (SEM): The surface topography of the uncoated and coated (optimized) microsphere were examined under SEM analytical electron microscope (Rajkot). The sample was loaded on copper sample holder, and sputter coated with carbon followed by gold. SEM was performed to characterize the surface morphology of formed microspheres (Philips-XL-20, The Netherlands). The parameters of SEM were acceleration voltage of 20 kV, chamber pressure of 0.6 mm Hg, original magnification ×800 [Figure 2a-e].

Drug polymer interaction

Drug-polymers interaction was studied by Fourier transform infrared spectroscopy using KBr pellets.

Stability studies

Stability studies were carried out at 45°C ± 0.50°C and 75% relative humidity for 90 days.[21]

RESULT AND DISCUSSION

The various batches have the average particle size in the range of 143–208 μm. Whereas Carr's index in between 12.69% ±0.42 and 27.11% ±0.73% and Hausner's ratio with in 1.40 and angle of repose was found with in the range of 21.26 ± 0.48–28.27 ± 1.09 microspheres to show flow property while formulating in the dosage form [Table 2]. The maximum percentage yield was found of F3 batch was noted

Table 2: Micromeritic study for formulation F1–F20

Formulations	Angle of repose	Bulk density (g/cm^3)	Tap density (g/cm^3)	Compresibility index (%)	Hausner's ratio	Particle size (μm)
F1	21.26±0.48	0.57±0.69	0.72±1.02	20.83±0.19	1.26	143
F2	23.15±0.39	0.52±0.83	0.63±0.69	17.46±0.53	1.21	145
F3	24.43±0.75	0.53±1.06	0.69±0.53	23.18±0.28	1.30	150
F4	23.72±0.49	0.43±0.73	0.59±0.83	27.11±0.73	1.37	171
F5	25.14±0.85	0.51±0.49	0.67±0.97	23.88±0.42	1.31	150
F6	26.62±1.01	0.56±0.58	0.71±1.05	21.12±0.51	1.26	162
F7	23.35±0.92	0.49±0.63	0.66±0.49	25.75±0.37	1.34	171
F8	27.51±0.75	0.58±0.16	0.70±0.75	17.14±1.08	1.20	179
F9	26.37±1.05	0.53±0.42	0.68±1.08	22.05±0.71	1.28	159
F10	22.17±0.39	0.51±0.93	0.63±0.68	19.04±0.62	1.23	162
F11	25.59±0.59	0.54±1.06	0.67±0.79	19.40±0.58	1.24	170
F12	28.27±1.09	0.48±0.78	0.59±0.58	18.64±0.43	1.22	182
F13	26.18±0.83	0.61±0.19	0.75±0.67	18.66±0.57	1.22	148
F14	24.63±0.73	0.57±0.37	0.66±0.83	13.63±0.28	1.15	152
F15	28.21±0.48	0.55±0.29	0.63±1.15	12.69±0.42	1.14	163
F16	23.73±0.93	0.56±0.57	0.68±0.43	17.64±0.39	1.21	181
F17	26.17±1.02	0.42±0.65	0.59±1.14	28.81±0.71	1.40	155
F18	27.64±0.67	0.54±0.83	0.67±0.86	19.40±0.37	1.24	171
F19	24.48±0.78	0.59±1.04	0.71±0.79	16.90±0.48	1.20	193
F20	25.19±0.89	0.52±0.41	0.65±0.53	20.00±0.68	1.25	208

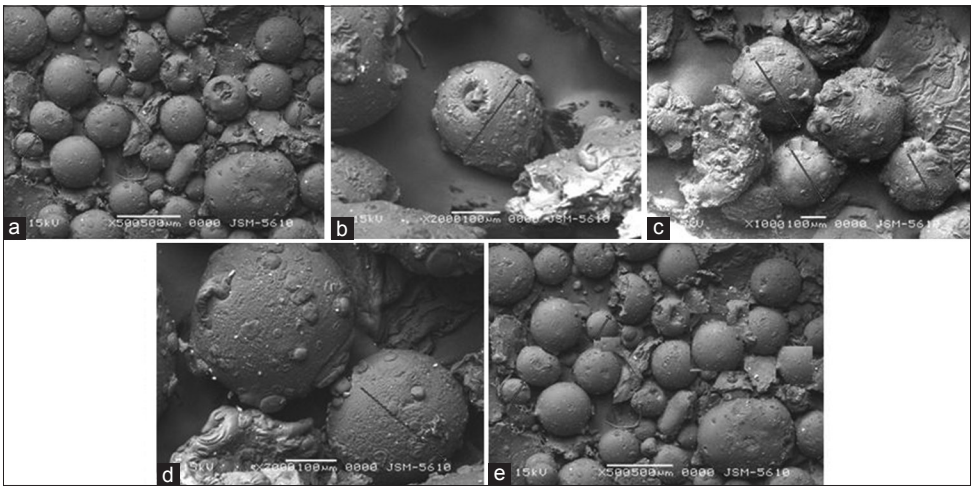

Figure 2: (a) Scanning electron microscopy photomicrographs of floating microspheres diltiazem and polycarbonate), (b) Scanning electron microscopy photomicrographs of diltiazem and acrycoat, (c) Scanning electron microscopy photomicrographs of diltiazem and ethyl cellulose, (d) Scanning electron microscopy photomicrographs of floating microspheres of diltiazem and hydroxypropyl methycellulose 4KM, (e) Scanning electron microscopy photomicrographs of floating microspheres of diltiazem and chitosan

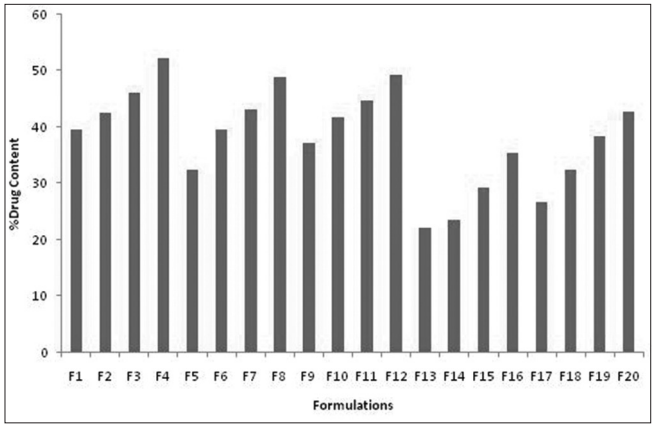

Figure 3: Effect of polymers on drug content of microsphere

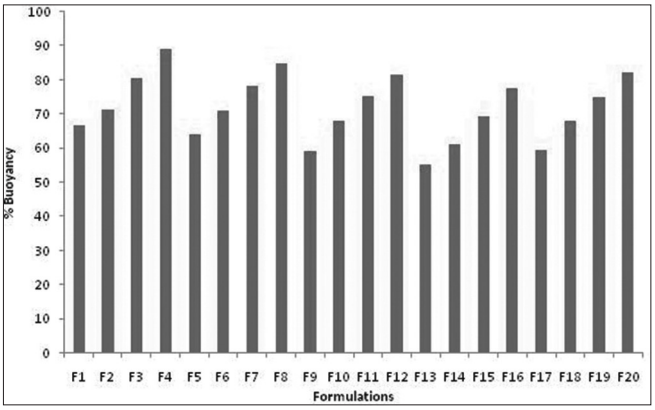

Figure 4: Effect of polymers on buoyancy of microsphere

to be 76.29% among all the batches. It was found that average percentage yield was >55% for all [Table 3 and Figure 3]. Buoyancy of batch F3 microspheres was found to be 80.53%, which indicates that most of the microspheres were still floatable after 12 h because of their low density and internal voids [Table 3 and Figure 4].

The microspheres of batch F4 formulation showed an entrapment of 88.15% while remaining formulation 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 and Figure 5]. Release of the drug from floating microspheres was evaluated at pH 1.2 using DTZ HCl as model drug. The drug release rate of DTZ HCl was almost linear with time for the first 10 h and gradually decreased with the afterwards [Figures 6-10]. 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

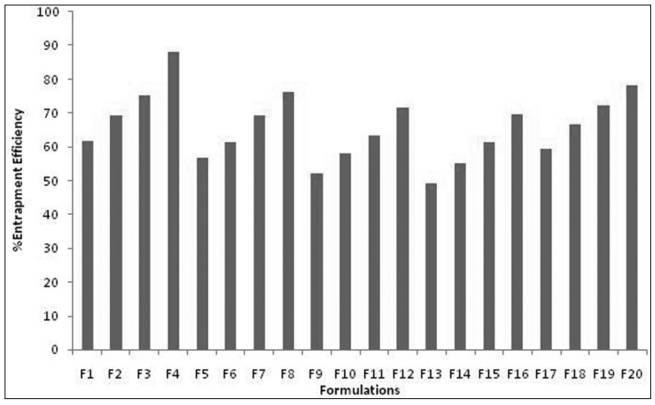

Figure 5: Effect of polymers on entrapment efficiency of microsphere

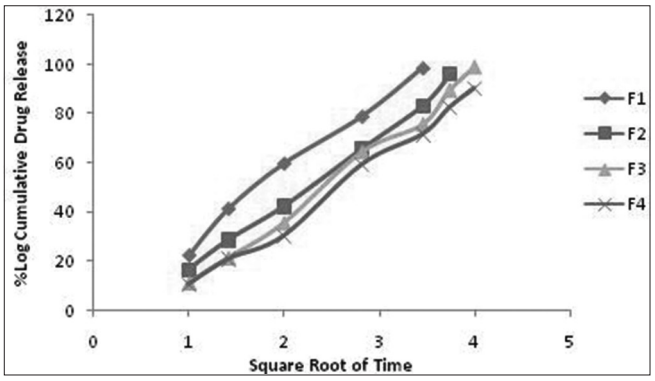

Figure 6: *In vitro* drug release of batches F1–F4 according to Higuchi's model

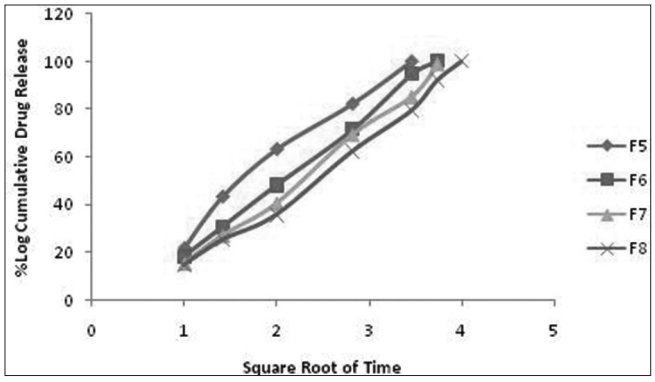

Figure 7: *In vitro* drug release of batches F5–F8 according to Higuchi's model

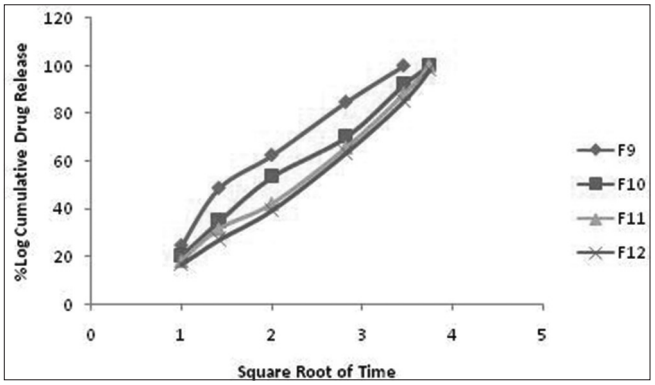

Figure 8: *In vitro* drug release of batches F9–F12 according to Higuchi's model

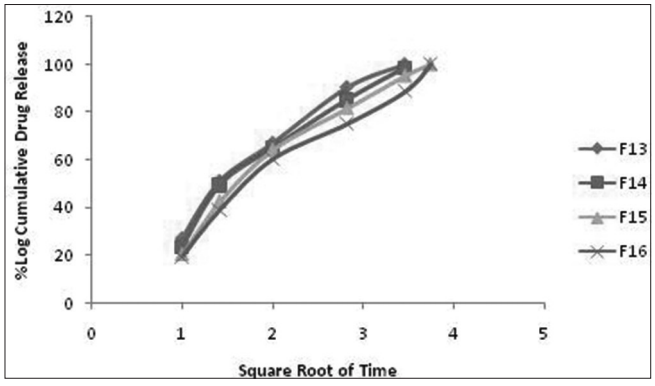

Figure 9: *In vitro* drug release of batches F13–F16 according to Higuchi's model

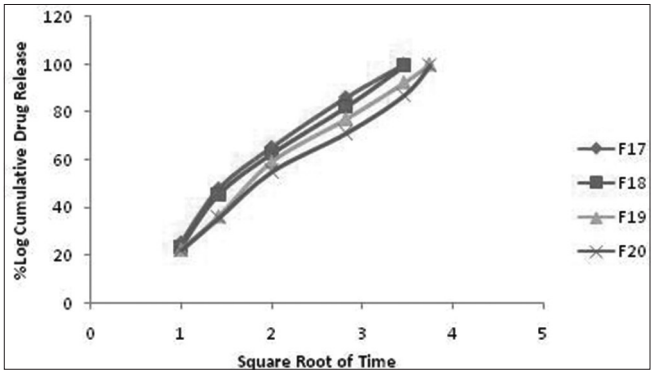

Figure 10: *In vitro* drug release of batches F17–F20 according to Higuchi's model

Table 3: Percentage yield and percentage buoyancy

Formulations	Drug content (%)	Entrapment efficiency (%)	Percentage buoyancy
F1	39.61	61.82	66.64
F2	42.52	69.43	71.48
F3	46.23	75.35	80.53
F4	52.18	88.15	89.24
F5	32.42	56.63	64.25
F6	39.53	61.42	71.15
F7	43.26	69.28	78.24
F8	48.93	76.31	84.73
F9	37.16	52.29	59.12
F10	41.83	58.19	68.24
F11	44.72	63.43	75.19
F12	49.35	71.62	81.47
F13	22.17	49.25	55.14
F14	23.48	55.16	61.25
F15	29.32	61.52	69.43
F16	35.47	69.58	77.58
F17	26.75	59.28	59.62
F18	32.43	66.73	68.24
F19	38.51	72.18	75.14
F20	42.82	78.34	82.25

solvent from the polymer to 450, which is an appreciable limit for matrix. This hollow nature was also responsible for the microspheres floating capability in simulated gastric fluids [Figure 2]. Infrared interpretation showed that there was no interaction between drug and polymers. The stability study showed that drug degradation was <5%, means the formulation was stable one and exhibit minimal degradation for a period of 3 months.

CONCLUSION

Micromeritics study shows good results for floating microspheres. Floating microspheres of F3 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 98.72% in 12 h for floating microspheres of F3 batch was obtained. Floatation was achieved for the entire study period.

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