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Research Article

## Formulation Development and Evaluation of Floating Microsphere of Acyclovir

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### ABSTRACT

The guanine derivative antiviral drug acyclovir (ACV) is one of the oldest molecules laying successful market until date, being commercially available in various dosage forms for oral, topical and parenteral administrations. Clinical application of this drug is superior to new antiviral agents due to its potential values such as suppression of recurrence, safety profile, minimal drug interactions and being inexpensive. ACV is slightly water soluble, less permeable and poorly bioavailable, yet more potential antiviral molecule. The present study involves preparation and evaluation of floating microspheres using ACV as a model drug for improving the drug bioavailability by prolongation of gastric retention time. Ethyl cellulose, hydroxyl propyl methyl cellulose microspheres loaded with ACV were prepared by solvent diffusion evaporation method. The microspheres had smooth surfaces with free-flowing and good-packing properties. The yield of the microspheres (F1-F6) was range from 62.23±0.85 to 73.32±0.65% and ethyl cellulose microspheres entrapped the maximum amount of the drug. Scanning electron microscopy confirmed their hollow structures with sizes in 198.3 nm. The prepared microspheres (F3) exhibited prolonged drug release and percentage buoyancy was found to 76.65±0.52. The formulated batches were evaluated for percentage yield, particle size measurement, flow properties, percent entrapment efficiency, swelling studies. The formulations were subjected to stability studies and In-vitro release and release kinetics data was subjected to different dissolution models. It was concluded that developed floating microspheres of ACV offers a suitable and practical approach for prolonged release of drug over an extended period of time and thus oral bioavailability, efficacy and patient compliance is improved.

**Keywords:** Acyclovir, Solvent diffusion evaporation method, Ethyl cellulose, Hydroxyl propyl methyl cellulose

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### INTRODUCTION

Oral route of administration is the most convenient and widely used method of drug administration and the development of stomach specific oral controlled-release drug delivery systems is a challenging job due to the variation of pH in different segments of the gastrointestinal tract, the fluctuation in gastric emptying time and the difficulty of localizing an oral delivery system in a selected region of the gastrointestinal tract. Rapid gastrointestinal transit can prevent the absorption of complete drug in the absorption zone and reduce the efficacy of the administered dose since the majority of drugs are absorbed in stomach or the upper part of small intestine [1,2]. To overcome the above discussed issues, many types of oral controlled drug delivery systems having prolonged gastric residence times have been reported such as: floating drug dosage systems (FDDS) [3-7], swelling or expanding system[8], mucoadhesive

systems[9,10], modified-shape systems[11], high-density systems and other delayed gastric emptying devices[12]. FDDS have lower density than gastric fluids and thus remain buoyant in the stomach fluid without affecting the gastric emptying for a prolonged period of time. While the system is floating in the gastric fluid, the drug is released slowly from the system at a desired rate. Materials used for FDDS include carbon dioxide gas-forming agents (carbonate or bicarbonate compounds) [8, 13], highly swellable hydrocolloids and light mineral oils [14,15]. Multiple unit systems and floating systems prepared by solvent evaporation methods have also been developed [12, 16-20]. However, it has been shown that products based on a multiple unit system comprising many small units have advantages over single -unit preparations such as matrix tablets [21]. The gastric emptying of multiple unit dosage forms occur gradually, in a more consistent manner, with less individual variation [2, 22]. Multiple unit dosage forms

also have the potential to distribute widely over a large area in the stomach and small intestine, thus yielding a more predictable drug release by suppressing the effect of many variables in the gastrointestinal environment. As multiple unit dosage forms consist of many small units, less risk of dosage dumping is expected [23]. Acyclovir [9-(2-hydroxyethoxymethyl)guanine; Zovirax] is a widely used antiviral drug for treating infectious diseases, such as genital herpes, chicken pox, varicella zoster infections, and herpes keratitis caused by herpes simplex virus. Oral absorption of acyclovir is highly variable, with an average bioavailability of 20–26.7% in humans [24–26]. Moreover, due to its short half-life ( $t_{1/2}$ ) of approximately 2.5 h, repeated administration of high-dose acyclovir is usually required to achieve therapeutic efficacy. Floating microspheres are one of the multiparticulate delivery system and are prepared to obtain prolonged or controlled drug delivery to improve bioavailability and to target drug to specific sites. Microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing site effects, decreasing dosing frequency and improving patient compliance [27].

## MATERIAL AND METHODS

### Material

Acyclovir was obtained as a gift sample from Macleods Pharmaceuticals, Mumbai. Dichloromethane, ethanol and isopropyl alcohol were purchased from E. Merck (India) Ltd., Mumbai. Ethyl cellulose, hydroxyl propyl methyl cellulose was purchased from Loba Chem. Pvt. Ltd, Mumbai. Double

distilled water was prepared freshly and used whenever required. All the chemicals used in this work were of analytical grade.

### Methods

#### Determination of $\lambda_{\max}$ of ACV

Accurately weighed 10 mg of drug was dissolved in 10 ml of 0.1 N HCl solutions in 10 ml of volumetric flask. The resulted solution 1000 $\mu$ g/ml and from this solution 1 ml pipette out and transfer into 10 ml volumetric flask and volume make up with 0.1 N HCl solution prepare suitable dilution to make it to a concentration range of 5–25 $\mu$ g/ml. The spectrum of this solution was run in 200–400 nm range in U.V. spectrophotometer (Labindia-3000+). A graph of concentration Vs absorbance was plotted.

#### Preparation of floating microsphere of ACV

Floating microspheres loaded with acyclovir were prepared using solvent diffusion-evaporation method using HPMC and EC in different ratio like 1:0.5, 1:1.5, 1:2 w/w. Drug and polymer in proportion of drug and polymers were dissolved in 1:2 mixture of solvent system of ethanol and dichloromethane. This clear solution was poured slowly in a thin stream into the aqueous solution of 1% polyvinyl alcohol. The emulsion was continuously stirred for 3 h at a speed of 500 rpm at 27 $\pm$ 2 $^{\circ}$ C. The floating microspheres were collected by decantation, while the non-floating microspheres were discarded. The microspheres were dried overnight at 40 $\pm$ 2 $^{\circ}$ C and stored in desiccator. The compositions of the formulations were shown in Table 1.

**Table 1 Formulations of the floating microspheres of ACV**

Sr. No	Formulation Code	Acyclovir (mg)	HPMC (mg)	EC (mg)
1.	F1	100	100	50
2.	F2	100	100	150
3.	F3	100	100	200
4.	F4	100	100	100
5.	F5	100	150	100
6.	F6	100	200	100

### Evaluation of microspheres

#### Microscopic Observation of prepared Microsphere

An optical microscope (Cippon, Japan) with a camera attachment (Minolta) was used to observe the shape of the prepared microsphere formulation.

#### Percentage Yield

The prepared microspheres with a size range of 1 $\mu$ m to 1000 $\mu$ m were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres.

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} \times 100$$

#### Drug Entrapment

The various formulations of the floating microspheres were subjected for drug content. 10 mg of floating microspheres from all batches were accurately weighed and crushed. The

powder of microspheres were dissolved in 10 ml 0.1 N HCl and centrifuge at 1000 rpm. This supernatant solution is then filtered through whatmann filter paper No. 44. After filtration, from this solution 0.1 ml was taken out and diluted up to 10 ml with 0.1 N HCl. The percentage drug entrapment was calculated using calibration curve method

#### Floating behavior

Ten milligrams of the floating microspheres were placed in 0.1 N HCl (100 ml). The mixture was stirred at 100 rpm in a magnetic stirrer. After 10 h, the layer of buoyant microsphere was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in desiccators until a constant weight was obtained. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

$$\text{Percent buoyancy} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

### Measurement of mean particle size

The mean size of the microspheres was determined by Photo Correlation Spectroscopy (PCS) on a submicron particle size analyzer (Malvern Instruments) at a scattering angle of 90°. A sample (0.5mg) of the microspheres suspended in 5 ml of distilled water was used for the measurement

### Determination of zeta potential

The zeta potential of the drug-loaded microspheres was measured on a zeta sizer (Malvern Instruments) by determining the electrophoretic mobility in a micro electrophoresis flow cell. All the samples were measured in water at 25°C in triplicate.

### In-vitro Release Studies

The drug release rate from floating microspheres was carried out using the USP type II (Electro Lab.) dissolution paddle assembly. A weighed amount of floating microspheres equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCl (pH=1.2) maintained at 37 ± 0.5°C and stirred at 55rpm. One ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. The collected samples analyzed spectrophotometrically at 242 nm to determine the concentration of drug present in the dissolution medium [28,29].

### Drug release kinetic data analysis

Several kinetic models have been proposed to describe the release characteristics of a drug from matrix. The following three equations are commonly used, because of their simplicity and applicability. Equation 1, the zero-order model equation (Plotted as cumulative percentage of drug released vs time); Equation 2, Higuchi's square-root equation (Plotted as cumulative percentage of drug released vs square root of time); and Equation 3, the Korsmeyer-Peppas equation (Plotted as Log cumulative percentage of drug released vs Log time).

To study the release kinetics of Famotidine from the Floating microspheres the release data was fitted to these three equations

**Zero order equation:** When a graph of the cumulative percentage of the drug released from the matrix against time is plotted, zero order release is linear in such a plot, indicating that the release rate is independent of concentration.

$$Q_t = k_0 \cdot t \dots\dots\dots (1)$$

Where  $Q_t$  is the percentage of drug released at time  $t$  and  $k_0$  is the release rate constant;

#### First order equation:-

$$\ln (100-Q_t) = \ln 100 - k_1 \cdot t \dots\dots\dots (2)$$

Where  $k_1$  is the release rate constant;

#### Higuchi's equation (Wagner, 1969):-

$$Q_t = k_H \cdot t^{1/2} \dots\dots\dots (3)$$

Where  $k_H$  is the Higuchi release rate constant

#### Korsmeyer-Peppas:-

The curves plotted may have different slopes, and hence it becomes difficult to exactly pin-point which curve follows perfect zero order release kinetics. Therefore, to confirm the kinetics of drug release, data were also analyzed using Korsmeyer's equation.

$$Q_t/Q_\infty = k_{KP} \cdot t^n$$

Where  $Q_t/Q_\infty$  is the fraction of drug released at time  $t$ ,  $k_{KP}$  constant comprising the structural and geometric characteristics of the device and  $n$  is the release exponent.

The slope of the linear curve gives the 'n' value. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. The value of 'n' gives an indication of the release mechanism. When  $n = 1$ , the release rate is independent of time (typical zero order release / case II transport);  $n = 0.5$  for Fickian release (diffusion/ case I transport); and when  $0.5 < n < 1$ , anomalous (non-Fickian or coupled diffusion/ relaxation) are implicated. Lastly, when  $n > 1.0$  super case II transport is apparent. 'n' is the slope value of  $\log M_t/M_\infty$  versus  $\log$  time curve [30-32].

### Stability studies

Stability studies were carried out with optimized formulation which was stored for a period of 45 days at 4±1°C, RT and 40±1°C.

## RESULTS AND DISCUSSION

The  $\lambda_{max}$  of ACV was found to be 242 nm by using U.V. spectrophotometer (Labindia-3000+) in linearity range 5-25 µg/ml Fig.1, 2. The floating microspheres of ACV were prepared by solvent diffusion-evaporation method. Percentage yield of different formulation was determined by weighing the microspheres after drying. The percentage yield of different formulation was in range of 62.23±0.85 to 73.32±0.65% Table 2. The maximum percentage yield was found in formulation F3, 73.32±0.65 as compare to all formulation. The drug entrapment efficacies of different formulations were in range of 62.23±0.54 to 75.56±0.23 %w/w. The maximum percentage drug entrapment was found in formulation F3 (75.56±0.23 % w/w) Table 3. To assess the floating properties, the microspheres were placed in 0.1N hydrochloric acid. The microspheres floated for prolonged time over the surface of the dissolution medium without any apparent gelation. Buoyancy percentage of the microspheres was in the range of 55.65±0.65 to 76.65±0.52. The nature of the polymer influenced the floating behaviour of the microspheres Table 4. The maximum percentage yield, drug entrapment, percentage buoyancy and floating lag time was found to be formulation F3 in floating microsphere. The optimized formulation of F3 was subjected to further studies. The mean size of the microspheres was determined by photo correlation spectroscopy (PCS) on a submicron particle size analyzer (Horiba Instruments) at a scattering angle of 90°. The results of measurement of mean particle size of optimized formulation F3 of floating microsphere was found to be 198.3nm Fig. 3. Results of zeta potential of optimized formulation F4 of floating microsphere was found --35.8 mV Fig. 4.

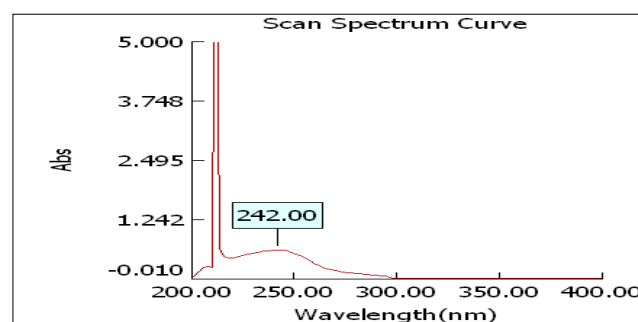


Figure 1 UV spectra of pure drug (ACV)

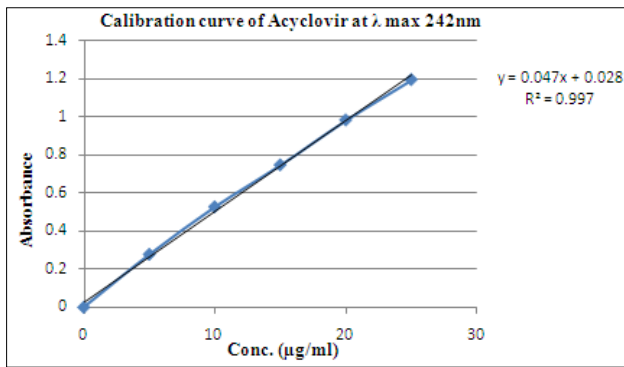


Figure 2 Calibration curve of ACV in 0.1 N HCl at 242 nm

Table 2 Percentage yield for different formulation

Formulation	Percentage Yield
F1	69.98±0.98
F2	70.12±0.95
F3	73.32±0.65
F4	65.56±0.58
F5	62.23±0.85
F6	66.56±0.32

Table 3 Drug entrapment for different formulations

Formulation	Drug entrapment (% w/w) of prepared microsphere
F1	65.56±0.95
F2	69.98±0.65
F3	75.56±0.23
F4	62.23±0.54
F5	59.98±0.52
F6	63.32±0.45

\*Average of three determination (n=3)

Table 4 Floating lag time and percentage buoyancy of floating microsphere

Formulation	Floating Lag Time (Sec.)	Percentage Buoyancy
F1	45±3	55.65±0.65 to 76.65±0.52
F2	49±2	66.65±0.69
F3	32±4	76.65±0.52
F4	45±3	56.65±0.47
F5	43±2	65.56±0.32
F6	48±3	73.21±0.45

Table 5 Release study data of formulation F1-F6

Time (hr)	Percentage Drug Release						29.98
	F1	F2	F3	F4	F5	F6	
0.5	33.25	30.25	25.56	29.98	20.23	15.56	39.98
1	46.65	41.25	30.56	39.98	26.65	23.32	46.65
2	59.98	52.36	42.23	46.65	31.25	33.32	63.32
4	73.23	69.98	60.32	63.32	46.65	45.56	80.56
6	89.98	85.56	75.56	80.56	53.32	51.48	92.23
8	99.23	90.23	82.56	92.23	63.32	56.65	99.23
10	-	99.89	89.98	99.23	72.23	65.56	-
12	-	-	98.85	-	85.56	73.32	29.98

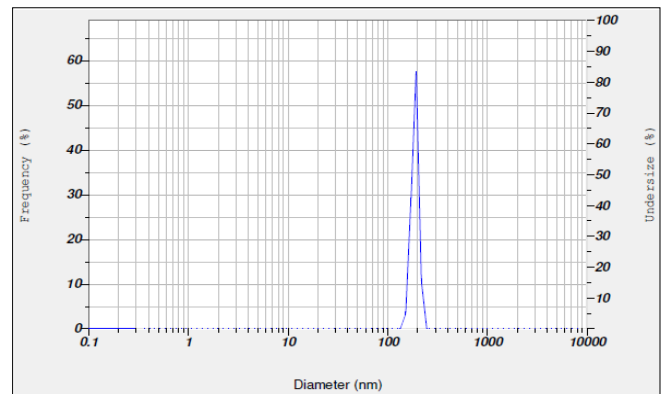


Figure 3 Particle size data of optimized microsphere formulation F3

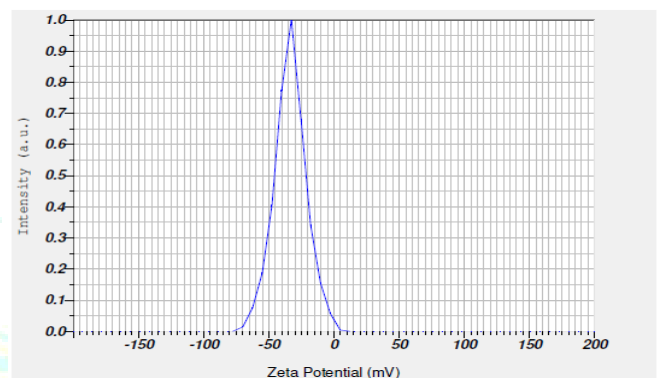


Figure 4 Zeta potential data of floating microsphere F3

The drug release from floating microspheres was found to be 98.85 % at the end of 12 h for F3 Table 5. The *In vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equation, in order to determine the mechanism of drug release. When the regression coefficient values were compared, it was observed that an 'r' value of microsphere was maximum zero order i.e 0.958 hence indicating drug releases from formulations was found to follow zero order for floating microsphere Table 6 & 7 and Fig. 5 & 6. According to ICH guidelines, 3 months accelerated stability study at 40±2°C and 75±5% RH optimized formulations (F3) was carried out. It showed negligible change over time for parameters like appearance, drug content, dissolution and assay etc., No significant difference observed in the drug content between initial and formulations stored at 40±2°C & 75±5% RH for 3 months.

Table 6 Release Kinetics of optimized formulation of microsphere F-3

Time (h)	Square Root of Time(h) <sup>1/2</sup>	Log Time	Cumulative% Drug Release	Log Cumulative % Drug Released	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	25.56	1.408	74.44	1.872
1	1	0	30.56	1.485	69.44	1.842
2	1.414	0.301	42.23	1.626	57.77	1.762
4	2	0.602	60.32	1.780	39.68	1.599
6	2.449	0.778	75.56	1.878	24.44	1.388
8	2.828	0.903	82.56	1.917	17.44	1.242
10	3.162	1	89.98	1.954	10.02	1.001
12	3.464	1.079	98.85	1.995	1.15	0.061

Table 7 Comparative study of regression coefficient for selection of optimized Formulation F-3

Release Kinetics	Zero order	First order
R <sup>2</sup>	0.958	0.866

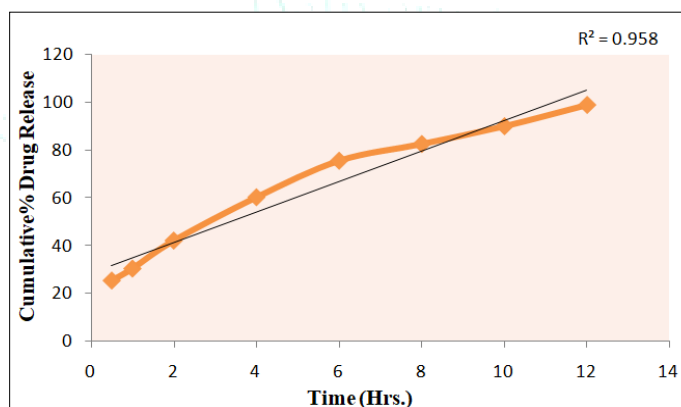


Figure 5 Zero order release kinetics

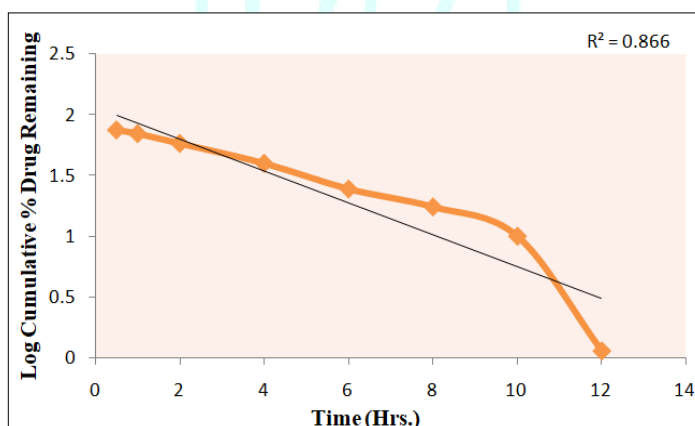


Figure 6 First order release kinetics

**CONCLUSION**

In vitro data obtained for floating microspheres of ACV showed excellent floatability, good buoyancy and prolonged drug release. Microspheres of different size and drug content

could be obtained by varying the formulation variables. Thus, the prepared floating microspheres may prove to be potential candidates for multiple-unit delivery devices adaptable to any intragastric condition.

## REFERENCES

1. Kaushik K, C haurasia D, Chaurasia H, Mishra SK, Bhardwaj P. Development and characterization of floating alginate beads for gastroretentive drug delivery system. *Acta Pharma Sci* 2011; 53(4): 551-562.
2. Tadros MI. Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: development, optimization and in vitro-in vivo evaluation in healthy human volunteers. *Eur J Pharm Biopharm* 2010; 74(2): 332-339.
3. Baumgartner S, Kristl J, Vrečer F, Vodopivec P, Zorko B. Optimisation of floating matrix tablets and evaluation of their gastric residence time. *Int J Pharm* 2000; 195(1-2): 125-135.
4. Bulgarelli E, Forni F, Bernabei MT. Effect of matrix composition and process conditions on casein-gelatin beads floating properties. *Int J Pharm* 2000; 198(2): 157-165.
5. Davoudi ET, Noordin MI, Kadivar A, Kamalidehghan B, Farjam AS, Javar HA. Preparation and characterization of a gastric floating dosage form of capecitabine. *Biomed Res Int* 2013; doi: 10.1155/2013/495319.
6. Singh BN, Kim KH. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. *J Control Release* 2000; 63(3): 235-259.
7. Garg R, Gupta G. Progress in controlled gastroretentive delivery systems. *Trop J Pharm Res* 2008; 7(3): 1055-1066.
8. Chen J, Park K. Synthesis of fast-swelling, superporous sucrose hydrogels. *Carbohydr Polym* 2000; 41(3): 259-268.
9. Shaikh R, Singh TRR, Garland MJ, Woolfson AD, Donnelly RF. Mucoadhesive drug delivery systems. *J Pharm Bioallied Sci* 2011; 3(1): 89-100.
10. Boddupalli BM, Mohammed ZNK, Nath RA, Banji D. Mucoadhesive drug delivery system: an overview. *J Adv Pharm Technol Res* 2010; 1(4): 381-387.
11. Kedzierewicz F, Thouvenot P, Lemut J, Etienne A, Hoffman M, Maincent P. Evaluation of peroral silicone dosage forms in humans by gamma-scintigraphy. *J Control Release* 1999; 58(2): 195-205.
12. Rouge N, Allémann E, Gex-Fabry M, Balant L, Cole ET, Buri P, et al. Comparative pharmacokinetic study of a floating multiple-unit capsule, a high density multiple-unit capsule and an immediate-release tablet containing 25 mg atenolol. *Pharm Acta Helv* 1998; 73(2): 81-87.
13. Prajapati PH, Nakum VV, Patel CN. Formulation and evaluation of floating matrix tablet of stavudine. *Int J Pharm Investig* 2012; 2(2): 83-89.
14. Chaturvedi K, Umadevi S, Vaghani S. Floating matrix dosage form for propranolol hydrochloride based on gas formation technique: development and in vitro evaluation. *Sci Pharm* 2010; 78(4): 927-939.
15. Murata Y, Sasaki N, Miyamoto E, Kawashima S. Use of floating alginate gel beads for stomach-specific drug delivery. *Eur J Pharm Biopharm* 2000; 50(2): 221-226.
16. Jagtap YM, Bhujbal RK, Ranade AN, Ranpise NS. Effect of various polymers concentrations on physicochemical properties of floating microspheres. *Indian J Pharm Sci* 2012; 74(6): 512-520.
17. Jain AK, Jain CP, Tanwar YS, Naruka PS. Formulation, characterization and in vitro evaluation of floating microspheres of famotidine as a gastro retentive dosage form. *Asian J Pharm* 2009; 3(3): 222-226.
18. El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Preparation and evaluation of ketoprofen floating oral delivery system. *Int J Pharm* 2001; 220(1-2): 13-21.
19. El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Development of floating microspheres to improve oral bioavailability of cefpodoxime proxetil. *Int J Pharma* 2001; 220: 13-21.
20. Wakde PH, K asliwal RH, Mane SB. Design and fabrication of gastroretentive bilayer floating tablet of propranolol HCl using natural polymer. *Int J Pharm Sci Res* 2013; 4(12): 4715-4728.
21. Pandya N, Pandya M, Bhaskar VH. Preparation and in vitro characterization of porous carrier-based glipizide floating microspheres for gastric delivery. *J Young Pharm* 2011; 3(2): 97-104.
22. Jagdale SC, Agavekar AJ, Pandya SV, Kuchekar BS, Chabukswar AR. Formulation and evaluation of gastroretentive drug delivery system of propranolol hydrochloride. *AAPS PharmSciTech* 2009; 10(3): 1071-1079.
23. Hussain MN, Masum MAA, Akhter S, Sharmin F, Reza MS. Formulation and evaluation of gastro retentive floating tablets of simvastatin using hydrophilic rate retardant. *Bangladesh Pharm J* 2012; 15(2): 119-126.
24. de Miranda P, Blum MR. Pharmacokinetics of acyclovir after intravenous and oral administration. *J Antimicrob Chemother.* 1983; 12 Suppl B:29-37.
25. Steingrimsdottir H, Gruber A, Palm C, Grimfors G, Kalin M, Eksborg S. Bioavailability of aciclovir after oral administration of aciclovir and its prodrug valaciclovir to patients with leukopenia after chemotherapy. *Antimicrob Agents Chemother.* 2000; 44(1):207-9. PMID: 10602752
26. Bras AP, Sitar DS, Aoki FY. Comparative bioavailability of acyclovir from oral valacyclovir and acyclovir in patients treated for recurrent genital herpes simplex virus infection. *Can J Clin Pharmacol.* 2001; 8(4):207-11. PMID: 11743593
27. Haznedar S, Dortunc B. Preparation and in vitro evaluation of eudragit microspheres containing acetazolamide. *Int J Pharm* 2004; 269(1): 131-140.
28. Tanwar Y S, Naruka P S, Ojha G R. Development and evaluation of floating microspheres of verapamil hydrochloride. *Brazilian Journal of Pharmaceutical Sciences* vol. 43, n. 4, out./dez., 2007, 529-534.
29. Deepa MK, Karthikeyan M. Cefpodoxime Proxetil Floating Microsphere: Formulation and In vitro Evaluation. *Iran J Pharm Sci* 2009; 5(2):69-72.
30. Brahamankar DM, Jaiswal SB. Biopharmaceutics and pharmacokinetics a treatise, pharmacokinetics: basic consideration. 2nd ed. Vallabh Prakashan; 2009. pp. 240e3.
31. Higuchi T. Mechanism of sustained action medication, theoretical analysis of rate of release of solid drugs dispersed in solid matrices. *J Pharm Sci* 1963; 52:1145e9.
32. Korsmeyer RW, Gury R, Doelker E, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymer. *Int J Pharm* 1983; 15:25e35.