Research Article

Formulation and Evaluation of Gastroretentive Floating Drug Delivery System of an Acyclovir

Shivanand K*[1], Kishor S[1] and Divakar Goli[1]

[1]Acharya & B. M Reddy College of Pharmacy, Acharya Dr. Sarvepalli Radhakrishnan Road, Soladevanahalli, Bangalore–560 090

ABSTRACT

Acyclovir is an antiviral drug used in the treatment of Herpes simplex infection and Varicella zoster infection. Acyclovir has shorter half life, having maximum absorption in stomach and upper part of the small intestine. Due to low gastric retention time, the bioavailability of drug is low as the large portion of drug misses the absorption window. The purpose of this study was to develop a gastroretentive floating drug delivery system to prolong the gastric residence time after oral administration, at a particular site and controlling the release of drug especially useful for achieving controlled plasma level as well as improving bioavailability. Formulations were designed using hydroxypropyl methylcellulose (HPMC K15M, HPMC K100M) and xanthan gum as release-retarding polymer(s) and sodium bicarbonate and tartaric acid as a gas former. Swelling ability, floating behaviour and drug release studies were conducted in simulated gastric fluid. The tablets showed acceptable physicochemical properties. Drug release from the tablets was dependant on the ratio and type of the polymer used in the formulation. Swelling studies indicated significant water uptake and contributed in drug release and gastroretention. The higher viscosity polymer had been seen to inhibit the release of acyclovir from the floating drug delivery system. Best formulation was checked for stability studies for 2 months which showed no significant changes in the parameters.

Keywords: Acyclovir, HPMC, Xanthan gum, Gastroretentive floating drug delivery.

INTRODUCTION

Gastric residence time (GRT) is an important factor affecting the drug bioavailability from dosage forms. Because of the short gastric emptying time, numbers of drug delivery systems are suffering with the low drug release in its absorption window that ultimately leads to scarce bioavailability of the administered dose.[1] Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients. The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, flotation, sedimentation, expansion modified shape systems or by the simultaneous administration of pharmacological agent, that delay gastric emptying.[2] Among these systems, floating drug delivery system have been most commonly used. Floating drug delivery system has less density [1.004 gm/cm^3] than gastric fluid so they buoyant in fluid and show sustained release.[3]

Herpes Simplex Virus (HSV) is a member of family of Herpes Viridae, a DNA virus. There are two types of Herpes Simplex Viruses (HSV). Viz HSV type 1 and type 2. HSV type 1 is the herpes virus that is usually responsible for cold sores of the mouth, the so called "fever blisters". HSV type 2 is the one that most commonly causes genital herpes. The drugs that are commonly used for herpes simplex are Acyclovir, Valaclovir and Famciclovir. Acyclovir, the first agent

Received Date : 27-05-2013
Revised Date : 7-10-2013
Accepted Date : 11-10-2013

DOI: 10.5530/rjps.2013.3.5

Address for correspondence
Dr. Shivanand Kalyanappa*
Prof. & HOD, Department of Pharmaceutics
Acharya & B M Reddy College of Pharmacy,
Acharya Dr. Sarvepalli Radhakrishnan road,
Soladevanahalli,
Bangalore-560 090
Mob No. +91-9481479977
E-mail:
shivanand@acharya.ac.in

www.rjps.in

to be licensed for the treatment of herpes simplex virus infections, is the most widely used drug for infections such as cutaneous herpes, genital herpes, chicken pox, varicella zoster infections.

The presently available conventional therapy is associated with a number of drawbacks such as highly variable absorption and low bioavailability (30%) after oral administration. The main problem with the therapeutic effectiveness of acyclovir is its absorption, which is highly variable and dose dependent thus reducing the bioavailability to 30% and half life is 3 hrs. Acyclovir is soluble in acidic pH and is predominantly absorbed from stomach.[4]

In context of the above principles, a strong need was recognized for the development of a dosage form to deliver the drug in the stomach and to increase the efficiency of the drug, providing sustained action. The present investigation applied a systematic approach to the development of gastroretentive floating dosage form.

MATERIALS AND METHODS

Acyclovir was obtained as gift sample from Bakul Pharma Pvt Ltd, Mumbai. HPMC (K15 M, K100 M) and Xanthan gum were obtained as a gift sample from KAPL, Bangalore. Sodium bi carbonate, tartaric acid, polyvinyl pyrrolidine K30, magnesium stearate, talc were taken from karnataka fine chem, Bangalore. All other chemicals used in the study were of analytical grade.

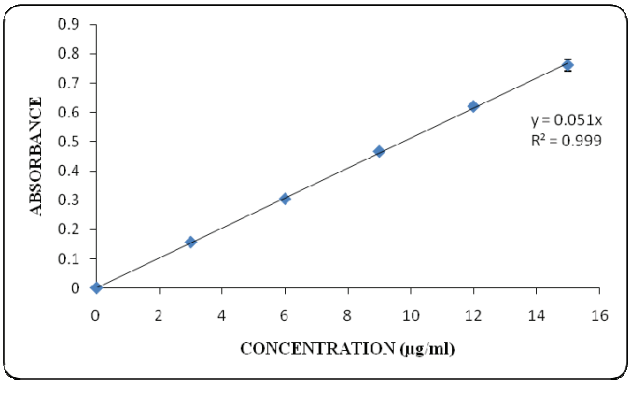

Figure 1: Calibration curve of Acyclovir in Simulated gastric fluid.

Estimation of Acyclovir: Accurately weighed 50 mg of Acyclovir was made to dissolve in simulated gastric fluid and the solution was made up to 50 ml with simulated gastric fluid. From this stock solution 10 ml was withdrawn and transferred into 100 ml volumetric flask. Volume was made with simulated gastric fluid in order to get standard stock solution containing 100 µg/ml. Take the standard stock solution, then a series of dilutions of 0.3, 0.6, 0.9, 1.2 and 1.5 ml were taken in separate 10 ml volumetric flasks and the volume was made up by simulated gastric fluid. Absorbance of these solutions was measured against blank of simulated gastric fluid at 255 nm for Acyclovir using UV-Spectrometer. Then a graph was plotted by taking concentration on x-axis and absorbance on y-axis which gives a straight line (Figure 1).

Preparation of gastroretentive floating tablets of Acyclovir: Gastroretentive floating tablets containing Acyclovir were prepared by direct compression technique using varying concentrations of different grades of HPMC and xanthan gum as release retardant polymers with sodium bicarbonate and citric acid as a gas generating agent (designated as F1 to F7 in Table 1). All the ingredients were accurately weighed and passed through sieve number 30 accordingly. Then, except Magnesium stearate all other ingredients were blended uniformly in glass mortar, after sufficient mixing of drug as well as other components, magnesium stearate was added, as post lubricant and further mixed for additional 2–3 minutes. Tablets were compressed on a Rotary tablet punching machine using flat surfaced, round shaped punches of 12 mm diameter.

Evaluation of tablets

The formulated tablets were evaluated for the following physicochemical characteristics (Table 2).

Table 1: Formulation Chart of Gastroretentive Floating Tablets of Acyclovir

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)
Acyclovir	200	200	200	200	200	200	200
HPMC K15M	-	70	140	35	35	105	105
HPMC K100M	105	70	35	140	35	105	-
Xanthan gum	105	70	35	35	140	-	105
Sodium bicarbonate	120	120	120	120	120	120	120
Tartaric acid	30	30	30	30	30	30	30
PVP K30	30	30	30	30	30	30	30
Talc	5	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5	5

Tablet thickness: Thickness of tablets is important for uniformity of tablet size. Thickness was measured using screw gauze on randomly selected samples.[5]

Tablet hardness: The resistance of tablet for shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Pfizer hardness tester.[5]

Friability: Friability is the resistance of the tablet to withstand the effect of abrasion and shock. Roche friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again and the percentage loss in tablet weight was determined.[5]

Weight variation: Twenty tablets were weighed individually and the average weight was determined. Then percentage deviation from the average weight was calculated. According to IP standards, not more than two of the individual tablets deviate from the average weight by more than the percentage shown in the table 6 and none deviates by more than twice that percentage.[6]

Uniformity of drug content: Weigh and finely powder 20 tablets. To a quantity of the powdered tablets containing 0.1 g of Acyclovir add 60 ml of 0.1 M sodium hydroxide and disperse with the aid of ultrasound for 15 minutes. Add a sufficient quantity of 0.1 M sodium hydroxide to produce 100 ml, mix well and filter. To 15 ml of the filtrate add 50 ml of water and 5.8 ml of 2 M hydrochloric acid and sufficient water to produce 100 ml. To 5 ml of the solution add sufficient 0.1 M hydrochloric acid to produce 50 ml and mix well. Measure the absorbance of the resulting solution at the maximum at 255 nm, using 0.1 M hydrochloric acid in the reference cell.[7]

Floating lag time: The floating lag time was carried out in a beaker containing 100 ml of 0.1 N HCl as a testing medium maintained at 37°C. The time required for the tablet to rise to the surface and float was determined as floating lag time.[8] The floating lag time of tablets depend upon the type and amount of polymers used. For floating system, the ideal matrix forming polymer should be highly permeable to dissolution media in order to initiate rapid generation of CO_2 and should be permeable for CO_2 to promote floating properties.[8]

Floating time: Floating time was the time, during which the tablet floats in 0.1 N HCl dissolution medium (including floating lag time).[8]

Swelling characteristics: The swelling properties of floating tablets containing drug were determined by placing the tablets in the USP dissolution testing apparatus II, in 900 ml of 0.1 N HCl at 37 ± 0.5°C, rotated at 50 rpm. The tablets were removed periodically from dissolution medium, blotted to remove excess water and weighed. Swelling characteristics were expressed in terms of percentage water uptake (WU %).[8]

$$WU\ \% = \frac{\text{Wt. of swollen tablet} - \text{Initial wt. of the tablet}}{\text{Initial wt. of the tablet}} \times 100$$

Dissolution studies: The release rate of acyclovir from floating tablets was determined using USP dissolution testing apparatus II (paddle type). The dissolution test was performed using 900 ml of simulated gastric fluid containing at 37 ± 0.5°C and 50 rpm. Aliquot volume was withdrawn from the dissolution apparatus hourly for 12 h and the samples were replaced with fresh dissolution medium. After filtration, the amount of drug released was determined from the standard calibration curve of pure drug.[9]

Kinetics modelling of drug dissolution profiles: The *in vitro* release data obtained were fitted in to various kinetic models. Correlation coefficients of formulation F3 batch showed higher correlation with zero order plots than higuchi and first order. So predominant drug release mechanism is controlled release.

RESULTS AND DISCUSSION

FTIR studies: The FTIR studies of the pure drug and the drug-polymer physical mixture was carried out to study the interaction between the drug and the polymer used. The FTIR spectrums of the pure drug (alone) and with the polymers are depicted in the Figure 5, 6, 7 and the Figure 8 respectively. The FTIR spectrum of the pure drug shows the characteristic FTIR peaks at 752 cm^{-1} (N–H bending), 1308 cm^{-1} (C=N stretching), 1631 cm^{-1} (C=O stretching), 1540 cm^{-1} (N–H bending). As all the FTIR peaks of the drug were observed in the drug: HPMC K15 M, drug: HPMC K100 M and drug: Xanthan gum (physical mixture), the FTIR studies revealed the absence of drug- polymer interaction in the solid state.

Evaluation of tablets: The objective of the present study was to prepare gastroretentive floating tablets of an antiviral drug (Acyclovir). These tablets were developed to prolong the gastric residence time and to increase the bioavailability of the drug. Acyclovir is chosen as a model drug because it is greater absorption in the stomach and upper part of the small intestine. The tablets were prepared by direct compression method, using polymers such as HPMC K15 M, HPMC K100 M and Xanthan gum. Tablets were evaluated for physical characteristics such as hardness, thickness, weight variation and floating capacity. The *in vitro* release characteristics were evaluated for 12hrs. Totally

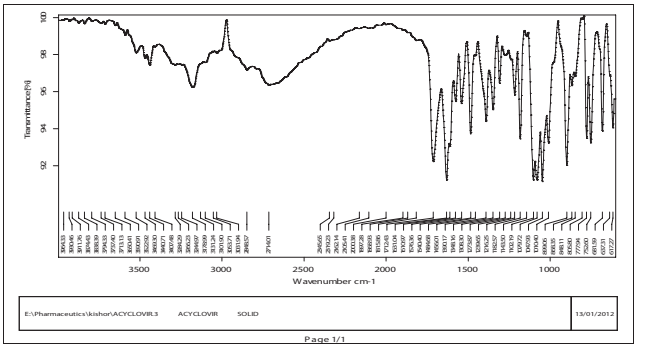

Figure 5: FT-IR (ATR) spectra of pure Acyclovir.

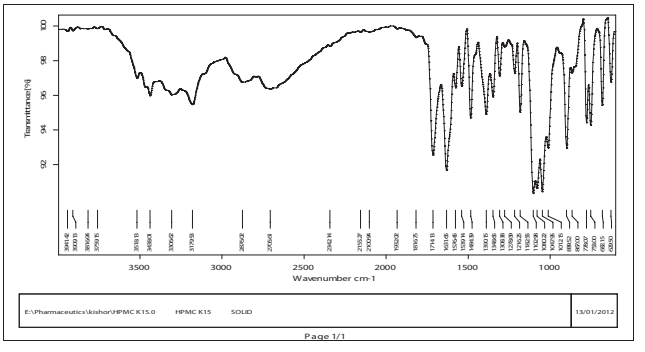

Figure 6: FT-IR (ATR) spectra of Acyclovir with HPMC K15M.

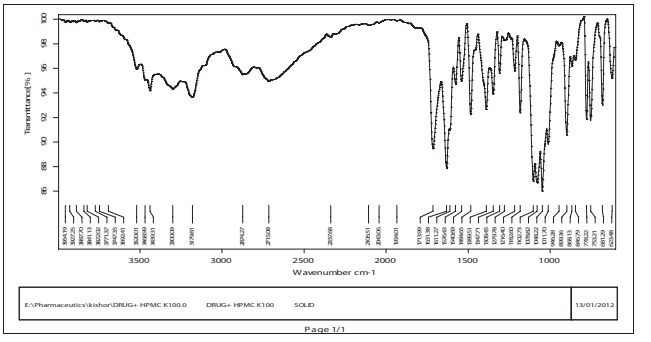

Figure 7: FT-IR (ATR) spectra of Acyclovir with HPMC K100M.

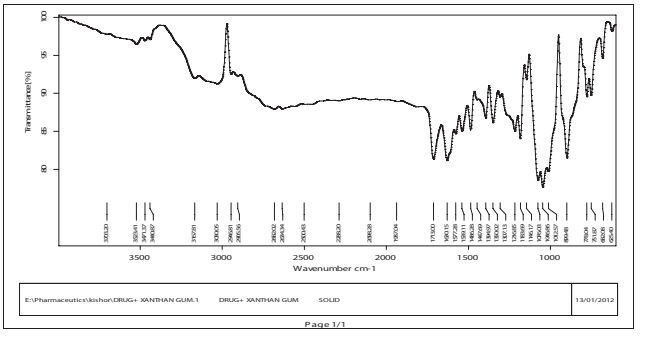

Figure 8: FT-IR (ATR) spectra of Acyclovir with Xanthan gum.

7 different formulations of Acyclovir were prepared by using different polymers like HPMC K15 M, HPMC K100 M and Xanthan gum (Table 1). All the formulations fulfilled the specifications of the various quality control parameters (Table 2): weight variation, hardness, thickness, friability, drug content, floating lag time and total floating time. The values of hardness of the different formulations ranged from 6.2 ± 0.30 kg/cm^2 to 6.8 ± 0.52 kg/cm^2.

The values of thickness of the different batches ranged from 3.56 ± 0.02 mm to 3.58 ± 0.03 mm. The values of friability of the different batches ranged from 0.202 to 0.435 % loss which was less than 1% as per official requirement of IP. All the batches exhibited uniformity of drug content. The values of drug content of the different formulations ranged from 98.80 to 101.30% which was within the required limits. The values of floating lag time of all the formulations (Table 2) ranged from 49.00 ± 1.00 sec to 150.66 ± 2.51 sec. All the formulations exhibited good matrix integrity. For floating system, the ideal matrix forming polymer should be highly permeable to dissolution media in order to initiate rapid generation of CO_2 and should be permeable for CO_2 to promote floating properties. The sodium bicarbonate and tartaric acid was used as a gas generating agent in order to float the tablet. The sodium bicarbonate and tartaric acid induces CO_2 generation in the presence of dissolution medium (0.1N HCl). The gas generated is trapped and protected within the gel formed by hydration of the polymer, thus decreasing the density of the tablet below 1 gm/ml and the tablet becomes buoyant.

Swelling characteristics: The percentage water uptake (%WU) of the formulations varied from 140.06 ± 3.44% to 158.81 ± 1.58% at 6th h. The percentage water uptake was found to improve by increasing the concentration of Xanthan gum in formulations.

***In vitro* drug release studies:** The release of Acyclovir from floating tablets varied according to the types and proportion of matrix forming polymers.

HPMC K15 M based formulations: In HPMC K15 M based formulations it has been concluded that an increase in the proportion of matrix forming polymer HPMC K15 M, increases the viscosity of gel and also it retards the drug release which leads to better control of polymers on the release of Acyclovir. The drug release was good with formulation F3 which was 96.17 ± 1.56 % in 12 h from among the formulations.

HPMC K100 M based Formulations: In HPMC K100M based formulations it has been concluded that an increase in the proportion of matrix forming polymer HPMC K100 M, increases the swelling and viscosity of the gel and also it retards the drug release from the polymer matrix. The drug release was good with formulation F4 which was 90.82 ± 1.67% in 12 h from among the formulations. Among the HPMC grades, the tablets prepared with an increased proportion of HPMC K15 M along with other polymers in equal proportion showed a drug release of 84.08 ± 1.66 % in

Table 2: Physico chemical parameters of gastroretentive floating tablets of an Acyclovir

Formulation code	Thickness (mm)	Hardness (kg/cm²)	Friability (% loss)	Weight Variation (mg)	Drug content (%)	Floating Lag Time (sec)	Floating Time (h)
F1	3.56 ± 0.02	6.3 ± 0.11	0.398	601.39 ± 4.06	100.32	59.33 ± 2.51	>12
F2	3.57 ± 0.03	6.4 ± 0.56	0.321	600.31 ± 4.87	99.90	69.21 ± 1.16	>12
F3	3.56 ± 0.04	6.7 ± 0.88	0.218	599.74 ± 5.11	100.23	49.00 ± 1.00	>12
F4	3.57 ± 0.06	6.4 ± 0.14	0.312	601.41 ± 5.08	99.25	59.33 ± 2.52	>12
F5	3.58 ± 0.03	6.6 ± 0.7	0.286	602.19 ± 4.21	100.70	150.66 ± 2.51	>12
F6	3.58 ± 0.03	6.8 ± 0.52	0.202	598.96 ± 4.08	98.80	93.33 ± 2.52	>12
F7	3.56 ± 0.03	6.2 ± 0.30	0.435	600.21 ± 4.79	101.30	62.66 ± 3.05	>12

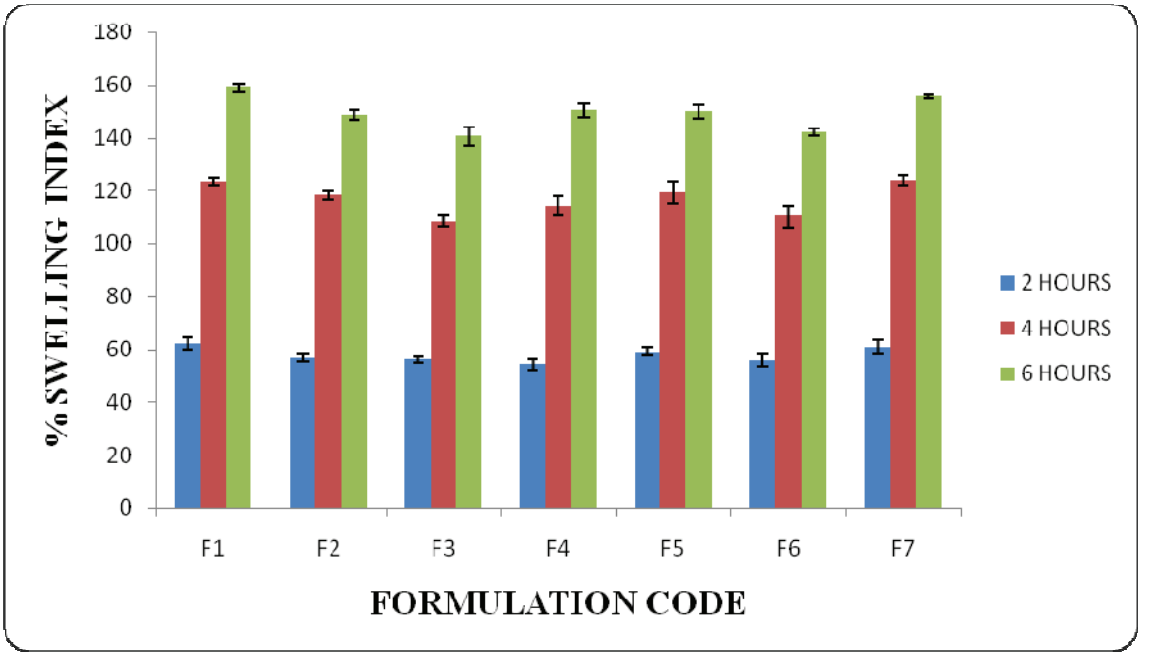

Figure 2: Swelling index of gastroretentive floating tablets of acyclovir.

12 h and tablets prepared with an increased proportion of HPMC K100 M along with other polymers in equal proportion showed a drug release of 82.88 ± 1.44% in 12 h. From this it is concluded that high degree of swelling of the polymer due to water uptake, which increases the swelling and viscosity, retards the drug release from the polymer matrix.

Xanthan gum based Formulations: In Xanthan gum based formulations, it has been concluded that an increase in the proportion of the matrix forming polymer xanthan gum, increases the swelling and viscosity of the gel and also it retards the drug release. The higher the swelling due to water uptake the more it retards the release of drug from the matrix. The duration of drug release was slower with formulation F5 which was only about 88.68 ± 2.75% in 12 h from among the formulations.

CONCLUSION

Formulations were developed by using release rate controlling and gel forming polymers like HPMC (K15M, K100M) and Xanthan gum by direct compression method with the incorporation of sodium bicarbonate as gas generating agent. Formulation F3 prolonged the drug release for longer period of time of 12 h and it showed a drug release of 96.17 ± 1.56%. The *in vitro* release data obtained were fitted in to various kinetic models. Correlation coefficients of formulation F3 showed higher correlation with zero order plot. So, predominant drug release mechanism is controlled release.

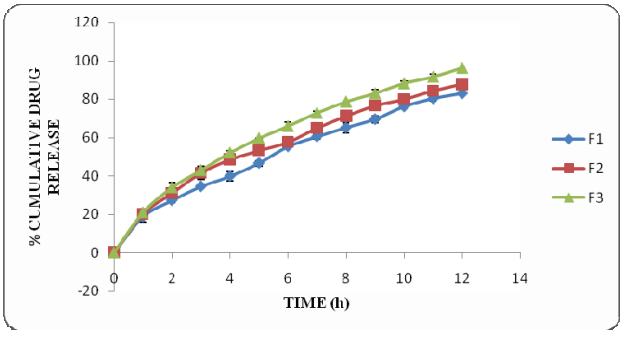

Figure 3: Cumulative drug release profile of acyclovir gastroretentive floating tablets from formulation 1 to formulation 3.

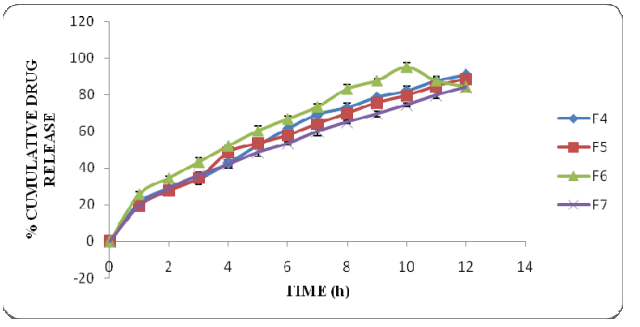

Figure 4: Cumulative drug release profile of acyclovir gastroretentive floating tablets from formulation 4 to formulation 7.

So formulation F3 is selected as a best formulation. The most satisfactory formulation had showed no major change in physicochemical properties, drug content, floating properties and *in vitro* dissolution pattern after storage at 30 ± 2°C / 65 ± 5 % RH and at 40 ± 2°C / 75 ± 5 % RH, there was no change in the above parameters during stability studies for two months. Therefore, it was concluded that the most satisfactory formulation satisfied the physicochemical parameters, floating properties, drug content requirement, *in vitro* drug release profile requirements and stability requirements.

ACKNOWLEDGEMENT

We are thankful to Bakul Pharma Pvt Ltd, Mumbai for donating gift sample of Acyclovir and KAPL, Bangalore for donating gift sample of HPMC (K15M, K100M) and Xanthan gum. We are thankful to the Chairman, Principal, and faculty of Acharya & BM Reddy College of pharmacy, Bangalore for their support during this project.

REFERENCES

1. Raja MD, Narra Kishore, Dhanalekshmi UM, Senthil kumar C , Rangaraj G, Neelakanta Reddy P, et al. Formulation and *in vitro* evaluation of floating alginate gel beads for site specific delivery of acyclovir. J Global Trends Pharma sci. 2011; 2(1):31–42.
2. Mayavanshi AV, Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs: a review. Res J Pharm Tech. 2008; 1(4): 345–8.
3. Singh LP, Rajesh KS, Umalkar DG, Chauhan VK, Rana V, Vasava KS. Floating effervescent tablet: review. J. Pharm. Biomedical Sci. 2011; 5(5):1–6.
4. Devi KV, Bhosale UV. Formulation and optimization of polymeric nano drug delivery system of acyclovir using 3^2 full factorial design. Int. J. Pharm. Res. 2009; 1(1): 644–53.
5. Leon Lachman et al; The theory and practice of industrial pharmacy. 3rd edition. Mumbai: Varghese Publishing House. 1990: 296–302.
6. Indian Pharmacopoeia. Government of India, Ministry of Health and Family Welfare. Vol. ii Delhi: Controller of Publications. 1996: 182.
7. British Pharmacopoeia. London: British Pharmacopoeia commission office; 2009: 2394–5.
8. Patel MP, Patel MM, Patel DH, Patel KN. Formulation development, optimization and evaluation of famotidine floating matrix tablets. Int. J. Pharm. Sci. Drug Res. 2009; 1(2):85–90.
9. Patil VS, Gaikwad PD, Banker VH, Pawar SP. Formulation and evaluation of floating matrix tablet of locally acting h2-antagonist. Int. J. Pharmacy Tech. 2010; 2(3):528–40.
10. Rang HP, Dale MM, Ritter JM, Flower RJ. Pharmacology. 6th edition. United Kingdom: 2007: 684–5.
11. Satoskar RS, Bhandarkar SD, Rege NN. Pharmacology and Pharmacotherapeutics. 21st edition. India: 2009:792–4.
12. Raymond C, Paul J, Weller P. Handbook of Pharmaceutical Excipients. 4th edition. London Pharmaceutical Press. 2003: 346–90.
13. Puneeth KP, Kavitha K, Tamizh MT. Development and evaluation of rosiglitazone maleate floating tablets using natural gums. Int. J. Pharm Tech Res. 2010; 2(3):1662–9.
14. Sauzet C, Bruno MC, Nicolas M, Kister J, Piccerelle P, Prinderre P. An innovative floating gastro retentive dosage system: formulation and in vitro evaluation. Int. J. Pharm. 2009; 378(1):23–9.