Research Article
CODEN (USA): IJPLCP

[Naveen et al., 4(3): March., 2013]
ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES

# Formulation design and *in vitro* evaluations for stomach specific drug delivery system of anti retroviral drug-acyclovir

**N. Raghavendra Naveen*, T. S. Nagaraja, D. R. Bharathi and J. Naga Subba Reddy**
Department of Pharmaceutics, SJM College of Pharmacy, Chitradurga, (Karnataka) - India

## Abstract

Floating matrix tablets or stomach specific drug delivery systems are designed 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. Due to low gastric retention time, the bioavailability of acyclovir is low as the large portion of drug misses the absorption window. The objective of this study was to develop a stomach specific drug delivery system of acyclovir using gas-forming agent like sodium bicarbonate and polymers like different grades of HPMC and xanthun gum. Tablets were prepared by direct compression using different concentrations of HPMC and xanthun gum. Tablets were evaluated for their physical characteristics, *viz*., hardness, friability, weight variation and floating properties. The floating lag time of all the formulations was within the prescribed limit (<10 minutes). All the formulations showed good buoyancy and swelling index properties. From *in vitro* drug release studies, it is concluded that all the formulation retarded the release of drug for twelve hours except AF-1 formulation. AF-8 formulation with 30% xanthun gum shows more controlled release of 60.22% at the end of 12hrs when compared to all other formulations.

Key-Words: Acyclovir, HPMC, Xanthun gum, *In vitro* drug release studies

## Introduction

Various approaches have been proposed to control the gastric residence of drug delivery systems in the upper part of the GIT including floating drug delivery systems (FDDS) [1, 2] high density DDS [3] mucoadhesive systems [4, 5, 6], swelling and expanding DDS [7], modified shape systems [8] and other delayed gastric devices [9]. FDDS is a gastroretentive dosage form (GRDF), which can prolong the gastric residence time (GRT) to produce an acceptable drug bioavailability [10, 11]. FDDS or hydrodynamically balanced systems have a bulk density lower than gastric fluid and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time [8].

Acyclovir is a potent antiviral drug with low toxicity used in treatment of herpes simplex infection & varicella zoster infection. It has maximum absorption in the stomach, and half life is 3 hrs. It is widely prescribed for the treatment of Herpes simplex virus infections, as well as in the treatment of Herpes zoster (shingles). Bioavailability of acyclovir is 10–20% when given orally owing to an important first pass metabolism.

*** Corresponding Author**
Email: raghavendra.naveen@gmail.com

Inorder It has an elimination half-life of 2-3 hours and has an absorption zone from the upper intestinal tract. Due to low gastric retention time, the bioavailability of drug is low as the large portion of drug misses the absorption window. Floating matrix tablets are designed 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 [12].

## Material and Methods

### Materials

Acyclovir was obtained as gift sample from Strides Arco, Bangalore. All grades of HPMC and Xanthan gum were obtained from Yarrow Chemicals, Mumbai. Sodium bi carbonate obtained from Fisher scientific, Mumbai. All other chemicals used in the study were of analytical grade.

### Method

#### Direct compression technique

The composition of different formulations of acyclovir floating tablets shown in Table 1. The powder mixture contains drug, controlled release polymers as for the formulae and lactose was used as the diluent, sodium bicarbonate added as effervescent agent. The blend was lubricated with magnesium

stearate for 3-5 min and talc was added as glidant. Then the mixed blend was then compressed into tablets by direct compression method using 8mm punches on a rotary tablet punching machine.

**EVALUATIONS**

**Pre compression parameters [13]**

The flow properties of blend (before compression) were characterized in terms of angle of repose, tapped density, bulk density, Carr's index and Hausner ratio.

**Post compression parameters[13]**

**(Physical Evaluation of Acyclovir Floating Tablets [13]**

The prepared floating tablets were evaluated for uniformity of weight using 20 tablets, Hardness (Monsanto tester), Friability using 10 tablets (Roche Type friabilator).

***In vitro* floating lag time**

The in vitro buoyancy was determined by floating lag time. The tablets were placed in a 100 ml beaker containing 0.1N HCl. The media was kept in stagnant condition and the temperature was maintained at 37°C. The time required for the tablet to rise to the surface and float was determined as floating lag time.

**Buoyancy / Floating test**

The randomly selected tablet from each formulation was kept in a 100ml beaker containing simulated gastric fluid pH 1.2 and temperature was maintained at 37±0.5°C, throughout the study. The duration of floating (floating time) is the time the tablet floats in the dissolution medium (including floating lag time which is the time required for the tablet to rise to the surface) is measured by visual observation.

**Determination of swelling index**

From each formulation, one tablet was weighed and placed in a beaker containing 200ml of 0.1N HCl buffer solution. After each hour the tablet was removed from beaker and weighed. The percentage weight gain by the tablet was calculated by using the formula.

$$\% SI = \frac{W_t - W_0}{W_0} X\ 100$$

S.I = Swelling index

Wt = Weight of tablet at time t

W0 = Weight of tablet before immersion

***In vitro* drug release**

The release of Acyclovir from floating tablets was determined by using Dissolution type II test apparatus.

The dissolution medium: 900 ml 0.1N HCl

Temperature : 37 ± 0.5°C

RPM : 50.

At specified time intervals, samples of 5 ml were withdrawn from the dissolution medium and that amount was replaced with fresh medium to maintain the volume constant. The samples were filtered and diluted to a suitable concentration with 0.1 N HCl. The absorbances of the diluted samples were measured at 255 nm for Acyclovir by using UV-Visible double beam spectrophotometer.

## Results and Discussion

**Pre compression parameters**

The powder blend of all formulations are evaluated for precompression parameters like angle of repose ,tapped density, bulk density, Carr's index and Hausner ratio. Results were given in table 2, which indicated good flow properties.

**Post compression parameters**

**Hardness of tablets:**

Hardenss of all formulations were found to be in the range 3.28 to 4.5 kg/cm$^2$.

**Friability Test:**

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

**Buoyancy / Floating test**

All the tablets were prepared by the effervescent approach. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in the presence of the dissolution medium (0.1N hydrochloric acid). The combination of sodium bicarbonate and citric acid provided desired floating ability and therefore this combination was selected for the formulation of the floating tablets.

The tablet floating lag time (FLT) was found to be minimum 15s and total floating time more than 12h. The floating lag time may be explained as a result of the time required for dissolution medium to penetrate the tablet matrix and develop the swollen layer for entrapment of $CO_2$ generated in situ. The tablet mass decreased progressively due to liberation of $CO_2$ and release of drug from the matrix. On the other hand, as solvent front penetrated the glassy polymer layer, the swelling of polymers caused an increase in volume of the tablet. The combined effect is a net reduction in density of the tablets, which prolongs the duration of floatation beyond 12h.

**Swelling index**

The swelling of the polymers used could be determined by water uptake of the tablet. The complete swelling was achieved by the end of 10 hours, so percent swelling was determined at the end of 10 hours for all the developed formulation. The values of swelling index of various batches were evaluated as shown in figure 1. There was a

significant increase in the percent swelling of the tablet with increase in concentration of polymers. After 10 hours swelling index was observed between 100.24 to 240.61 %.

***In vitro* dissolution studies**

The initial batches [AF1-AF2], made with HPMC K4M alone showed the complete release in 9 to 12 hrs. Tablets formulated with HPMC K15M alone (AF3), showed 94.17%.drug release in 12 hrs and where a formulation AF-4 showed a drug release in 12 hrs with 79.22% due to more concentration of HPMC K15M. Tablets formulated with HPMC K100M alone (AF-5), showed 82.26% drug release in 12 hrs and where a formulation AF-6 showed a drug release in 12 hrs with 66.38% due to more concentration of HPMC K100M. The formulations [AF7-AF8], made with xanthun gum showed controlled drug release of 74.25% and 60.22 at the end of 12hrs.

## Conclusion

Nowadays, controlling the drug release by gastroretentive drug delivery system has become the most popular method. A Gastroretentive system means retention of the drug in the GIT for long period of time and sustaining the effect of drug. There are various approaches to increase the gastric retention time of dosage form and floating system is one of the approaches for delivery of drugs which are absorbed from stomach and upper small intestine.

Acyclovir has less bioavailability and half life is 3 hrs and it has maximum absorption in the stomach so it is formulated as effervescent floating drug delivery system. For anti-retroviral therapy, the drug has to administer for long period of time and due to this more drug will be accumulated in the body, which ultimately increases the side effects. This targeted delivery of the drug through FDDS reduces the dose, duration of therapy and also the side effects. Natural polymer xanthun gum shows more controlled drug release (74.25 to 60.22% at the end of 12hrs) than other grades of HPMC. All grades of HPMC shows controlled drug release up to 10 to 12hrs.

## Acknowledgement

The authors are thankful to Dr.Shivamurthy Murugha Sharanaru, President, SJM Vidya Peetha for providing all necessary facilities through the Principal, SJM college of Pharmacy.

## References

1. X. Q. Xu, M. J. Sun, F. Zhi, *et al*. Floating matrix dosage form for phenoporlamine hydrochloride based on gas forming agent: *in vivo* and *in vitro* evaluation in health volunteers. Int. J. Pharm., 2006, 310: 139-145.
2. Y. Sato, Y. Kawasaki, H. Takeuchi, *et al*. *In vitro* evaluation of floating and drug releasing behaviors of hollow microspheres (microballons) prepared by the emulsion solvent diffusion method. Eur. J. Pharm. Biopharm., 2004, 57: 235-343.
3. **A.** J. Möes. Gastroretentive dosage forms. Crit. Rev. Ther. Drug Carrier Syst., 1993, 10: 143-159.
4. T. Dürig, R. Fassihi. Evaluation of fl oating and sticking extended release delivery systems: an unconventional dissolution test. J. Control. Rel., 2000, 67: 37-44.
5. M. Chavanpatil, P. Jain, S. Chaudhari, *et al*. Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofl oxacin. Int. J. pharm., 2006, 316: 86-92.
6. J. Wang, Y. Tabata, D. Bi, *et al*. Evaluation of gastric mucoadhesive properties of animated gelatine microspheres. J. Control. Rel., 2001, 73: 223-231.
7. M. Chavanpatil, P. Jain, S. Chaudhari, *et al*. Development of Sustained release gastroretentive drug delivery system of ofl oxacin: *in vitro* and *in vivo* evaluation. Int. J. Pharm., 2005, 304: 178-184.
8. B. N. Singh, K. H. Kim. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J. Control. Rel., 2000, 63: 235-259.
9. S. J. Hwang, H. Park, K. Park. Gastric retentive drugdelivery systems. Crit. Rev. Ther. Drug Carrier Syst., 1998, 15: 243-284.
10. L. Whitehead, J. T. Fell, H. L. Sharma, *et al*. Floating dosage forms: an *in vivo* study demonstrating prolonged gastric retention. J. Control. Rel., 1998, 55: 3-12.
11. P. L. Bardonnet, V. Faivre, W. J. Pugh, *et al*. Gastroretentive dosage forms: overview and special case of Helicobactor pylori. J. Control. Rel., 2006, 111: 1-18.
12. Devi Kusum V, Bhosale U.V. Formulation and optimization of polymeric Nano drug delivery system of acyclovir using $3^2$ Full factorial design. International Journal of PharmTech Research 2009; 1: 644-653.
13. T. Akelesh, S.B.Sapkal, R.Sivakumar, R.Jothi, R.Venkatnarayanan. Formulation development of gastro retentive floating tablet of acyclovir using natural gums. Der Pharmacia Lettre, 2011, 3(1):254-261.

**Table: 1: Formulation of acyclovir floating tablets**

| Ingredients(mg) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 |
|---|---|---|---|---|---|---|---|---|
| ACYCLOVIR | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| HPMCK4M | 45 | 90 | - | - | - | - | - | - |
| HPMC K15M | - | - | 45 | 90 | - | - | - | - |
| HPMC K 100M | - | - | - | - | 45 | 90 | - | - |
| Xanthun gum | - | - | - | - | - | - | 45 | 90 |
| $NaHCO_3$ | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| Citric Acid | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Mg. Stearate | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Talc | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Lactose | 114 | 69 | 114 | 69 | 114 | 69 | 114 | 69 |
| **Total weight** | 300 | 300 | 300 | 300 | 300 | 300 | 300 | 300 |

**Table 2: Pre compression evaluations for powder blend**

| | Angle of repose (θ)* | Bulk density (g/ml)* | Tapped density(g/ml)* | Carr`s index (%) | Hausner's ratio.* |
|---|---|---|---|---|---|
| **$AF_1$** | 28.32± 0.341 | 0.4033±0.014 | 0.4763± 0.017 | 14.61± 1.67 | 1.1810±0.026 |
| **$AF_2$** | 27.46± 0.173 | 0.4152±0.045 | 0.4792± 0.026 | 12.32± 1.53 | 1.1541±0.023 |
| **$AF_3$** | 26.28± 0.174 | 0.4186±0.024 | 0.4696± 0.084 | 12.37± 1.65 | 1.1218±0.023 |
| **$AF_4$** | 25.62 ±0.218 | 0.3912±0.016 | 0.4602± 0.036 | 13.48± 1.32 | 1.1763±0.062 |
| **$AF_5$** | 28.27 ±0.284 | 0.4106±0.052 | 0.4894 ±0.028 | 14.32± 1.71 | 1.1919±0.025 |
| **$AF_6$** | 25.82± 0.215 | 0.3807±0.029 | 0.4549± 0.039 | 13.63± 1.39 | 1.2067±0.034 |
| **$AF_7$** | 26.65± 0.055 | 0.4237±0.011 | 0.4901± 0.010 | 13.55± 1.88 | 1.1567± 0.003 |
| **$AF_8$** | 28.32± 0.225 | 0.4310±0.008 | 0.5050± 0.016 | 14.65± 1.95 | 1.1716± 0.023 |

All values are expressed as mean ± SD, n=3

Table 3: Post compression evaluations for prepared tablets

| Formulation code | Hardness (kg/cm$^2$) | Average weight (mg) | Friability (%) | Floating lag time (sec) | Total floating time (h) |
|---|---|---|---|---|---|
| $AF_1$ | 3.46 | 303 | 0.68±0.032 | 18 | >24 |
| $AF_2$ | 3.28 | 301 | 0.63±0.010 | 15 | >24 |
| $AF_3$ | 3.55 | 299 | 0.74±0.014 | 20 | >24 |
| $AF_4$ | 3.89 | 300 | 0.57±0.041 | 24 | >24 |
| $AF_5$ | 4.15 | 302 | 0.58±0.027 | 27 | >24 |
| $AF_6$ | 4.28 | 303 | 0.66±0.062 | 31 | >24 |
| $AF_7$ | 4.24 | 301 | 0.74±0.021 | 30 | >24 |
| $AF_8$ | 4.50 | 302 | 0.77±0.054 | 36 | >24 |

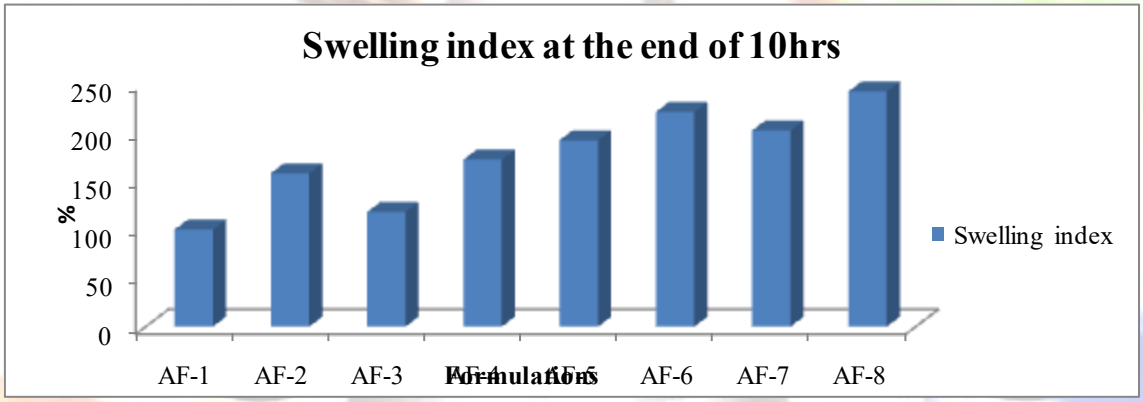


Fig. 1: Comparison of swelling index of all formulations at the end of 10 hrs

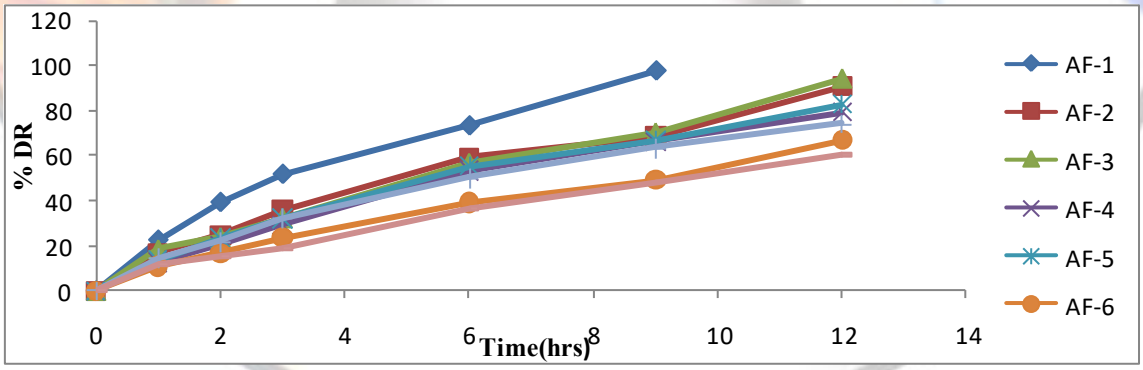


Fig. 2: *In Vitro* drug release profile of all formulations