WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 18, 798-810. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATON OF FLOATING TABLET OF ACYCLOVIR

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Article Received on
26 August 2018,

Revised on 16 Sept. 2018,
Accepted on 06 October 2018

DOI: 10.20959/wjpr201818-13488

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ABSTRACT

Floating drug delivery Systems has received considerable interest in the past few decades as they were overcome the drawbacks of conventional drug delivery system like frequent dosing, low bioavailability etc. relative to fast gastric-emptying time. wet granulation method was used for preparation of floating tablets. An optimum floating drug delivery System was defined as a system that remains in the stomach for sufficient interval of time and releases the active medicament in a sustained manner. These remain floating on the gastric contents. Thus resulting in prolonged pharmacological effect the improving the bioavailability of drug. The aim of writing this research was to prepare optimized floating tablets of Acyclovir which were evaluated for various parameters like Weight Variation, Hardness, Friability, Angle of Repose, Flow Rate, Bulk density, Tapped Density, Carr‟s Index, Thickness, Diameter, floating lag time, duration of floating time, In-vitro drug release studies, data treatment, in- vivo and Stability Studies of floating tablets.

KEYWORDS: Floating tablets**,** bioavailability, Gastro retentive, prolonged release.

INTRODUCTION

Floating drug delivery systems have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased gastric retention time and control of the fluctuation in plasma drug concentration.[1] Gastroretentive drug delivery systems are designed to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal

tract.[2] Modified release drug delivery system with prolonged residence time in the stomach is of particular interest for drugs- acting locally in the stomach; having an absorption window in the stomach or in the upper part of small intestine; those unstable in the intestinal or colonic environments; or those having low solubility at high pH values.[3] Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action A controlled drug delivery system with prolonged residence time in the stomach is of particular interest for drugs.[4] The controlled gastric retention of solid dosage forms may be achieved by mucoadhesive systems that causes bio adhesion to stomach mucosa.[5] Floating systems, swelling and expanding systems, modified-shape systems, high density systems and other delayed gastric emptying devices.[6] The important point in the development of oral controlled release dosage forms is not just to prolong the delivery of the drug more than 12 hours, but to prolong the presence of the dosage forms in the stomach or upper gastrointestinal tract unit all the drug is released for desire period of time. A rational approach to enhance bioavailability and improve pharmacokinetic and pharmacodynamics profile is to retain the drug reservoir above its absorption area, i.e. In the stomach and to release the drug in a controlled manner, so as to achieve zero order kinetics for a prolonged period of time, one of the most feasible approaches for achieving a prolonged and predictable drug delivery profile is to control the gastric residence time in GIT.[7,8,9]

The present study is to develop and optimize floating tablet of drug acyclovir. Acyclovir is selected as a drug candidate for this study as its bioavailability is low and half-life range from 2 to 4 hours necessitating frequent administration. Acyclovir is used for treatment of Herpes simplex virus and varicella zoster virus infection. It can be taken by mouth. Common side effects include nausea and diarrhea. Potentially serious side effects include kidney problems and low platelets. It is generally considered safe for use in pregnancy with no harm having been observed. Floating tablets have emerged as the power full means of improving the bioavailability and providing sustained release and avoiding the adverse effects of many drugs. Floating tablets have proved to be potential approach for gastric retention. These systems have special advantage for the drug that are primarily absorbed from the upper part of GIT. So with an improved knowledge of formulation development aspect, physiochemical and pharmacological prospects of drug there is lot of future scope for designing of optimum floating drug delivery system.

Advantages

1. Drug that have narrow absorption window in the GIT(gastro intestinal Tract) will have poor absorption.[10,11]
2. The development process is affected by several nature of gastric empting as highly variable nature of gastric emptying process.[12,13]
3. Oral sustain release dosage forms deliver drug for longer period of time and help to produce therapeutic effect for more than 12 hr for those drugs which are having low plasma half-life.[14]

MATERIALS AND METHOD

Materials

Acyclovir was received from Yarrow Chem. Products Mumbai. Hydroxyl propyl methyl cellulose (HPMC K4MCR) was received from Colorcon Asia Pvt. Ltd. Goa. Carbopol 934P was received from Arihant Trading co. Mumbai. Lactose was received from CDH, New Delhi and sodium bicarbonate was received from S.D. Fine-Chem. Ltd, Mumbai. All ingredients used were of analytical grade.

Identification of Drug by UV Spectroscopy Determination of λmax of Acyclovir

The stock solution of Acyclovir was prepared by using by using 100mg in 100ml of 0.1 N HCl (pH 1.2) in 100 ml volumetric flask. The drug was dissolved by gentle shaking. Then 1 ml of solution was taken out and volume was making up to 100 ml with 0.1N HCl (pH 1.2). From this stock solution 1-10 µg/ml concentration range solutions were made. The resulting dilution were scanned between 200-400nm on Shimadzu- 1700E UV Spectrophotometer against 0.1N HCl solution as blank.

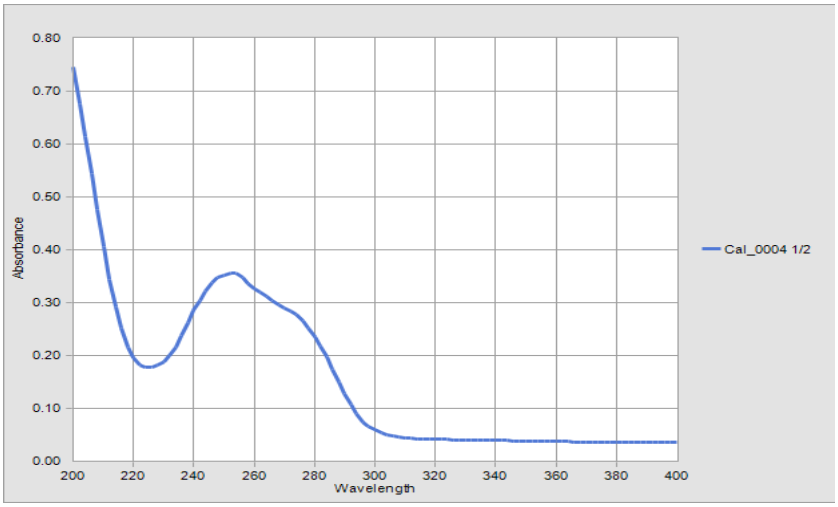

Fig.1 Spectrum of Acyclovir in 0.1N HCl (λmax 252nm).

Method

Floating tablets were prepared by the wet granulation method. The granules were prepared by wet granulation method. First of all ingredients were accurately weighed. Then accurately weighed quantities of acyclovir, HPMC-K4MCR, lactose, sodium bicarbonate were mixed homogeneously using glass –mortar and pestle. The wet granulation was done with ethanol (95%). Wet mass will be passed through a 40-mesh screen and dried in a hot air oven at 40°C over night. The dried granules will be sized through 40/60, mesh and blended with magnesium stearate (approx,1% w/w) using lactose as filler and channeling agent. Sodium bicarbonate will be used was used as a gas generating agent, here ethanol is used as granulating agent.

Evaluation of Granules[15,16,17,18]

- **Angle of repose (θ)**

It is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height „h, above a flat horizontal surface to which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of the

$$\text{Angle of repose } (\Theta) = \tan^{-1}(H/R)$$

funnel. The angle of repose was then calculated using following equation.(The results are shown in table No. 2).

Where,

H= Height of the pile R= Radius of the pile.

- **Bulk density**

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured in to graduate measuring cylinder through large funnel and volume was measured, which is called initial bulk volume. It is expressed in gm/ml and is given by the formula.(The results are shown in table No. 2).

$$\text{Bulk density} = M/Vo$$

Where,

M = mass of the powder

Vo = bulk volume of the powder.

- **Tapped density**

10 gm of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed in gm/ml and is given by.(The results are shown in table No. 2).

$$\textbf{Tapped density} = M/V_t$$

Where,

M = mass of the powder

V_t = final tapping volume of the powder.

- **Compressibility Index (Carr's Index)**

Compressibility Index is used as an important parameter to determine the flow behavior of the powder. It is indirectly related to the relative flow property rate, cohesiveness and particle size. It is simple, fast and popular method for predicting flow characteristic. Carr"s index can be represented by equation.(The results are shown in table No.2).

$$\textbf{Carr's Index (\% Compressibility)} = \frac{P_t - P_b}{P_t} \times 100$$

Where;

P_b= Bulk Density.

P_t = Tapped Density.

Formulation of Floating tablet

Table 1: Formulation table of floating tablet of acyclovir.

Ingredients (in mg)	Formulation code (F)			
	F1	F2	F3	F4
Acyclovir	200	200	200	200
HPMC K4MCR	170	180	190	200
Carbopol 934 NF	10	10	10	10
Sodium bicarbonate	15	15	15	15
Lactose	30	30	30	30
Magnesium stearate	2	2	2	2
Tablet weight (mg)	427	437	447	457

Characterization of Floating Tablets

- **Dimensional Analysis**

The thickness and diameter of tablets was determined using Vernier caliper. Twenty tablets from each batch were used and average values were calculated. (The results are shown in

table No. 4 and fig No.2).

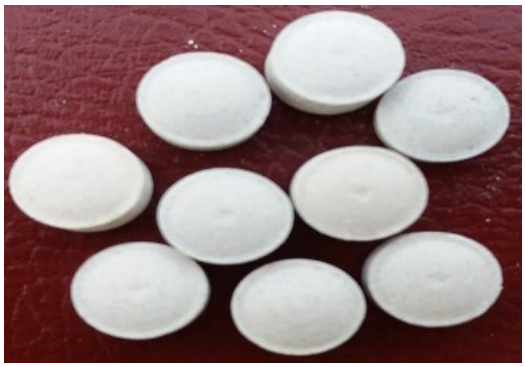

Fig. 2: floating tablets.

Hardness[19]

Tablet hardness and strength are the essential to see that the tablet can with the shock and stress during manufacturing packing and transportation, and while handled by the patient. To test the hardness of the tablet Monsanto tester was used. (The results are shown in table No.3).

- **Friability**[20]

Friability is tested for a tablet to observe whether the tablet is stable to abrasion or not, it was tested by using Roche friabilator. This is made up of a plastic drum fixed with a machine which rotated at 25 rpm for 100 revolutions. And then the twenty tablets which were weighed prior to the test are taken out of the drum and cleaned with a cloth and weighed once again, the weight variation must not be less than 0.5 to 1.0% for a conventional tablet. (The results are shown in table No.3).

- **Weight Variation test (U.S.P.)**[21]

Take 20 tablets were weighed individually. Average weight was calculated and compared with the individual tablet weight. The tablet passes the U.S.P. test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. (The results are shown in table No.3).

- **Floating lag time and Duration floating time**[22]

Floating lag time (FLT) and total floating time (TFT) of floating tablets were measured visually in dissolution apparatus type II containing100 ml 0.1 N HCl with a paddle rotated at 50 rpm (pH 1.2) at 37 ± 0.5°C. (The results are shown in table No.4).

- **Swelling index**[23]

The prepared tablets were placed in a glass containing 200 ml of 0.1 N HCl at 37 ± 0.5°C. The percentage of swelling at different time interval was calculated by the following equation.

$$\text{Weight variation \%} = \frac{\text{Weight of tablet} - \text{Initial weight of tablet}}{\text{Initial weight of tablet}} \times 100$$

- **Drug content uniformity testing**

The uniformity of drug content test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets with in a batch.

The drug content of the tablet was determined by triturating 20 tablets powder equivalent to average weight was added to 100ml of 0.1 N HCl, forwarded by starring for 30 minutes The solution was filtered through a Whatman filter paper no. 41, diluents solubility and the absorbance of resultant solution was measured using double beam UV-spectrophotometer (Shimadzu, UV-1700, Japan) at 252 nm using 0.1 N HCl as blank. The average drug content is calculated. The formula-

$$\text{Drug content} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

- **In-vitro Dissolution Studies**

An In vitro dissolution study of acyclovir floating tablet was carried out by USP dissolution testing apparatus Π (Paddle Type). the dissolution test was perform using 900 ml of 0.1 N HCl at 37±0.5ºC at 75 rpm, 1 ml of liquid was withdrawn from the dissolution apparatus at different predetermined time intervals (0,1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 18, hours) and the sample were replaced filtered through the Whatman filter paper No. 41 and analyzed at 252 nm using UV-spectrophotometer (Shimadzu, UV-1700, Japan) cumulative % drug release and calculated using an equation obtained from a calibration curve. (The results are shown in fig, 3).

In-vivo Studies

The in vivo study was performed as per the guidelines approved by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), ministry of social justice and Empowerment, Government of India. The institutional Animals Ethical

Committee (Registration No. BU/Pharm/IAEC/a/17/03) approved the protocol for study.

In-vivo studies was conducted using Albino rat (Wister rats) and plasma concentration time profile of acyclovir floating tablet will be determined using UV spectrophotometer.

The Albino rats were divided in 3 groups. Each group containing 2 animals. Rats were kept on fasting 12hrs before drug administration. Water was given ad libitum throughout the study.

The 1st group was kept as control and will be given normal saline solution. The 2nd group was given calculated doseof floating tablet of acyclovir.

The 3rd group was given marketed formulation of acyclovir.

[Albino rats were given Formulation which was equivalent to 4 mg drug (according to 13.3 mg/kg body weight)].

Then blood samples were collected from tail all three groups 0.5 ml of pre-dose blood sample will be collected 15 min before drug administration. Later the blood samples were collected at 1, 2, 4, 8, 10,12 up to 24 hours. Then after suitable processing and dilution. The samples were analyzed for drug content by UV spectrophotometer at 252nm.(The results are shown in fig.8).

RESULTS AND DISCUSSION

Table 2: Pre-compressional parameter of formulated granules.

Formulation Code (F1)	Angle of Repose(θ)	Flow Rate (mg/sec.)	Bulk density (gm/cm^3)	Tapped Density	Carr's Index
F1	22.70±1.80	1.10±0.2	0.662±0.18	0.817±1.06	20.32
F2	25.95±1.74	0.98±0.11	0.648±0.16	0.887±1.01	23.22
F3	24.89±1.16	1.18±0.17	0.651±0.29	0.826±0.50	18.64
F4	26.12±1.04	0.91±0.16	0.624±1.08	0.801±0.18	22.10

Table 3: Post -compressional parameter of floating tablets of Acyclovir.

Formulation Code (F1)	% Weight Variation*	Hardness ($kg/cm^{2)}$*	% Friability
F1	± 3.9%	6.40 ± 0.16	0.524
F2	±3.2%	6.37 ± 0.45	0.564
F3	± 4.4 %	6.53 ± 0.57	0.572
F4	± 3.7%	6.63 ± 0.58	0.482

Table 4: Post-compressional parameter of floating tablets of Acyclovir.

Formulation Code(F)	Diameter (mm)	Thickness (mm)	Floating Lag time (sec.)*	Duration of Floating time (hrs.)*
F1	8.99±0.03	4.12±0.01	99± 2.87	19.33 ± 2.05
F2	8.97±0.01	4.10±.0.05	94 ± 3.27	21.50 ± 1.87
F3	8.98±0.02	4.08±0.03	88 ± 2.85	23.33 ± 0.62
F4	8.99±0.01	3.69±0.04	70 ± 2.49	24.08 ± 0.95

In-vitro Dissolution Studies

In-vitro drug release study of acyclovir from Formulation Code F1, F2, F3 & F4; was performed in 0.1N HCl (pH 1.2). The graph is shown in fig .1 Thus Formulation F4 provides better sustained release behavior than other formulations. (The results are shown in fig.3).

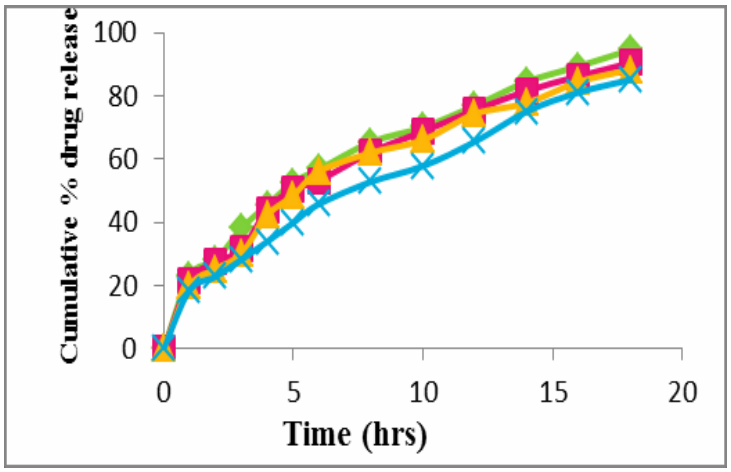

Fig. 3: Release Profile of Acyclovir in 0.1N HCl (pH 1.2) for Formulation Code F1,F2, F3, & F4.

Data Treatment

The data obtained from the in vitro dissolution study were fitted to zero order first order, Higuchi and Korsmeyer- peppas equations. All release kinetic models were applied on the formulation code F1, F2, F3 and F4 due to their satisfactory release behavior the selection criteria for model was based on goodness of fit of the data and residual some of the secures. The formulations are best fitted to higuchi‟s pattern of drug release and also show good linearity to first order kinetics.

(The results are shown in fig.4, 5, 6, 7 and table No.5).

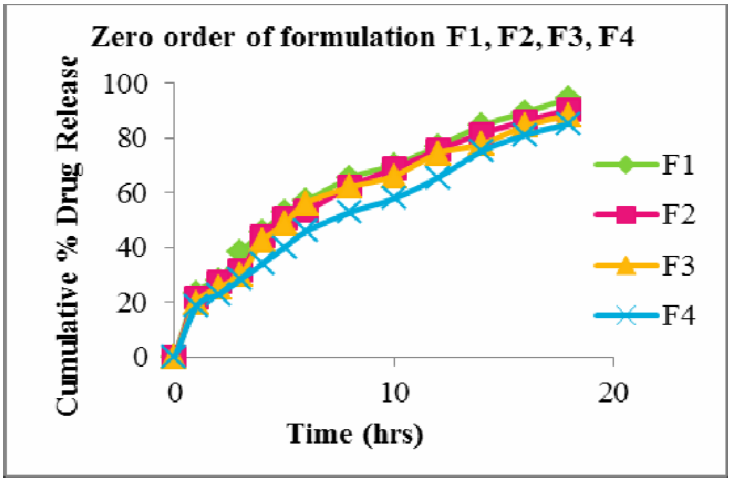

Fig. 4: Zero Order Kinetic Treatment of Formulation F1, F2, F3, F4.

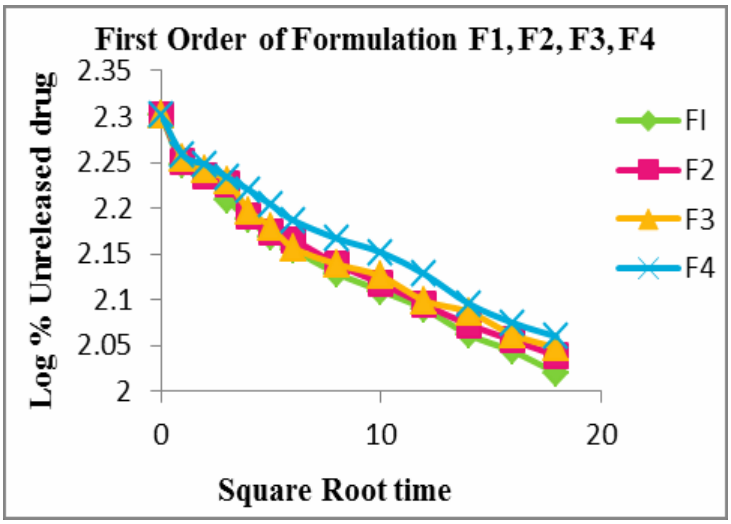

Fig. 5: First Order Kinetic Treatment of Formulation F1, F2, F3, F4.

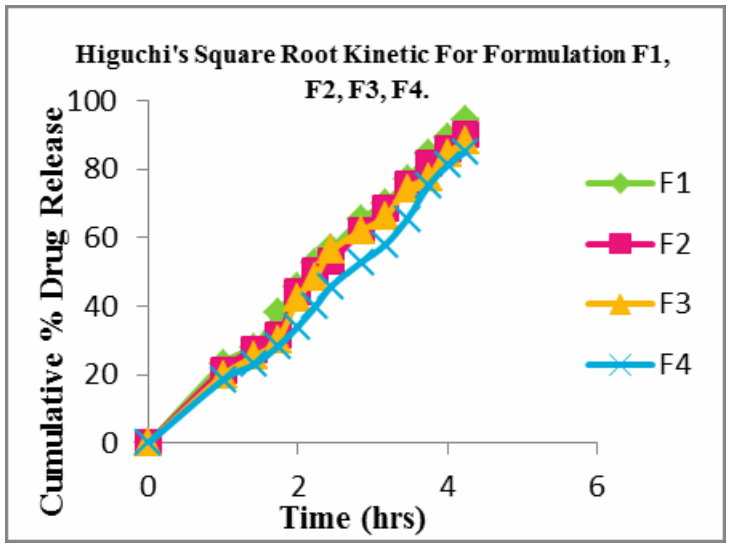

Fig. 6: Higuchi's Square Root Kinetic Treatment of Treatment of Formulation F1,F2,F3,F4.

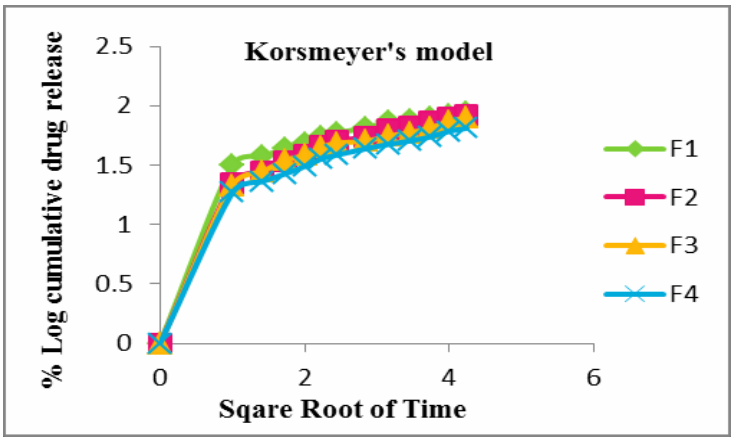

Fig. 7: Korsmeyer's Equation Kinetic Treatment of Dissolution Data of Floating Tablet of Acyclovir.

Table 5: Data Treatment

Formulation code (F)	Zero Order Kinetic	First Order Kinetic	Higuchi's	Korsmeyer's
F1	y = 4.555x+21.07 R^2 = 0.913	y = -0.014x +2.257 R^2 = 0.959	y = 22.46x -0.017 R^2 = 0.996	y=0.319x + 0.841 R^2 = 0.617
F2	y = 4.469x+19.25 R^2 = 0.918	y = -0.013x +2.261 R^2 = 0.958	y = 21.95x -1.125 R^2 = 0.994	y=0.334x + 0.732 R^2 = 0.698
F3	y = 4.382x+18.56 R^2 = 0.910	y = -0.013x + 2.262 R^2 = 0.949	y = 21.57x -1.635 R^2 = 0.990	y=0.321 x + 0.742 R^2 = 0.675
F4	y = 4.288x+14.01 R^2 = 0.959	y = -0.012x + 2.274 R^2 = 0.982	y = 20.55x -4.386 R^2 = 0.990	y=0.312x + 0.687 R^2 = 0.697

In-vivo study

The In-vivo studies conducted on Albino rat (Wister rats) indicated that the prepared formulation F4 of acyclovir floating tablet showed pharmacological effect up to 24 hrs in contrast to marketed preparation of Acyclovir which showed its effect only up to 8 hrs.

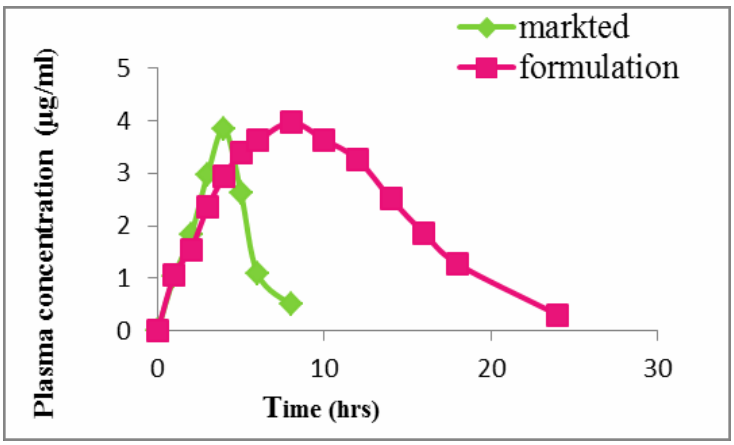

Fig. 8: Plasma drug concentration profile of Marketed Preparation and Prepared Formulation F4 of Acyclovir.

Stability Studies

There was no significant color change or change in general appearance at the end of 8 weeks, indicating that the formulations were stable.

CONCLUSION

Floating tablets have emerged as the power full means of improving the bioavailability and providing sustained release and avoiding the adverse effects of many drugs. Floating tablets have proved to be potential approach for gastric retention. These systems have special advantage for the drug that are primarily absorbed from the upper part of GIT. So with an improved knowledge of formulation development aspect, physiochemical and pharmacological prospects of drug there is lot of future scope for designing of optimum floating drug delivery system.

ACKNOWLEDGEMENT

The authors thankful to the institute of pharmacy Bundelkhand University, Jhansi for providing the facility to conduct the study and thanks to Mr. Abhishek Gupta.

CONFLICT OF INTEREST: Nil.

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