JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

Formulation and Optimization of Acyclovir Floating Tablet

Thakkar Aatish, Patel Nishith*, Dr. M. B. Patel

Department of Pharmaceutical Technology, A-One Pharmacy college, Ahmedabad, Gujarat, India

ABSTRACT:

The present research work aims to formulation of floating and in-vitro evaluation of acyclovir floating tablet using direct compression method. The potential ingredients used as floating, swallable polymer are HPMC K100 LV and Psyllium Husk with gas generating agent Sodium Bicarbonate. Psyllium husk was specially treated to improve its direct compression property. Simplex lattice design was used to carry out optimization. Seven batches were prepared using three independent variable F lag and Cumulative % release 5 h& 10h as independent variables. Regression analysis showed significant coefficients at $P < 0.05$. The final optimized batch was generated using polynomial equation and 2D Plots. Release kinetics of optimized batch revealed that drug release mechanism follows non- fickain, anomalous diffusion (n=0.5-0.85) and tablets were testes for 3 month accelerated stability study. Cumulative % release before and after Stability batches were tested by t test which shows significant result tcal<ttab. Thus gastroretentive floating drug delivery tablets of acyclovir using HPMC, Psyllium husk and Sodium bicarbonate shows promising drug delivery system.

KEYWORDS: HPMC K100LV, Psyllium Husk, Simplex Lattice design, acyclovir, floating, gastro retentive

Article history:
Received 25 Mar 2014
Accepted 28 April 2014
Available online 13 May 2014

For Correspondence:

Mr. Nishith Patel

Department of Pharmaceutics & Pharmaceutical Technology, A-One Pharmacy College, Ahmedabad, Gujarat, India

Email: nish11586@yahoo.com

(www.jpsbr.org)

INTRODUCTION: [1, 2, 3, 4]

Acyclovir is an antiviral agent widely used for the treatment of herpes simplex and varizella zoster. It is an analog of guanine. Its structure differs from other analogs of nucleosides in which contain only a portion of it as the carbohydrate ring is replaced by an open chain Is regarded as a prodrug, since its original form is inactive, and its metabolites are active antiviral substances.the mechanism of action of acyclovir is shown in figure 1

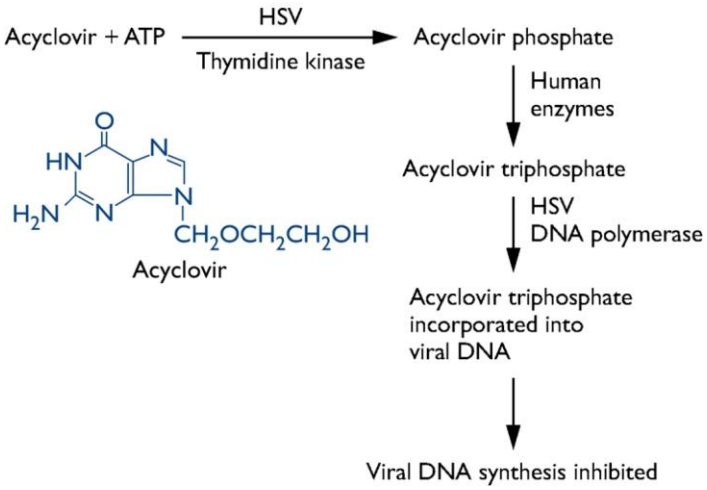

Figure 1 Mechanism of Action of acyclovir

Aciclovir is poorly water soluble and has poor oral bioavailability (15–30%), hence intravenous administration is necessary if high concentrations are required. When orally administered, peak plasma concentration occurs after 1–2 hours. Aciclovir has a high distribution rate; protein binding is reported to range from 9 to 33%.[1] The elimination half-life of aciclovir is approximately 3 hours and its oral bioavailability is low, 20% in average. Acyclovir is absorbed only in the upper part of the small intestine. It is renally excreted, partly by glomerular filtration and partly by tubular secretion. Due to that behavior the recommended oral dosage of acyclovir immediate release is 200 or 400 mg every 5-6 hours.

The floating gastro retentive drug delivery system can be retained in the stomach and assists in improving delivery of drugs that have a limited absorption in the gastrointestinal regions. This system helps in continuously releasing drugs before it reaches the absorption region, over prolonged time period. Thus it will increase the oral bioavailability and decrease the dosage frequency.

FACTORS CONTROLLING GASTRIC RETENTION AND FLOATING OF DOSAGE FORMS: [1, 5-8]

If drug or food do not emptied from stomach that means it will retain in the stomach. Therefore Gastric retention depends on gastric emptying for the given drug. The stomach itself having intersubject and intrasubject variability for gastric emptying and that is because all individuals take foods, drinks, drugs of different type, different kind, in different quantity at different time and time interval. Once the journey of drug starts in GI track its fate will be quite unpredictable because of following variables present along with dosage.

1. **Type of food intake:** Oily. Oil free, digestible, indigestible, calorie content, Solid content, and temperature
2. **Stomach Physiology:** Stomach size, pH, contents
3. **Stomach mode:** fed state or fasting state
4. **Individual variation:** Eating habit, mental behavior, mental status, stress during eating, Physical activity, Frequency of intake, Age Gender, Diseased condition
5. **Dosage Variation**:
   - **a.** Size & shape of dosage so that do not easily pass through pyloric antrum. Dosage forms having a diameter of more than 7.5 mm show a better gastric residence time compared with one having 9.9 mm.
   - **a.** Density of dosage form (A density of < 1.0 gm/ cm^3 is required to exhibit floating property)

POTENTIAL DRUG CANDIDATES FOR GASTRORETENTIVE DRUG

DELIVERY SYSTEMS:

1. Absorption from upper GIT e.g. Ciprofloxacin.
2. Drugs those are locally active in the stomach e.g., antacids, misroprostol, Amoxicillin. etc.
3. Drugs that have narrow absorption window in gastrointestinal tract (GIT) e.g. L-DOPA, para amino benzoic acid, furosemide, riboflavin etc.
4. Drugs those are unstable in the intestinal or colonic environment e.g. captopril, ranitidine HCl, metronidazole.
5. Drugs that disturb normal colonic microbes e.g. antibiotics against Helicobacter pylori.
6. Drugs that exhibit low solubility at high pH values e.g. diazepam, chlordiazepoxide, verapamil HCl.

MATERIALS AND METHODS

Acyclovir (Torrent Research Centre, Bhat, India), Psyllium husk, Lactose (Cambridge Health Care Ltd, Ahmedabad, India), HydroxyPropyle Methyl Cellulose K100LV, magnesium stearate (Astron chemical Pvt. Ltd., Mumbai) Microcrystalline Cellulose(Chem Doc chemicals) were used.

Preparation of Tablets

Acyclovir floating tablets were prepared by mixing Psyllium husk, HydroxyPropyle Methyl Cellulose K100LV, sodium bicarbonate, Microcrystalline Cellulose and lactose with 200 mg acyclovir. Simplex design was used to optimise final formula for acyclovir floating tablet.

Simplex design [9, 10]

Three variables X1 as the amount of HPMC K100 LV (mg); X2 as the amount of sodium bicarbonate (mg); X3 as the amount of Psyllium Husk (mg) were selected as independent variables. Seven batches (S1-S7) were prepared and their final formulas are shown in table 1 Floating lag time (Flag) and the time required for 80% drug dissolution (t80) were taken as responses, as dependant factor. Raw material mixed together in octagonal blender, passes through required sieves. 1% w/w Mg Stearate and 2% w/w Talc were added to blend mixture

and tablets were prepared by direct compression technique.

Table 1 Formulation batches of SLD S1 to S7

Excipients (mg)	S1	S2	S3	S4	S5	S6	S7
Drug	200	200	200	200	200	200	200
HPMC (100cps)	100	50	50	75	50	75	50
Psyllium Husk(%)	50	50	100	75	75	50	50
Sod. Bicarbonate	50	100	50	50	75	75	50
MCC	50	50	50	50	50	50	50
Lactose	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Each batch contains 1% w/w Mg Stearate and 2% w/w Talc Total weight of tablet 515 mg

Hardness and friability test

The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. Friability is the measure of tablet strength. Roche Friability Test apparatus was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

$$\% \textbf{ loss} = \frac{\textbf{Initial weight of tablets} - \textbf{Final weight of tablets}}{\textbf{Initial weight of tablets}} \times \mathbf{100}$$

Uniformity of Weight [11]

The USP weight variation test is run by weighing 20 tablets individually. Calculating the average weight and comparing the individual tablet weight to the average. The tablet meet the USP test, if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

In-vitro buoyancy studies: [11]

Floating characteristics of tablets were determined in a USP dissolution apparatus II (paddle) in an acidic environment at 37±0.5 ◦C and 50rpm. The floating lag time (FLT) as well as total floating time (TFT) were determined visually using a timing mechanism.

Swelling studies:

The swelling behavior of tablets were measured in glass containing 200 ml of HCL (0.1 N) which was maintained at 37±0.5 ◦C. At regular time intervals, the tablets were removed from glass and the percentage of swelling was calculated using the following equation.

$$\% \text{ swelling} = \frac{W_2 - W_1}{W_1} \times 100 \quad \ldots\ldots(7)$$

Where, W_2 is the weight of the swollen tablets, and

W_1 is the initial weight of the tablets.

Drug content and physical evaluation*:*

The drug content of the tablets was determined using 0.1N HCl as a solvent,and the samples were analyzed spectrophotometrically (Shimadzu, 1800, Japan) at 252nm .

In-vitro dissolution studies:[11]

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 0.1N HCL, at 37 ± 0.5°C and 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 h, and the samples were replaced with fresh dissolution medium. The samples were passed through Whatman filter paper and the absorbance of these solutions was measured at 252 nm

RESULTS AND DISCUSSION

The Prepared floating tablets were evaluated for their hardness, friability, weight variation, drug content, swelling index, floating lag time, total floating time and *In Vitro* drug release study in 0.1 N HCl up to 12 h were performed. All formulation batches shows total floating time more than 12 h, good hardness ranges between 4 to 6 kg/cm^2, friability in range and less than 1 % from 0.325 to 0.959 %. The deviation from the mean weights of prepared tablet were found to be within the prescribed limits.(Table 2)

Table 2 Evaluation of simplex lattice design acyclovir tablets

Batch	Weight variation(mg)	Friability (%)	Hardness (kg/cm2)	Drug Content (%)	Floating lag Sec.
S1	513±0.52	0.325	4.0-5.0	98.51	145
S2	514±0.23	0.537	4.0-5.0	99.12	132
S3	515±0.63	0.593	4.5-5.5	98.45	110
S4	514±0.5	0.667	5.0-6.0	98.27	160
S5	516±0.47	0.794	4.5-5.5	99.45	129
S6	515±0.12	0.959	4.0-5.0	98.36	127
S7	516±0.16	0.549	5.0-6.0	98.24	118

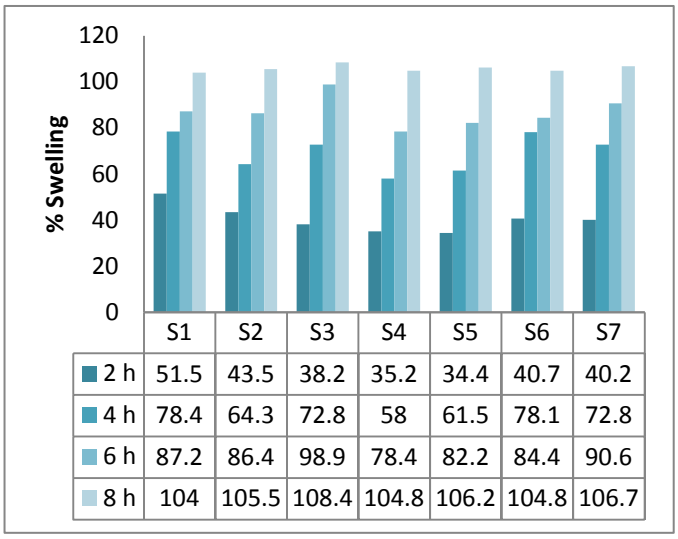

Figure 2 Swelling Index of Simplex lattice acyclovir tablets

Table 3 Effect on dependent variable on Simplex Lattice design layout

Batch No.	Transformed fraction of Coded Values†			Observed Values of		
	X_1	X_2	X_3	Y_1 F_{lag}	Y_2 (t_5)	Y_3 (t_8)
S1	1	0	0	145	40.29	63.75
S2	0	1	0	132	49.30	80.80
S3	0	0	1	110	32.22	52.78
S4	0.5	0.5	0	160	40.57	64.13
S5	0	0.5	0.5	129	35.03	57.28
S6	0.5	0	0.5	127	40.56	60.14
S7	0.33	0.33	0.33	118	39.47	57.16

Table 4 Coded Values and Actual Values for Independent Variables

Coded Values†	Actual Values (mg)		
	X1	X2	X3
1	100	100	100
0	50	50	50

Table 5 Summary of results of regression analysis

Coefficients for F_{lag}

Response	b_1	b_2	b_3	b_{12}	b_{23}	b_{13}	b_{123}
FM	0	-13†	-35†	86†	32†	-2†	-662.188†
RM		-13	-35	86	32	-2	-662.188

FM indicates full model; RM, reduced model.†Response is insignificant at P = <0.05.

Coefficients for Y_{t8}

Response	b_1	b_2	b_3	b_{12}	b_{23}	b_{13}	b_{123}
FM	0	17.05†	-10.97†	-32.58†	-38.04†	7.5†	-47.944†
RM		17.05	-10.97	-32.58	-38.04	7.5	-47.944

Table 6 Testing the model by F Test for Y1

	For Y_1 F_{lag}					
	DF	SS	MS	R^2	F	P
Regression						
FM	7	2052.5	293.214	1	2.71026E+31	3.24E-50
RM	5	1387.06	277.412	0.675791	1.667544501	0.000325
Error						
FM	3	3.79E-29	1.26E-29			
RM	4	665.4389	166.3597			

Table 6 Testing the model by F Test for Y2

For Y_2 (t_8)						
	DF	**SS**	**MS**	**R^2**	**F**	**P**
Regression						
FM	7	549.9132	78.55902	1	7.44E+33	1.34E-34
RM	6	549.9132	91.65219	1		
Error						
FM	3	3.7E-32	1.23E-32			
RM	3	0	0			

A polynomial equation was granted by linear multiple regression that quantitatively explain the effect of different variables on dissolution

$$Y_1F_{lag} = (0)X_1 + (-13)X_2 + (-35)X_3 + 86X_1X_2 + 32X_2X_3 - 2X_1X_3 - 662X_1X_2X_3$$

.The equation for reduced model is,

$$Y_1 (F_{lag}) = -13X_2 - 35X_3 + 86X_1X_2 + 32X_2X_3 - 2X_1X_3 - 662X_1X_2X_3$$

All coefficients were found to be significant at P < 0.05. except P1 Further, the results for testing model in portions (reduced model) are shown in Table.5 The critical value of F_{tab}**is 9.55** (df = 2, 3) at P value of 0.05.Since the calculated value **(F = 1.667)** is less than the critical value (F = **9.55**), it may be concluded that the all interaction term b_2, b_3, b_{12}, b_{23}, b_{13} andb_{123}contribute significantly to the prediction of Y F_{lag} and can be retained in the reduce model.

A polynomial equation was granted by linear multiple regression that quantitatively explain the effect of different variables on dissolution.

$$Y_2 (t_8) = (0)X_1 + 17.05X_2 + (-10.97)X_3 + (-32.58)X_1X_2 + (-38.04)X_2X_3 + 7.5X_1X_3 - 47.94X_1X_2X_3$$

The equation for reduced model is,

$$Y_2 (t_8) = 17.05X_2 + (-10.97)X_3 + (-32.58)X_1X_2 + (-38.04)X_2X_3 + 7.5X_1X_3 - 47.94X_1X_2X_3$$

All coefficients were found to be significant at P < 0.05 except P1 Further, the results for testing model in portions (reduced model) are shown in Table.6 hence they were kept in the full model to generate the reduced model. The results of statistical analysis are shown in Table 6 the critical value of F_{tab} is 10.12 (df = 1, 3) at P value of 0.05.Since the calculated value (F =7.43) is less than the critical value (F = 10.12). The equations were further validated using check point batches. The obtained values from equation were similar with practically obtained data.

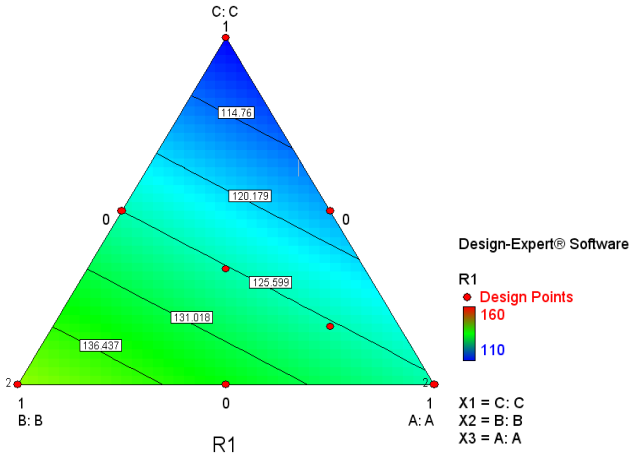

Figure 3 2 D graphical model for dependant factor Y1

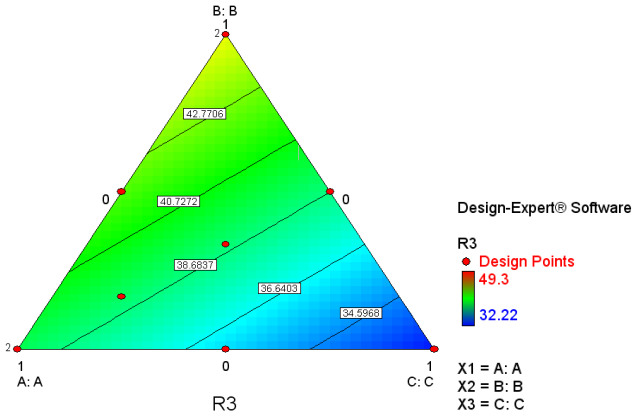

Figure 4 2 D graphical model for dependant Y2

From 2D graphical model it is clearly visible that all three variables show their concentration power over responses. In figure 3 clearly shows that as the concentration of sodium bicarbonate increases floating lag time increases. In figure 4 shows good cumulative % release as concentration of Psyllium husk increases compare to increase in concentration of HPMC.

With the help of equation and counter plot optimized batch was derived the prepared tablet was tested for kinetic of drug release. The result of the regression from zero order, first order, higuchi model, hixon model and krosmeyer peppas model (Table 7) showed that floating tablets of Acyclovir releases the drug by anamolous diffusion (0.5-.85).

Table 7 Release kinetics of optimized batch [12-16]

DRUG RELEASE KINETICS DATA			OPTIMIZED BATCH
Sr. no.	**Kinetic Model**	**Parameters**	
1	**Zero order**	R^2	**0.9958**
		Slope	7.3094
		Intercept	6.9660
2	**First order**	R^2	**0.9776**
		Slope	0.0720
		Intercept	1.1986
3	**Higuchi**	R^2	**0.9671**
		Slope	30.62
		Intercept	-19.45
4	**Hixon-Crowell**	R^2	**-0.99580**
		Slope	-2.43647
		Intercept	31.011
5	**Korsmeyer and Peppas**	R^2	0.9825
		Slope	0.6554
		Intercept	-0.7884
		n	0.65054

This study reflected that floating tablet of acyclovir using Psyllium husk can be promising in combination with synthetic polymers and gas-generating agent and the hydrophilic polymer such as HPMC K100LV and psyllium husk plays an important role for the formulation of FDDS.

ACKNOWLEDGEMENTS

The authors would like to thank Torrent Research Centre, Bhat, India for providing API support for the project. The authors would like to thank **Dr. Mandev B. Patel**, principal of A-One Pharmacy College, Anasan, Ahmedabad for providing all facilities and constant encouragement.

REFERENCES

1. Oral Controlled Release Formulation Design and Drug Delivery: Theory to Practice, edited by Hong Wen, Kinam Park, Published by John Wiley & sons. New Jersey
2. http://www.drugbank.ca/drugs/APRD00567 accessed on 25 September 2013
3. http://es.wikipedia.org/wiki/Aciclovir accessed on 30 September **2013**
4. P Susantakumar1, Gaur A and Sharma P. Comparative Acyclovir IR 800 Mg Tablet in Healthy Indian Adult Volunteers Under Fasting and Non-fasting Conditions. J Bioequiv Availab 2011, 3:6
5. Arrora S, Ali J, Khar RK, Baboota S. Floatng drug delivery systems: A review. AAPS Pharm Sci Tech. 2005; 6(3): 372-390.
6. Vyas SP, Khar RK. Gastroretentive systems. In: Controlled drug Delivery. Vallabh Prakashan, Delhi, India. 2006; 197-217.
7. Rao NG, Katta S, Reddy MS, "Overview on Floating Drug Delivery System." American Journal of Pharmtech Research, 2013, 3(2), 145-169.
8. Moes AJ. Gastric retention systems for oral drug delivery. Business Briefing: Pharmatech. 2003: 157-59.
9. Mandlik S K, Adhikari S. Application of Simplex Lattice Design in Formulation andDevelopment of Buoyant Matrices of Dipyridamole. Journal of App Pharma.Sci.**2012**. 2 (12) 107-111
10. Patel D. M, Patel N. M, Pandya N. N., Jogani P D. Gastroretentive Drug Delivery System of Carbamazepine: Formulation Optimization Using Simplex Lattice Design: A Technical Note. AAPS PharmSciTech 2007; 8 (1)
11. United State Pharmacopoeias 30 U.S.P. NF 25 2007, "The official Compendia of Standard" Asian edition.
12. Mario, G. and Gabriele G., "Mathematical Modeling and Controlled Drug Delivery: Matrix Systems" Current Drug Delivery, (2005) 2, 97-116.
13. US Food and Drug Administration, Guidance for Industry; SUPAC–MR Modified Release Solid Oral Dosage Forms, Scale–up and Post–approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation, Rockville, MD USA, 1997.
14. Banakar U. V. Pharmaceutical Dissolution Testing, Swarbrick J., Drug and the Pharmaceutical Sciences, *Volume 49*, Marcel Dekker, New York, 1992Pg: 407.
15. O'Hara, T., Dunne, A., Butler, J. and Devane, J., A review of methods used to compare dissolution profile data Pharm. Sci. Technol. Today, (1998) 1:5, 214–223.
16. Ertan, G., Karasulu, H. Y., Karasulu, E., Ege, M. A., Kose, T. and Guneri, T., "A new in vitro/in vivo kinetic correlation method for nitrofurantoin matrix tablet formulations." Drug Dev. Ind. Pharm., (2000) 26:7, 737–743