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Formulation development of gastro retentive floating tablet of acyclovir using natural gums

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ABSTRACT

The aim of present study was to develop gastro-retentive floating tablet of Acyclovir by direct compression method. Floating tablets of Acyclovir was developed by using gas forming agents like sodium bicarbonate and natural gums like Locust bean gum, Sodium alginate and Xanthan gum by effervescent technique. Various combinations of floating polymers were used in this formulation. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, in vitro buoyancy , buoyancy lag time and dissolution studies. The formulation optimized for different concentration of natural gums like Locust bean gum, Sodium alginate and Xanthan gum. The results of in vitro release studies showed that optimized formulation F7 could sustain drug release (99.08%) for 16 hr and remain buoyant for 24 hr. Optimized formulation F7 contained 60% of Locust bean gum and 40% Sodium alginate out of total floating polymer while amount of Xanthan gum is same in all 7 batches. F7 formulation fitted best for Korsemeyer – Peppas model and showed no significant change in physical appearance, drug content, floatability or in vitro dissolution pattern after storage at 45 °C/75% RH for two months.

Keywords : Acyclovir, gastro retentive floating tablet, Stability studies

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INTRODUCTION

The real issue in the development of oral controlled release dosage forms is not just to prolong the delivery of drugs for more than 12 hours, but to prolong the presence of the dosage forms in the stomach or upper gastrointestinal tract until all the drug is released for desire period of time. Rapid GI transit could result in incomplete drug release from the drug delivery device in the absorption zone leading to diminished efficacy of the administered dose[1]. Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices[2,3]. The principle of buoyant preparation offers a simple and practical approach

to achieve increased gastric residence time for the dosage form and sustained drug release. Acyclovir is an antiviral drug, belonging to the deoxiguanosine family. 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. It has an elimination half-life of 2-3 hours and has an absorption zone from the upper intestinal tract. The recommended adult oral dosage of acyclovir is 200 mg twice daily or 400 mg once daily. The effective treatment of genital herpes simplex requires administration of 1000 mg of acyclovir in 5 divided doses per day. An alternative dose of 800 mg leads to plasma fluctuations; thus a sustained release dosage form of acyclovir is desirable. The short biological half-life of drug (~2.0-3.0 hours) also favors development of a sustained release formulation[4]. Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose can be achieved with floating drug delivery system[5].

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 Acyclovir dosage forms.

MATERIAL AND METHODS

Materials

Acyclovir was obtained as gift sample from FDC Pvt.Ltd, Goa. Locust bean gum and Sodium alginate were obtained from RVS College, Sulur, and Coimbatore. Xanthan gum was obtained from VAMA pharma, Nagpur. Sodium bi carbonate, polyvinyl pyrrolidine, magnesium stearate, talc, aerosol were taken from VAMA pharma, Nagpur. All other chemicals used in the study were of analytical grade.

Method

Direct compression technique

The composition of different formulation of Acyclovir floating tablets shown in table 1. Floating tablets were prepared by direct compression technique. The sodium alginate, locust bean gum, Xanthan gum, sodium bicarbonate, and the active ingredient were mixed homogeneously. Magnesium stearate, talc and Aerosil were added as a lubricant and the powder was compressed into tablets using CADMACH multi punch tablet machine.

Evaluation of Acyclovir floating tablets

(i) Precompression parameters of Acyclovir blend

The flow properties of blend (before compression) were characterized in terms of angle of repose[6] ,tapped density, bulk density[7], Carr's index[8] and Hausner ratio.

(ii) Physical Evaluation of Acyclovir Floating Tablets

Two tablets from each formulation were randomly selected and organoleptic properties such as colour, odour, taste, and shape were evaluated. Thickness and diameter of ten tablets were measured using Vernier calipers. The prepared floating tablets were evaluated for uniformity of weight using 20 tablets, Hardness (Monsanto tester)[9], Friability using 10 tablets (Roche Type friabilator) [10].

(iii) Drug Content Estimation

The drug content in each formulation was determined by triturating 20 tablets and to a quantity of the powdered tablets containing 0.1g of acyclovir adds 60 ml of 0.1m sodium hydroxide and disperses with the aid of ultrasound for 15 minutes. Add a sufficient quantity of 0.1m sodium

hydroxide to produce 100 ml, mix well and filter. To 25 ml of the filtrate add 50 ml of water and 5.8 ml of 2M Hcl and sufficient water to produce 100 ml. To 5ml of the solution add sufficient 0.1 m hydrochloric acid to produce 50ml and mix well measure the absorbance so the resulting solution at the maximum at 255nm, l appendix II B, using 0.1m hydrochloric acid in the reference cell. Calculate the content of $C_8H_{11}N_5O_3$ taking 560 as the value of A (1%, 1cm) at the maximum at 255 nm.

(iv) In Vitro Buoyancy Studies

The *in vitro* buoyancy was determined by floating lag time, per the method described by Rosa *et al.* The tablets were placed in a 100 ml beaker containing 0.1N Hcl. The time required for the tablet to rise to the surface and float was determined as floating lag time. The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time.

(v) In Vitro Dissolution Studies

The release rate of Acyclovir from floating tablets was determined using *United States Pharmacopoeia* (USP) Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1N hydrochloric acid, at 37 ± 0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with 0.1N hydrochloric acid. Absorbance of these solutions was measured at 255 nm using a Thermospectronic-1 UV/V is double-beam spectrophotometer..

(vi) In Vitro Drug Release Kinetic Studies

Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero order[11], first order[12], Higuchi square root[13], Korsmeyer- Peppas model[14].The criteria for selecting the most appropriate model was chosen on the basis of goodness of fit test.

RESULTS AND DISCUSSION

(i)Compatibility studies of Acyclovir

Acyclovir was subjected to Drug – Excipients compatibility studies with various excipients like Sodium alginate, locust bean gum, xanthan gum, Sodium bicarbonate, magnesium stearate, and talc. The mixtures have shown no colour change and lumping.

(ii)Precompression parameters of Acyclovir granules

The formulations showed good flow property and **Carr's** index (table 2). Angle of repose ranged from 24.1^0 ±0.7 to 25.1^0 ±0.1 and the **Carr's** index ranged from 15.50±0.32 to 32.39±0.27. The Bulk Density and Tapped Bulk Density of the prepared granules ranged from 0.465±0.012 to 0.551±0.015 and 0.598±0.058 to 0.710±0.036 respectively. The results of angle of repose indicates good flow property of the granules and the value of carr's compressibility index further showed support for the flow property.

(iii)Post compression parameters of Acyclovir floating Tablets

The shape of the tablets of all formulations remained off white, smooth, flat faced circular with no visible cracks. The hardness of the tablets was measured by Pfizer tester (Biological museum, Mumbai, India) and was in between 4.8 ± 0.02 to 5.0± 0.04 kg/cm^2. The friability was measured by Friabilator (Roche Type Friabilator) and was found to be 0.499 ±

0.02 to 0.7± 0.03%, which is an indication of satisfactory mechanical resistance of the tablets. The drug content estimations showed values in the range of 99.12 ± 0.04 to 99.75± 0.04% as shown in Table3 which reflects good uniformity in drug content among different formulations. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits of ±7.5% of the weight. The results are shown in table 3. All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality.

(vi)In vitro buoyancy studies

The results for floating time are presented in table 4. From the study of floating properties, it was observed that the floating lag time ranges from 15 to 120 seconds and tablet of each batch remained buoyant up to 16 hours, during which the tablets lost their integrity and the size of swollen matrix gel drastically reduced.

(v)In vitro release studies

In vitro dissolution studies of all the formulations of floating tablets of Acyclovir were carried out in 0.1N HCl. The study was performed for 20h and cumulative drug release was calculated at every one hour time interval. In vitro dissolution studies of all the formulations are shown in figure 1. Two different natural gums (Table 1) were used to prepare floating tablets. It was observed that the type of natural gum influences the drug release pattern. All the formulations contained equal amount of gas generating agent (sodium bi carbonate) . A significantly higher rate and extent of drug release was observed from the batches based on Locust bean gum and sodium alginate. Varying the amount of Xanthan gum affect the drug release.

(vi) Analysis of release mechanism

The drug release data of optimized formulation (F7) were fitted to models representing Higuchi's, zero order, first order and Korsmeyer's- peppas equation kinetics to know the release mechanisms. The results are shown in Table 5 .In the present study, in vitro release profiles could be best expressed by Higuchi's equation as optimized formulation (F7) showed good linearity indicates that diffusion is dominant mechanism of drug release with these formulations. The release profile of F7 formulation compared with various kinetic models which is shown in figure 2 .

Table I: Composition of different floating tablet formulation of Acyclovir tablets

Formulation code	Ingredients	Formulation code						
		Single polymer		Combination batches				
		F_1	F_2	F_3	F_4	F_5	F_6	F_7
1	Acyclovir	200	200	200	200	200	200	200
2	Sodium alginate	270	-	135 50%	68 25%	202 75%	160 60%	110 40%
3	Locust bean gum	-	270	135 50%	202 75%	68 25%	110 40%	160 60%
4	Xanthan gum	220	220	220	220	220	220	220
5	Sodium bi carbonate	136	136	136	132	136	136	136
6	PVP	25	25	25	25	25	25	25
7	Talc	12	12	12	12	12	12	12
8	Magnesium stearate	25	25	25	25	25	25	25
9	Aerosil	12	12	12	12	12	12	12
	Total weight	900	900	900	900	900	900	900

(vii) Stability Study of Optimized Formulation (F7)

The optimized floating tablets (F7) were selected for stability study on the basis of in vitro buoyancy and in vitro drug dissolution studies. The tablets were investigated at 45°C/75% RH for 2 months. From the data, the formulation is found to be stable under the conditions mentioned before since there was no significant change in the percentage amount of drug content (Table 6). Thus, it was found that the floating tablets of Acyclovir (F7) were stable under these storage conditions for at least 2months.The dissolution profile of F7 formulation at initial level and after two months are shown in figure 3.

Table II: Results of pre compression flow properties of granules of Acyclovir

Formulation code	Angle of Repose(θ) ± SD	Bulk density (g/cc) ± SD)	Tapped density (g/cc) ± SD	Carr's index ± SD	Hausner Ratio
F1	24.1^0 ±0.7	0.525±0.011	0.689±0.096	23.80±0.77	1.312
F2	25.1^0 ±0.6	0.487±0.004	0.666±0.041	26.87±0.53	1.367
F3	30.3^0 ±1.1	0.515±0.114	0.689±0.031	25.25±0.79	1.337
F4	26.3^0 ±0.6	0.545±0.012	0.645±0.016	15.50±0.32	1.183
F5	25.3^0 ±0.8	0.480±0.016	0.710±0.036	32.39±0.27	1.479
F6	29.4^0 ±0.2	0.465±0.012	0.598±0.058	22.24±0.13	1.286
F7	25.1^0 ±0.1	0.551±0.015	0.684±0.032	19.44±0.09	1.241

Table III: Results of post compression properties of Acyclovir floating tablets

Formulation code	Uniformity of Weight (mg)	Hardness (kg/cm2)	Friability (%)	Drug content (mg)
F1	901.2 ± 0.01	5.0 ± 0.02	0.7 ± 0.03	99.12 ± 0.04
F2	900.6 ± 0.29	4.9 ± 0.02	0.5 ± 0.01	98.96 ± 0.02
F3	900.7 ± 0.34	5.0 ± 0.04	0.6 ± 0.02	98.92 ± 0.07
F4	902.8 ± 0.26	4.8 ± 0.02	0.6 ± 0.02	99.44 ± 0.02
F5	903.1 ± 0.02	5.0 ± 0.02	0.5 ± 0.04	98.13 ± 0.12
F6	900.6 ± 0.36	4.9 ± 0.04	0.499 ± 0.02	99.27 ± 0.04
F7	903.0± 0.34	5.0± 0.04	0.5± 0.02	99.75± 0.04

Table IV: Results of in vitro buoyancy studies of Acyclovir Floating Tablets

Formulation code	Floating lag time (S)	Total floating time (h)
F1	120±1.52	>16
F2	15±1.0	>16
F3	60±0.57	>16
F4	30±2.08	>16
F5	120±2.0	>16
F6	60±2.08	>16
F7	90±2.06	>16

Table V: Kinetic Release Data of Different Model for Optimized Formulation (F7)

Model	Slope	R^2
Zero order	4.8534	0.8411
First order	-0.2064	0.7829
Higuchi	-0.0317	0.9462
Korsemeyer-Peppas	21.8789	0.9971
Matrix	0.9963	19.9415

Table VI: Stability study (45 °C/75%RH) of Optimized Formulation (F7)

Parameters	1st month	2nd month	3rd month
Physical appearance	White flat smooth faced	White flat smooth faced	White flat smooth faced
Weight variation (mg)	903.0± 0.34	903.0± 0.34	903.0± 0.34
Hardness (Kg/Cm^2)	5.0± 0.04	4.9± 0.04	4.9± 0.04
Friability (%)	0.6 ± 0.02	0.56 ± 0.02	0.58± 0.02
Drug content (%)	99.45± 0.04	98.76± 0.02	98.25± 0.03
Buoyancy lag time(s)	92±2.06	93±1..04	94±0..06
Total floating time(hrs)	16	16	16
Buoyancy on disturbing	Float	Float	Float

Fig I. Comparative Dissolution Profile of Batch F1 to F7 in 0.1N Hcl

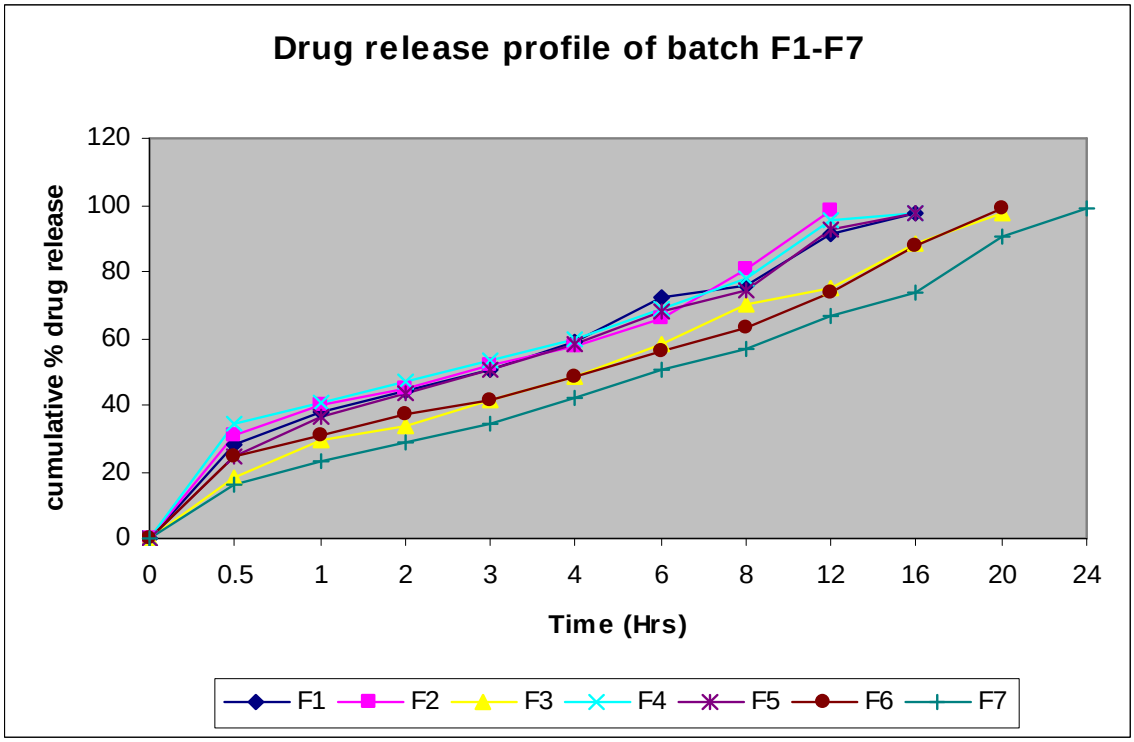


Fig II. Release profile of batch F7 with model fitting

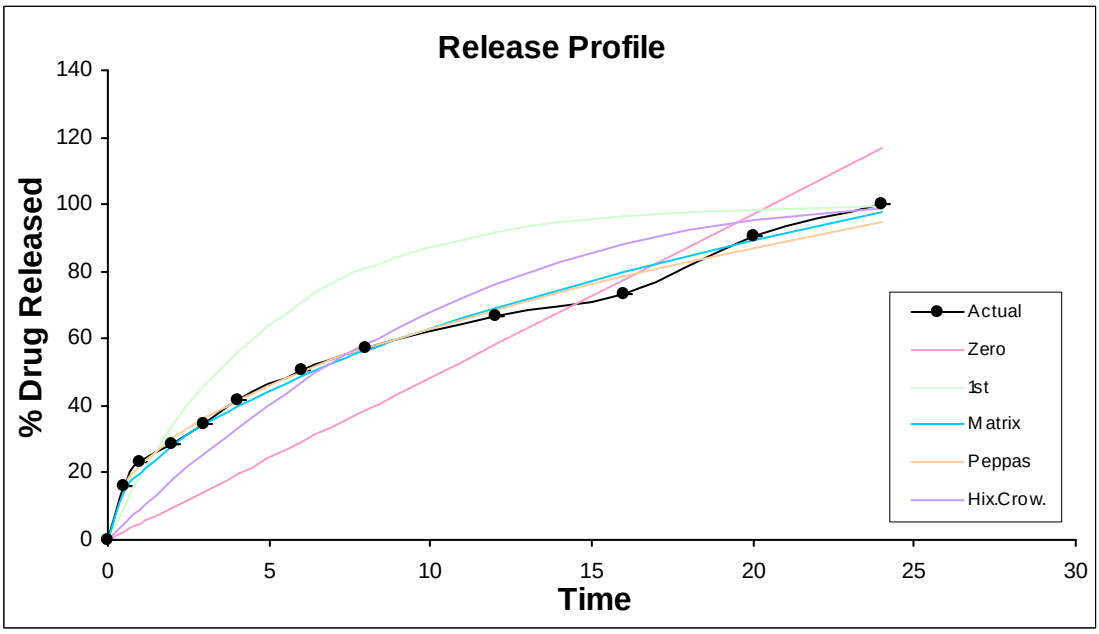
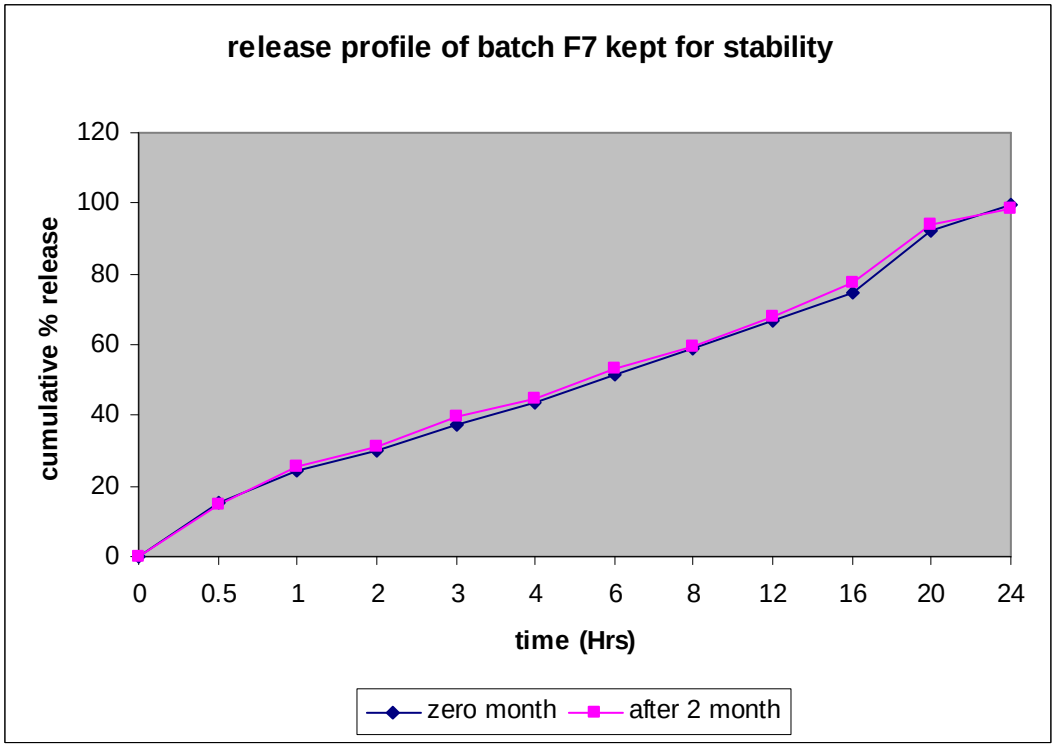


Fig III. Dissolution profile of batch F7 kept on stability at 40°C/75% RH



CONCLUSION

In the present study Acyclovir floating tablets by wet granulation method using natural gums like Xanthan gum ,Locust bean gum and Sodium alginate was developed. Formulation (F7) containing 40% Sodium alginate and 60% Locust bean gum showed controlled drug release for 16hrs, emerging as best formulation. Mechanism of drug release of optimized formulation (F7) found to be Zero order non fickian diffusion. Good stability was observed for 2 months during

stability studies. Thus, results of the current study clearly indicate, a promising potential of the Acyclovir floating system as an alternative to the conventional dosage form.

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