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DESIGN AND EVALUATION OF FLOATING DRUG DELIVERY BASED ON MATRIX TABLET OF ACYCLOVIR

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ABSTRACT

Floating tablets of Acyclovir were developed to prolong gastric residence time, leading to an increase in drug bioavailability. Tablets were prepared by direct compression technique, using polymers hydroxypropyl methylcellulose HPMC (K100M) and HPMC (K15M). Tablets were evaluated for physical characteristics, weight variation, thickness, hardness and friability; drug content, swelling, floating properties and *in-vitro* drug release for 12 h. Tablets exhibited sustained and prolonged drug release profiles while floating over the dissolution medium. The best formulation was selected based on *in-vitro* drug release rate.

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Key Words

Acyclovir, Floating matrix tablet, Swelling Index, HPMC

INTRODUCTION

Floating drug delivery systems were first described by Davis in 1968.^[1] It is possible to prolong the gastric residence time of drugs using these systems. Several techniques are used to design gastro retentive dosage forms. These include floating, swelling, inflation, adhesion, high-density systems and low density systems that increase the gastric residence time.^[2-3] Gastric retention is useful for drugs which (i) act locally; (ii) have a narrow absorption window (Various dosage forms developed for gastric retention include, floating tablets^[4], pellets^[5], floating granules^[6], floating microspheres.^[7-8] Gastro retentive floating drug delivery system (GFDDS) is systems which are retained in the stomach for longer period of time. In this investigation, an attempt was made to design floating tablets of Acyclovir using different polymers along with a gas-generating agent.

Acyclovir (INN) is a synthetic deoxyguanosine analog and it is the prototype antiviral agent that is activated by viral thymidine kinase. Acyclovir triphosphate competitively inhibits viral DNA polymerase and competes with the natural deoxyguanosine triphosphate, for incorporation into viral DNA. Once incorporated, acyclovir triphosphate inhibits DNA synthesis by acting as a chain terminator.

In this study, an attempt was made to design and formulate the floating matrix tablets of Acyclovir so as to increase its gastric retention thereby ensuring slower and complete release of Acyclovir. Also, attempts were made to assess the effect of semi synthetic polymers, HPMC (K100M) and HPMC (K15M) on the release rate of drug. Sodium bicarbonate and Citric acid were used as a gas generating agent.

OBJECTIVE

The purpose of this work is to develop a Floating Matrix Tablet to prolong gastric retention time for effective drug delivery system.

EXPERIMENTAL WORK

Materials

Acyclovir was obtained as gift sample from Matrix Labs, Sinnar, India. HPMC of two different viscosity grades HPMC (K100M), HPMC (K15M) were received from Colorcon Asia Pvt. Ltd. Microcrystalline cellulose S.D Fine Chemical, Mumbai, India. Other ingredients used were of analytical grade.

METHODS

Drug-excipient compatibility Studies

Ftir

The infrared spectra of Acyclovir, physical mixture of drug and excipient which were recorded between 400 to 4000 cm⁻¹ on FTIR. The IR spectra for the test samples were obtained using KBr disk method using an FTIR spectrometer.

Preparation of floating tablets

Floating tablets of Acyclovir were prepared by direct compression method employing Sodium bicarbonate and Citric acid used as gas-generating agent. HPMC (K100M), HPMC (K100M) were used as polymers as rate retarding material. Drug of required quantity was accurately weighed and polymers blended thoroughly using glass mortar and pestle manually in geometric proportion and then Sodium bicarbonate and Citric acid was mixed thoroughly. Magnesium stearate was added to the blend as a lubricant. Matrix tablets were prepared by direct compression method on Cadmach 16 station automatic tablet compression machine. Average weight of the tablets 500 mg was kept constant.

Table 1. Composition of Acyclovir floating tablets

Formulation (mg/tablet)	Drug	HPMC (K100M)	HPMC (K15M)	Gas forming agent	Magnesium Stearate	MCC
F1	200	100	-	-	6	194
F2	200	150	-	-	6	144
F3	200	200	-	-	6	94
F4	200	-	100	-	6	194

F5	200	-	150	-	6	144
F6	200	-	200	-	6	94
E7	200	100	-	50	6	144
E8	200	100	-	100	6	94
E9	200	150	-	50	6	94
E10	200	150	-	100	6	44
E11	200	200	-	50	6	44
E12	200	200	-	100	-	-
E13	200	-	100	50	6	144
E14	200	-	100	100	6	94
E15	200	-	150	50	6	94
E16	200	-	150	100	6	44
E17	200	-	200	50	6	44
E18	200	-	200	100	-	-

CHARACTERIZATION

Weight variation, thickness, hardness and friability determination

The weight variation of tablets were determined, thickness was measured using digital screw gauge (Mitutoyo, Japan) friability was carried out on Roche friabilator and Hardness was measured by using Pfizer hardness tester.^[9-10]

Assay of Acyclovir

Twenty tablets were taken and powdered, powder equivalent to one tablet was taken and was allowed to dissolve in 100 ml of 0.1N Hydrochloric acid (HCl). The solution was filtered, diluted suitably and analyzed using UV/visible spectrophotometer (Systronics 2201) at 252 nm.

Determination of swelling index

The swelling index of tablets was determined in 0.1N HCl at room temperature. The swollen weight of the tablet was determined at predefined time intervals. The swelling index was calculated by the following equation:

$$\text{Swelling index} = \frac{W_t - W_0}{W_0}$$

Where,

W_0 = initial weight of tablet,

W_t = weight of tablet at time t.

Each experiment was performed in triplicate and the mean and standard deviation (SD) were calculated.

In-vitro buoyancy studies

The *in-vitro* buoyancy was determined by floating lag time. 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 taken as the floating lag time. The experiments were conducted in triplicate.

In-vitro drug release studies

The release of Acyclovir was studied using USP dissolution apparatus I (Labindia, India). The dissolution media was 900 ml 0.1N HCl maintained at $37 \pm 0.5^\circ\text{C}$ with rotation speed of 50 rpm. Aliquots of 10 ml was collected at predetermined time intervals and replenished with an equivalent volume of fresh medium. The samples were filtered through a filter paper and diluted suitably with 0.1N HCl and were analyzed using UV/visible spectrophotometer at 252 nm. The results are expressed as mean \pm S.D (n=3).

Kinetic modeling of drug release

The suitability of several equations, which are reported in the literature to identify the mechanism(s) for the release of Acyclovir, was tested with respect to the release data. The data were evaluated according to the following equations.

Sr. No.	Model	Equation
1	Zero order (Chen and Hao 1998)	$F = k t$
2	First order (Shah et al. 1987)	$\ln F = k t$
3	Higuchi (Higuchi 1961)	$F = k t^{0.5}$
4	Korsmeyer and Peppas model (Korsmeyer et al. 1983)	$F = k t^n$

Results and Discussion

Compatibility Study

From the results of FTIR studies there are no significant changes observed when pure drug, HPMC (K100M), HPMC (K15M), and physical mixture were subjected to FTIR study. As shown in figure.1-3.

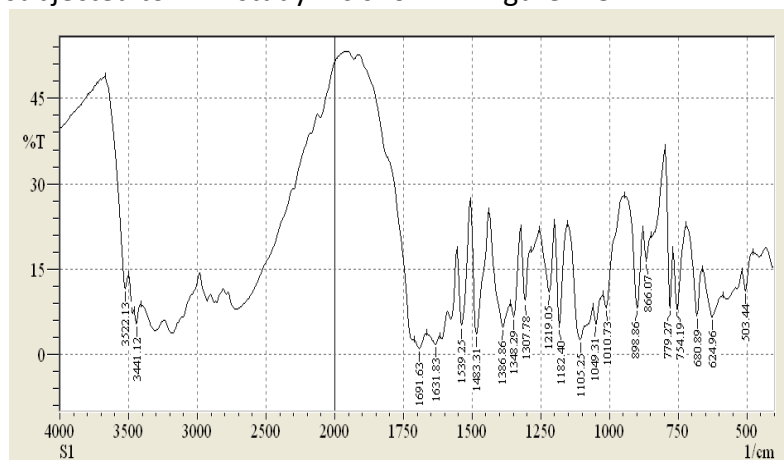


Figure 1. FTIR Spectra of Acyclovir

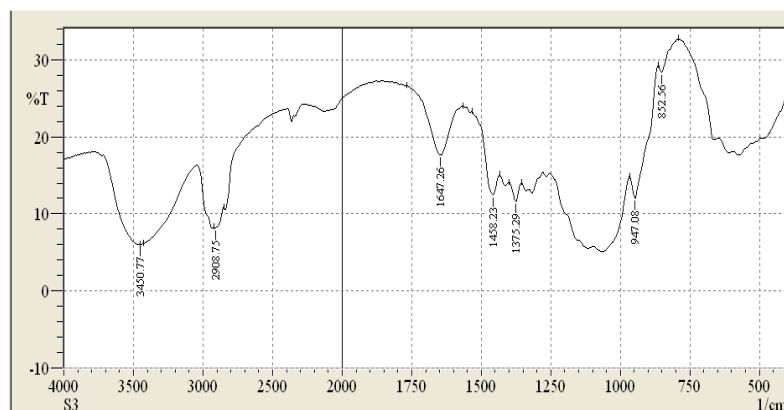


Figure 2. FTIR Spectra of HPMC (K15M)

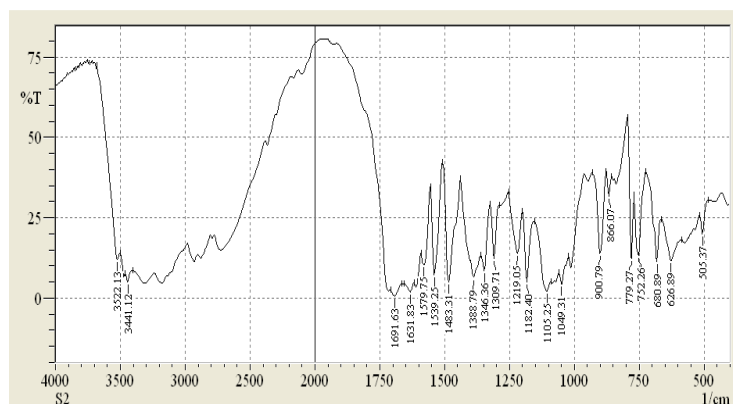


Figure 3. FTIR Spectra of Physical Mixture

Physical properties of the compressed floating tablet systems

The floating tablets of Acyclovir were prepared by effervescent technique using HPMC (K100M), HPMC (K15M), Microcrystalline cellulose, Sodium bicarbonate and Citric acid along with magnesium stearate. The results of weight variation, thickness variation and assay of floating tablets are shown in Table 2. The weight variation and thickness of the all the formulations were found to be within limits. Hardness of tablets was found to be between 7.46 to 8.12 kg /cm². The friability was below 1% for all formulations, indicating good mechanical resistance of the tablet. The drug content varied between 98.27 to 99.88 % in all tablets with low standard deviation indicating content uniformity of the prepared batches.

Table 2. Physicochemical parameters of the prepared formulations

Formulations	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm ²)	Friability (%)	Drug content (%)
F1	500±0.1	5.02±0.15	8.12±0.14	0.7	99.78±1.23
F2	498±0.26	5.02±0.16	8.12±0.15	0.2	97.27±1.34
F3	501±0.5	5.02±0.17	8.13±0.16	0.4	98.23±1.24
F4	500±0.10	5.02±0.14	8.12±0.17	0.3	97.45±1.20
F5	498±0.68	5.02±0.12	8.14±0.13	0.7	98.23±1.26
F6	499±0.45	5.02±0.15	7.89±0.11	0.34	94.23±1.18
E7	499±0.64	5.02±0.16	7.55±0.12	0.1	99.25±1.15
E8	499±0.5	5.02±0.03	7.46±0.18	0.4	98.27±1.26
E9	501±0.57	5.02±0.03	7.76±0.15	0.34	99.88±1.30
E10	501±0.13	5.02±0.32	7.26±0.11	0.56	99.78±1.56
E11	500±0.16	5.02±0.23	7.55±0.19	0.14	98.27±1.34
E12	499±0.87	5.02±0.20	7.42±0.16	0.36	98.27±1.76
E13	499±0.78	5.02±0.15	7.82±0.12	0.71	99.32±1.41
E14	498±0.5	5.05±0.05	8.12±0.15	0.5	99.88±1.36
E15	498±0.96	5.02±0.10	8.11±0.14	0.78	98.56±1.40
E16	500±0.45	5.02±0.18	8.22±0.11	0.62	99.76±1.20
E17	501±0.23	5.02±0.15	8.12±0.12	0.32	97.67±1.36
E18	500±0.21	5.02±0.16	8.13±0.15	0.42	98.46±1.20

*All values expressed as mean are S.D., n=3

Buoyancy studies

The formulated tablets on immersion in 0.1N HCl media, they remain buoyant for more than 12 h with a lag time of 15 to 18 sec. Sodium bicarbonate and Citric acid was added as a gas generating agent. The optimized concentration of effervescent mixture utilized aided in the buoyancy of all tablets. This may be due to the fact that effervescent mixture in tablets produced carbon

dioxide that was trapped in swollen matrix, thus decreasing the density of the tablet below 1 making the tablets buoyant. All the batches showed good in vitro buoyancy. The results of the in vitro buoyancy study of batch E7-E18 are shown in Table 3. That clearly indicates the floating lag time (15 sec) of the Acyclovir tablet and the floating and swelling tendency of the formulation.^[11]

Table 3. Results of Floating Time of E7-E18

Sr. No.	Buoyancy time in seconds	Floating Time (hr)
E7	30	>12
E8	18	>12

E9	25-30	>12
E10	15-25	>12
E11	30	>12
E12	15-18	>12
E13	25-30	>12
E14	15	>12
E15	30	>12
E16	15-18	>12
E17	25-30	>12
E18	15-20	>12

Swelling Index^[12]

In order to study the swelling index of the floating tablet, all the tablets were kept in 100 ml of 0.1N HCl

and the swelling behaviour of tablets after 1 hr, 2 hrs, 4 hrs, 6 hrs, 8 hrs was studied. The results are shown in Table 4

Table 4. Results Swelling Study of Tablets

Time in hours	Formulation											
	E7 (%)	E8 (%)	E9 (%)	E10 (%)	E11 (%)	E12 (%)	E13 (%)	E14 (%)	E15 (%)	E16 (%)	E17 (%)	E18 (%)
1	54	40	34	45	50	55	47	40	39	55	60	55
2	67	64	70	78	65	68	65	84	89	75	70	75
4	95	90	99	96	78	85	79	96	95	90	84	85
8	99	128	110	116	90	104	90	124.6	110	115	120	106

In-vitro Drug Release Studies

Effect of HPMC (K100M)

In order to investigate the release rate with HPMC (K100M) this is prepared in the ratio of 1:0.5, 1:0.75 and 1:1. The formulations F1-F3 were subjected to dissolution studies as shown in Figure 4.

From the Figure 4. the formulation F1 showed drug release rate 85.22 % in 12 hr, F2 showed 82.66 % drug release rate in 12 hr and F3 showed 79.82 % drug release rate in 12 hrs. It was concluded that the drug release rate decreases as the concentration of polymer increases.

Effect of HPMC (K15M)

In order to investigate the release rate with HPMC (K15M), which prepared in the ratio 1:0.5, 1:0.75 and 1:1. The formulations F4-F6 were subjected to dissolution studies as shown in Figure 5.

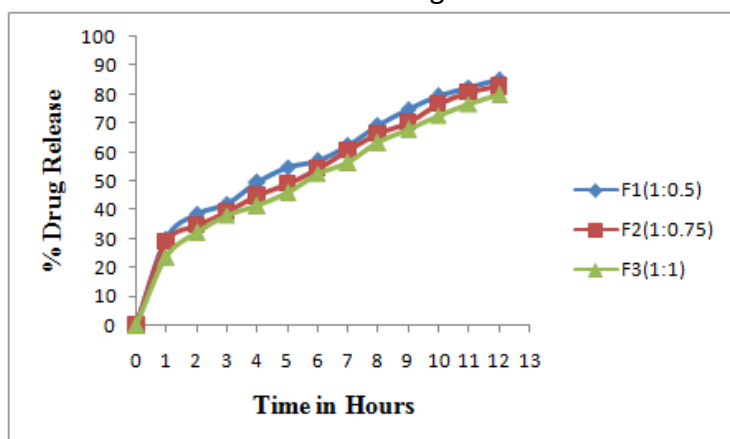


Figure 4. Results of *in-vitro* Drug Release Rate Profile of F1- F3

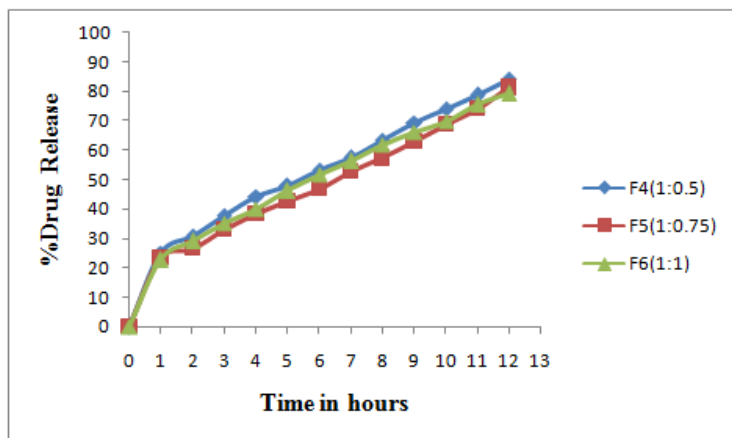


Figure 5. Results of *in-vitro* Drug Release Rate Profile of F4- F6

From the Figure 5 and the formulation F4 showed drug release rate 84.16 % in 12 hr, F5 showed 81.31 % drug release rate in 12 hr and F6 showed 79.20 % drug release rate in 12 hrs. It was concluded that the drug release rate decreases as the concentration of polymer increases.

Effect of Sodium bicarbonate and Citric acid on HPMC (K100M) prepared formulations

In order to study the combine effect of Sodium bicarbonate and Citric acid with HPMC (K100M) and the formulation which is prepared in the ratio 1:0.5:0.25, 1:0.5:0.5, 1:0.75:0.25, 1:0.75:0.5, 1:1:0.25, 1:1:0.5. The formulations E7-E12 were subjected to dissolution studies as shown in Figure 6.

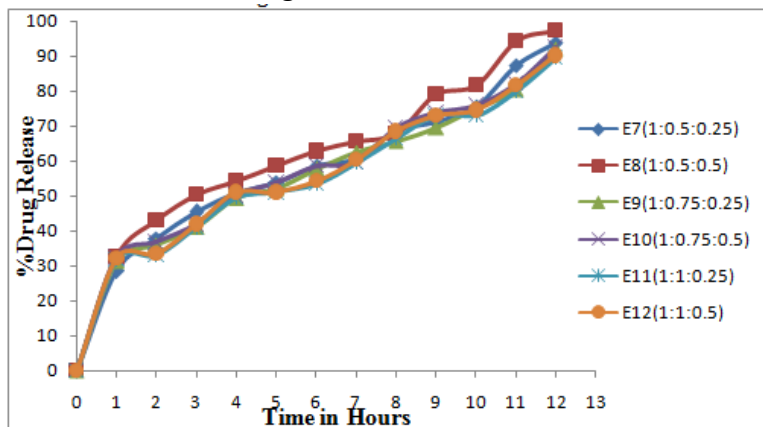


Figure 6 Results of *in-vitro* Drug Release Rate Profile of E7- E12

From the Figure 6 the formulation E7 showed 93.70 % drug release rate in 12 hrs, E8 showed 97.31 % drug release rate in 12 hrs, E9 showed 91.99 % drug

release in 12 hrs, E10 showed 92.36 % drug release rate in 12 hrs, E11 showed 89.41 % drug release rate in 12 hrs, E12 showed 90.34% drug release rate in 12 hrs. It was concluded that the concentration of HPMC (K100M) increases and the drug release rate decreases similarly as the concentration of gas forming agent increases the drug release rate also increases.

Effect with Sodium bicarbonate and Citric acid on HPMC (K15M) prepared Formulations

In order to study the combine effect of Sodium bicarbonate and Citric acid with HPMC (K15M) and the formulation which is prepared in the ratio 1:0.5:0.25, 1:0.5:0.5, 1:0.75:0.25, 1:0.75:0.5, 1:1:0.25, 1:1:0.5. The formulations E13-E18 were subjected to dissolution studies as shown in Figure 7.

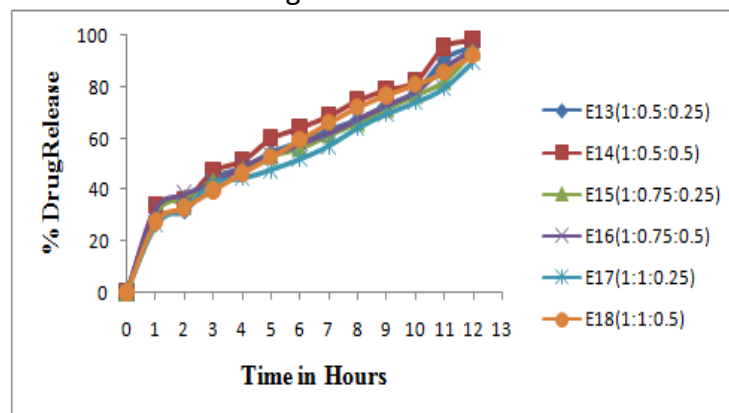


Figure 7. Results of *in-vitro* Drug Release Rate Profile of E13- E18

From the Figure 7. the formulation E13 shows 95.46 % drug release in 12 hrs, E14 shows 98.31 % drug release in 12 hrs, E15 shows 93.78 % drug release in 12 hrs, E16 shows 94.42 % drug release in 12 hrs, E17 shows 89.70 % drug release in 12 hrs, E18 shows 92.15 % drug release in 12 hrs. It was concluded that the concentration of HPMC (K15M) increases the drug release rate decreases and similarly the concentration of gas forming agent increases the drug release rate also increases.

Drug Release Kinetics

Dissolution data of the optimized formulations was fitted to various mathematical models (Zero-order, First order, matrix, Peppas and Hix. Crowell) in order to describe the kinetics of drug release rate. Higher the

value of regression coefficient (R^2) was chosen as criteria for selecting the most appropriate model. The

dissolution data of was found to fit well into zero order release kinetics as shown in Table 5.

Table 5. Release Kinetics of Optimized Formulations

Formulation	R^2				
	Zero order	First order	Matrix	Peppas	Hix.-Crow.
E7	0.6508	0.6739	0.9781	0.9970	0.6663
E8	0.8273	0.8561	0.9815 n=0.4131	0.9774	0.9293
E9	0.8176	0.8465	0.8934	0.7892	0.8376
E10	0.8216	0.8264	0.9535	0.8709	0.8078
E11	0.8687	0.8764	0.9276	0.9761	0.9510
E12	0.8498	0.9408	0.9872	0.9710	0.9566
E13	0.9063	0.9334	0.9805	0.9823	0.9631
E14	0.8772	0.8681	0.9916 n=0.4703	0.9794	0.9520
E15	0.8628	0.9389	0.9810	0.9800	0.9590
E16	0.8683	0.9165	0.9784	0.9755	0.9541
E17	0.9073	0.9739	0.9677	0.9789	0.9777
E18	0.9253	0.9666	0.9738	0.9950	0.9777

Conclusion

An attempt was made to develop a floating drug delivery system of Acyclovir using HPMC (K100M) and HPMC (K15M) as gel-forming polymer, Sodium bicarbonate and Citric acid as gas generating agent. Drug excipient study was carried out to investigate the possible interactions between drug and polymers. Results of FTIR, indicated that there is no incompatibility, can be used to manufacture the tablet

formulation with desired *in-vitro* floating time and dissolution.

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