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RESEARCH ARTICLE

Development and Evaluation of Gastro-Retentive Floating Acyclovir Tablets

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ABSTRACT

In the present study an attempt was made to prepare acyclovir floating tablets. Acyclovir floating tablets (200mg) were prepared by direct compression method using HPMC, sodium carboxy methyl cellulose and carbopol with an effervescent base (sod. Bicarbonate and citric acid). FTIR study confirmed the absence of any drug/polymer/excipients interactions. The prepared floating tablets were evaluated for hardness, weight variation, thickness, friability, drug content uniformity, buoyancy lag time, total floating time, swelling index and in vitro dissolution studies. Among all the 12 formulations F1, F2, F3, F4, F5, F6, F10, F11, F12 showed good floating property while formulations F7, F8, F9 showed moderate floating while all the 12 formulations showed controlled drug release. Stability studies were carried out for F4 and F10, both the formulations showed good stability. It was observed that F4 and F10 gave maximum drug release upto 97.17% within 24 hrs.SEM study indicates that both the tablets F4 &F10 have smooth and uniform surface before the dissolution study, but after the dissolution study, the Tablet F4 which was prepared withsod.CMC has shown erosion of the polymer matrix. But the Tablet F10 have shown spongy like structure, the matrix was swollen and pores were created.

KEYWORDS

Gastro-retentive, Acyclovir, Swelling Index, Gas Generating Agent

INTRODUCTION

The goal in designing sustained and controlled release is to reduce frequency of dosing or increase effectiveness of the drug by localization at site of action, reducing dose frequency, providing uniform drug delivery.[1] The current controlled release technology had made it possible to release drugs at a constant release rate for longer periods of time ranging from days to years. However, this benefit had not satisfied a variety of important drugs that

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- Are locally active in the stomach,
- Have an absorption window in the stomach or in the upper small intestine,
- Are unstable in the intestinal or colonic environment, or
- Exhibit low solubilities at high pH values.

These limits promoted the development of gastro retentive drug delivery systems (GRDDS). Besides being able to continually and sustainably deliver drugs to the small intestinal absorption window, the improvements provided from GRDDS include: achieving a greater and prolonged therapeutic effect and thus reducing the frequency of administration periods,

providing a more effective treatment of local stomach disorders, and minimizing both lower-tract inactivation of the drug and drug effects on the lower intestinal flora.[1]

From the recent scientific and patent literatures that an increased interest in novel oral controlled release dosage forms that designed to be retained in the GIT for a prolonged and predictable period of time exists today Several approaches are currently utilized in the prolongation of the gastric residence times (GRT), including floating drug delivery systems (FDDS), low-density systems, raft systems incorporating alginate gels, bioadhesive or mucoadhesive systems, high-density systems, super porous hydrogels and magnetic systems. The FDDS is one of the most leading methodologies in gastro retentive drug formulations.[2]

Floating drug delivery systems (FDDS) or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and 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 GRT and a better control of the fluctuations in plasma drug concen tration.[2]

MATERIAL AND METHODS

Acyclovir was received as a gift sample from Lincoln Pvt. Ltd., Gujrat. Hydroxy propyl methyl cellulose was obtained from Yarrow chemicals, Mumbai. Sodium carboxy methyl cellulose, microcrystalline cellulose and carbopol was obtained from international Mumbai.

Methods

Standard Calibration Curve for Acyclovir in pH (1.2) 0.1 N HCl

Solution 1st: Accurately weighed 100 mg of Acyclovir (pure drug) was dissolved in sufficient quantity of 0.1N HCl and the volume was made upto 100 mL with 0.1N HCl (1000 µg/mL). Further dilution was made to give stock solution 100µg/ml.[4]

Solution2nd: From this 1st stock solution, 1 ml was pipetted out and transferred in to a 100 ml volumetric flask and volume was made up to 100 ml with 0.1 N HCl which contained the concentration of 10 µg/ml (2nd stock solution). From 2nd stock solution aliquots equivalent to 1-5 µg (1, 2, 3, 4 and 5 ml) were pipette out in to a series of 10 ml volumetric flask and volume was made up to 10 ml with 0.1 N HCl. The absorbance of these solutions was measured against the 0.1 N HCl as blank at 255nm using UV-Visible double beam spectrophotometer.[3,4]

Preparation of Floating Tablets

Floating tablets has been prepared by direct compression method. HPMC, Sodium carboxy methyl cellulose, Carbopol, sodium bicarbonate, citric acid, microcrystalline cellulose and the active ingredient were sieved through sieve no. 60 and mixed homogeneously. Magnesium stearate, talc were added as a lubricant and the powder was compressed into tablets using Rotary tablet punch machine punch.[5]

Pre Compression Evaluation of Powder

Bulk Density and Tapped Density

Both loose bulk density and tapped bulk density were determined. A 2gm of granules from each formula, previously light Shaken for the break of any agglomerates formed, was introduced into the 10ml of measuring cylinder. After noting its initial volume, cylinder was allowed to fall down its own weight from the hard surface from a height of 2.5cm at 2 sec Intervals.

$$\text{LBD} = \frac{\text{Weight of the powder}}{\text{Volume of the packing}}$$

$$\text{TBD} = \frac{\text{Weight of the powder}}{\text{Tapped volume of packing}}$$

Percentage Compressibility or Carr's Index

$$\text{Carr's Index (\%)} = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100$$

Table 1: Composition of Formulation F1 to F12

Formulation Code	Drug (Mg)	HPMC (Mg)	Sod. CMC (mg)	Carbopol (mg)	$NaHCO_3$ (mg)	Citric acid (mg)	MCC (mg)	Lactose (mg)	Total Wt. (mg)
F1	200	160	-	-	50	25	25	40	500
F2	200	140	-	-	50	25	25	60	500
F3	200	120	-	-	50	25	25	80	500
F4	200	-	80	-	50	25	25	120	500
F5	200	-	70	-	50	25	25	130	500
F6	200	-	60	-	50	25	25	140	500
F7	200	-	-	100	50	25	25	100	500
F8	200	-	-	120	50	25	25	80	500
F9	200	-	-	140	50	25	25	60	500
F10	200	80	40	-	50	25	25	80	500
F11	200	-	100	50	50	25	25	50	500
F12	200	100	-	50	50	25	25	50	500

Angle of Repose

The fixed funnel and free standing cone methods employ a funnel that is secured with its tip at a given height, h, which was kept above graph paper that is placed on a flat horizontal surface. With r being the radius, of base of conical pile, angle of repose can be determined by following equation:[6]

$$\theta = \tan^{-1} (h/r)$$

Hardness Test

The measured hardness of tablets of each batch ranged between 4.1 to 4.5 kg/cm^2. This ensures good handling characteristics of all batches.

Friability Test

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

Weight Variation Test

20 tablets were randomly selected and weighed individually than average wt. of the tablets was calculated. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits of ± 5% of the weight.

The weights of all the tablets were found to be uniform with— low standard deviation values.[7]

Test for Content Uniformity

Tablet containing 500mg of drug is dissolved in 100 ml of 0.1N HCl taken in volumetric flask. The drug is allowed to dissolve in the solvent.

The solution was filtered, 1 ml of filtrate was taken in 50 ml of volumetric flask and diluted up to mark with 0.1N HCl and analyzed spectrophotometrically at 255nm.[8]

In Vitro Dissolution Studies

The dissolution test was performed using 900 ml of 0.1N HCl at 37° ± 0.5°C and 100 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus and the samples were replaced with fresh dissolution medium. The samples were filtered and the absorbance of these solutions was measured at 255 nm using a UV/Visible spectrophotometer. The Cumulative percentage drug release was plotted against time to determine the release profile.[9]

In Vitro Residence Time

In vitro residence time was determined by floating lag time, total floating time for floating of tablets floating lag time test was performed to check the floating behavior. The tablets were dropped in the dissolution medium, i.e., 0.1 N HCl and the time taken by them to come to the surface of the dissolution medium, i.e., time taken for floating on surface was reported.[10,11]

Determination of Swelling Index

The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using the dissolution medium was 100 ml 0.1N HCl (pH 1.2). After 0.5, one, two, three, four, and five, each tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, AX 120). Swelling index was calculated by using the following formula.[12]

$$\text{Swelling index} = \frac{\text{(Wet weight of tablet - Dry weight of tablet)}}{\text{Dry weight of tablet}}$$

Scanning Electron Microscopy

Scanning electron microscopy was performed to characterize the surface morphology of the formed tablets and this was done by using a JSM 6100 JEOL Scanning electron microscope at 20 kV. Prior to examination, samples were gold-coated to render them electrically conductive and examined under the microscope.[13]

Drug-Polymer Interaction by FT-IR

Drug polymer interaction was studied by taking FT-IR. Infrared spectra of acyclovir, HPMC and drug floating tablets were carried out by using KBR pellet technique and were recorded on a shimadzu FT-IR spectrometer.[14]

RESULTS AND DISCUSSION

Calibration Curve of Acyclovir in 0.1N HCl Solution

Table 2: Absorbance data for the calibration curve of acyclovir in 0.1N HCl

Sl.No.	Concentration (µg/ml)	Absorbance
1.	0	0
2.	1	0.053
3.	2	0.116
4.	3	0.166
5.	4	0.231
6.	5	0.289

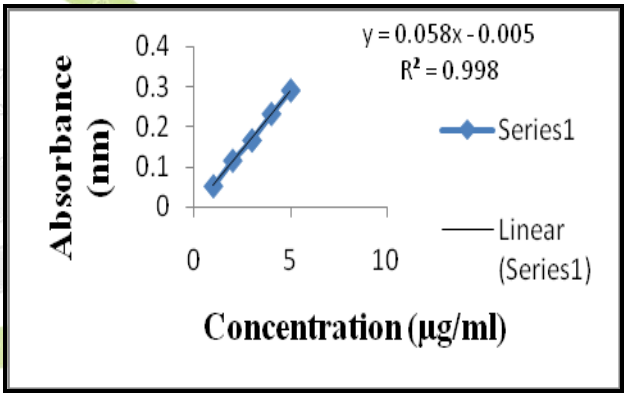

Figure 1: Standard calibration curve of Acyclovir in 0.1N HCl

IR Spectrum

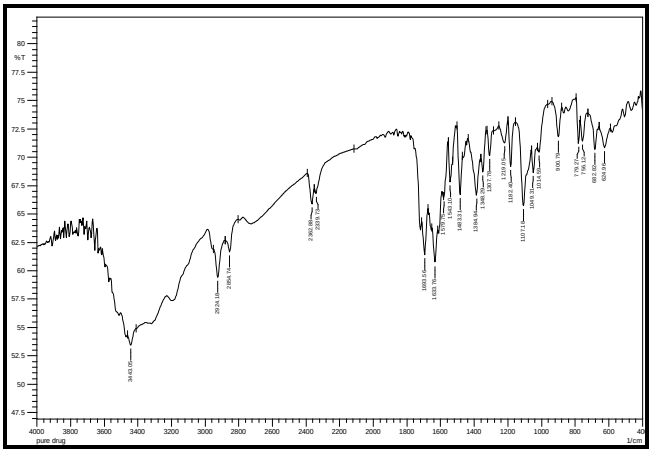

Figure 2: IR spectrum of pure drug

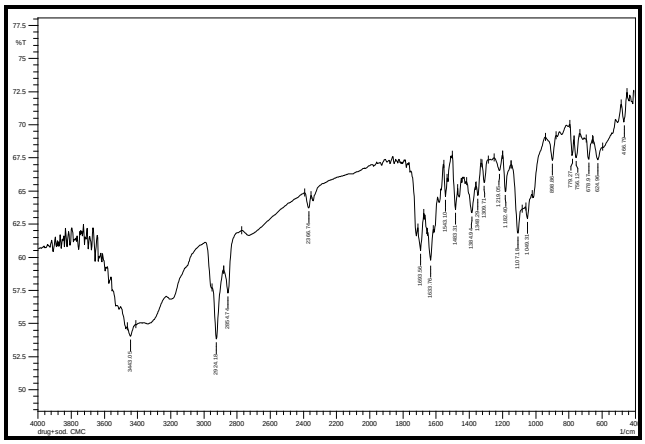

Figure 3: IR spectrum of drug + sodium CMC

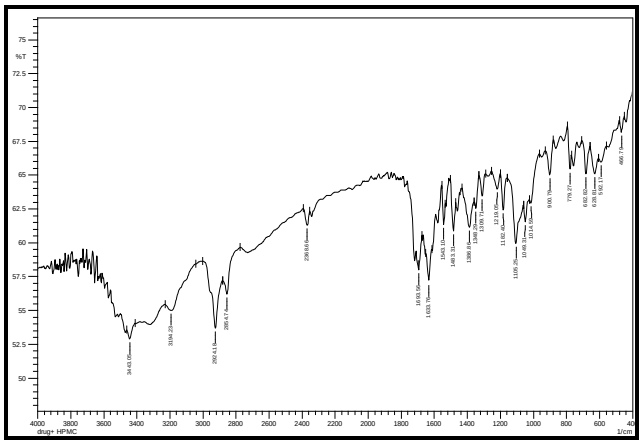

Figure 5: IR spectrum of drug + HPMC

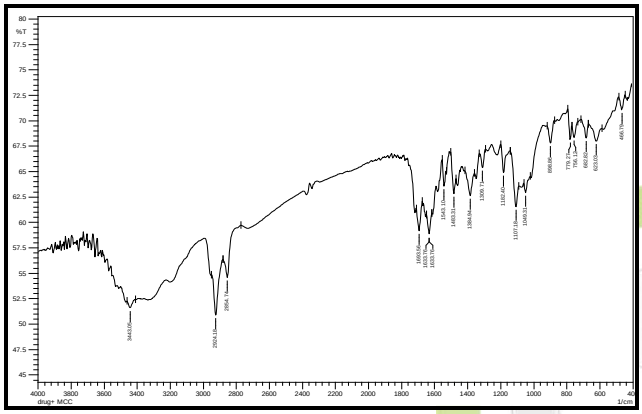

Figure 4: IR spectrum of drug + microcrystalline cellulose

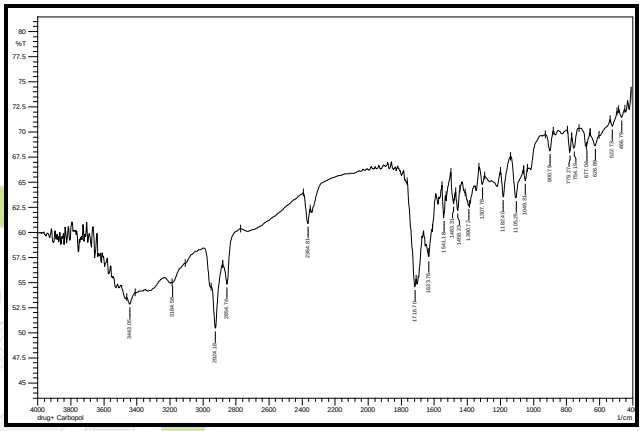

Figure 6: IR spectrum of drug + carbopol

Pre-Compression Evaluation of Acyclovir Floating Tablets

Table 3: Pre-compression parameters of Acyclovir floating tablets

Formulations	Bulk density (g/ml	Tapped density (g/ml)	Carr's compressibility index (%)	Angle of Repose (Ø)
F1	0.55	0.62	11.29	15.60
F2	0.48	0.63	23.0	25.60
F3	0.47	0.632	25.39	30.17
F4	O.490	0.65	24.6	30.1
F5	0.58	o.62	6.45	16.69
F6	0.49	0.63	7.9	17.7
F7	0.57	0.63	9.5	26.56
F8	0.59	0.68	13.23	27.51
F9	0.66	0.66	7.04	16.08
F10	0.57	0.64	10.93	21.09
F11	0.65	0.77	15.58	23.62
F12	0.55	0.61	9.8	17.17

Evaluation of Tablets

Table 4: Evaluation data of Acyclovir floating tablets

Formulation	Thickness (mm) n=20	Weight variation n=20	Hardness (Kg/cm^2)	Friability %	Floating time (hrs)	Floating lag time	Drug content (%)
F1	2.788± 0.057	489.5±0.933	6.3±0.5	0.4± 0.057	22	60 sec	97
F2	2.948± 0.066	488± 0.882	6.0±0.1	0.32± 0.055	18	75 sec	90.35
F3	2.904± 0.055	487.5± 0.825	6.0±0.5	0.56± 0.015	12	90 sec	94.1
F4	2.724± 0.000	491.5± 0.887	5.8±0.7	0.44± 0.010	18	80 sec	99.6
F5	2.835± 0.057	491.5±0.833	5.6±0.5	0.85± 0.011	16	95 sec	98.65
F6	3.154± 0.010	493.5± 0.951	5.4±0.8	0.80± 0.090	13	70 sec	97.0
F7	3.258± 0.049	487.5± 0.887	6.2±0.5	0.52± 0.060	7	120 sec	89.35
F8	2.687± 0.052	485.7± 0.833	6.0±0.3	0.81± 0.011	6-5	145 sec	89.0
F9	2.876± 0.057	488.5± 0.812	6.1±0.5	0.73± 0.010	5	160 sec	89.9
F10	3.3892±0.000	489.5± 0.852	5.6±0.5	0.56± 0.017	>24	45 sec	99.2
F11	2.751± 0.100	486.5± 0.812	6.0±0.3	0.89± 0.010	8-12	90 sec	89.45
F12	2.893± 0.100	489.5±0.933	6.3±0.7	0.93± 0.010	12-18	120 sec	94.8

Table 5: Swelling index of acyclovir floating tablets

Time (hr.)	0.5	1.0	2.0	3.0	4.0	5.0
F1	22.48	36.54	52.61	64.65	80.72	94.77
F2	19.60	33.33	48.47	61.60	76.78	96.94
F3	16.46	31.52	43.57	60.64	75.70	91.76
F4	25.75	38.83	50.90	64.98	81.08	93.15
F5	24.74	35.81	48.89	65.99	78.06	93.15
F6	18.95	38.10	48.18	62.29	77.41	85.48
F7	17.47	28.51	42.57	58.63	72.69	84.73
F8	13.68	23.13	39.63	53.92	67.00	81.08
F9	9.47	20.56	32.05	49.19	63.91	77.41
F10	15.55	27.47	40.41	66.46	75.96	100.60
F11	11.11	19.79	34.35	49.89	65.56	78.99
F12	27.51	42.57	57.63	68.47	91.76	161.0

Table 6: *In vitro* drug release of formulations F1 to F12

Time hr.	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0.5	17.64	14.06	11.45	15.58	12.69	10.08	10.52	7.53	5.95	19.65	15.98	10.51
1.0	20.45	19.56	16.07	17.52	15.95	13.52	11.38	9.39	8.30	21.48	17.13	12.59
1.5	29.65	24.45	20.68	20.59	18.08	17.62	13.90	11.85	10.85	24.56	20.52	16.18
2.0	36.78	28.17	23.95	23.78	22.49	20.98	16.38	14.52	12.98	27.69	22.60	22.64
3	41.53	30.19	27.58	27.02	27.48	22.90	20.56	19.90	15.50	31.32	25.90	28.93
4	46.51	34.50	32.65	32.50	34.49	26.51	25.12	22.38	19.85	37.45	29.30	35.65
5	51.70	39.45	39.95	41.80	40.91	31.45	30.06	27.85	25.90	45.30	34.35	42.90
6	56.12	43.41	45.34	48.37	45.43	37.63	36.52	33.90	30.94	54.85	40.69	50.61
7	63.32	48.65	52.50	55.52	50.98	44.92	44.15	40.54	36.90	62.95	47.85	57.63
8	71.50	54.45	60.90	61.50	58.50	51.49	49.90	46.58	47.50	71.32	55.68	65.98
9	79.02	59.95	69.63	69.15	70.39	60.30	58.56	57.30	59.30	79.35	64.32	73.95
10	84.35	67.31	77.16	81.85	77.40	69.90	67.90	65.98	68.52	87.52	69.56	85.38
12	89.19	77.65	84.62	88.30	87.59	80.05	78.42	76.65	79.30	93.69	78.90	89.06
24	95.56	86.59	90.90	96.51	94.68	92.56	87.30	87.52	88.63	97.45	87.37	91.17

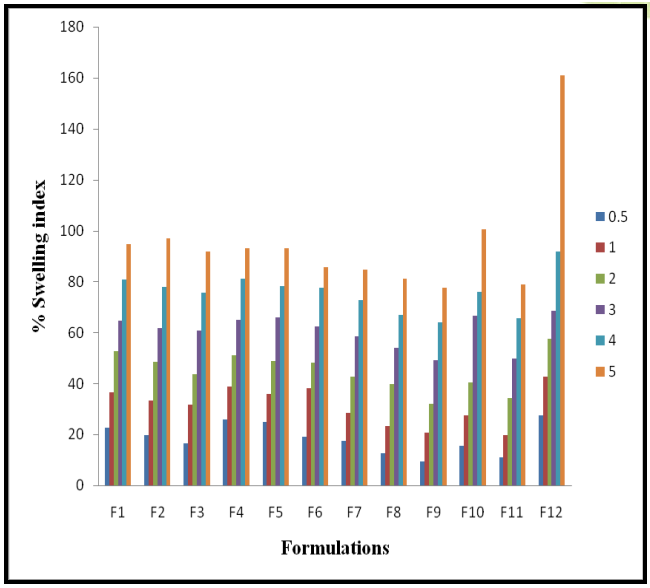

Figure 7: Swelling index of acyclovir floating tablets

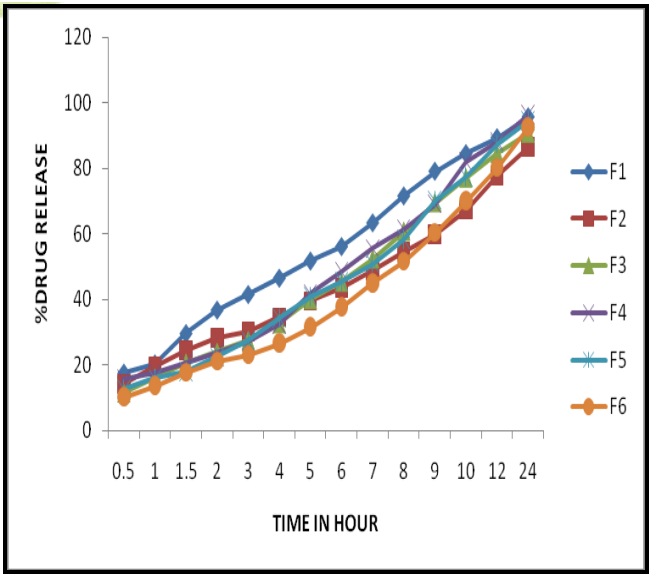

Figure 8: % drug released Vs. time plots (zero order) of formulations F1, F2, F3, F4, F5, F6

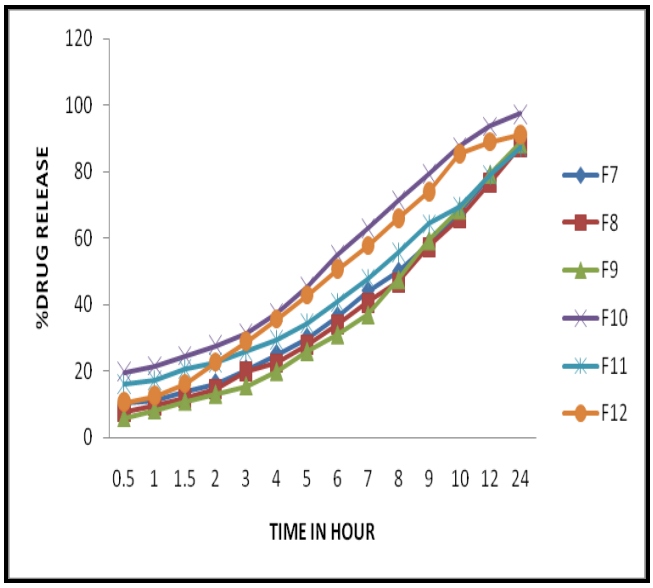

Figure 9: % drug released vs. time plots (zero order) of Formulations F5, F6, F7, F8, F9, F10, F11, F12

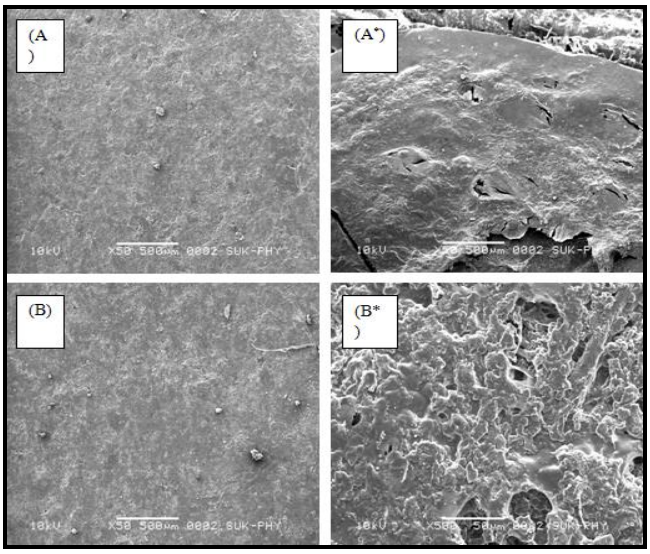

Figure 10: Scanning electron microscopic photographs of F4 tablets before (A) and after (A*) dissolution, F10 tablets before (B) and after (B*) dissolution experiment

Table 7: Kinetic values of Acyclovir floating tablets

Formulation	Zero order equation		First order equation		Higuchi equation		Korsemeyer's equation	
	n	r	n	R	n	r	N	R
F1	0.1879	0.8684	-4.83	-0.4190	0.0418	0.9751	0.6667	0.7414
F2	0.2333	0.9162	-2.2090	-0.1760	0.0497	0.9840	0.7083	0.7507
F3	0.1966	0.9000	-3.4609	-0.2902	0.0420	0.9701	0.7250	0.8079
F4	0.1905	0.9077	-4.7672	-0.4367	0.0404	0.9697	0.7054	0.7826
F5	0.1935	0.9103	-4.1927	-0.3712	0.0409	0.9714	0.7229	0.8084
F6	0.2111	0.9353	-3.4408	-0.2972	0.0434	0.9692	0.7469	0.8229
F7	0.2132	0.9267	-2.4991	-0.2089	0.0440	0.9640	0.7560	0.8378
F8	0.2137	0.9353	-2.4701	-0.2059	0.0436	0.9618	0.7694	0.8734
F9	0.2012	0.9268	-2.7594	-0.2343	0.0408	0.9472	0.7642	0.8956
F10	0.1777	0.8191	-5.2118	-0.4948	0.0386	0.9627	0.6739	0.7495
F11	0.2191	0.9148	-2.5073	-0.2037	0.0461	0.9697	0.7147	0.7636
F12	0.1758	0.8741	-3.8485	-0.3322	0.0383	0.9596	0.7239	0.8421

r: correlation coefficients, n: release mechanism

Table 8: Stability studies

S.N	Time	Drug content											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	0	97	90.35	94.1	99.6	98.65	97.0	89.35	89.0	89.9	99.2	89.45	94.8
2	1 month	96.57	87.01	92.54	97.20	96.31	87.80	87.45	88.59	87.54	97.50	86.3	91.8

DISCUSSION

The main aim of this work was to develop new floating tablets of Acyclovir to increase its oral bioavailability by prolonging its gastric residence time and allowed to float in the stomach for a long period.

In the present dissertation floating tablets of Acyclovir were prepared by direct compression method using three semi-synthetic polymers HPMC, Sodium CMC, and Carbopol.

Acyclovir floating tablets were prepared using HPMC (F1, F2 & F3), Sod.CMC (F4, F5 & F6), Carbopol (F7, F8 & F9), HPMC & Sod. CMC (F10), Sod. CMC & Carbopol (F11), HPMC & Carbopol (F12).

The powder evaluation suggested that all the prepared powders exhibited good flow properties, as the angle of repose value were less than 30^0. A good packing ability of the powder was indicated by carr's compressibility index. The weight, Thickness and drug contents of all the tablets were found to be uniform. The hardness was in the range of 5.4 to 6.3 kg/cm^2andfriability was in the range of 0.32 to 0.93 % and drug content was in the range of 89.0 % to 99.6 %.

The FTIR study indicated that the characteristics peaks related to drug were also noticed in the spectra of drug & other polymers. Hence there is no drug –polymer interaction.

Among all the formulations F4 & F10 formulations were optimized based on floating time and drug release profile. The floating study of the prepared tablets was carried out in 0.1N HCL buffer and the results are shown.

Formulation F4 containing Sod. CMC and formulation F10 containing combination of HPMC & sod. CMC found to be best not only in floating behavior but also in best drug release profile.

The polymers used were of low density, highly swellable in shortest possible time and which upon contact with water; a hydrogel layer is formed to act as a gel would be gel boundary for the release of drug. Mixture of citric acid and sodium bicarbonate was incorporated in the formulation in such a way that when it contact with the acidic gastric contents, CO_2 is liberated and gets entrapped in swollen polymers, which provides buoyancy to the dosage form.

The swelling study of the prepared tablets was carried out in 0.1N HCl buffer and the results are shown. The swelling behavior of tablets was expressed as the ratio of initial weight of tablet to the final weight of swollen tablet as a function of time. In formulations maximum swelling was seen with the formulation containing HPMC along with Sod. CMC (F10) &HPMC along with Carbopol (F12). Results indicate that as the concentration of HPMC increases the swelling index increases.

The scanning electronic microscopy was used to know the surface texture of polymeric matrix before and after the dissolution studies. Both the tablets F4 (A) and F10 (B) have shown smooth and uniform surface before the dissolution study. But after the dissolution study, both the tablets has become porus & rough.

The in-vitro drug release study was performed using dissolution rate test apparatus in 0.1 N HCl (pH 1.2) till end of the study.

The dissolution profiles are given in Figure 8 to 10and data are presented in Table. From dissolution data it is evident that designed formulations have displayed in the range of 86.59% to 97.45% drug release in 24hrs.

Among all the formulations, formulation F4 containing Sod.CMC & formulation F10 containing HPMC & Sod.CMC showed maximum drug release of 96.51% and 97.45% respectively at the end of 24 hr.

All the formulation prepared, released the drug by zero order (higher R^2 value than first order).

To know the diffusion mechanism the slope values of peppas equation were calculated for all the formulations and were in the range of 0.666 to 0.7694. The calculated slope values are more than 0.5 in all the cases suggesting that the drug was released by non-fickian diffusion mechanism.

All the formulation was subjected for short term stability studies. It was observed for drug content at 40^0 for 1 month. There are no physical changes in appearance, flexibility and colour. The % of degradation with respect to drug content was2-3% thus the formulations were stable. Stability data were given in table. Based on the results of evaluations data of all the 12 formulations F4 & F10 were optimized because of their good gastro retentive property in the stomach and sustained release data.

CONCLUSION

It can be concluded from this study that, the prepared tablets are resourceful delivery systems for acyclovir. This study has shown promising results, further, they exists a scope for pharmacokinetic evaluation in experimental animals.

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