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FORMULATION AND EVALUATION OF FLOATING TABLETS OF ACYCLOVIR USING NATURAL POLYMERS

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ABSTRACT

The aim of the present work is to formulate and evaluate floating tablet of acyclovir using natural polymers by direct compression method. The floating tablets of Acyclovir were prepared by direct compression method, *Hibiscus rosa sinensis* (HRS) leaves mucilage and xanthum gum used as a natural rate controlling agents. Sodium alginate used as a semi-synthetic rate controlling agent. Different excipient are used to formulate tablets. The physicochemical parameters like pre-compression and post-compression evaluation were performed as per pharmacopoeia standards and compatibility study was done by FTIR method. The release data were subjected to different models in order to evaluate their kinetics and release mechanism. The FTIR spectral analysis showed that there was no drug interaction with formulations additives. Pre-compression parameters showed good flow properties. Post compression parameters shown good results. Formulation F_3 and F_9 showed good results throughout the study. Short term stability studies on the formulations F_3 and F_9 indicated that there are no significant change in the hardness, friability, disintegration time, drug content and *in-vitro* drug release study. Result revealed that the floating tablet of acyclovir containing rate controlling agents such as xanthum gum with conc. 21% (F_3) and mucilage of *Hibiscus rosas sinesis* leaves with conc. 21% (F_9) are showed shorter floating lag time and better cumulative drug release profile as compared to sodium alginate.

KEYWORDS: Gastro retentive floating tablet (GRFT); Acyclovir; *Hibiscus rosa sinensis (*HRS); Natural polymers; Floating drug delivery system (FDDS).

INTRODUCTION

Oral route is considered as the most convenient route of drug delivery. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed. Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site.[1] The enthusiasm designed for controlled drug release is necessary to uphold the secure effective drug concentration in the body for an extended time period. For most favorable performance, drug concentration in the body should be maintained on top of the effective level and under the toxic level.[2]

Floating drug delivery system (FDDS) is of particular interest for drugs which act locally in the stomach, are primarily absorbed in the stomach, are poorly soluble at an alkaline pH, have a narrow window of absorption and are unstable in the intestinal or colonic environment.[3] Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids (1.00 g/cm^3) 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.[4] Acyclovir is an antiviral drug having highly selective and low in cytotoxicity. This is commonly used in the treatment of Herps Simplex virus and Herps Zoster virus infection.

The aim of current study was to develop floating tablet of acyclovir using different natural and semi-synthetic rate controlling agents to improve bioavailability, therapeutic efficacy and patient compliance.

MATERIALS AND METHODS

Materials

Acyclovir was generously gifted by Biomedica Remidies, Punjab. *Hibiscus rosa-sinensis* leaves are collected from local area of Bagalkot, India and mucilage was extracted in pharmaceutical lab, xathan gum, sodium alginate, HPMC K4M, sodium bicarbonate, citric acid, talc, magnesium stearate and CMC are used for the formulation of tablets. All reagents

and chemicals used were of laboratory grade.

Methods

Extraction of *Hibiscus rosa-sinensis* mucilage

The fresh young leaves of *Hibiscus rosa-sinensis* were collected, washed with water to remove dirt and debris, and shade dried for 25 days. The dried leaves were ground to a fine powder. 10gm of leaf powder soaked in 100ml water for 5-6 hours, boiled for 30 minutes and allow to stand for 1 hour to complete release of mucilage into water. The mucilage was extracted using eight fold muslin cloth bag to remove the mark from the solution. Acetone (in the volume of three times to the volume of filtrate) was added to precipitate the mucilage. The mucilage was separated, dried, in an oven at 40 ºC, passed through #80 sieve and stored in desiccators at room temperature for further use.

Purification of *Hibiscus rosa-sinensis* mucilage

The crude mucilage (1%) was obtained after extraction which was centrifuged at 10000 rpm, decanted and precipitated in acetone following 1:2 ratio mucilaginous solution:acetone ratio, washed with isopropyl alcohol with 1:1 volume ratio and finally it was dried.[5-6]

Formulation of Acyclovir floating tablet

Floating tablets of acyclovir were prepared by direct compression method, in this powder blends of active ingredient and suitable excipient, which flow uniformly in the die cavity and forms a firm compact was prepared as per the composition shown in the below table. Powdered drug was mixed with *Hibiscus rosa- sinensis* mucilage, Xanthum gum, Sodium alginate, as a rate controlling agents in 17%, 19% and 21%, sodium bicarbonate and citric acid are used as gasifying agents, HPMC K4M used as release retardant, talc used as a gliding, magnesium stearate as a lubricant, CMC is used as diluents. All the powders were mixed well and compressed in single station tablet punching machine to obtain the tablets. Each tablet weighed 600mg.

Evaluation of tablets

Recompression parameters

Precompressional studies were carried out by standard methods. The flow property were characterized in terms of angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio.[7]

Postcompression parameters

Compressed tablets were then evaluated for thickness, hardness, weight variations and friability. Diameter and thickness were measured by using digital Vernier caliper. Hardness was measured by Monsanto type hardness tester. Weight variation is carried out in single pan balance. Friability testing was done by using Roche friabilator.[7]

***In vitro* buoyancy study**

The tablets were placed in 250 ml beaker containing 0.1N HCL. The time required for the tablets to rise to the surface and float was determined as floating lag time. The time between introduction of tablet and its buoyancy in 0.1N HCL and the time during which the tablet remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called floating lag time (FLT) or buoyancy lag time (BLT) and total duration of time by which dosage form remain buoyant is called total floating time (TFT).[8]

Swelling Index

The tablets were weighed individually and placed separately in petri dish containing 5mL of 0.1N HCl and incubated at 37∘C±1∘C. At regular 2h time intervals until 12h, the tablets were moved from petridish, and the excess surface liquid was removed carefully using the tissue paper. The swollen floating tablets were then reweighed and % swelling index (SI) was calculated using the following formula[9]:

$$\text{Swelling index} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

Drug content

Three tablets weighed and crushed in a mortar then weighed powder contain equivalent to 100mg of drug transferred in 100ml of 0.1 N HCL. Subsequently, the solution in volumetric flask was filtered suitable dilutions will be carried out. And final solution was analyzed at 255.5nm using UV- visible spectrophotometer Shimadzu UV- 2450, Japan.[10]

***In-vitro* drug release study**

In-vitro drug release was studied using Lab India Dissolution Apparatus (LABINDIA DS 8000, India), in 900ml of 0.1 N HCL, maintained at 37°C for 12 hours, at 100 rpm. 1ml of sample was withdrawn after specified time from dissolution medium. Collected samples were analyzed spectrophotometrically at measured wavelength of 255.5nm, and cumulative percent drug release was calculated. Drug release profile was studied using percentage drug release versus time (hr) plot.[11]

Kinetic study

The rate and mechanism of release of acyclovir from the prepared floating tablets were analyzed by fitting the dissolution data into following equations.

Zero order kinetics $Qt = Q0 + k0t$

First Order Kinetics $= InQ0 - k1$

Higuchi's Model $Qt = kH\sqrt{t}$

Hixon-Crowell $Q01/3 - Qt1/3 = kst$

Peppas Model $Qt/Q\infty = kktn$

Where,

Qt: amount of drug released in time t, Q0: initial amount of drug in the Tablet, Qt/Q∞: fraction of drug released at time t, k0; k1; kH; kk; kst: release rate constants, n: the release exponent indicative of the mechanism of drug release.[12]

Fourier Transform Infra-red Spectroscopy

The FTIR absorption spectra in the range of 4000-400 cm^{-1} for pure drug, drug with excipient in 1:1 ratio and the final formulation were obtained using Ker disc method (Broker alpha II) and observed for characteristic peaks of drug.[13]

Stability Studies

Stability studies of pharmaceutical products were done as per ICH guidelines. These studies are designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions. In order to determine the change in *in-vitro* release profile on storage, stability study of formulation code F_3, F_6 and F_9 was carried out at 40°C in a humidity chamber having 75% RH. The samples were withdrawn after a period of 15 days, 30 days, 45 days and 60 days. Formulations are evaluated for change in hardness, friability, disintegration time, drug content and *in-vitro* drug release pattern.[14]

RESULTS AND DISCUSSION

In the present study 9 formulations with variable concentration of polymer were prepared and evaluated for physiochemical parameters. The formulated batch compositions were shown in table no.1.

The angle of repose was performed by funnel method. All the formulations were found in the range of 22.61° to 29.68°. Bulk density was found to be in range of 0.48 to 0.90 gm/ml, and

Tapped density was found to be 0.56 to 1.00 gm/ml. The carr's index of all the formulations lies within the range of 7.77% to 14.94 and Hausner's ratio ranged from 1.08 to 1.17. These values indicate that the prepared granules exhibited good flow properties. The preformulation studies were shown in table no.3.

All formulations passed weight variation test as per pharmacopoeia limits. The friability was below 1% for all the formulations, which indicates good mechanical resistance of tablets. The hardness for different formulations was found to be between 6.8 to 7.2 kg/cm^2. The post formulation studies were shown in table no.4.

The drug content estimation data for all the formulations were found to be 96.4% to 99.4% (which indicates they are in official limits ± 5%). The floating lag time of all the formulations was found to be 32 to 55 sec. The total floating time of all the formulations was found to be >24 hrs. The results were depicted in table no.5.

The Swelling Index of all the formulations was found to be 82.12% to 93.66%. at the end of 12 hours. The results were depicted in table no.6.

Drug release profile was studied using percentage drug release versus time (hr) plot. Formulations F1, F2, F3, F4, F5, F6, F7, F8, and F9 showed 58.64, 55.06, 51.50, 65.01, 63.62, 61.45, 49.25, 47.42 and 44.18 release of drug respectively at 12 hours and the results were depicted in table no.7.

The compatibility study was performed by IR Spectroscopy to study the interaction of polymers with Acyclovir. The FTIR spectroscopy was employed to ascertain the compatibility between drug and polymers. All the IR spectra shown in Fig 2 to 9. By correlation, the interpreting the results, it indicates that drug is compatible with formulation components. The FTIR spectral analysis showed that there was no drug interaction with formulations additives of the tablet as there is no variation and shift in bands, it can be justified there is no interaction between drug and polymer.

The regression coefficient (R) value for Zero order, First order, Higuchi, Peppas, Hixson crowell models for all the formulations were shown in table no. 20. The formulations F1, F2, F4, F7 and F8 follows peppas model, formulations F3, F5, F6 and F9 follows Zero order kinetics and the results were depicted in table no.8.

On the basis of drug content, *in- vitro* release study, floating lag time, total floating time, formulations F3, F6 and F9 were subjected for stability studies as per ICH guidelines. There was no significant change in hardness, friability, disintegration-time, drug content and *in-vitro* release study. The results were depicted in table no.9.

According to the obtained results, the floating tablets of Acyclovir containing rate controlling agents like *Hibiscus Rosa sinensis* and xanthum gum shows the better rate controlling capacity compared to sodium alginate. The gas generating component sodium bicarbonate interacts with an acid source citric acid by contact with gastric fluid to generate carbon dioxide. In the present invention, HPMC K4M used along with gas generating agent to enhance buoyancy. Tablets prepared by direct compression method were found to be good without chipping, capping and sticking.

Table 1: Composition of floating tablets of Acyclovir.

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Acyclovir	200	200	200	200	200	200	200	200	200
Xanthum gum	100	115	130	----	----	----	----	----	----
Sodium alginate	----	----	----	100	115	130	----	----	----
H.R.S	----	----	----	----	----	----	100	115	130
HPMC K4M	135	120	105	135	120	105	135	120	105
Sodium bicarbonate	90	90	90	90	90	90	90	90	90
Citric Acid	45	45	45	45	45	45	45	45	45
Magnesium stearate	6	6	6	6	6	6	6	6	6
Talc	12	12	12	12	12	12	12	12	12
CMC	12	12	12	12	12	12	12	12	12

Table 2: Absorbance data for the standard calibration curve of Acyclovir in 0.1 N HCl at 255.5nm.

SI. NO.	CONCENTRATION (µg/ml)	ABSORBANCE.
0	0	0
1.	2	0.143
1.	4	0.206
2.	6	0.302
3.	8	0.394
4.	10	0.510
5.	12	0.603
6.	14	0.712
7.	16	0.821
8.	18	0.924

Table 3: Physical properties of acyclovir formulations.

Formulation.	Angle of Repose. (ɵ)	Bulk-Density. (g/cc)	Tap-Density. (g/cc)	Carr's Index. (%)	Hausner's Ratio.
F1	27.02	0.48	0.56	14.28	1.16
F2	29.68	0.90	1.00	10.00	1.11
F3	28.81	0.83	0.90	7.77	1.08
F4	24.66	0.78	0.87	10.34	1.11
F5	25.31	0.68	0.75	9.33	1.10
F6	23.88	0.73	0.82	10.97	1.12
F7	22.61	0.82	0.96	14.58	1.17
F8	24.13	0.74	0.87	14.94	1.17
F9	29.68	0.66	0.74	10.81	1.12

Table 4: Evaluated for thickness, hardness, uniformity of weight variation.

Formulation.	Thickness. (mm) ± SD	Hardness. (kg/cm^2) ± SD	Weight Variation. (mg) ± SD	Friability. (%) ± SD
F1	3.55±0.11	6.9±0.15	597.3±1.12	0.87±0.10
F2	3.59±0.15	7.0±0.11	600.4±1.62	0.88±0.06
F3	3.51±0.13	6.9±0.14	601.8±0.23	0.70±0.14
F4	3.55±0.08	6.8±0.08	600.4±0.25	0.73±0.08
F5	3.59±0.09	7.0±0.10	600.2±0.12	0.63±0.06
F6	3.59±0.10	7.1±0.11	598.0±0.65	0.69±0.12
F7	3.42±0.12	7.2±0.08	600.5±0.64	0.92±0.15
F8	3.45±0.15	7.0±0.13	599.8±0.20	0.88±0.12
F9	3.40±0.12	7.2±0.14	600.1±0.36	0.96±0.04

Table 5: Evaluated for floating lag time, total floating time, drug- content.

Formulations.	Floating Lag time (sec) ± SD	Total Floating time (hr)	Drug Content. (%)
F1	36±2.88	>24	98.8
F2	35±1.52	>24	99.4
F3	32±1.00	>24	97.6
F4	45±1.15	>24	96.4
F5	43±0.57	>24	99.2
F6	42±1.15	>24	96.6
F7	45±1.52	>24	98.2
F8	40±0.57	>24	97.6
F9	36±1.00	>24	98.8

Table 6: Swelling index of acyclovir formulations.

	Swelling Index (%)								
Time (hr.)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	25.41	11.68	18.73	23.33	26.24	25.87	24.11	25.32	22.00
2	27.37	16.52	21.55	40.00	41.36	35.22	32.42	34.21	28.96
3	31.60	19.19	32.83	45.00	51.16	36.89	35.55	43.25	34.52
4	33.61	33.72	48.59	52.00	56.31	43.07	41.42	49.85	41.36
5	37.62	41.23	51.24	63.33	62.79	53.58	47.26	53.32	48.58
6	48.49	48.24	58.04	66.33	68.43	59.76	54.66	59.47	56.21
7	57.19	56.92	67.49	70.16	71.76	62.27	59.87	65.14	62.84
8	59.03	63.60	70.81	73.50	73.75	71.83	66.23	71.69	68.74
9	69.06	73.62	74.19	75.00	79.06	76.54	74.55	79.84	74.95
10	82.44	87.14	82.42	93.66	84.05	82.12	79.98	84.12	80.01

Table 7: *in-vitro* dissolution study.

Time (hr.)	**% Cumulative drug release**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	5.70	5.68	5.86	5.44	4.95	4.62	5.33	5.42	4.17
2	11.97	11.41	11.32	12.29	12.76	15.73	12.74	15.45	10.24
3	18.44	18.49	17.39	18.89	18.10	16.69	17.60	17.74	15.54
4	23.14	22.02	20.85	23.35	21.20	19.62	22.36	22.11	17.88
5	28.69	27.37	26.56	28.86	25.61	25.52	25.81	26.59	20.49
6	32.78	31.68	30.55	31.01	29.36	27.67	28.39	29.51	25.43
7	36.53	35.06	33.13	37.18	34.42	33.61	32.37	33.39	27.41
8	40.41	39.78	37.85	41.69	36.96	39.37	36.65	36.79	31.39
9	45.39	45.03	41.09	47.25	44.47	42.62	40.74	41.54	32.44
10	49.5	47.77	44.29	54.28	54.79	50.45	42.66	43.44	38.47
11	54.39	51.03	48.12	59.90	58.43	55.63	46.66	45.55	42.40
12	58.64	55.06	51.50	65.01	63.62	61.45	49.25	47.42	44.18

Table 8: Kinetics of drug release of Acyclovir floating tablet.

Code.	**Zero Order. (R value)**	**First Order. (R value)**	**Higuchi. (R value)**	**Peppas. (R value)**	**Hixson Crowell. (R value)**	**Best Fit Model.**
F1.	0.9942	0.9965	0.9510	0.9970	0.9958	Peppas
F2.	0.9921	0.9949	0.9547	0.9965	0.9940	Peppas
F3.	0.9975	0.9930	0.9596	0.9898	0.9920	Zero Order
F4.	0.9978	0.9977	0.9329	0.9978	0.9967	Peppas
F5.	0.9939	0.9924	0.9199	0.9924	0.9930	Zero Order
F6.	0.9908	0.9905	0.9235	0.9784	0.9907	Zero Order
F7.	0.9841	0.9881	0.9660	0.9919	0.9868	Peppas
F8.	0.9797	0.9843	0.9684	0.9845	0.9828	Peppas
F9.	0.9932	0.9912	0.9523	0.9911	0.9926	Zero Order

Table 9: Stability studies of F_3 F_6 and F_9 formulation at 40°C± 2°C / 75% RH±5%.

Formulation	Tested after time (days)	Hardness (kg/cm^2)	Friability (%)	Floating Test		Drug Content (%)	Cum. % Drug Released (at 12th hours)
				BLT (sec)	TFT (hrs)		
F3	15	6.9	0.70	35	>10	97.4	51.48
	30	6.9	0.72	37	>10	97.0	51.28
	45	6.8	0.73	38	>10	96.8	50.66
	60	6.8	0.75	39	>10	96.7	50.12
F6	15	7.1	0.73	42	>10	96.5	61.43
	30	7.0	0.75	44	>10	96.4	61.22
	45	6.8	0.76	44	>10	96.2	61.01
	60	6.8	0.76	45	>10	96.2	60.74
F9	15	7.2	0.95	46	>10	98.7	44.12
	30	7.1	0.95	47	>10	98.5	43.92
	45	7.1	0.97	49	>10	98.5	43.58
	60	7.0	0.97	50	>10	98.4	43.19

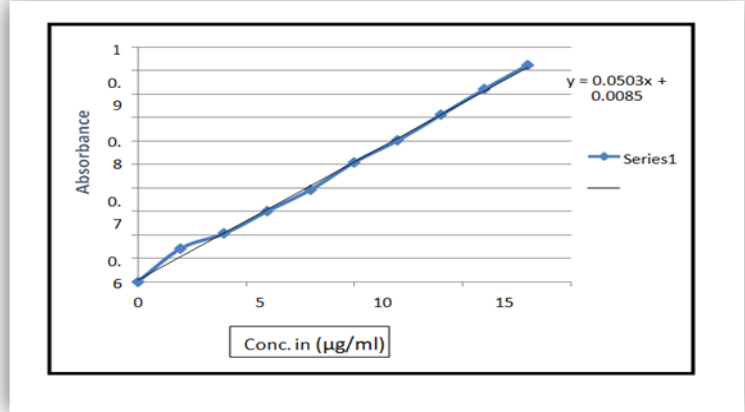

Fig. 1: Calibration curve of Acyclovir in 0.1 N HCL at 255.5nm.

Fourier Transform Infrared spectroscopy

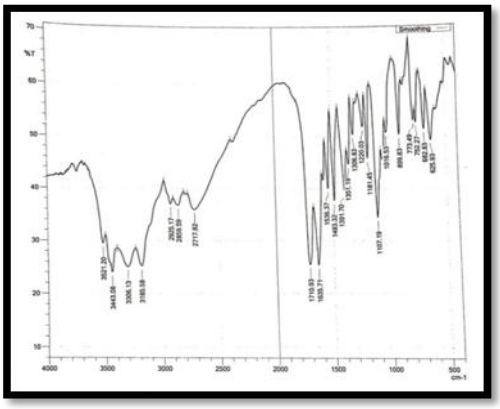

Fig. 2: Acyclovir

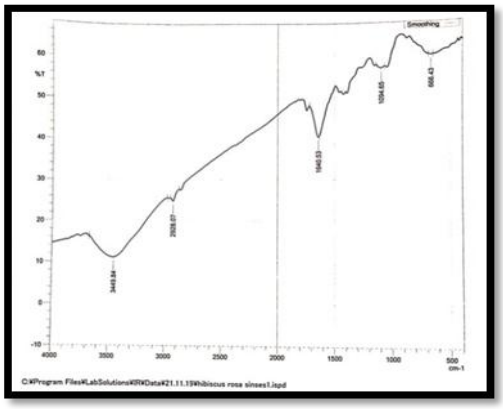

Fig. 3: HRS

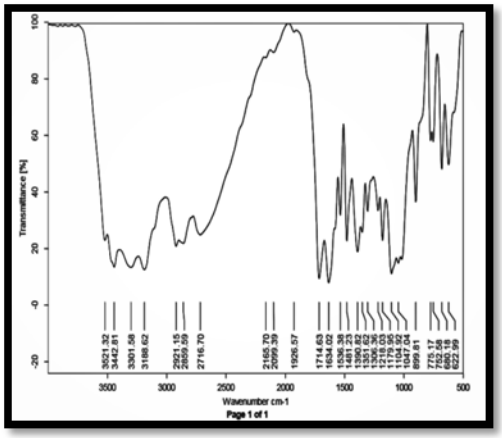

Fig. 4: Acyclovir + Xanthum gum

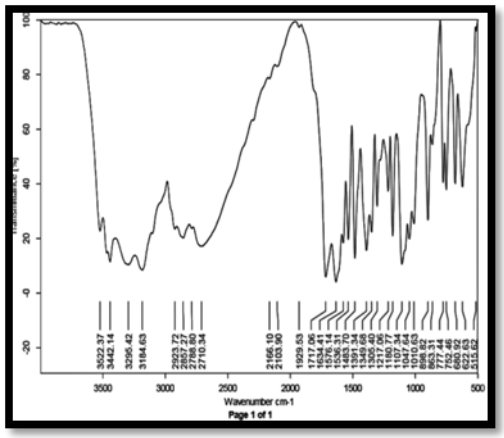

Fig. 5: Acyclovir + Sodium alginate

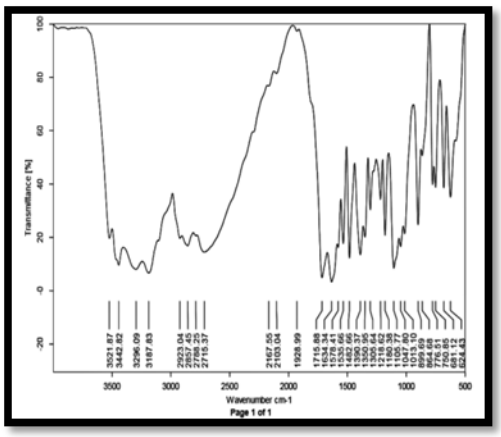

Fig. 6: Acyclovir + HRS

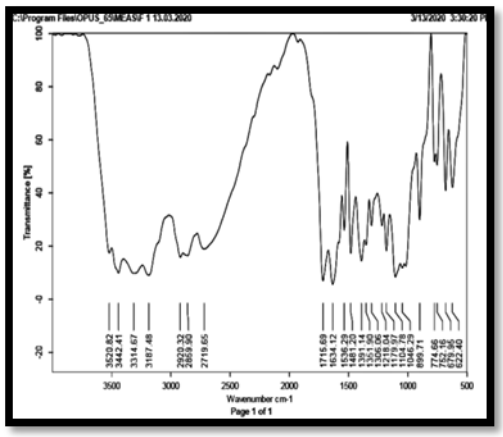

Fig. 7: F1 formulation

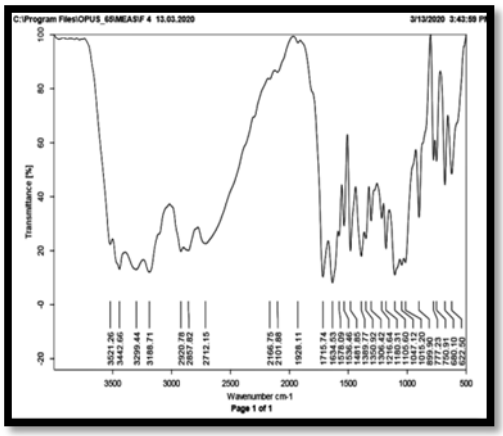

Fig. 8: F4 formulation

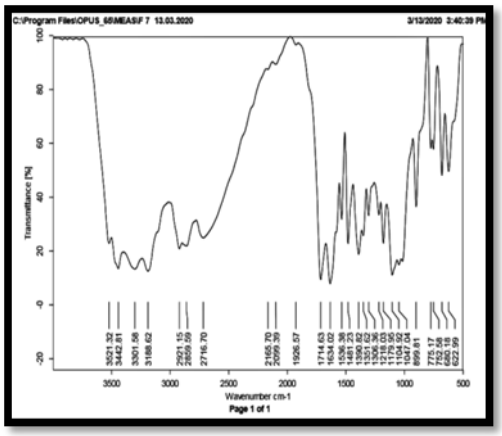

Fig. 9: F7 formulation

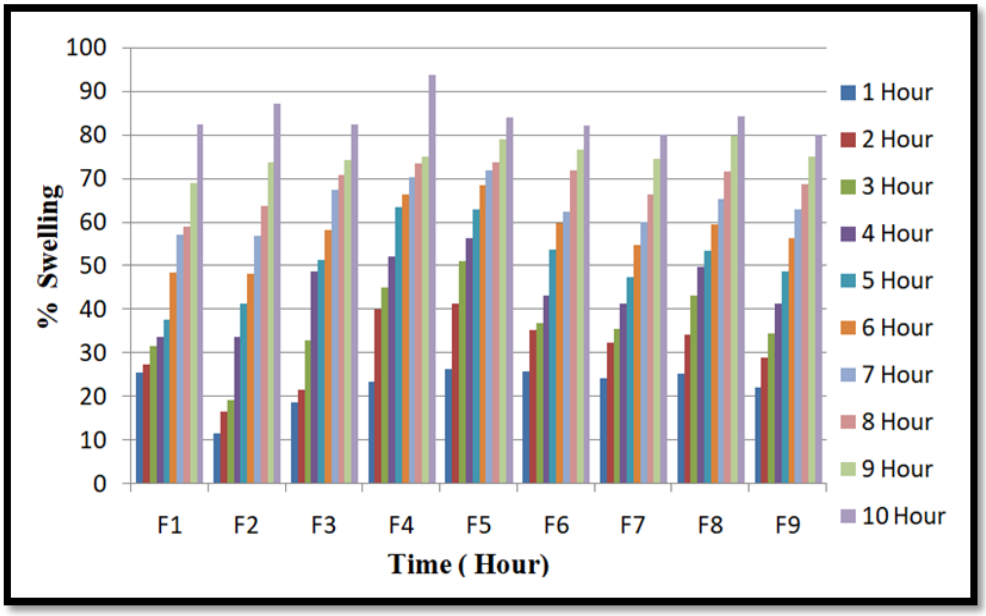

Fig. 10: Graphical representation of swelling index.

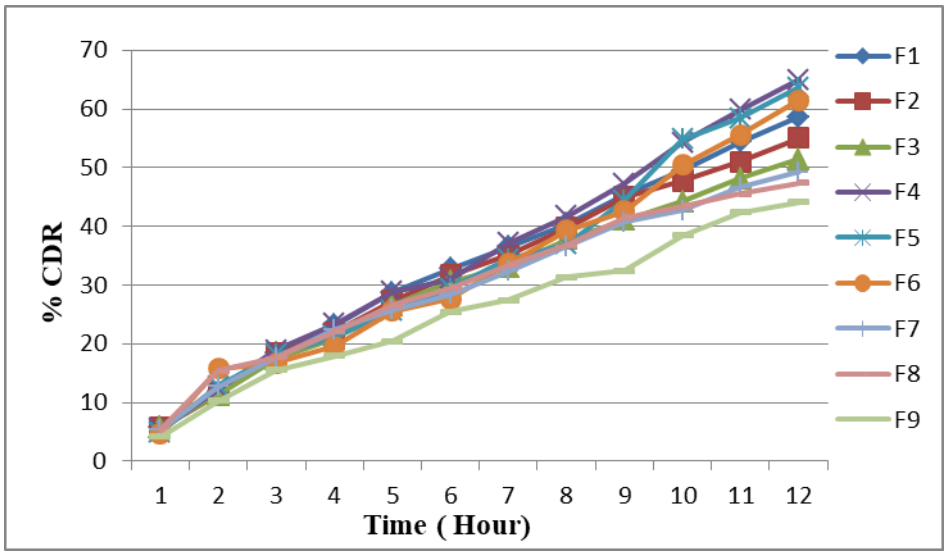

Fig. 11: Cumulative percentage drug release vs time.

CONCLUSIONS

Acyclovir floating tablets were successfully formulated and evaluated. The work is carried out using natural polymers with different concentrations. FTIR studies proved that there is no chemical interaction between acyclovir and polymers. The developed floating tablets of acyclovir are used to prolong the drug release for more than 12 h, thereby improving bioavailability and patient compliance. The *in-vitro* drug release studies revealed the drug release from the formulation depended upon the polymer used and their concentration. The sustained drug release with better floating was achieved with natural polymers.

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