FORMULATE AND EVALUATE FAMCICLOVIR FLOATING TABLETS

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ABSTRACT : Floating drug delivery system of famciclovir was developed to prolong gastric residence time, target stomach mucosa and increase drug bioavailability by using different polymers like HPMC E15, Xanthan gum, methyl cellulose and compritol 888 ATO with different concentration. Famciclovir capable of floating in the gastric condition were formulated and evaluated. The gel bits were prepared by wet granulation method by employing sodium bicarbonate and citric acid as effervescence generating agent. Drug and polymer compatibility were studied by subjecting physical mixtures of drug and polymers to FT IR studies. The formulation variables like hardness, polymer, concentrations and shape of the tablets were optimized to achieve the floating nature of the tablet in stomach for 24 hours. In addition, ethyl cellulose was also included in this formulation to evaluate their release characteristics. Among all the formulations F6 formulation 1 which contain 20% HPMC E15 was selected as optimized formulation because the drug release up to 12 hours exhibited better buoyancy and less floating lag time
KEY WORDS: Famciclovir, Floating matrix tablets, Methyl cellulose, HPMC E15, Compritol 888 ATO

I.INTRODUCTION

Oral drug delivery is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance, and cost-effective manufacturing process[1]. Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms[2, 3] The design of floating drug delivery Systems (FDDS) should be primarily aimed to achieve more predictable and increased bioavailability. Now-a-days most of the pharmaceutical scientist is involved in developing the ideal FDDS[4]. This ideal system should have advantage of single dose for the whole duration of treatment and it should deliver the active drug directly at the specific site. Scientists have succeeded to develop a system and it encourages the scientists to develop control release tablet.[5] Control release implies the predictability and reproducibility to control the drug release, drug concentration in target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.[6] Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.[7]Aim of the study is to formulate and evaluate Famciclovir floating tablets using different polymers like HPMC E15, xanthan Gum, Guar Gum and Compritol 888 ATO in different ratios. To formulate and evaluate floating tablets of Famciclovir, using different ratios. To carry out the drug Excipient - Compatibility studies To analyse the release pattern of the drug by fitting the dissolution data into various exponential equations. Famciclovir is used to treat infections caused by certain types of viruses.[8] It treats shingles caused by herpes zoster. It also treats outbreaks of herpes simplex that cause cold sores around the mouth, sores around the anus, and genital herpes. In people with frequent outbreaks of genital herpes, famciclovir is used to help reduce the number of future episodes. Famciclovir is an antiviral drug. However, it is not a cure for these infections. The viruses that cause these infections continue to live in the body even between outbreaks. Famciclovir decreases the severity and length of these outbreaks.[9]

II.MATERIALS AND METHODS

2.1 MATERIALS

Famciclovir was collected as a gift sample from Hetero labs, Hyderabad polymers and other excipients were purchased from SD Fine Chemicals Ltd.,Mumbai.

2.2 METHODOLOGY

Preparation of floating tablets

All formulations were prepared by Direct Compression method. All ingredients like HPMC E15, Xanthan Gum, Guar Gum, and Compritol 888 ATO were sieved and weighed properly. Floating tablets contained the mixture of sodium bicarbonate, citric acid as a matrix material. To begin the mixture that provided floating was placed on the die cavity and a preparatory pressing was made. The tablets were compressed with a hardness of 4kg/ sqcm in a hand press with a 12 mm diameter punch[10]

Table : 1 Composition of Famciclovir floating Tablet

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Famciclovir	50	50	50	50	50	50	50	50	50	50
HPMC E15	25	---	---	---	---	50	---	---	---	---
Xanthan Gum	---	25	---	---	---	---	50	---	---	---
Guar Gum	---	---	25	---	---	---	---	50	---	---
Compritol 888 ATO	---	---	---	25	---	---	---	---	50	---
Methyl Cellulose	---	---	---	---	25	---	---	---	---	50
Ethyl Cellulose	50	50	50	50	50	50	50	50	50	50
MCC	40	40	40	40	40	40	40	40	40	40
Lactose	40	40	40	40	40	15	15	15	15	15
Sodium Bicarbonate	20	20	20	20	20	20	20	20	20	20
Citric Acid	10	10	10	10	10	10	10	10	10	10
Mannitol	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	3	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2	2
Total weight	250	250	250	250	250	250	250	250	250	250

EVALUATION OF TABLETS[11,12]

The formulated tablets were evaluated for the following physicochemical parameters:

Weight Variation: Formulated tablets were tested for weight uniformity. 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was compared with average weight to ascertain whether it is within permissible limits or not.

Hardness: Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the tablet was compressed a pointer rides along a gauge in the barrel to indicate the force.

Friability: The Roche friability test apparatus was used to determine the friability of the tablets twenty pre-weighed tablets were placed in the apparatus, which was given 100 revolutions after which the tablets were reweighed. The percentage friability was calculated[13].

Drug Content: Five tablets of each formulation were weighed and powdered. The quantity of powder was equivalent to 100 mg. The equivalent weight furosemide was transferred into 100 ml volumetric flask and by using methanol as the extracting solvent and samples were analyzed spectrophotometrically[14].

Buoyancy / Floating Test:

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form 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).

In-Vitro floating studies[15] :

Tablets were placed in a 100 ml flask at pH1.2 and both the time needed to go upward and float on the surface of the fluid and floating duration was determined. Table no 7 shows the floating lag time and floating time of prepared formulations.

In-Vitro Release Studies[16,17] :

Dissolution studies were carried out for all the formulations combinations in triplicate, employing USP XXVII paddle method and 0.1 N HCl as the dissolution medium at 75 rpm and 37 ± 0.5 ^{o}C. A 5 ml aliquot of sample was withdrawn periodically at suitable time intervals and the volume replaced with an equivalent amount of the plain dissolution medium. The samples were analyzed spectrophotometrically at 225 nm. The current study involved unequal time intervals in the entire 12 hours dissolution span.

Released kinetics[18,19]: The analysis of the drug release mechanism from a pharmaceutical dosage form is an important but complicated process and it is practically evident in case of matric system. As a model-dependant approach, the dissolution data was fitted to five popular release models such as zero-order, first-order, diffusion and exponential equations, which have been described in the literature. The order of drug release from matrices was described by using zero order and first order kinetics. The mechanism of drug release from matrices was studied by using Higuchi equation, erosion equation and Pappas-korsemeyer equation.

Zero order release kinetics: It defines a linear relationship between the fraction of drug released versus time.

$$Q = k_O\ t$$

A plot of the fraction of drug released against time will be linear, if the released obeys the zero order released kinetics.

First order release kinetics: Wagner assuming that the exposing surface area of a tablet decreasing exponentially with time during dissolution process, suggested that drug released from most of the slow released tablets could be described adequately by apparent first order kinetics. The equation that describes the first order kinetics is

$$In\ (I-Q) = -k_1\ t$$

Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the released obeys first order released kinetics.

Higuchi Equation: It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$$Q = k_2\ t^{1/2}$$

Where k_2 is the release rate constant

Power law: In order to define a model, which would represent a better fit for the formulation, dissolution data was further analyzed by Pappas and Koresemeyer equation.

$$M_t / M_\alpha = k\ t^{n}$$

A plot between log of M_t / M_α against log time will be linear if the release obeys Pappas and Korsemeyer equation and the slope of this plot represents 'n' value.

III. RESULTS AND DISCUSSION:

DRUG -POYMER COMPATABILITY STUDIES BY FT -IR :

The compatibility between the drug and optimized formulation was evaluated using FT IR Peak matching method. The IR spectra of pure drug, polymer and physical mixture respectively. From the infrared Spectra it is clearly evident that there were no interactions of the drug.

Figure :1 IR Spectrum of Pure Famciclovir

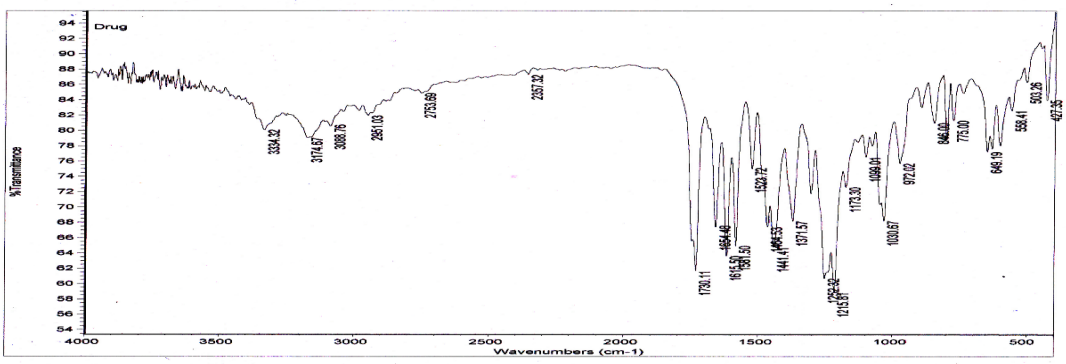


Figure : 2 IR Spectrum of Pure HPMC E15

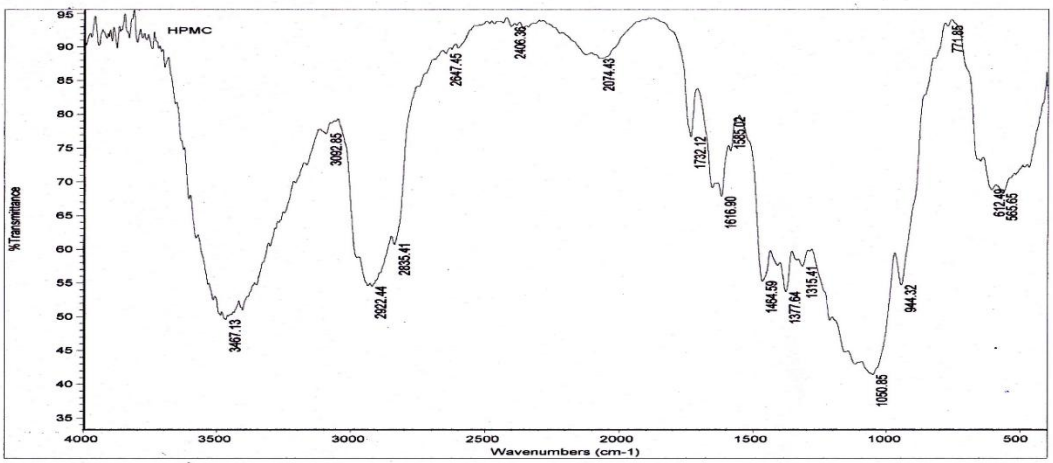
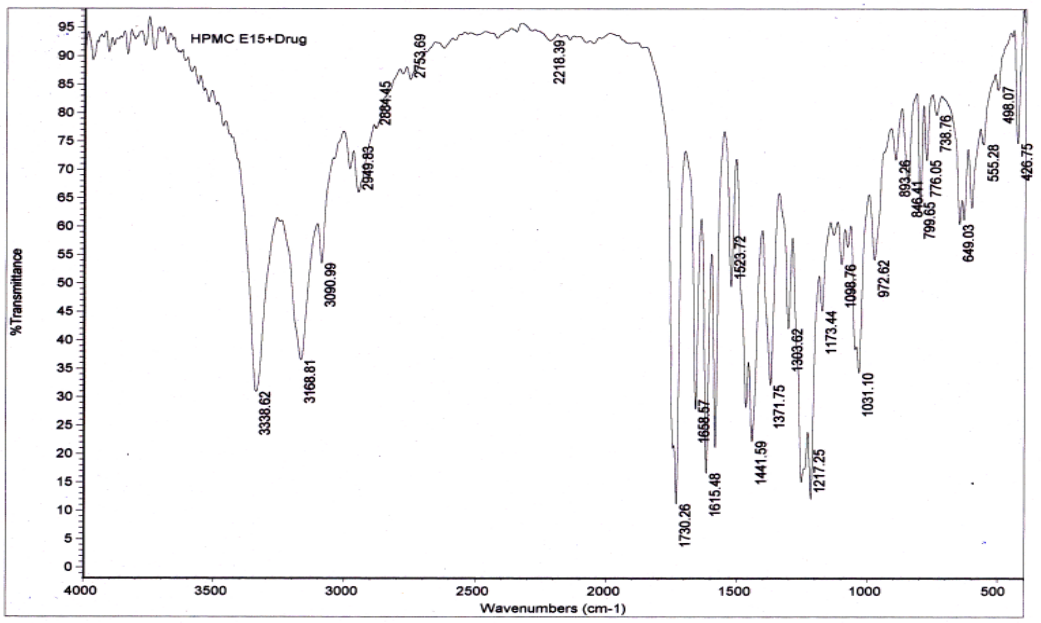


Figure :3 IR Spectrum of Pure Famciclovir with HPMC E15



Micrometric properties of powders:

The powders of different formulations were evaluated for angle of repose, bulk density, tapped density and compressibility index and the results were noted

Table 2 : Micromeritic Properties Of Powders

FORMULATION	Angle of Repose	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)
F1	$28^o.73'\pm 0.15$	0.485± 0.003	0.614± 0.008
F2	$27^o.52'\pm 0.32$	0.475± 0.002	0.652± 0.003
F3	$28^o.99'\pm 0.45$	0.497± 0.004	0.632± 0.006
F4	$29^o.52'\pm 0.92$	0.485± 0.002	0.695± 0.004
F5	$27^o.47'\pm 0.23$	0.452± 0.004	0.552± 0.009
F6	$27^o.63'\pm 0.12$	0.457± 0.005	0.562± 0.006
F7	$29^o.25'\pm 0.98$	0.487± 0.003	0.587± 0.004
F8	$27^o.85'\pm 0.25$	0.456± 0.003	0.616± 0.007
F9	$28^o.13'\pm 0.85$	0.482± 0.005	0.652± 0.008
F10	$29^o.74'\pm 0.56$	0.465± 0.006	0.653± 0.005

In process parameters of Tablets:

Tablets of all the formulations were subjected to many in process evaluation parameters such as Physical appearance, thickness, content uniformity, weight variation, hardness and friability.

Table 3 : In Process parameters results of Formulated Famciclovir Tablets:

FORMULATION	AVG. WT (MG)	HARDNESS (KG/CM^2)	Disintegration Time (Min)	Friability (%)	% Drug Content	Thickness (mm)
F1	249	4.1	2	0.29	102.9	2.21
F2	250.2	3.3	5	0.40	100.1	2.31
F3	249	4.6	60	0.38	100.1	2.25
F4	248	3.9	27	0.33	99.89	2.27
F5	251	4.1	20	0.20	99.5	2.24
F6	249.3	4.5	13	0.47	99.95	2.22
F7	249.2	4.5	9	0.30	100.2	2.20
F8	248.2	5.0	22	0.32	99.24	2.24
F9	249.6	5.2	19	0.20	98.26	2.22
F10	250.3	4.8	18	0.10	96.86	2.24

In vitro Dissolution Studies: Dissolution studies were carried out for all the formulations combinations in triplicate, employing USP XXVII paddle method and 0.1 N HCl as the dissolution medium at 75 rpm and 37 ± 0.5 ^oC. A 5 ml aliquot of sample was withdrawn periodically at suitable time intervals and the volume replaced with an equivalent amount of the plain dissolution medium. The samples were analyzed spectrophotometrically at 225 nm for 12 hours. Five different polymers and their combinations were used to prepare floating matrix tablets. It was observed that the type and concentration of polymer influences the drug release pattern. The cumulative percent of drug released in F1 formulation is 98.26% in 10 hours. It was observed that among all the formulations the cumulative percent of drug released in F6 formulation is 99.48% in 12 hours & accurate release patterns observed in case of F6 formulation which was prepared by at 20% concentration of HPMC E15.

Table 4 : Dissolution data of Famciclovir floating tablets of F1, F2, F3, F4, F5 formulations:

TIME (hrs)	Cumulative Percentage Amount of drug Dissolved				
	F1	**F2**	**F3**	**F4**	**F5**
0.5	48.02±0.77	32.04±1.25	50.26±0.23	20.08±0.23	19.26±0.12
1	49.12±0.75	39.24±1.43	58.26±0.15	29.26±0.87	30.28±0.85
2	50.52±1.01	40.28±1.09	65.17±0.67	38.32±0.89	42.72±0.69
3	53.54±1.12	43.72±1.06	68.12±1.26	49.48±1.22	52.55±0.58
4	58.18±0.42	45.84±0.73	70.42±1.12	68.62±1.10	58.28±1.12
5	61.16±0.24	47.26±0.24	72.30±0.96	74.54±0.98	66.16±0.72
6	63.42±1.02	50.28±1.09	73.70±0.25	79.60±0.52	70.42±0.36
7	70.26±1.36	89.26±0.93	80.62±0.47	85.82±0.45	78.83±0.52
8	79.26±0.23	99.82±0.24	81.28±0.36	90.90±0.32	82.26±0.67
9	82.48±0.82	----	97.82±0.45	99.72±0.11	83.08±0.61
10	98.26± 0.54	----	----	----	98.26±0.22
11	----	----	----	----	----
12	----	----	----	----	----

Table 5 : Dissolution data of Famciclovir floating tablets of F6, F7, F8, F9, F10 formulations:

TIME (hrs)	Percentage Amount of drug Dissolved				
	F6	F7	F8	F9	F10
0.5	**19.24±0.85**	20.18±0.58	50.28±0.48	38.16±0.18	42.17±0.56
1	**28.38±0.45**	32.32±1.26	53.63±0.19	49.26±0.37	48.83±0.62
2	**35.42±0.98**	38.48±1.30	59.52±0.60	53.48±0.56	52.92±0.71
3	**47.85±1.32**	40.19±0.56	62.54±1.03	54.54±1.10	68.68±0.62
4	**55.92±0.57**	43.62±0.54	65.02±1.06	62.32±1.12	74.54±1.14
5	**68.62±0.98**	49.83±0.38	67.19±0.98	38.27±0.97	80.28±0.62
6	**72.78±0.98**	55.92±0.89	68.23±0.45	72.48±0.59	84.66±0.40
7	**79.52±1.26**	62.62±0.95	69.56±0.49	80.53±0.42	89.26±0.52
8	**83.13±0.32**	70.36±0.12	71.26±0.54	82.84±0.36	93.38±0.68
9	**87.28±0.89**	86.42±1.01	72.32±0.47	90.08±0.18	95.42±0.62
10	**90.72± 0.85**	99.28±0.97	97.82±1.10	98.28±0.86	99.22±0.74
11	**95.30±0.54**	----	----	99.28±0.47	----
12	**99.48 ±1.01**	----	----	----	----

In vitro buoyancy Studies:

The in vitro buoyancy was determined by floating lag time and total floating time. The Tablets were placed in a 100 ml flask at pH1.2 and both the time needed to go upward and float on the surface of the fluid and floating duration was determined. In all formulations sodium bicarbonate was added as a gas generating agent. Sodium bicarbonate in presence Citric acid generates CO_2. The generated gas is trapped or protected within gel, formed by hydration of polymer, thus decresing the density of the tablet. As the density falls below 1, the tablet becomes float on gastric fluids. Formulations F1 & F6 which are prepared by HPMC E15 higher floating duration up to 12 hours in compare to the other formulations. F6 formulation shows lesser floating lag time i.e only 20 sec. the floating lag time and floating time of prepared formulations.

Table 6 : Results of In vitro buoyancy Studies:

FORMULATION	Buoyancy Lag Time (min)	Total Floating Time (hrs)
F1	1	12
F2	6.0	6
F3	3.5	8
F4	3.0	8
F5	15	10
F6	20 sec	<12
F7	8	8
F8	12.5	10
F9	1	10
F10	8	8

Figure :4 Dissolution data of Famciclovir floating tablets of F1, F2, F3, F4, F5 formulations

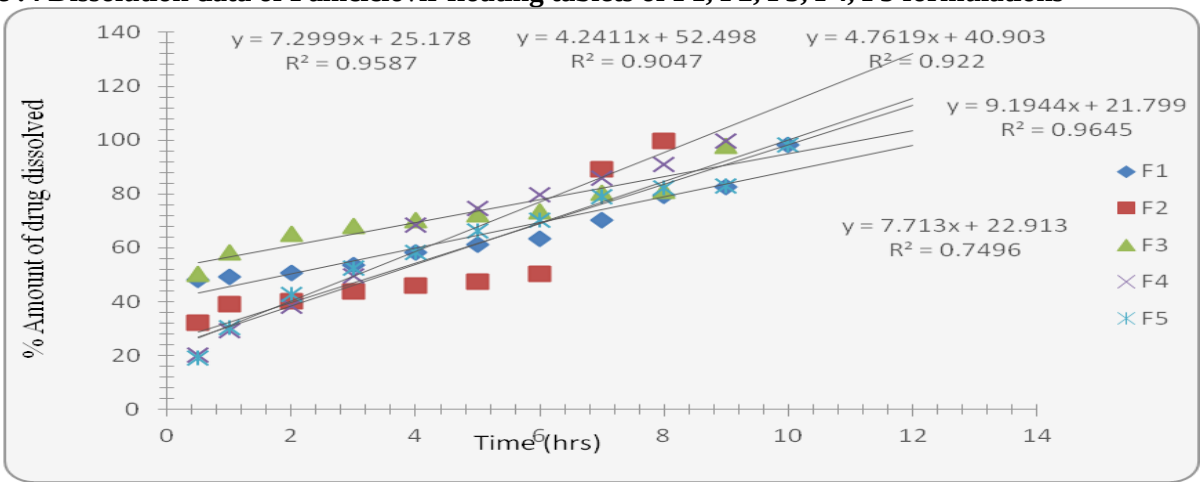
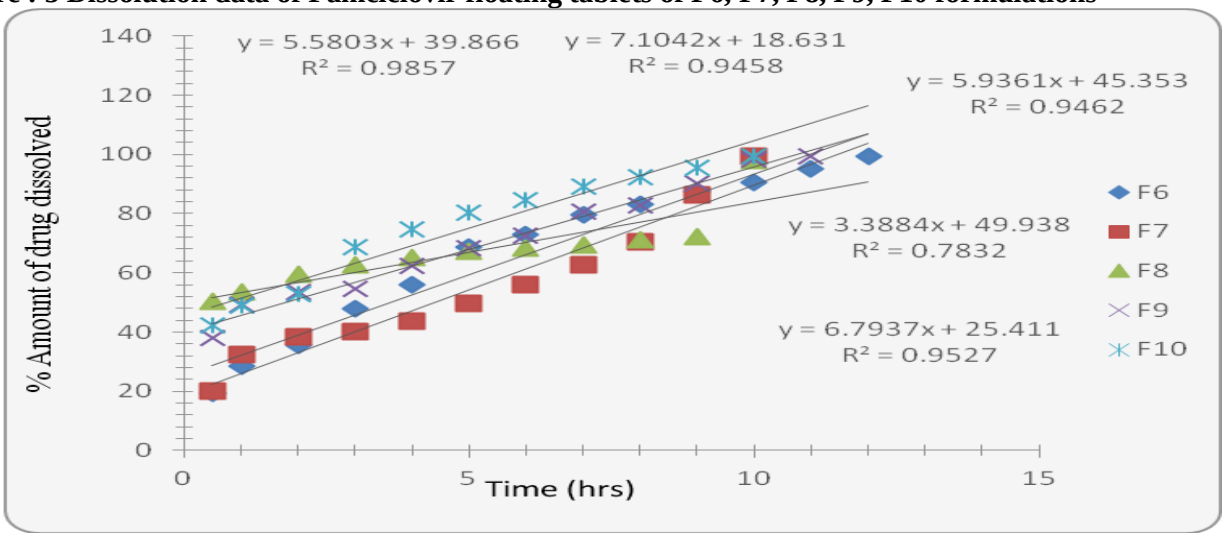


Figure : 5 Dissolution data of Famciclovir floating tablets of F6, F7, F8, F9, F10 formulations



Release kinetics :

In vitro release data were treated with zero order, first order and Higuchi & Korsmeyers -Peppas equation as shown in the table no:. As r values of zero order kinetics shown greater values than r values of first order kinetics, it is evident that the drug release from Famciclovir tablets followed zero order kinetics. All the formulations except F3, F5 follows erosion model. In order to understand the mechanism of drug release the in vitro release data was fitted to Korsmeyer's-Peppas release model. Interpretation of diffusion co. efficient (n) values enlights in understanding the release mechanism from the dosage forms. If n value is <0.45 for fickian release, >0.45 and < 0.89 for non fickian release. 0.89 for case II release and >0.89 for super case II type release. The value of n fell within the range of 0.159 to 0.746 indicates that follows fickian or non- fickian transport type of release. The optimize formulation F6 follows non fickian type release.

IV. SUMMARY & CONCLUSION

Prepared tablets showed acceptable weight variation, hardness & content uniformity. A lesser floating lag time and a prolonged floating duration could be achieved by using different polymers. Among all the formulations F1 and F2 containing HPMC E 15 has lesser floating lag time and prolonged duration. Among these two formulations F6 have lesser floating lag time and accurate amount of drug release can be observed. The drug release was further controlled by the presence of sodium bicarbonate with citric acid by the generation of carbon dioxide. The optimized formulation F6 was subjected to FI IR compatibility studies, which indicates no chemical interaction between drug and excipient. In the present work floating tablets of Famciclovir are formulated to provide sustained release of drug with the aim of providing an effective and safe therapy for viral infections with a reduced dose, increased bioavailability, Suitable drug release pattern for several hours by reduced length of treatment. On conclusion, this novel drug delivery system i.e., floating system offers a valuable dosage form which delivers the

drug at a controlled rate and at a specific site. The floating dosage form was found to be a feasible approach in delivering Famciclovir to the upper gastrointestinal tract to maximize the drug absorption due to the presence of a biological window comprised of the upper gastrointestinal tract.

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