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FORMULATION AND DEVELOPMENT OF FAMCICLOVIR SUSTAINED RELEASE TABLETS USING VARIOUS RETARDING POLYMERS

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ABSTRACT

Sustained release tablets of Famciclovir were formulated by using HPMC K15M and Ethyl cellulose. The tablets were evaluated for Preformulation studies like angle of repose, bulk density, compressibility index and physical characteristics like hardness, weight variation, friability and drug content. In-vitro release of drug was performed in 0.1 N HCL and phosphate buffer pH 6.8 for twelve hours. All the physical characters of the fabricated tablet were within acceptable limits. The tablet with Ethyl cellulose (F5) shows a better sustained drug release (99.23%) was obtained with the matrix tablet. It is cleared through the dissolution profile of Famciclovir from matrix tablets prepared using different polymers were indicated a low in the polymer ratio retarded the drug release to a greater extent.

Key words: Famciclovir, HPMC K15M, Ethyl cellulose, Wet granulation and sustained release tablets.

1. INTRODUCTION

A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body[1]. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action[2]. The term therapeutic substance also applies to an agent such as gene therapy that will induce in vivo production of the active therapeutic agent. Sustained release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect[3]. The advantage of administering a single dose of a drug that is released over an extended period of time to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use. The first sustained release tablets were made by Howard Press in New Jersy in the early 1950's. The first tablets released under his process patent were called 'Nitroglyn' and made under license by Key Corp. in Florida[4]. Sustained release, prolonged release, modified release, extended release or depot formulations are terms used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose[5]. The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or to a specified target organ[6].

2. METHODOLOGY

The materials used in the present investigation were either ACS/AR/LR grade or the best possible Pharma grade.

Materials Used

Table-1: List of Materials Used

Name of the Material	Source
Famciclovir	Procured From Abbott. Provided by SURA LABS, Dilsukhnagar, Hyderabad.
HPMC K 15	Merck Specialities Pvt Ltd, Mumbai, India
Ethyl Cellulose	Merck Specialities Pvt Ltd, Mumbai, India
MCC	Colorcon Asia private Ltd. Goa, India
Talc	Merck Specialities Pvt Ltd, Mumbai, India

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PVP-K30	Sri Krishna Pharmaceuticals Ltd, India
Magnesium Stearate	Merck Specialities Pvt Ltd, Mumbai, India

Equipments Used

Table-2: List of Equipment's Used

Name of the Equipment	Manufacturer
Weighing Balance	Sartorius
Tablet Compression Machine (Multistation)	Lab Press Limited, India.
Hardness Tester	Monsanto, Mumbai, India.
Vernier Callipers	Mitutoyo, Japan.
Roche Friabilator	Labindia, Mumbai, India
Dissolution Apparatus	Labindia, Mumbai, India
UV-Visible Spectrophotometer	Labindia, Mumbai, India
pH meter	Labindia, Mumbai, India
FT-IR Spectrophotometer	Per kin Elmer, United States of America.

Identification Tests:

Analytical Method Development:

U V Spectra:

100mg of Famciclovir pure drug was dissolved in 100ml of Methanol (stock solution) 10ml of above solution was taken and make up with100ml by using 0.1 N HCL (100µg/ml). From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml) and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer[7]. The solution was scanned in the range of 200 – 400nm.

Preparation of Calibration Curve:

100mg of Famciclovir pure drug was dissolved in 100ml of Methanol (stock solution)10ml of above solution was taken and make up with100ml by using 0.1 N HCL (100µg/ml).From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 5, 10, 15, 20 and 25 µg/ml of Famciclovir per ml of solution. The absorbance of the above dilutions was measured at 300 nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R2) which determined by least-square linear regression analysis[8]. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Preparation of 0.1 N HCl: Accurately measured 8.5 mL of concentrated hydrochloric acid was added to 1000 mL of distilled water.

Preparation of pH 6.8 phosphate buffer:

Preparation of 0.2 M sodium hydroxide solution: Accurately weighed 8 g of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed.

Dissolved 6.805 g of potassium dihydrogen orthophosphate in to 800mL of Purified water and mixed. Added 112mL of 0.2M NaOH solution in to this solution, diluted to volume with purified water. Then adjusted the pH of this solution to 6.8 with 0.2M NaOH solution.

Preformulation Parameters

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced[9]. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was

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carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel[10]. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

Tan θ = h / r Tan θ = Angle of repose

h = Height of the cone, r = Radius of the cone base

Table-3: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting[11]. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

Bulk Density = M / Vo

Where, M = weight of sample

Vo = apparent volume of powder

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit[12]. The tapped density was calculated, in gm per L, using the formula:

Tap = M / V

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of Powder Compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value[13]. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk Density Tap = Tapped Density

Table-4: Carr's Index Value (as per USP)

Carr's Index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

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Formulation Development of Tablets:

Preparation of Famciclovir Matrix Tablets

All the matrix tablets, each containing 250 mg of Famciclovir, were prepared by wet granulation method[14-18].

Procedure: Wet granulation: Drug and the diluent (MCC) were sifted through sieve No. 40 manually and mixed well to ensure the uniformity of premix blend. Several drug diluent premixes were then mixed with the selected ratio of polymer(s), previously sifted through sieve No. 40, for 5 minutes. Premix blend was wet granulated with 5% w/v solution of PVP K-90 in a mortar. The wet mass was passed through No.18 sieve. The wet granules were dried at 55°C ± 5°C for 1 hour in a hot-air oven and the dried granules were sieved through No.22 sieve.

These granules were blended with lubrication mixture (Magnesium stearate and Talc) and compressed using 10 station rotary tableting machine, equipped with flat-faced, round punches of 9-mm diameter.[19]

Table-5: Formulation Composition for Tablets

Ingredients(mg)	Formulation Codes							
	F1	F2	F3	F4	F5	F6	F7	F8
Famciclovir	250	250	250	250	250	250	250	250
HPMC K 15	15	30	45	60	-	-	-	-
Ethyl cellulose	-	-	-	-	20	40	60	80
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Talc	4	4	4	4	4	4	4	4
PVP-K30	10	10	10	10	10	10	10	10
Magnesium Stearate	5	5	5	5	5	5	5	5
Total weight	500	500	500	500	500	500	500	500

All the quantities were in mg

Total Tablet Weight = 500 mg

Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content[20-23].

Weight Variation Test: To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage[24]. The mean and deviation were determined. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Table-6: Pharmacopeial Specifications for Tablet Weight Variation

Average weight of tablet(mg) (I.P)	Average weight of tablet(mg) (U.S.P)	Maximum percentagedifference allowed
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

Hardness: Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness[25]. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness: Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance[26]. Average thickness for core and coated tablets is calculated and presented with deviation.

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Friability: It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Reweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations)[27]. At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2) / W] × 100

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Determination of Drug Content: Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of drug were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with media[28]. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

In Vitro Drug Release Studies Dissolution Parameters:

Apparatus	--	USP-II, Paddle Method
Dissolution Medium	--	0.1 N HCL, pH 6.8 Phosphate buffer
RPM	--	50
Sampling intervals (hrs)	--	0.5,1,2,3,4,5,6,7,8,10,11,12
Temperature	--	37°c + 0.5°c

Procedure: 900ml 0f 0.1 HCL was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c + 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCL were removed and pH 6.8 phosphate buffer was added process was continued from up to 12 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media was replaced[29-31]. Suitable dilutions were done with media and analyzed by spectrophotometrically at 300 and 305 nm using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model[32].

Zero Order Release Rate Kinetics: To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

F = Ko t

Where, 'F' is the drug release at time't', and 'Ko' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation Log (100-F) = kt

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release[33].

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

F = k t1/2

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model: The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line[34].

$Mt/ M\infty = K\ tn$

Where, $Mt/ M\infty$ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for Supercase II transport, n > 1. In this model, a plot of log ($Mt/ M\infty$) versus log (time) is linear[36-37].

Hixson-Crowell release model: $(100\text{-}Qt)^{1/3} = 1001/3– K_{HC.t}$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

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Drug – Excipient Compatibility Studies Fourier Transform Infrared (FTIR) Spectroscopy: The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in IR spectrophotometer and the IR spectrum was recorded from 4000 cm to 550 cm-1. The resultant spectrum was compared for any spectrum changes[38-40].

3. RESULTS AND DISCUSSION

The present study was aimed to develop sustained release tablets of Famciclovir using various polymers. All the formulations were evaluated for physicochemical properties and in vitro drug release studies.

Analytical Method

Standard Graph of Famciclovir (Table. 7) has shown good linearity with R2 values 0.998 and 0.998 in 0.1 N HCl (Fig.1) and pH 6.8 buffer (Fig.2) respectively under λmax of 300nm, which suggests that it obeys the "Beer-Lambert's law".

Table-7: Observations for graph of Famciclovir in 0.1N HCL

Conc. (mcg/mL)	Absorbance	
	0.1N HCl at (300nm)	6.8 pH Buffer at (305nm)
0	0	0
5	0.122	0.128
10	0.258	0.246
15	0.356	0.352
20	0.456	0.461
25	0.572	0.578
30	0.686	0.682

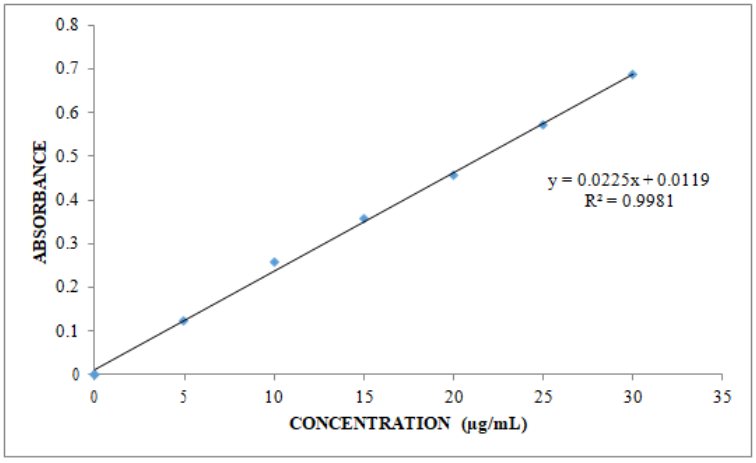

Fig-1: Standard graph of Famciclovir in 0.1 N HCl

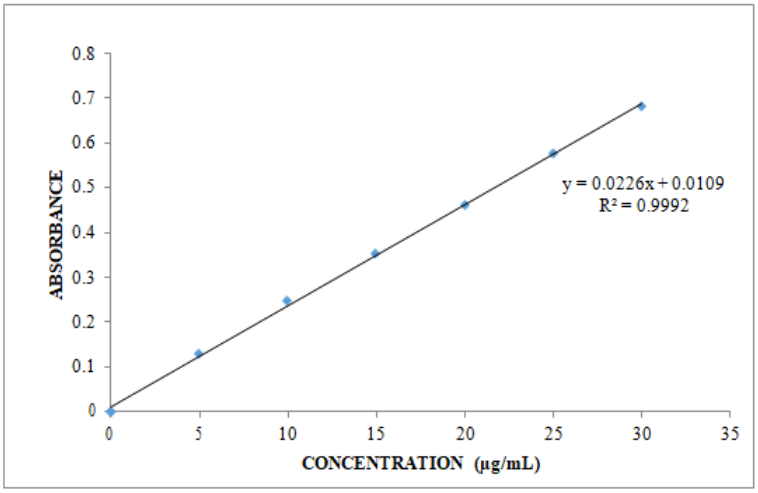

Fig-2: Standard graph of Famciclovir in 6.8 pH buffer

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Preformulation Parameters of Powder Blend

Table-8: Pre-Formulation Parameters of Core blend

Formulation code	Angle of repose (Ɵ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's ratio
F1	24.72 ± 0.01	0.345 ± 0.018	0.401 ± 0.012	13.97 ± 0.01	1.16 ± 0.02
F2	19.66 ± 0.02	0.332 ± 0.002	0.375 ± 0.015	11.46 ± 0.01	1.13 ± 0.01
F3	20.16 ± 0.015	0.465 ± 0.015	0.532 ± 0.001	12.59 ± 0.01	1.14 ± 0.01
F4	21.41 ± 0.01	0.421 ± 0.002	0.492 ± 0.002	14.43 ± 0.02	1.17 ± 0.02
F5	20.60 ± 0.015	0.382 ± 0.001	0.439 ± 0.002	12.98 ± 0.01	1.15 ± 0.01
F6	20.36 ± 0.015	0.523 ± 0.002	0.604 ± 0.017	13.41 ± 0.02	1.15 ± 0.01
F7	19.98 ± 0.01	0.348 ±0.001	0.401 ± 0.001	13.22 ± 0.01	1.15 ± 0.01
F8	40.13 ± 0.01	0.412 ±0.015	0.530 ±0.021	22.23 ± 0.01	1.29 ± 0.01

All the values represent n=3

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.332 ± 0.002 to 0.523 ± 0.002 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.375 ± 0.015 to 0.604 ± 0.017 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 14.43 ± 0.02 which show that the powder has good flow properties. All the formulations has shown the Hausner's ratio ranging between 1.13 ± 0.01 to 1.29 ± 0.01 indicating the powder has good flow properties.

Quality Control Parameters for Tablets:

Tablet quality control tests such as weight variation, hardness, friability, thickness and drug release studies in different media were performed on the compression tablet.

Table-9: In Vitro Quality Control Parameters for Tablets

Formulation Codes	Average Weight (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug Content (%)
F1	500.14	5.2	0.45	6.21	96.25
F2	498.82	4.1	0.38	5.49	98.12
F3	499.55	5.0	0.28	5.05	100.01
F4	496.72	4.7	0.20	6.56	98.59
F5	499.58	4.2	0.38	5.84	98.09
F6	497.89	5.6	0.30	6.11	95.83
F7	500.04	4.5	0.26	5.87	99.37
F8	500.27	5.1	0.18	5.39	98.14

Weight Variation Test: Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet. The average weight of the tablet is approximately in range of 496.72 to 500.27 mg, so the permissible limit is ±7.5% (>500 mg). The results of the test showed that, the tablet weights were within limit.

Hardness Test: Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 9. The results showed that the hardness of the tablets is in range of 4.1 to 5.6 kg/cm2, which was within IP limits.

Thickness: Thickness of three tablets of each batch was checked by using Micrometer and data shown in Table-9. The result showed that thickness of the tablet is raging from 5.05 to 6.56 mm.

Friability: Tablets of each batch were evaluated for percentage friability and the data were shown in the Table 9. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

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Drug Content: Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 95.83 – 100.01 %.

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

In Vitro Drug Release Studies

Table-10: Dissolution Data of Famciclovir Tablets

TIME	CUMULATIVE % OF DRUG RELEASE							
	F1	F2	F3	F4	F5	F6	F7	F8
In dissolution media 0.1 N HCL								
0	0	0	0	0	0	0	0	0
0.5	30.22	18.58	20.82	14.85	16.34	13.50	10.29	06.91
1	47.04	30.25	26.90	19.09	21.26	18.32	16.72	12.30
2	51.98	37.71	31.35	25.50	28.54	26.11	23.90	16.61
In dissolution media 6.8 Phosphate Buffer								
3	60.35	45.64	41.05	32.26	32.80	30.55	28.89	22.52
4	69.26	52.83	46.16	38.34	39.03	37.81	36.25	26.81
5	75.90	60.17	52.09	46.86	46.97	43.65	42.10	35.32
6	91.71	66.98	59.90	51.71	52.61	50.07	47.52	43.60
7	98.23	79.05	67.72	58.55	60.76	56.22	55.99	50.97
8		90.14	73.38	69.14	67.21	62.89	62.71	56.82
9		97.08	85.89	77.82	75.14	72.27	67.63	63.35
10			98.96	86.91	81.30	78.14	75.89	70.82
11				91.35	90.18	86.96	83.71	73.99
12				97.08	99.23	96.82	90.82	86.34

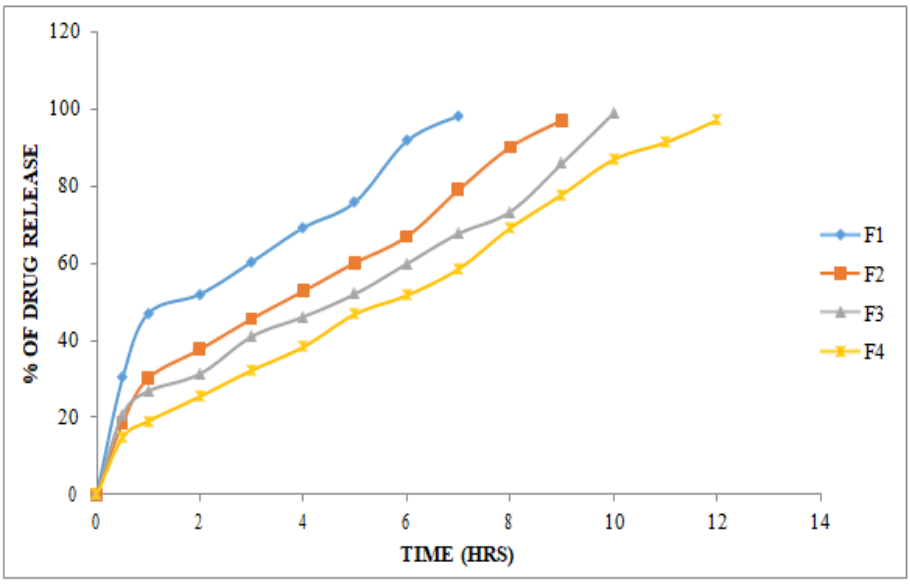

Fig-3: Dissolution Profile of Famciclovir (F1, F2, F3, F4 Formulations)

The results of release studies of formulations F1 to F4 are shown in Table 10 and Figure 3. The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. As the percentage of polymer increased, the kinetics of release decreased.

Formulation F1 composed of drug polymer ratio of 1:1, failed to sustain release beyond 7h. This formulation underwent erosion before complete swelling could take place. Formulations with drug polymer ratios 1:2 (F2), 1:3 (F3) have extended the drug release for 10h. Further increasing the ratio to 1:4 (F4), the release was sustained for 12 h.

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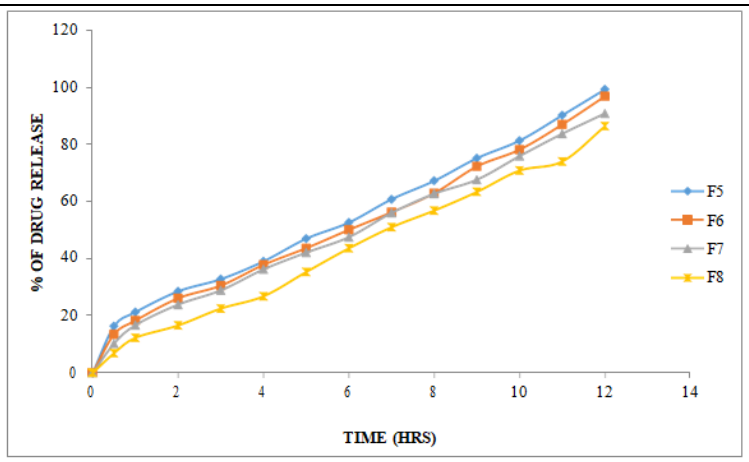

Fig-4: Dissolution Profile of Famciclovir (F5, F6, F7, F8 Formulations)

Hydrophobic Ethyl cellulose can be used as a matrix former for the formulation of sustained-release dosage forms. Batches containing ethyl cellulose (F5 to F8) as release retardant extended the release up to 12 hours with initial slow release. As drug polymer ratio increased, the release rate was decreased. During dissolution the erosion was observed. The results were shown in Table 10 and Figure 4.

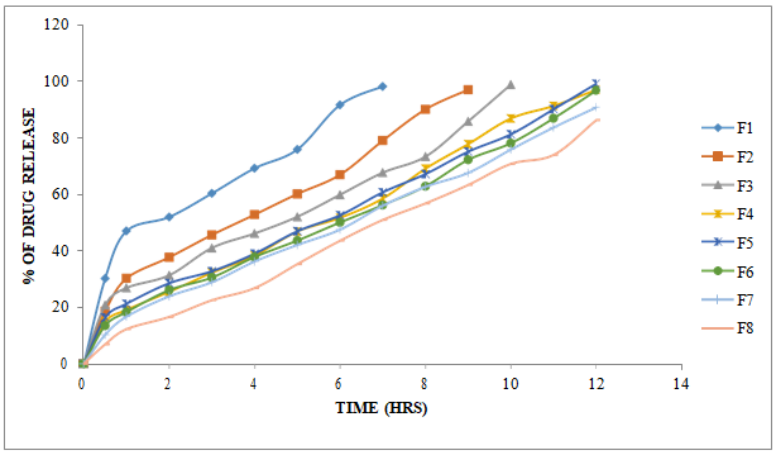

Fig-5: Dissolution Profile of Famciclovir (F1 to F8 formulations)

Out of total 8 batches, the drug release was extended up to 12 hours for the formulations F5. So, these formulations selected for further studies like kinetic data analysis.

Table-11: Release Kinetics:

CUMULATIVE(%) RELEASE Q	TIME(T)	ROOT(T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM % RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3 - Qt1/3
0	0	0	0	0	2.000	0	0	0	100	4.642	4.642	0.000
16.34	0.5	0.707	1.213	-0.301	1.923	32.680	0.0612	-0.787	83.66	4.642	4.374	0.268
21.26	1	1.000	1.328	0.000	1.896	21.260	0.0470	-0.672	78.74	4.642	4.286	0.355
28.54	2	1.414	1.455	0.301	1.854	14.270	0.0350	-0.545	71.46	4.642	4.150	0.492
32.8	3	1.73	1.516	0.47	1.827	10.933	0.0305	-0.484	67.2	4.642	4.06	0.576

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39.03	4	2.000	1.591	0.602	1.785	9.758	0.0256	-0.409	60.97	4.642	3.936	0.706
46.97	5	2.236	1.672	0.699	1.725	9.394	0.0213	-0.328	53.03	4.642	3.757	0.885
52.61	6	2.449	1.721	0.778	1.676	8.768	0.0190	-0.279	47.39	4.642	3.619	1.023
60.76	7	2.646	1.784	0.845	1.594	8.680	0.0165	-0.216	39.24	4.642	3.398	1.243
67.21	8	2.828	1.827	0.903	1.516	8.401	0.0149	-0.173	32.79	4.642	3.201	1.441
75.14	9	3.000	1.876	0.954	1.396	8.349	0.0133	-0.124	24.86	4.642	2.919	1.723
81.3	10	3.162	1.910	1.000	1.272	8.130	0.0123	-0.090	18.7	4.642	2.654	1.987
90.18	11	3.317	1.955	1.041	0.992	8.198	0.0111	-0.045	9.82	4.642	2.141	2.500
99.23	12	3.317	1.997	1.079	-0.114	8.269	0.0101	-0.003	0.77	4.642	0.917	3.725

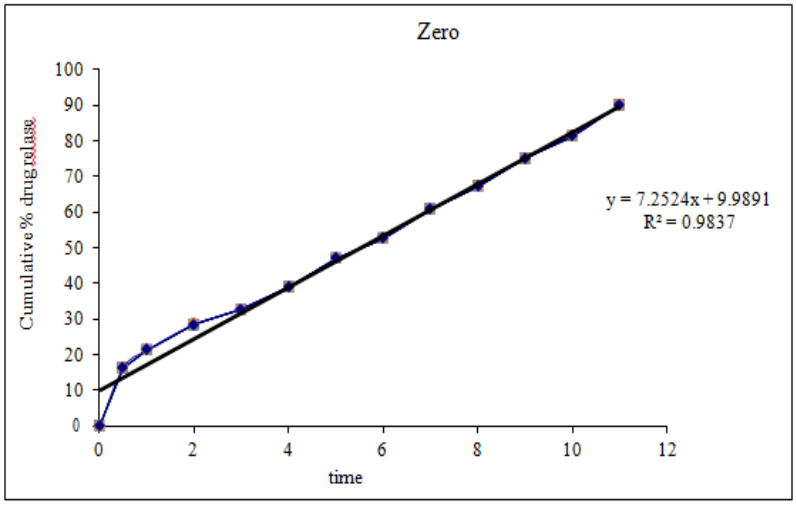

Fig-6: Zero Order Release Kinetics Graph

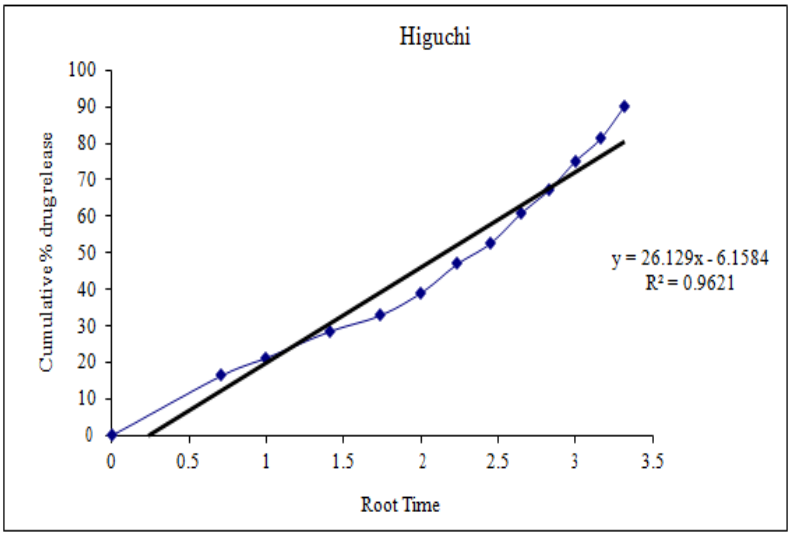

Fig-7: Higuchi Release Kinetics Graph

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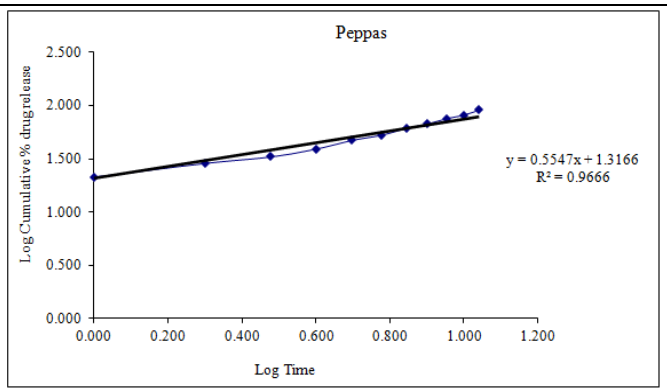

Fig-8: Peppas Release Kinetics Graph

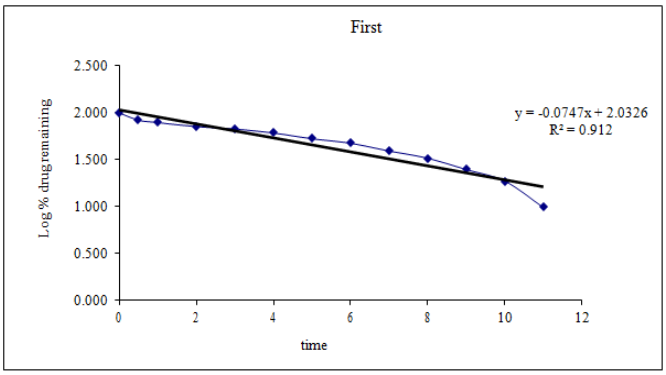

Fig-9: First Order Release Kinetics Graph

Optimised formulation F5 was kept for release kinetic studies. From the above graphs it was evident that the formulation F8 was followed Zero order release mechanism.

Drug – Excipient Compatibility Studies

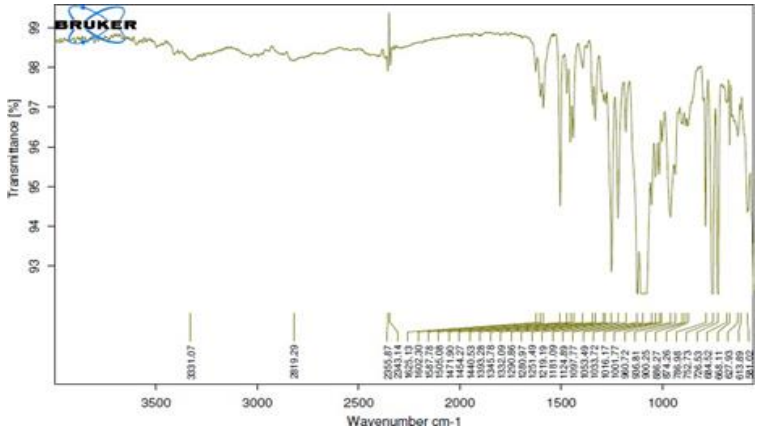

Fig-10: FT-TR Spectrum of Famciclovir Pure Drug

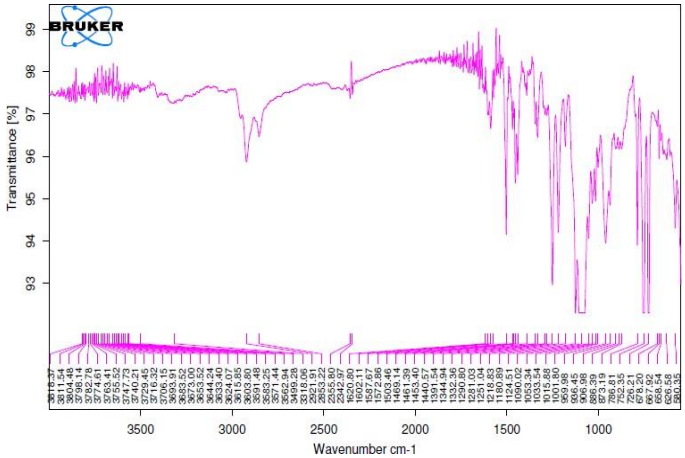

Fig-11: FT-IR Spectrum of Optimised Formulation

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

Famciclovir is also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

4. CONCLUSION

Famciclovir is a guanosine analogue antiviral drug used for the treatment of various herpesvirus infections, most commonly for herpes zoster (shingles). It is a prodrug form of Penciclovir with improved oral bioavailability. As the conventional doses release the Famciclovir in just few minutes and therefore the therapeutic concentrations are maintained for a short period of time generating a need for administration of another dose Therefore an attempt is made to maintain the therapeutic concentration for longer period of time. This is achieved by developing sustained release drug delivery system. These sustained release matrix tablets mainly prepared for release of the drug for longer period of time i.e., 12 hours and utilizing the drug to full extent avoiding unnecessary frequency of dosing. For the formulation of sustained release matrix tablet HPMC K 15M, Ethyl cellulose and PVP was used as matrix forming agents. Other excipients used are microcrystalline cellulose (diluents), Magnesium stearate (lubricating agent). Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers/excipients interactions. The prepared sustained release tablets were evaluated for hardness, Weight variation, thickness, friability, drug content uniformity, In-vitro dissolution studies. Formulation F5 is considered to be the optimized formulation Matrix tablets were compressed without any problem and do not require any change in ratio of excipients in formulation. Results of the present study demonstrated that both hydrophilic and hydrophobic polymers could be successfully employed for formulating sustained-release matrix tablets of Famciclovir. It was observed that Formulations F5 retained the drug release up to 12 hrs. All formulations were subjected for four different models viz. Zero order, First order, Higuchi matrix and Peppas model equations and all the formulations best fit in to the Zero order release mechanism by giving the values of diffusion exponent (n) in the range of 0.983 that indicate the formulation had release the drug by diffusion followed by erosion mechanism. Hence it can be concluded that twice a daily controlled release matrix tablet of Famciclovir having satisfactory sustained release profile which may provide an increased therapeutic efficacy. The developed formulation overcome and alleviates the drawback and limitation of sustained release preparations.

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