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RESEARCH ARTICLE OPEN ACCESS

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 Preformulating 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.

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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, 3]. 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[4]. 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 levelof a drug often translates into better patient compliance, as well as enhanced clinical efficacyof the drug for its intended use[5, 6]. 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.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. 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[7, 8]. Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. There are certain considerations for the preparation of extended release formulations:

- ✓ If the active compound has a long half-life, it is sustained on its own,
- ✓ If the pharmacological activity of the active is not directly related to its blood levels,
- ✓ If the absorption of the drug involves an active transport and
- ✓ If the active compound has very short half-life, then it would require a large amount of drug to maintain a prolonged effective dose.

The above factors need serious review prior to design.

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of pharmaceutical technology. It excludes complex production

procedures such as coating and Pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed[9]. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane-controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.

Rationale for extended-release dosage forms

Some drugs are inherently long lasting and require only once-a-day oral dosing to sustain adequate drug blood levels and the desired therapeutic effect. These drugs are formulated in the conventional manner in immediate release dosage forms. However, many other drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results. Multiple daily dosing is inconvenient for the patient and can result in missed doses, made up doses, and noncompliance with the regimen[10,11]. When conventional immediate-release dosage forms are taken on schedule and more than once daily, they cause sequential therapeutic blood level peaks and valleys (troughs) associated with the taking of each dose. However, when doses are not administered on schedule, the resulting peaks and valleys reflect less than optimum drug therapy. For example, if doses are administered too frequently, minimum toxic concentrations of drug may be reached, with toxic side effects resulting. If doses are missed, periods of sub therapeutic drug blood levels or those below the minimum effective concentration may result, with no benefit to the patient. Extended-release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended-release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period (Fig.1). The sustained plasma drug levels provided by extended-release products oftentimes eliminate the need for night dosing, which benefits not only the patient but the caregiver as well[12].

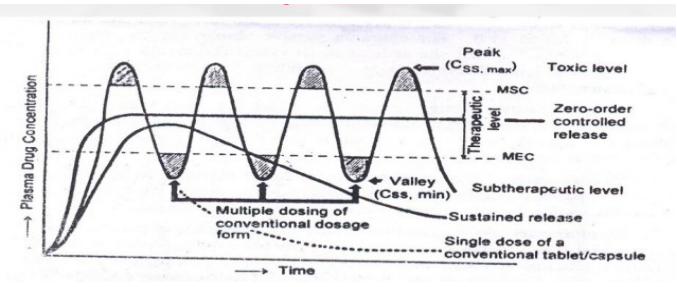


Figure 1. Hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations

Advantages of sustained release dosage forms

- The frequency of drug administration is reduced.
- Patient compliance can be improved.
- Drug administration can be made more convenient as well.
- The blood level oscillation characteristic of multiple dosing of conventional dosage forms is reduced.
- Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced.
- The characteristic blood level variations due to multiple dosing of conventional dosage forms can be reduced.
- The total amount of drug administered can be reduced, thus:
  - Maximizing availability with minimum dose;
  - Minimize or eliminate local side effects;
  - Minimize or eliminate systemic side effects;
  - Minimize drug accumulation with chronic dosing.
- Safety margins of high potency drugs can be increased a the incidence of both local and systemic adverse side effects can be reduced in sensitive patients.
- Improve efficiency in treatment.
  - Cure or control condition more promptly
  - Improve control of condition
  - Improve bioavailability of some drugs
  - Make use of special effects; e.g., sustain release aspirin for morning relief of arthritis by dosing before bed-time.

Disadvantages of sustained release dosage forms

- Probability of dose dumping.
- Reduced potential for dose adjustment.
- Cost of single unit higher than conventional dosage forms.
- Increase potential for first pass metabolism.
- Requirement for additional patient education for proper medication.
- Decreased systemic availability in comparison to immediate release conventional dosage forms.
- Poor invitro and invivo correlations.

MATERIALS

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- Colorconasia private Ltd. Goa, India, Talc- Merck Specialities Pvt Ltd, Mumbai, India, PVP-K30- Sri Krishna Pharmaceuticals Ltd, India, Magnesium- Stearate, Merck Specialties Pvt Ltd- Mumbai, India.

METHODOLOGY

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. The solution was scanned in the range of 200 – 400nm.

Preparation 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 (R^2)which determined by least-square linear regression analysis. 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 thequality 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. The various characteristics of blends tested as per Pharmacopoeia.

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. 8.1) has shown good linearity with R^2 values 0.998 and 0.998 in 0.1 N HCl (Fig.8.1) and pH 6.8 buffer (Fig.8.2) respectively under λmax of 300nm, which suggests that it obeys the "Beer-Lambert's law".

Table 1. 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

Table 2. 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

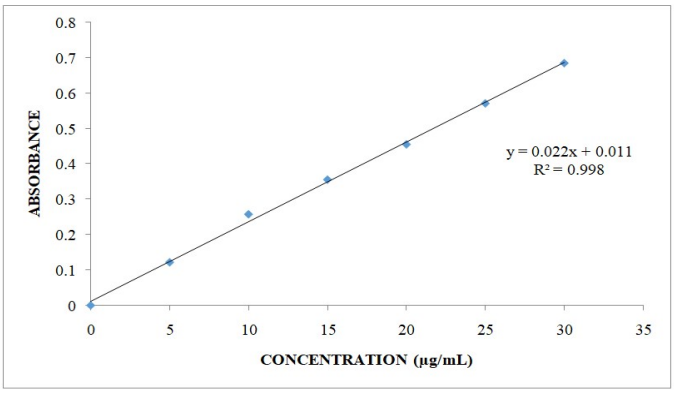


Fig. 2. Standard graph of Famciclovir in 0.1 N HCl

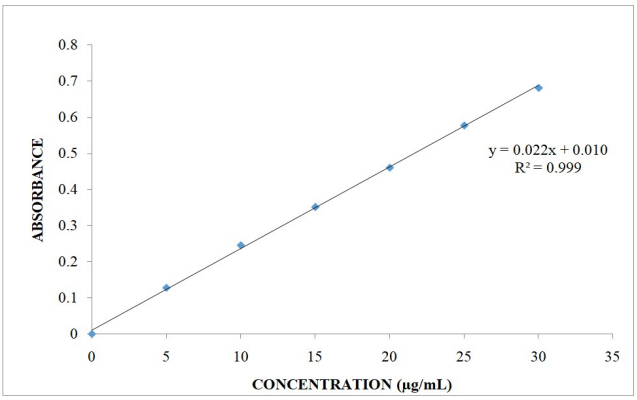


Fig.3. Standard graph of Famciclovir in 6.8 pH buffer

Preformulation parameters of powder blend

Table 3. Pre-formulation parameters of Core blend

Formulation code	Angle of repose (Θ)	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 hausners 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.

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 496.72to 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 8.4. The results showed that the hardness of the tablets is in range of 4.1 to 5.6 kg/cm^2, which was within IP limits.

Thickness: Thickness of three tablets of each batch was checked by using Micrometer and data shown in Table-8.4. 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 8.4. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

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.

Table 4. 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

***In Vitro* Drug Release Studies**

Table 5. 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

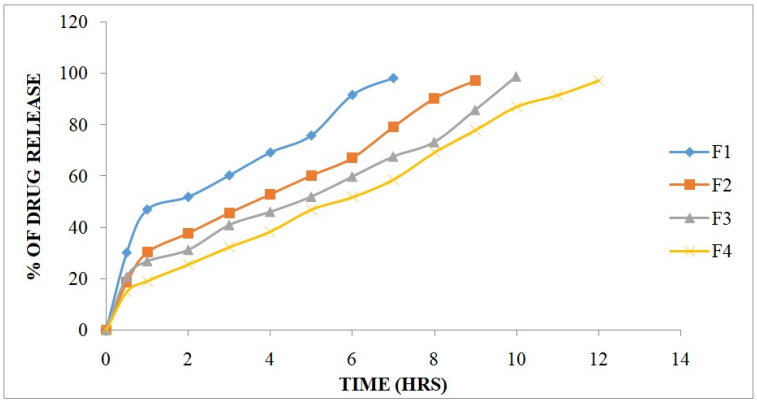
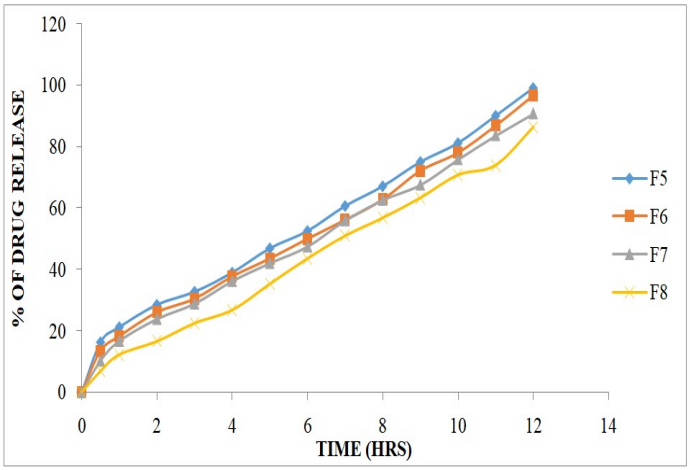


Fig. 4. Dissolution profile of Famciclovir (F1, F2, F3, F4 formulations)

The results of release studies of formulations F1 to F4 are shown in Table 8.5 and Figure 8.3. 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.

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 8.5 and Figure 8.4. 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.



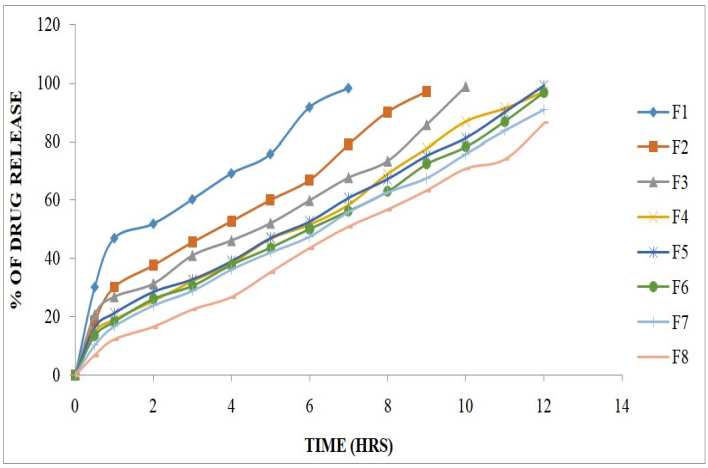
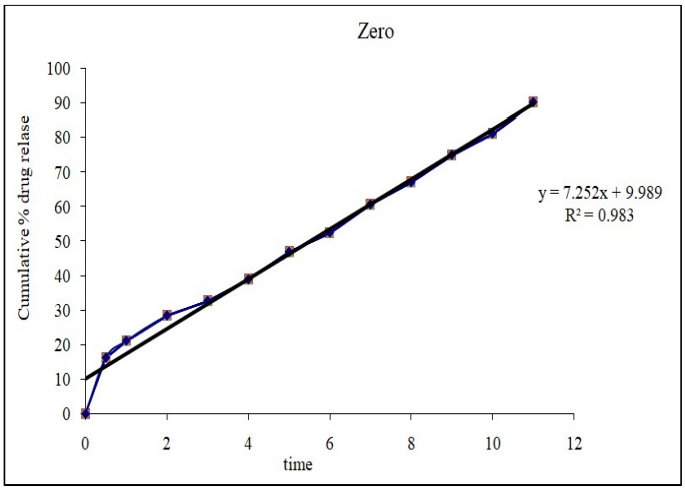


Fig. 5. Dissolution profile of Famciclovir (F5, F6, F7, F8 formulations) **Fig. 6. Dissolution profile of Famciclovir (F1 to F8 formulations)**

Table 6. 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	1.732	1.516	0.477	1.827	10.933	0.0305	-0.484	67.2	4.642	4.066	0.576
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



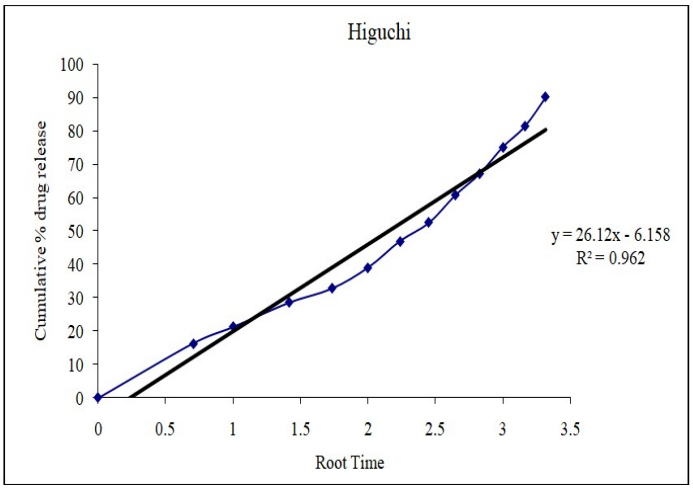


Fig. 6. Zero order release kinetics graph **Fig. 7. Higuchi release kinetics graph**

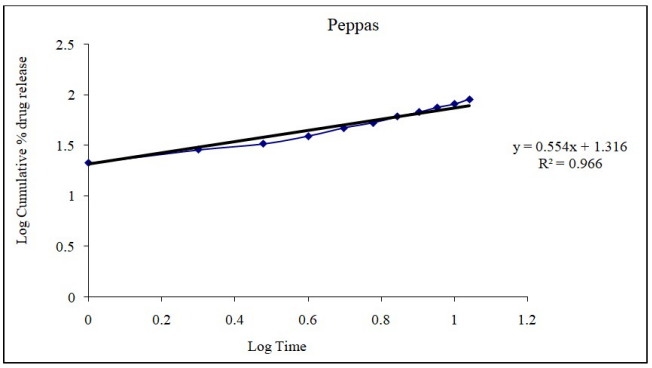


Fig. 8. Peppas release kinetics graph

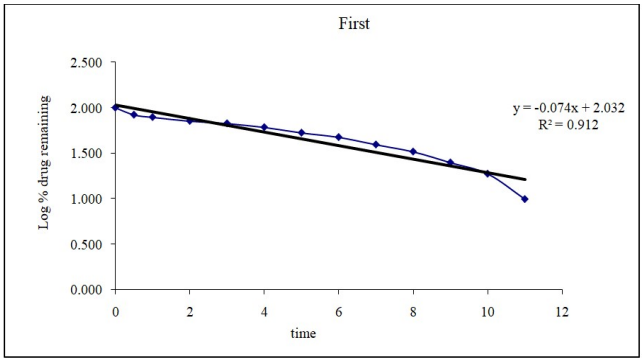


Fig.9. First order release kinetics graph

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

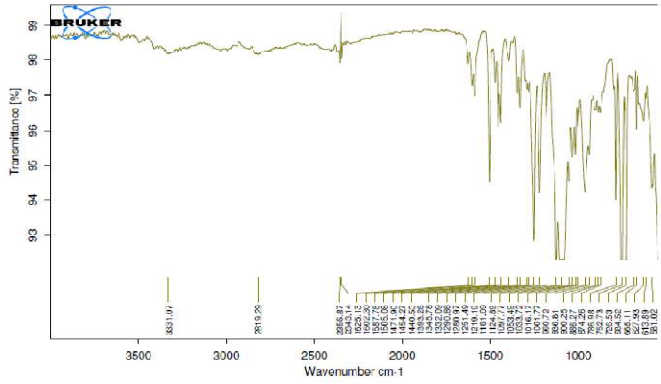


Fig. 10. FT-TR Spectrum of Famciclovir pure drug

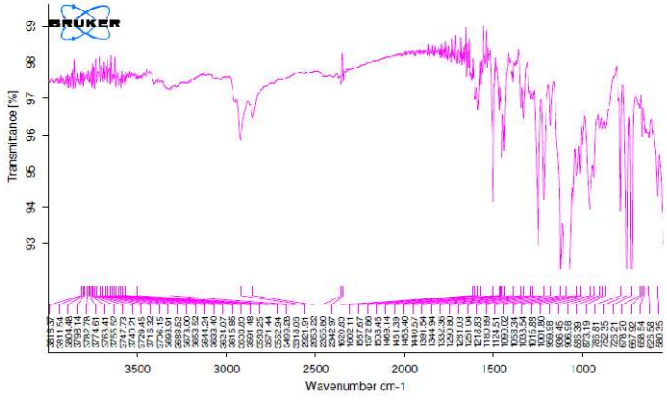


Fig. 11. FT-IR Spectrum of Optimised Formulation

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.

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/excipient's 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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