ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Formulation And Evaluation Of Famciclovir Sustained Released Matrix Tablets By Direct Compression Method.

Sheshikala Vaddepally, Naga Raju Potnuri*, JVC Sharma, and Swarupa Arvapalli.

Department of Pharmaceutics, Joginpally B.R. Pharmacy College, Yenkapally (V), Moinabad(M), R.R. Dist, Telangana, India.

ABSTRACT

The present study aimed to formulation and evaluation of Famciclovir sustained released tablets by using direct compression technique, to achieve a controlled and sustained drug release with reduced frequency of drug administration, reduced side effects and improved patient compliance. Famciclovir tablets were prepared by using natural polymer like Xanthan gum, Tamarind gum and Guar gum. All the batches (F1-F12) were evaluated for pre compression parameters, post compression and in vitro drug release characteristics. The drug release rates from tablets were compared with marketed formulations. The release kinetics and mechanism of drug release by regression coefficient analysis, higuchi constant and peppas exponential release model equation were also investigated. The Famciclovir released from the tablets follows higuchi diffusion mechanism and fickian transport system. The interactions between the drug, polymers and adjuvants during the direct compression technique are also investigated by using FT-IR examination.

Keywords: Famciclovir, Natural Gums, Higuchi diffusion and Fourier transform infrared spectroscopy (FT-IR).

https://doi.org/10.33887/rjpbcs/2019.10.3.47

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Sustained release dosage form is mainly designed for the maintenance of therapeutic blood concentration of the drug for extended period of time with minimum systemic adverse effects. The drugs having a low therapeutic index and short elimination half-life are preferred for preparation of sustained released formulations [1]. The objective of the present investigation was to develop the sustained release formulation of Famciclovir matrix tablets by using natural polymers like Xanthan gum, Tamarind gum and Guar gum are widely used. Sustained release system have benefits like greater patient compliance, avoiding multiple dosing, cost effectiveness, flexibility, increase the plasma drug concentration, avoidance side effects, broad regulatory acceptance and overcome the problems associated with conventional drug delivery system [2-3]. Famciclovir is a guanine analogue antiviral drug used for the treatment of various herpes virus infections, most commonly for herpes zoster (shingles). Medically it is used to treat the herpes zoster (shingles) [4] treatment of herpes simplex virus 2 (genital herpes) [5] herpes labialis (cold sores) in immunocompetent patients [6] and for the suppression of recurring episodes of herpes simplex virus 2. It is also indicated for treatment of recurrent episodes of herpes simplex in HIV patients. Famciclovir is marketed under the trade name Famvir.

Xanthan gum is widely used in oral and topical pharmaceutical formulations, cosmetics, and foods as a suspending and stabilizing agent [7–9]. It is also used as a suspending agent for conventional [10] dry [11] and sustained-release [12] suspensions. The functional category of xanthan gum is gelling agent, stabilizing agent, suspending agent, sustained-release agent and viscosity-increasing agent. Guar gum based three layer matrix tablets have been used experimentally in oral controlled release formulations [13] and it has also been investigated in the preparation of sustained release matrix tablets in the place of cellulose derivatives such as methylcellulose [14].

MATERIALS AND METHODS

Materials

Famciclovir was purchased from BMR Pharma & Chemical Suppliers, Hyderabad, Telangana, India. Xanthan gum, Tamarind gum and Guar gum were purchased from Strides Pharma Science Limited, Bangalore, Karnataka, India. Micro Crystalline Cellulose was purchased from coloran asia (P) Ltd, Goa, India. Other chemicals PVP K30, Talc, Magnesium stearate (Loba Chemie Pvt Ltd, Mumbai, Maharashtra, India) were obtained commercially and used as such.

Methods

Solubility studies of Famciclovir

Solubility studies of Famciclovir were determined by using water, pH 1.2, pH 6.8 and pH 7.4 phosphate buffers. Solubility studies were performed by taking excess amount of Famciclovir in beakers containing the solvents. The mixtures were shaken for 24 hours at regular intervals. The solutions were filtered by using whatman filter paper grade No: 41. The filtered solutions are analyzed spectrophotometrically and the Solubility study of Famciclovir was shown in Table No: 2 and Figure II. The solubility studies were observed that pH 1.2 buffer has more solubility than the other buffers and its Percentage solubility is 0.897±0.09%.

Famciclovir calibration curve

Famciclovir calibration curves were prepared by buffer pH 1.2 and pH 6.8 in the concentration range of 2-12µg/mL and they were analyzed spectrophotometrically **(**UV-Visible Double Beam Spectrophotometer**)** at 224.20 nm. The regression coefficient is 0.999 and graph was shown in Figure I.

Fabrication of Famciclovir matrix tablets

Famciclovir, Natural polymers (Xanthan gum, Tamarind, Guar gum), microcrystalline cellulose, PVP K30, magnesium stearate and talc were passed through sieve No# 60 separately. Twelve (F1-F12) formulations

with various polymer ratios were prepared by keeping Famciclovir as a constant for 250mg. The Composition of Famciclovir sustained released matrix tablets are shown in Table No: 1.

The Famciclovir formulations were prepared by direct compression technique and tablets were compressed in a cadmach single punch tablet compression machine. A weighed amount (500mg) of the powder was introduced in the die cavity and the die capacity was adjusted as required tablet weight 500mg. Compression force was adjusted to obtain the required hardness for 6 to 9 kg/cm^2. A batch of 30 tablets was prepared for all the Famciclovir formulations (F1-F12).

Drug-Excipients interaction studies

Pre-formulation studies are very important for the successful formulation of any dosage form. Differential Scanning Calorimetry (DSC), Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the evaluation of physicochemical compatibility and interactions, which helps in the prediction of interaction of the drug with polymers, binders and lubricants used in tablet formulations. Positive interactions sometimes have a beneficial effect as far as desired release parameters are concerned. Therefore, in the present studies Famciclovir, Natural Gums (Xanthan, Tamarind and Guar Gums) and excipients were used and analyzed for compatibility studies. Present investigation fourier transform infrared spectroscopy was used to determine any possible interactions between the Famciclovir, Polymers and excipients which were used and analyzed for compatibility studies.

EVALUATION

All the formulations (F1to F12) were evaluated for pre compression parameters (angle of repose, hausner ratio, compressibility index, bulk & tapped density) and post compression parameters (weight uniformity, thickness, hardness, friability and drug content uniformity).

In vitro dissolution studies

The dissolution studies of all formulations (F1-F12) were evaluated by using USP dissolution apparatus type-II. The medium was used for 900 mL of 0.1N hydrochloric acid for 2hrs, pH 6.8 phosphate buffer for upto 24 hrs. The temperature should be maintained at 37 ± 0.5°C with paddle stirred at 50 rpm and 5 mL of sample was withdrawn at different time intervals & at the same time an equivalent volume of medium (5 mL) was replaced on it, to maintain sink condition. The samples were analyzed by UV Visible spectrophotometer at 224.20nm.

Data Analysis

Three kinetics models like zero order (Eq-I), first order (Eq-II), and Higuchi equations (Eq-III) were applied to process in vitro data to find the equation with the best fit.

$$Q = K_0 t \quad \text{[Eq-I]}$$
$$Q = 100\ (1\text{-}e\text{-}K_1 t) \quad \text{[Eq-II]}$$
$$Q = K_H t_{1/2} \quad \text{[Eq-III]}$$

Where:
Q is the release percentage at time t.
K_0 is the zero order constant
K_1 is the first order constant and
K_H is the Higuchi constant.

To investigate the mechanism of Famciclovir released was done by plotting as cumulative Famciclovir released on Y-axis verses square root of time on X-axis described by higuchi, linearity was observed in graphs that indicates the mechanism of Famciclovir released is “diffusion controlled” [15]. The data was further analysed to the following empirical equation proposed by peppas [16]. $Mt/M\alpha=Kt^n$ [Eq-IV] Where: Mt is drug release at time t, Mα is the total amount of drug in formulation Mt/Mα is the fraction of drug release up to time t, K is the kinetic constant and n is the exponential constant.

ISSN: 0975-8585

RESULTS AND DISCUSSION

Pre compression parameters

Pre compression parameters of all the Famciclovir matrix tablets were shown in excellent flow properties and it shows satisfactory results. The angle of repose ranged from $22^0.34'$ to $26^0.45'$, hausner ratio ranged from 11.04 to 15.45, compressibility index ranged from 1.12 to 1.18%, bulk density ranged from 0.325 to 0.397g/cc and tapped density ranged from 0.289 to 0.337g/cc. The pre-compression parameters are summarized in Table No: 3.

Post compression parameters

Post compression parameters of all the Famciclovir matrix tablets were shown within in the limits and it shows satisfactory results. The weight uniformity ranged from 489.08 to 499.97mg, thickness ranged from 4.26 to 4.98mm, hardness ranged from 6.8 to 8.8 kg/cm^2, Friability ranged from 0.25 to 0.85%, and drug content ranged from 84.63 to 99.21mg/tablet and the results are shown in Table No: 4.

In Vitro release kinetic analysis

The first order plots of the all formulations (F1-F12) were indicated linear, so they followed first orders release kinetics. The slope of the line and corresponding first order constants (K) can be calculated, which is indicative of the release rate profile. The drug released from the matrix formulations were evaluated by using different kinetic models. The regression coefficient (A) and corresponding constants (K) obtained from higuchi constant. The regression coefficient (A) and corresponding constants (n) obtained from korsmeyer peppas models.

To investigate the mechanism of drug released from the Famciclovir formulations were done by plotting for square root of time on X-axis verses cumulative drug release on Y-axis as described by higuchi, for all matrix formulations (F1 to F12) were found to be linear, indicating the diffusion mechanism of drug released. The time on X-axis verses percent drug released on Y-axis profiles were fitted for the peppas equation. The “n” values of all the formulations (F1-F12) were less than 0.5, which indicates formulations follow Fickian diffusion mechanism. The Famciclovir formulation (F1-F12) drug released profiles were shown in Figure III to VI.

Compatibility studies by using FT-IR

The compatibility studies should be conducted by to check the whether any compatibility problems between drug (Famciclovir), natural polymers (Xanthan gum, Tamarind gum and Guar gum) and excipients (PVP K30, talc and magnesium stearate) used in present investigation. The Physical mixture of drug and polymers was characterized by FTIR spectral analysis for any physical as well as chemical alteration of drug characteristics. The FI-IR spectrums (Figure VII and VIII), it is clear that the characteristics peaks are seen in both pure drug (Famciclovir) and polymers (Xanthan gum, Tamarind gum and Guar gum) without any changes in their position, so there is no strong interactions between excipients, polymers and Drug.

ISSN: 0975-8585

Table No: 1: Composition of Famciclovir sustained released matrix tablets

S. No	INGREDIENTS (mg/tablet)	FORMULATIONS WITH CODE											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	Famciclovir	250	250	250	250	250	250	250	250	250	250	250	250
2	Xanthan Gum	30	60	90	120	--	--	--	--	--	--	--	--
3	Tamarind Gum	--	--	--	--	30	60	90	120	--	--	--	--
4	Guar Gum	--	--	--	--	--	--	--	--	30	60	90	120
5	Microcrystalline Cellulose (MCC)	196	166	136	106	196	166	136	106	196	166	136	106
6	PVP K30	20	20	20	20	20	20	20	20	20	20	20	20
7	Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2
8	Talc	2	2	2	2	2	2	2	2	2	2	2	2
9	Total weight (mg)	500	500	500	500	500	500	500	500	500	500	500	500

Table No: 2: Solubility studies of Famciclovir

S. No	Name of Solvent	Percentage of Solubility
1	Water	0.392±0.65
2	pH 1.2 Buffer	0.897±0.09
3	pH 6.8 Buffer	0.509±0.54
4	pH 7.4 Buffer	0.356±0.23

Table No: 3: Pre-Compression parameter of Famciclovir sustained released matrix tablets

S. No	FORMULATIONS	Angle of repose (0)	Hausner Ratio	Compressibility Index (%)	Density (g/cc)	
					Bulk	Tapped
1	**F1**	26.45±0.23	12.17±0.89	1.14±0.36	0.378±0.54	0.332±0.73
2	**F2**	26.08±0.45	13.20±0.23	1.15±0.37	0.356±0.66	0.309±0.36
3	**F3**	25.46±0.03	15.45±0.43	1.18±0.04	0.369±0.32	0.312±0.83
4	**F4**	23.99±0.78	11.04±0.24	1.18±0.58	0.359±0.67	0.305±0.64
5	**F5**	25.67±0.46	11.08±0.08	1.12±0.34	0.325±0.23	0.289±0.83
6	**F6**	25.09±0.21	13.16±0.56	1.15±0.95	0.342±0.87	0.297±0.78
7	**F7**	22.34±0.04	11.99±0.72	1.16±0.56	0.336±0.47	0.289±0.51
8	**F8**	26.45±0.56	12.59±0.02	1.14±0.59	0.397±0.23	0.304±0.83
9	**F9**	25.89±0.62	12.92±0.28	1.15±0.10	0.387±0.76	0.337±0.74
10	**F10**	26.41±0.42	13.33±0.21	1.15±0.09	0.360±0.97	0.312±0.78
11	**F11**	22.45±0.68	11.55±0.24	1.17±0.68	0.385±0.25	0.309±0.13
12	**F12**	24.23±0.26	13.23±0.48	1.15±0.34	0.378±0.53	0.328±0.90

All the values are expressed in Mean± SD, N=3

Table No: 4: Post Compression parameters of Famciclovir matrix tablets

S. No	FORMULATIONS	Weight Uniformity (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug Content (mg/tablet)
1	**F1**	499.84±0.245	4.26±0.08	7.8±0.02	0.52±0.02	97.26±0.02
2	**F2**	499.72±0.214	4.28±0.05	6.8±0.25	0.62±0.03	93.25±0.15
3	**F3**	498.45±0.254	4.98±0.69	8.2±0.31	0.45±0.15	84.63±0.63
4	**F4**	498.94±0.216	4.29±0.03	7.2±0.02	0.75±0.20	97.52±0.48
5	**F5**	499.44±0.202	4.30±0.03	8.6±0.03	0.26±0.45	92.36±0.52
6	**F6**	489.08±0.214	4.29±0.03	8.2±0.36	0.54±0.33	92.56±0.15
7	**F7**	499.97±0.245	4.41±0.02	8.4±0.41	0.65±0.25	99.21±0.36

ISSN: 0975-8585

8	**F8**	498.72±0.254	4.44±0.03	7.2±0.02	0.85±0.14	93.15±0.20
9	**F9**	499.75±0.214	4.28±0.07	7.1±0.06	0.62±0.68	89.18±0.75
10	**F10**	498.86±0.202	4.32±0.02	7.5±0.21	0.25±0.26	86.84±0.63
11	**F11**	499.72±0.254	4.34±0.05	8.1±0.23	0.51±0.21	92.15±0.15
12	**F12**	498.92±0.202	4.33±0.11	8.8±0.08	0.36±0.06	90.24±0.21

All the values are expressed in Mean± SD, N=3

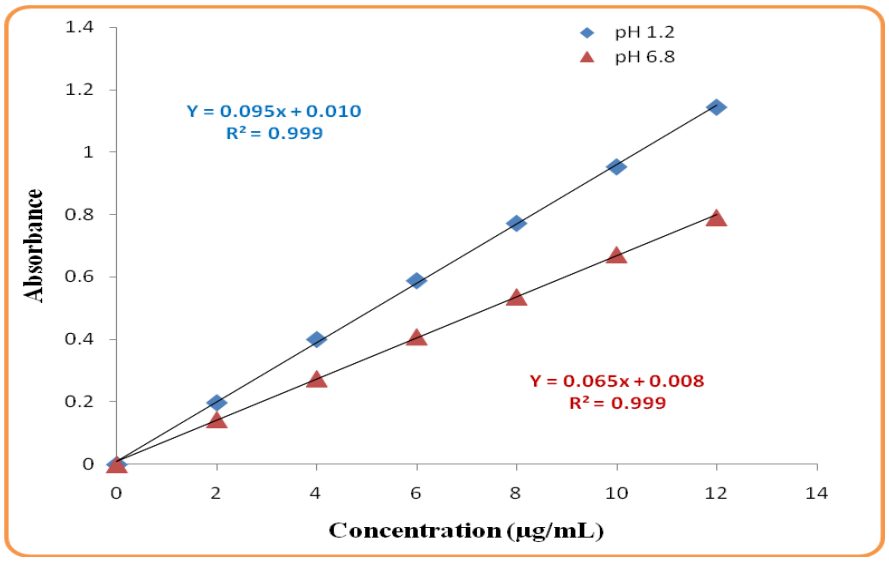

Figure I: Calibration curve of Famciclovir In pH 1.2 and pH 6.8 Buffers

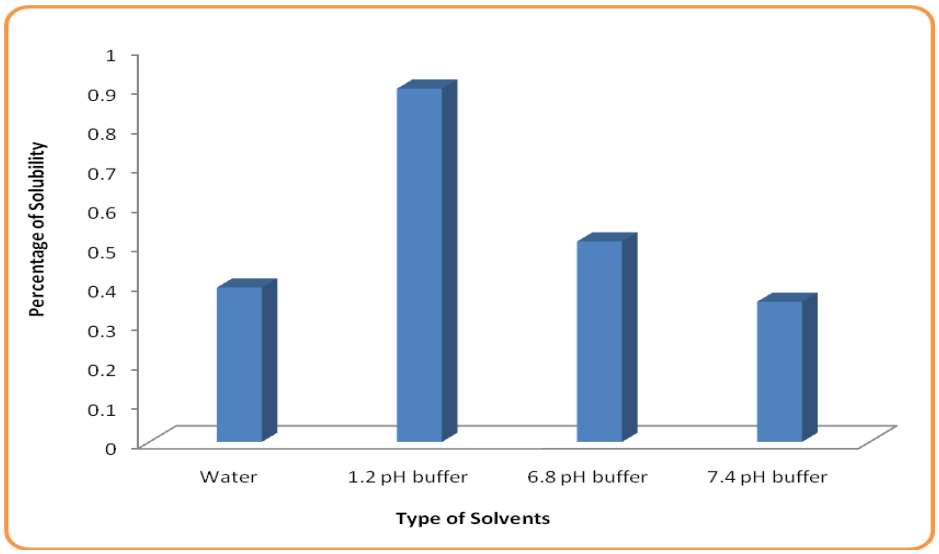

Figure II: Solubility studies of Famciclovir

ISSN: 0975-8585

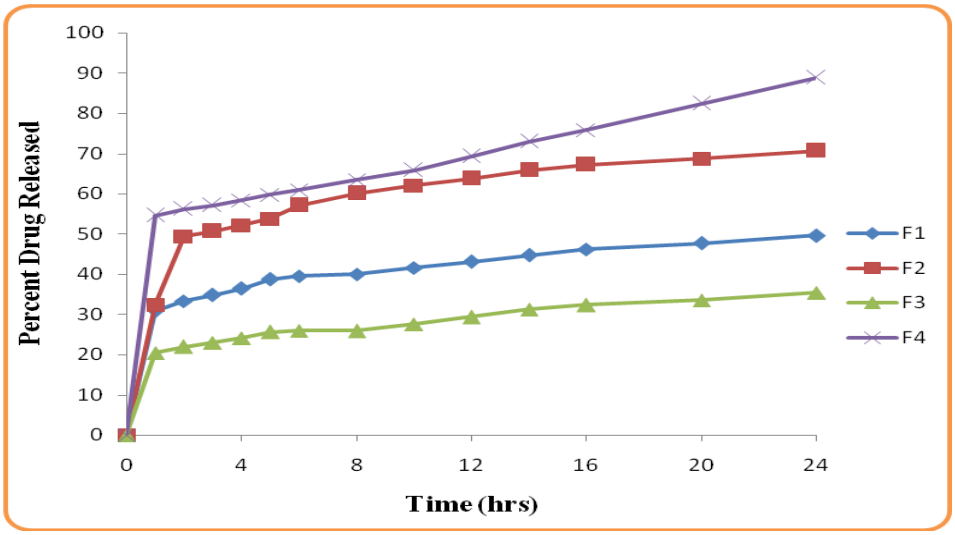

FIGURE III: Famciclovir released profiles (Xanthan Gum as a Polymer) of F1 to F4

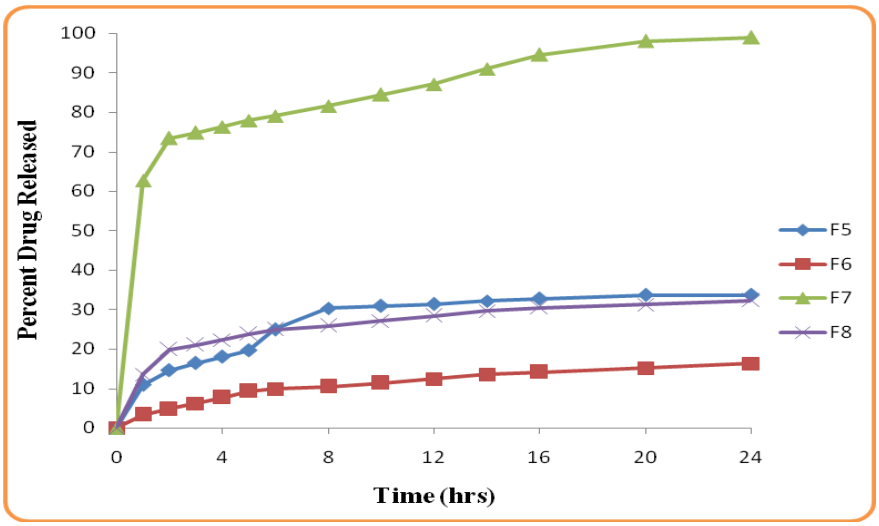

FIGURE IV: Famciclovir released profiles (Tamarind Gum as a Polymer) of F5 to F8

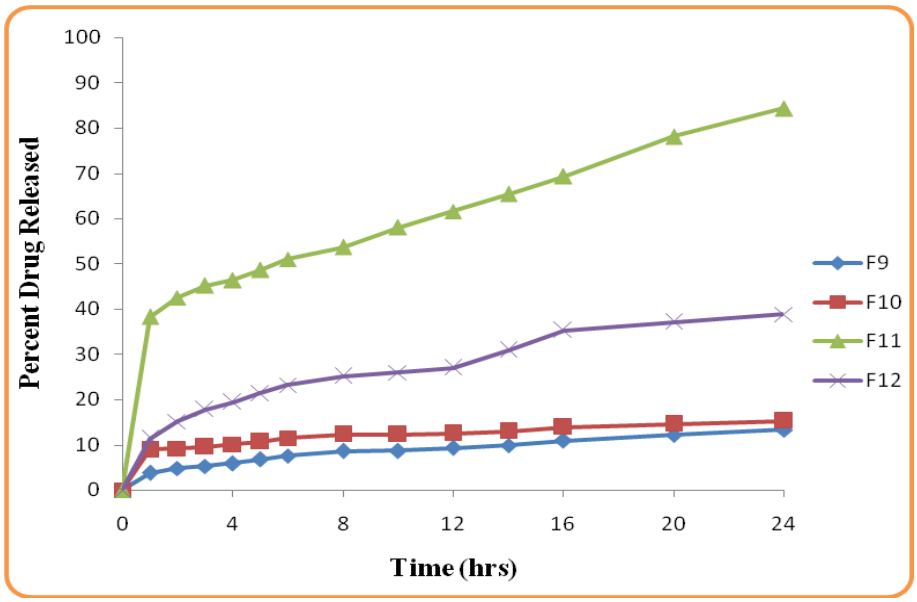

FIGURE V: Famciclovir released profiles (Guar Gum as a Polymer) of F9 to F12

ISSN: 0975-8585

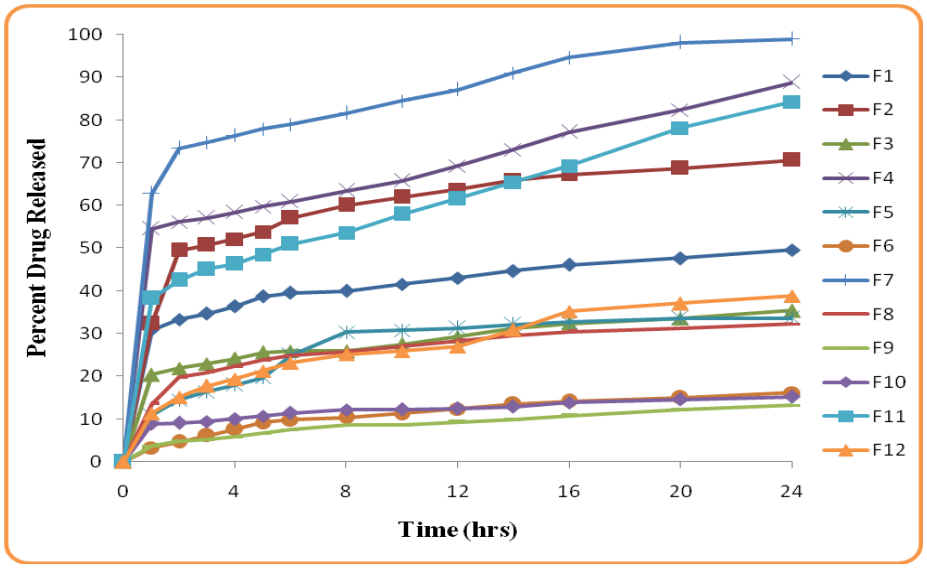

FIGURE VI: Comparison of Famciclovir released profiles for F1 to F12

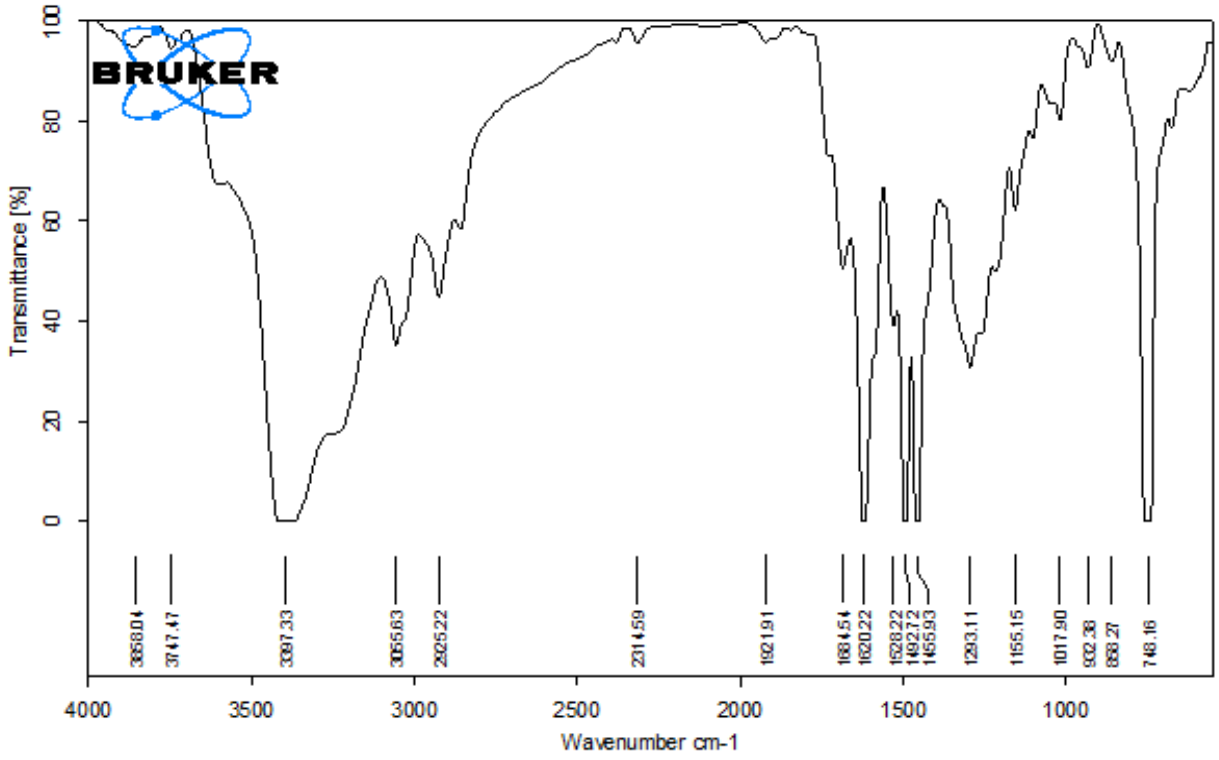

FIGURE VII: FTIR Spectrum of pure Famciclovir

ISSN: 0975-8585

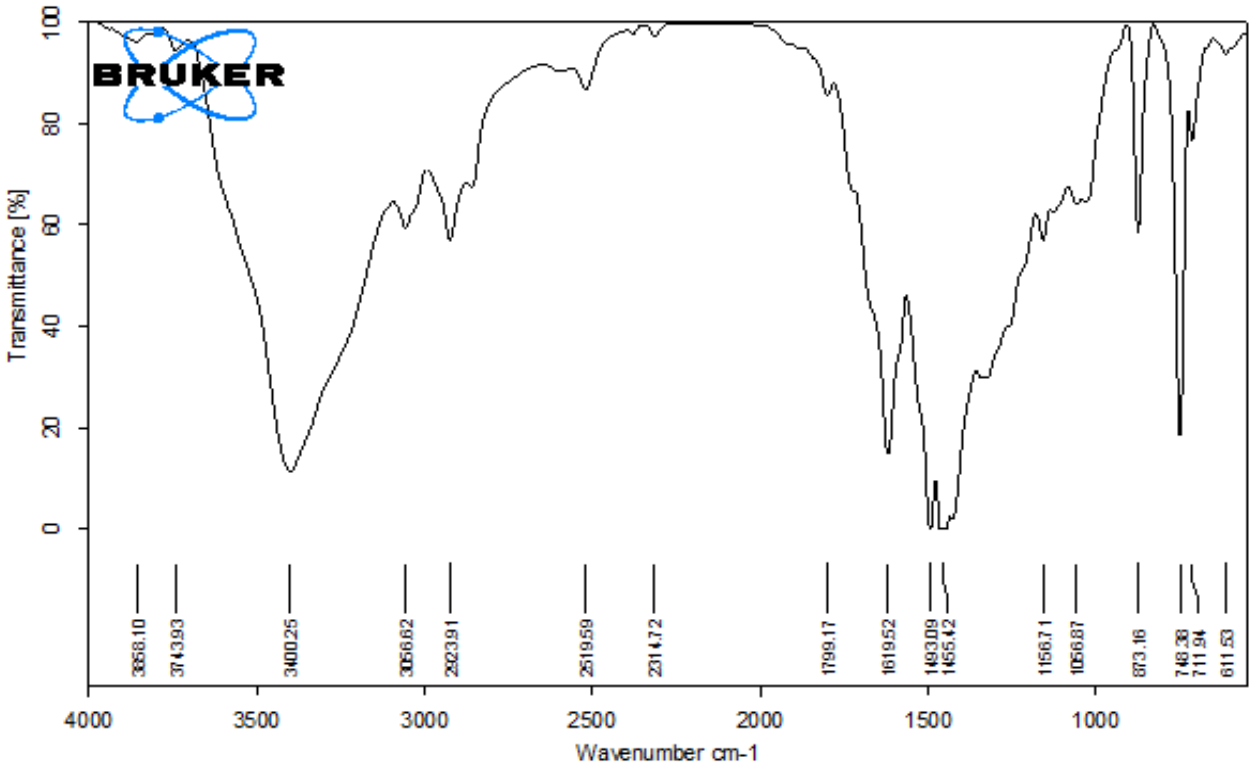

FIGURE VIII: FTIR Spectrum of Famciclovir and Polymers

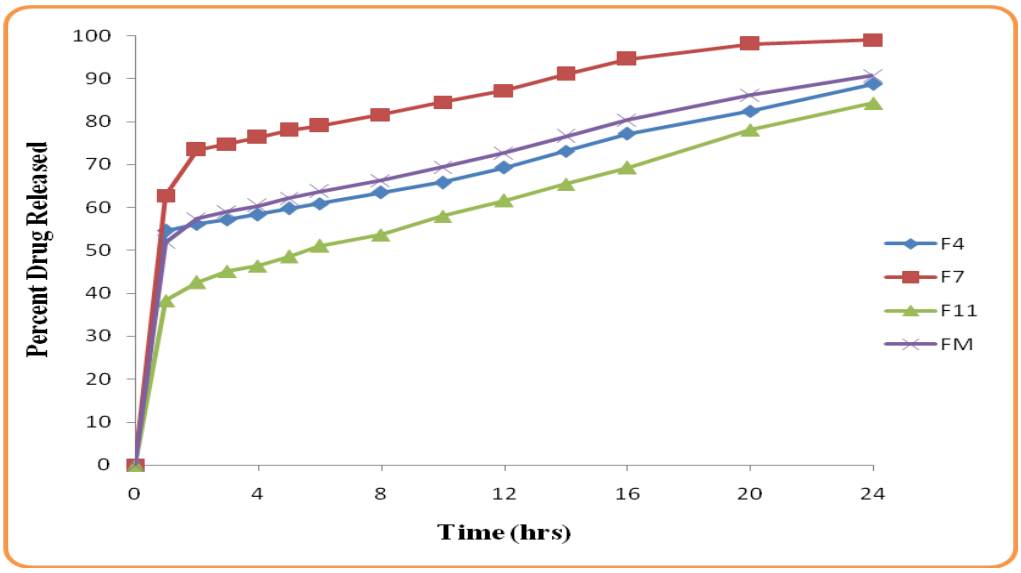

FIGURE IX: Comparison of the in vitro release of optimized formulations (F4, F7, F11) with market formulation (FM)

CONCLUSION

The present work to aim the formulation and evaluation of Famciclovir sustained released matrix tablets by direct compression technique. In this technique natural polymers like Xanthan gum, Tamarind gum and Guar gum were used as polymers for drug released upto extended time period. The Formulations F7 found to satisfy the desired criteria for Famciclovir released form matrix formulation. The Famciclovir released from matrix formulation and released mechanism followed for "first order kinetics & fickian transport mechanism" respectively. Finally to achieve a Famciclovir sustain released matrix tablets and drug released up to 24 hrs. Comparison of the optimized formulation (F7) with market formulation (FM) was shown in Figure IX.

ISSN: 0975-8585

REFERENCES

[1] M. George, I.V. Grass, and J.R. Robinson. “Sustained and controlled release drug delivery systems” Marcel Dekker, Newyork., 1978: 124-127.

[2] B. Mishra, J. Seena, S. Singh and C. Sankar. “Development & characterization of matrix tablets of ketorolac trometh amine. Indian pharm. 2003: 2: 86-89.

[3] K.R. Reddy, S. Mutalik and S. Reddy. “Formulation and in vitro evaluation of sustained release nicorandil matrix tablets.” AAPS pharm sci tech, 2003: 4(4): 480-488.

[4] S.K. Tyring, and R.A. Barbarash. "Famciclovir for the treatment of acute herpes zoster: Effects on acute disease and postherpetic neuralgia". Annals of Internal Medicine, 1995: 123 (2): 89-96.

[5] A.D. Luber, and J.F. Flaherty. "Famciclovir for treatment of herpesvirus infections". Annals of Pharmacotherapy. 1996: 30 (9): 978-985.

[6] S.L. Spruance and N. Bodsworth. "Single Dose, Patient-initiated Famciclovir: A Randomized, Double-blind, Placebo-controlled trial for episodic treatment of herpes labialis". Journal of the American Academy of Dermatology. 2006: 55 (1): 47-53.

[7] G. Bumphrey. ‘Extremely useful’ new suspending agent. Pharm J, 1986: 237: 665-671.

[8] B.K. Evans, Fenton May V. Keltrol (Letter). Pharm J. 1986: 237: 736-737.

[9] J.K. Chollet, M.J. Jozwiakowski, and K.R. Phares. Development of a topically active imiquimod formulation. Pharm Dev Technol, 1999: 4(1): 35-43.

[10] X.Q. Wang, Jia Huang, Jun dong Dai and Tao Zhang. “Long-term studies on the stability and oral bioavailability of cyclosporine A nanoparticle colloid”. Int J Pharm, 2006: 322(1-2): 146-153.

[11] M. Gabriels and Plaizier Vercammen. “J. Experimental designed optimisation and stability evaluation of dry suspensions with artemisinin derivatives for paediatric use”. Int J Pharm. 2004: 283(1-2): 19-34.

[12] V.B. Junyaprasert, and G. Manwiwattanakul. “Release profile comparison and stability of diltiazem resin microcapsules in sustained release suspensions”. Int J Pharm, 2008: 352 (1-2): 81-91.

[13] Al Saiden SM, Y.S. Krishnaiah, V. Satyanarayana, P. Bhaskar, and R.S. Karthikeyan. “Pharmacokinetic evaluation of guar gum based three layer matrix tablets for oral controlled delivery of highly soluble metoprolol tartrate as a model drug”. European Journal of Pharmaceutics and Biopharmaceutics, 2004: 58(3): 697-703.

[14] P. Khullar, R.K. Khar, and S.P. Agarwalet. “Guar gum as a hydrophilic matrix for preparation of theophylline controlled release dosage form”. Indian Journal of Pharmaceutical Sciences, 1999: 61(6): 342-345.

[15] T. Higuchi. “Mechanism of Sustained action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. Journal of Pharmaceutical Sciences, 1963: 52: 1145-1149.

[16] R.W. Korsmeyer, R. Gurny, E. Doelker, P. Buri and N.A. Peppas. “Mechanisms of solute release from porous hydrophilic polymers”. International Journal of Pharmaceutics, 1983: 15(1): 25-35.