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Formulation and *in vitro* characterization of letermovir extended-release tablets

K. Madhavi, Mohammed Omar*, Ramya Sri. S

Department of Pharmaceutics, Arya College of Pharmacy, Sangareddy, Telangana, India.
SuraPharma Labs, Dilsukhnagar, Hyderabad, Telangana-500060, India.

Address of Correspondence: Mohammed Omar

ABSTRACT

The aim of the present work was to develop an extended-release dosage form of Letermovir. Letermovir is an antiviral drug for the treatment of cytomegalovirus (CMV) infections. Letermovir tablets were prepared using hydrophobic and hydrophilic polymers like Badham Gum, Cashew nut tree gum and synthetic polymers Eudragit L- 100 and HPMC K4M, prepared by direct compression method and evaluated for various pre and post compression parameters. Hydrophobic matrix tablets failed to prolong the drug release, whereas Hydrophilic based matrix tablets showed good drug release. Whereas from the dissolution studies it was evident that the formulation (F7) showed better and desired drug release pattern i.e., 99.10 % in 12 hours. It contains the Eudragit L- 100 as extended release material. It followed peppas release kinetics mechanism.

Keywords: Letermovir, Badham Gum, Cashew nut tree gum, Eudragit L- 100, HPMC K4M, direct compression and Extended release system.

INTRODUCTION

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are 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. [1,2] There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug. If one were to develop an ideal drugdelivery system, two pre-requisites would be required: Firstly single dose for the duration of treatment whether for days or weeks as with infection, diabetes orhypertension. Second it should deliver the active entity directly to the site of action minimizing the side effects.

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.[3]

Extended release formulations make the drug available over extended time period after oral administration. The extended release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. By incorporating the dose for 24 hrs into one tablet/capsule from which the drug is released slowly. This formulation helps to avoid the side effects associated with low and high concentrations. The ideal drug delivery system should show a constant zero-order release rate and maintain the constant plasma concentrations.

It is desirable to maintain a therapeutic blood concentration in order to achieve the desirable pharmacological effects. To maintain a narrow range of therapeutic blood concentration it is desirable to have a dosage form that can deliver the drug in a more sustainable or controlled way to achieve the desired results. Extended release tablets and capsules are commonly taken 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 drugs that promptly produces the desired therapeutic effect, followed by gradual release of additional amount of drugs to maintain this effect over a predetermined period. The sustained plasma drug levels provided by extended release products often eliminate the need for night dosing, which benefits not only the patient but the patient but the caregiver as well.[4]

MATERIALS AND METHODS

Letermovir Procured From Aurobindo Pharma Pvt Ltd, India, Provided by SURA LABS, Dilsukhnagar, Hyderabad. Badham Gum from Merck Specialities Pvt Ltd, Mumbai, India. Cashew nut tree gum from Merck Specialities Pvt Ltd, Mumbai, India. Eudragit L- 100 from Merck Specialities Pvt Ltd, Mumbai, India. HPMC K4M from Merck Specialities Pvt Ltd, Mumbai, India. PVP K 30 from Merck Specialities Pvt Ltd, Mumbai, India. MCC102 from Merck Specialities Pvt Ltd, Mumbai, India. Mg. stearate from Merck Specialities Pvt Ltd, Mumbai, India. Talc from Merck Specialities Pvt Ltd, Mumbai, India.

METHODOLOGY

Analytical method development

Buffer Preparation

Preparation of 0.2M Potassium dihydrogen orthophosphate solution: Accurately weighed 27.218 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000mL of distilled water and mixed.

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

Preparation of pH 6.8 Phosphate buffer: Accurately measured 250ml of 0.2M potassium

Dihydrogen ortho phosphate and 112.5 ml 0.2M NaOH was taken into the 1000ml volumetric flask. Volume was made up to 1000ml with distilled water.

a) Determination of absorption maxima

100mg of Letermovir pure drug was dissolved in 100ml of 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with 100 ml by using 0.1 N HCL (stock solution-2 i.e 100µg/ml). From this 10ml was taken and make up with 100 ml of 0.1 N HCL (10µg/ml). Scan the 10µg/ml using Double beam UV/VIS spectrophotometer in the range of 200 – 400 nm.

b) Preparation calibration curve

100mg of Letermovir pure drug was dissolved in 15ml of Ethanol and volume make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCl (stock solution-2 i.e 100µg/ml). From this take 0.2, 0.4, 0.6, 0.8 and 1 ml of solution and make up to 10ml with 0.1N HCL to obtain 2, 4, 6, 8 and 10 µg/ml of Letermovir per ml of solution. The absorbance of the above dilutions was measured at 262nm 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.

Formulation development of Extended release Tablets

All the formulations were prepared by direct compression method. The compositions of different formulations are given in Table 1. The tablets were prepared as per the procedure given below and aim is to prolong the release of Azilsartan.

Procedure

1) Letermovir and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Table 1: Formulation of Extended release tablets

INGREDIENTS (MG)	FORMULATION CODES											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Letermovir	240	240	240	240	240	240	240	240	240	240	240	240
Badham Gum	100	200	300	-	-	-	-	-	-	-	-	-
Cashew nut tree gum	-	-	-	100	200	300	-	-	-	-	-	-
Eudragit L- 100	-	-	-	-	-	-	100	200	300	-	-	-
HPMC K4M	-	-	-	-	-	-	-	-	-	100	200	300
PVP K 30	10	10	10	10	10	10	10	10	10	10	10	10
MCC102	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Mg. stearate	8	8	8	8	8	8	8	8	8	8	8	8
Talc	9	9	9	9	9	9	9	9	9	9	9	9
Total Weight (mg)	650	650	650	650	650	650	650	650	650	650	650	650

Drug content

The amount of drug in tablet was important for to monitor from tablet to tablet, and batch to batch is to evaluate for efficacy of tablets. For this test, take ten tablets from each batch were weighed and powdered. Weighed equivalent to the average weight of the tablet powder and transferred into a 100 ml volumetric flask and dissolved in a suitable quantity of media. The solution was made up to the mark and mixed well. Then filter the solution. A portion of the filtrate sample was analyzed by UV spectrophotometer.

In vitro drug release studies

Apparatus --USP-II, Paddle Method
Dissolution Medium -- 0.1 N HCl, p H 6.8 Phosphate buffer
RPM --50
Sampling intervals (hrs)--0.5,1,2,3,4,5,6,7,8,10,11 and 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 media 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. Then 0.1 N HCl was replaced with pH 6.8 phosphate buffer and process was continued up to 12 hrs at 50 rpm. At specific time intervals, withdrawn 5 ml of sample and again 5ml media was added to maintain the sink condition. Withdrawn samples were analyzed at wavelength of drug using UV-spectrophotometer.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

Drug excipient interaction studies are significant for the successful formulation of every dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the assessment of physicochemical compatibility and interactions, which helps in the prediction of interaction between drug and other excipients. In the current study 1:1 ratio was used for preparation of physical mixtures used for analyzing of compatibility studies. FT-IR studies were carried out with a bruker FTIR facility.

RESULTS AND DISCUSSION

The present work was designed to developing extended tablets of Letermovir using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method

Standard graph of Letermovir in 0.1N HCl

The scanning of the 10µg/ml solution of Letermovir in the ultraviolet range (200-400 nm) against 0.1 N HCl blank gave the λ_{max} as 262nm. The standard concentrations of Letermovir (2-10µg/mL) prepared in 0.1N HCl showed good linearity with R^2 value of 0.998, which suggests that it obeys the Beer--Lamberts law.

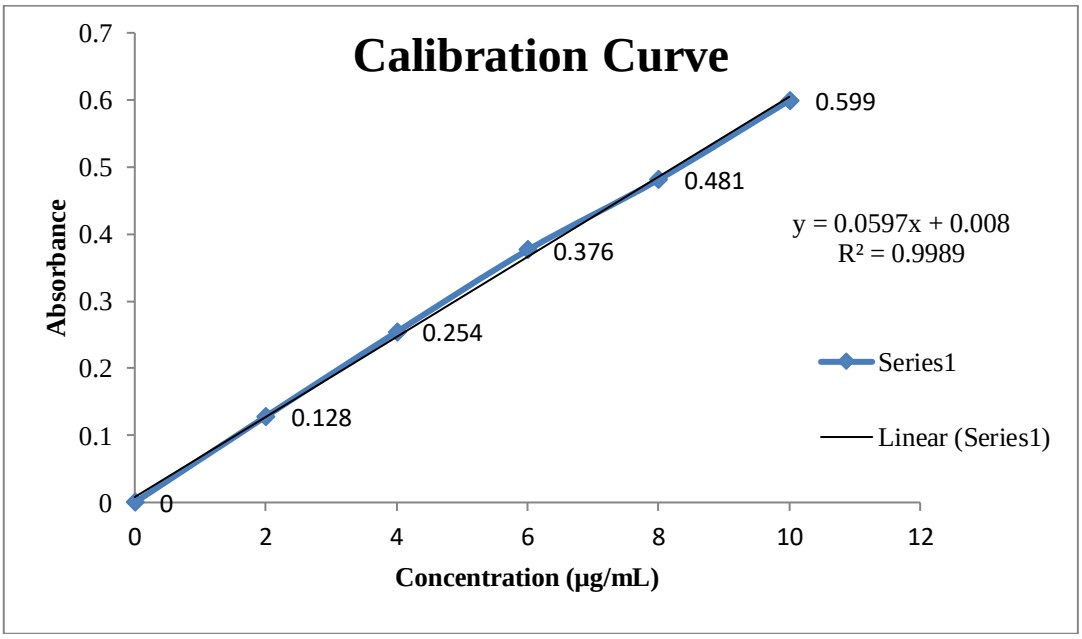

Fig 1: Calibration curve of Letermovir in 0.1 N HCl at 262 nm

Standard Curve of Letermovir in Phosphate buffer pH 6.8

The scanning of the 10µg/ml solution of Letermovir in the ultraviolet range (200-400nm) against 6.8 pH phosphate buffer as blank gave the λ_{max} as 264 nm. The standard concentrations of Letermovir (2-10µg/ml) prepared in 6.8 pH phosphate buffer showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

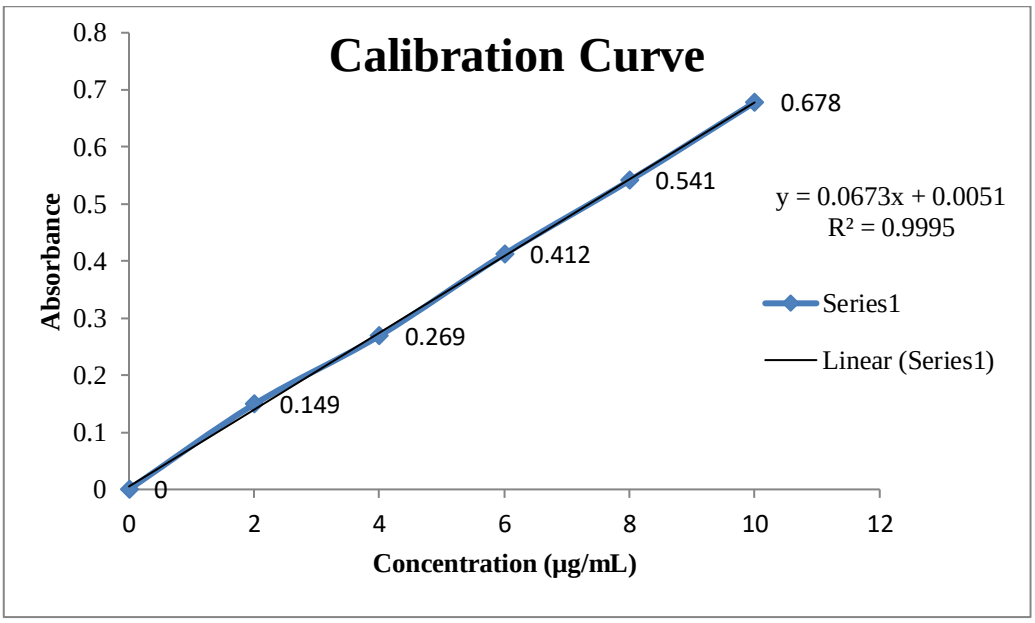

Fig 2: Calibration of Letermovir in Phosphate buffer pH 6.8

EVALUATION PARAMETERS

Pre-compression parameters

Table 6: Pre-compression parameters of powder blend

Formulation Code	Pre-compression parameters of powder blend				
	Angle of Repose	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner's Ratio
F1	25.8^0	0.532	0.657	19.45	1.17
F2	27.5^0	0.476	0.594	25.22	1.24
F3	29.5^0	0.456	0.633	27.51	1.38
F4	29.7^0	0.488	0.685	24.84	1.40
F5	29.9^0	0.461	0.661	27.75	1.43
F6	26.8^0	0.588	0.720	22.24	1.22
F7	27.3^0	0.567	0.705	18.33	1.24
F8	28.4^0	0.543	0.711	17.13	1.30
F9	29.6^0	0.477	0.660	23.52	1.38
F10	30.5^0	0.449	0.654	21.44	1.45
F11	30.3^0	0.484	0.698	18.71	1.44
F12	29.2^0	0.503	0.685	17.83	1.36

Tablet powder blend was subjected to various pre-compression parameters. The angle of repose values was showed from 25.8^0 to 30.5^0; it indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.449 -0.588 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.594 - 0.720 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 17.13 to 27.75 which showed that the powder has good flow properties. All the formulations were showed the hausner ratio ranging from 1.17 to 1.45 indicating the powder has good flow properties.

Post Compression parameters for tablets

Table 7: Post compression parameters of tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	648.53	5.2	0.24	5.15	98.32

F2	647.82	4.9	0.63	5.65	97.56
F3	649.31	4.6	0.41	5.41	98.75
F4	646.96	5.1	0.46	5.82	98.11
F5	649.20	5.8	0.30	5.44	98.24
F6	647.18	4.7	0.42	5.50	98.57
F7	648.37	4.5	0.21	5.82	98.46
F8	649.56	5.0	0.46	5.46	97.20
F9	648.75	4.3	0.52	5.28	96.38
F10	647.60	4.9	0.64	5.19	97.90
F11	648.10	5.2	0.42	5.22	98.51
F12	649.83	4.1	0.16	5.64	95.72

Weight variation and thickness

All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table 7. The average tablet weight of all the formulations was found to be between 646.96 to 649.83**.** The maximum allowed percentage weight variation for tablets weighing >650 mg is 1.5% and no formulations are not exceeding this limit. Thus all the formulations were found to comply with the standards given in I.P. And thickness of all the formulations was also complying with the standards that were found to be between 5.15 to 5.82.

Hardness and friability

All the formulations were evaluated for their hardness, using monsanto hardness tester and the results are shown in table 7. The average hardness for all the formulations was found to be between **(**4.1 to 5.8**)** Kg/cm^2 which was found to be acceptable. Friability was determined to estimate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the formulations were evaluated for their percentage friability using roche friabilator and the results were shown in table 7. The average percentage friability for all the formulations was between 0.16 and 0.64, which was found to be within the limit.

Drug content

All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown in table 7. The drug content values for all the formulations were found to be in the range of **(**95.72to 98.75**).** According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the FDT formulations comply with the standards given in IP.

In vitro *drug release studies*

The formulations prepared with different natural polymers by wet granulation method. The tablets dissolution study was carried out in paddle dissolution apparatus using 0.1N HCl for 2 hours and 6.8 pH phosphate buffers for remaining hours as a dissolution medium.

Table 8: Dissolution Data of Letermovir Tablets

TIME (H)	CUMULATIVE PERCENT DRUG RELEASED											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
0.5	10.58	14.79	18.58	21.51	08.85	11.38	33.60	17.86	10.31	12.59	20.15	07.51
1	18.31	16.14	20.89	27.37	12.43	16.52	38.19	20.62	15.10	20.13	23.96	16.39
2	26.15	28.70	28.37	30.14	19.99	21.81	49.52	27.31	22.68	28.35	30.36	21.04
3	32.28	36.57	35.21	43.71	26.51	27.68	53.96	30.53	30.78	32.52	35.98	27.58
4	40.98	39.96	42.79	48.96	31.97	35.50	60.37	37.94	35.48	38.98	41.99	34.65
5	45.65	44.25	47.65	57.21	38.74	37.49	67.82	48.36	41.94	43.11	45.69	41.21
6	51.23	53.57	56.35	60.15	43.59	43.21	72.65	53.78	46.87	45.95	50.99	46.57
7	63.82	58.12	63.17	65.89	50.24	48.15	79.29	60.33	52.10	49.31	57.10	52.78
8	70.65	61.24	68.20	70.64	56.30	53.25	81.66	63.39	60.87	54.68	62.98	60.14
9	76.87	66.59	79.48	75.40	61.25	57.92	84.25	67.59	65.85	58.29	65.74	63.97
10	80.41	70.17	85.90	85.76	66.71	62.79	90.33	71.48	70.32	66.91	79.90	68.72
11	84.05	89.56	90.10	91.24	72.95	65.57	96.21	76.55	73.92	78.39	85.81	71.49
12	90.79	96.32	98.14	96.46	87.20	71.83	99.10	84.95	79.40	81.89	97.89	75.35

From the dissolution data it was evident that the formulations prepared with Badham Gum as polymer were retarded the drug release more than 12 hours. Whereas the formulations prepared with lower concentration of Cashew nut tree gum retarded the drug release up to 12 hours in the concentration 100 mg. In higher concentrations the polymer was unable to retard the drug release. The Formulation Containing Eudragit L- 100 in 100 mg Concentration Showed good retarding

nature with required drug release in 12 hours i.e 99.10 %. Whereas the formulations prepared with lower concentration of HPMC K4M retarded the drug release up to 12 hours in the concentration 200 mg. In higher concentrations of the polymer was unable to retard the drug release.

Hence from the above dissolution data it was concluded that F7 formulation was considered as optimised formulation because good drug release (99.10%) in 12 hours.

Application of Release Rate Kinetics to Dissolution Data

Table 9: Release kinetics data for optimised formulation (F7)

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			2.000				100	4.642	4.642	0.000
33.6	0.5	0.707	1.526	-0.301	1.822	67.200	0.0298	-0.474	66.4	4.642	4.049	0.592
38.19	1	1.000	1.582	0.000	1.791	38.190	0.0262	-0.418	61.81	4.642	3.954	0.688
49.52	2	1.414	1.695	0.301	1.703	24.760	0.0202	-0.305	50.48	4.642	3.696	0.946
53.96	3	1.732	1.732	0.477	1.663	17.987	0.0185	-0.268	46.04	4.642	3.584	1.058
60.37	4	2.000	1.781	0.602	1.598	15.093	0.0166	-0.219	39.63	4.642	3.409	1.232
67.82	5	2.236	1.831	0.699	1.508	13.564	0.0147	-0.169	32.18	4.642	3.181	1.461
72.65	6	2.449	1.861	0.778	1.437	12.108	0.0138	-0.139	27.35	4.642	3.013	1.629
79.29	7	2.646	1.899	0.845	1.316	11.327	0.0126	-0.101	20.71	4.642	2.746	1.895
81.66	8	2.828	1.912	0.903	1.263	10.208	0.0122	-0.088	18.34	4.642	2.637	2.004
84.25	9	3.000	1.926	0.954	1.197	9.361	0.0119	-0.074	15.75	4.642	2.507	2.135
90.33	10	3.162	1.956	1.000	0.985	9.033	0.0111	-0.044	9.67	4.642	2.130	2.511
96.21	11	3.317	1.983	1.041	0.579	8.746	0.0104	-0.017	3.79	4.642	1.559	3.082
99.1	12	3.464	1.996	1.079	-0.046	8.258	0.0101	-0.004	0.9	4.642	0.965	3.676

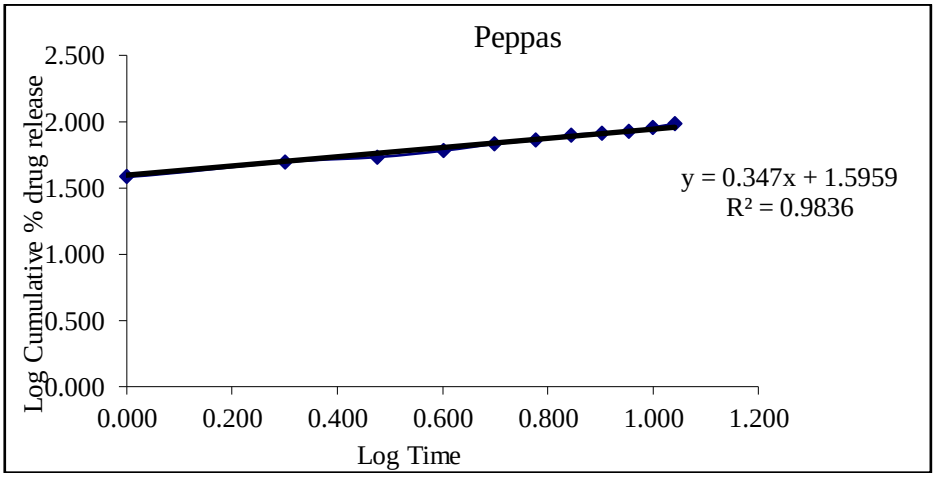

Fig 3: Graph of peppas release kinetics

Optimised formulation F7 was kept for release kinetic studies. From the above graphs it was evident that the formulation F7 was followed peppas release mechanism.

Drug and Excipient Compatability Studies
FTIR STUDY

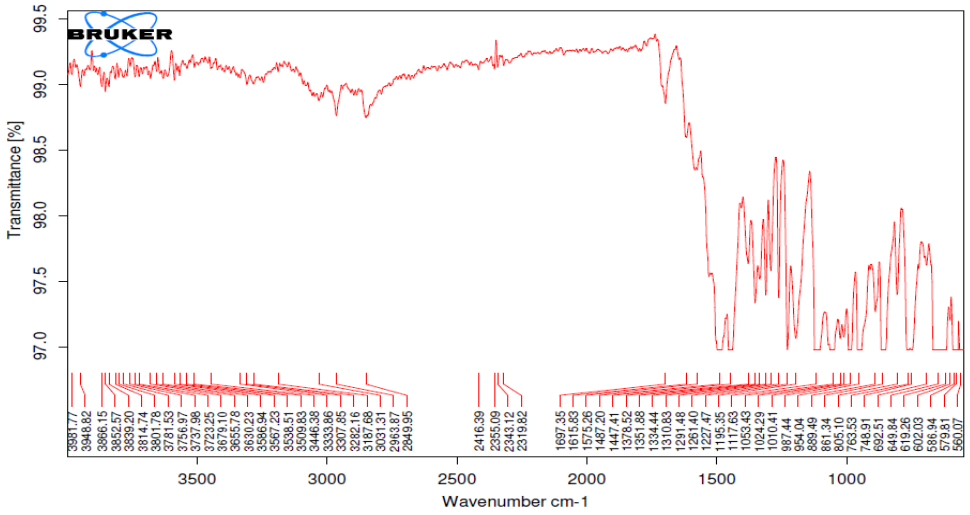

Fig 4: Ftir graph of pure drug of Letermovir

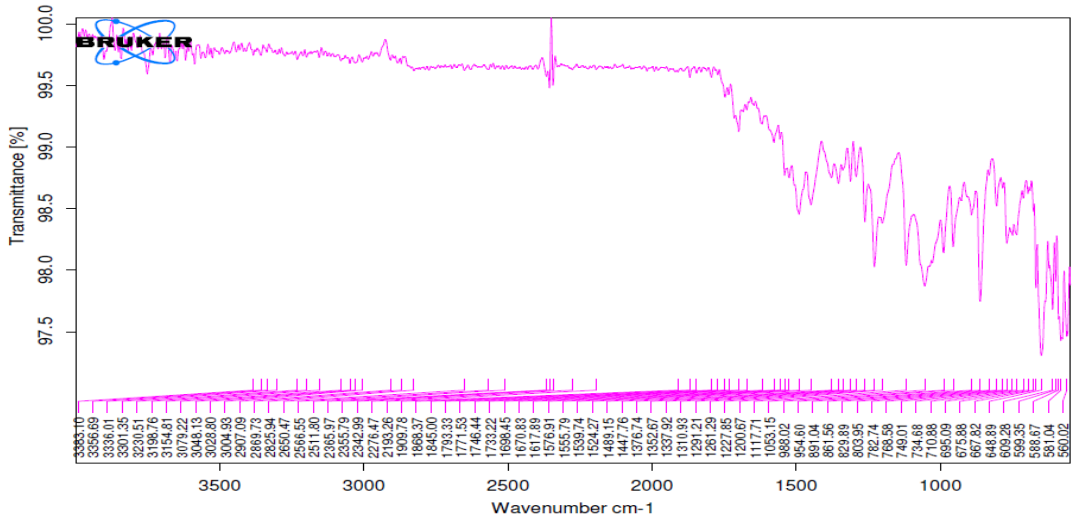

Fig 5: FTIR Spectrum of optimised formulation

From the above studies it was found that there was no shifting in the major peaks which indicated that there were no significant interactions occurred between the Letermovir and excipients used in the preparation of different Letermovir extended release formulations. Therefore the drug and excipients are compatible to form stable. Formulations under study, The FTIR spectra of Letermovir and physical mixture used for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence they were compatible.

CONCLUSION

The results of the study demonstrate that natural polymers Badham Gum, Cashew nut tree gum and synthetic polymers Eudragit L- 100 and HPMC K4M. It is evident from the results that an extended tablet prepared with combination of natural and synthetic polymer is a better system for 12 hr extended release of a highly ethanol soluble drug like Letermovir. All the formulations were prepared by direct compression method. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. FTIR studies concluded that there is no drug-polymer interaction. *In vitro* dissolution studies showed extended released 99.10 % 12 hours, the optimized formulation, F7 which contained Eudragit L- 100 has shown *in vitro* Letermovir release up to 12 hours. Followed by peppas diffusion mechanism and the formulations maintained integrity throughout the dissolution study.

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