ejpmr, 2019,6(1), 410-419

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

FORMULATION AND EVALUATION OF RAFT FORMING TABLETS OF LAMIVUDINE

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Article Received on 01/11/2018 **Article Revised on 22/11/2018** **Article Accepted on 12/12/2018**

ABSTRACT

The aim of the current project was to formulate and evaluate **raft forming tablets** containing lamivudine as an **API.** It is a nucleoside reverse transcriptase inhibitor (NRTI), belonging to the class of organic compounds known as 3'-thia pyrimidine nucleosides. It is an anti-retro viral medication used in the treatment and prevention of HIV/AIDS and chronic Hepatitis B. Raft forming tablets were developed to prolong the gastric residence time, increase drug absorption, patient compliance and to decrease the dosing frequency thus decrease the risk of drug resistance and toxicity. Lamivudine tablets were prepared by direct compression method using various polymers such as HPMC, luctoman, sodium alginate, carbopol. In order to study the interaction between drug and selected excipients FT-IR and DSC studies were carried out. Fourteen different formulations of lamivudine were prepared using different ratios of polymers. The formulations formed were examined for hardness, thickness, friability, weight variation, drug content uniformity, % cumulative drug release, *in-vitro* buoyancy studies, raft strength etc. The formulation FLS1 showed highest percentage drug release for a prolonged period of 8 hrs. The drug release mechanism of the optimized formulation was studied by fitting the acquired drug release data into various kinetic models. The release profile was found to be best fitted in zero order model with an R^2 value of 0.998. The n value for the Korsmeyer- peppas model was found to be >0.89, thus declaring that the drug release mechanism followed was super case II transport. Stability studies were performed on FLS1 for a period of 3 months and was found to be stable.

KEYWORDS: lamivudine, RDDS, raft strength, buoyancy studies.

INTRODUCTION

Raft forming systems

It is a novel approach of GRDDS. The synonym of raft is a flat configure, usually built of logs or barrels that sails on water. Here also, we are reflecting upon a dosage form that drifts on gastric liquid of stomach.[1]

The method involved in raft growth is the development of a viscous cohesive gel in contact with the gastric juices, wherein every portion of the dosage form expands forming raft.[2] Caco3 is used as raft strengthener.[3] The calcium ions liberated by it interact with sodium alginate to produce an insoluble gel.[4] Diverse polymers, principally various polysaccharides are used as raft forming agents ex: xanthan gum, carbopol, alginicacid, pectin, chitosan, isapgol and sodium alginate.[5]

Raft drifts on the gastric juices because of its low bulk density created by co_2 formation.

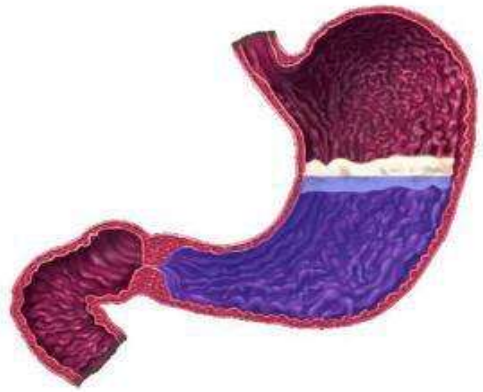

Fig. I: raft formation.

It is a nucleoside reverse transcriptase inhibitor (NRTI) and zalcitabine analog. It is an anti-retroviral medication used to prevent, treat HIV/AIDS and chronic hepatitis B. The half life ($t_{1/2}$) and protein binding are the major considerations for formulation of a sustained release dosage form. The plasma protein binding is 36% which are considerably low making it suitable to be formulated as sustained release raft forming tablets.

The current experiment is aimed at prolonging the gastric residence time, increasing drug absorption, patient compliance, decreasing the dosing frequency thus decreasing the risk of drug resistance and toxicity.

MATERIALS AND METHODOLOGY

Materials

Lamivudine was received from Nicholas Priamal, Telangana. $NaHCO_3$, $CaCO_3$, Anhydrous lactose, MCC, HPMC K100M, Sodium alginate, carbopol, Magnesium stearate and talc were obtained from S.D. Fine chemicals, Mumbai. Luctoman was received as gift sample from lucid pharmaceuticals, Hyderabad.

Preparation of raft forming floating tablets

Lamivudine raft forming floating tablets were prepared by direct compression technique. Accurately weighed quantities of lamivudine, $NaHco_3$, $CaCo_3$, MCC, HPMC K100M, luctoman (modified guar gum), sodium alginate, guar gum, lactose monohydrate (diluents) were sifted through # 60 to get uniform size particles. All the ingredients were mixed thoroughly in a blender. After sufficient blending, talc (glidant) and magnesium stearate (lubricant) were added and mixed further for few minutes. The blended mixture was compressed/punched into tablets weighing 500mg, using tablet punching machine with 6mm round punches by CADMACH Machinery.

Table I: Composition of lamivudine tablets with combination of HPMC, Sodium alginate and carbopol (mg).

Ingredients	FHS1	FHS2	FHS3	FHS4	FHC1	FHC2	FHC3	FHC4
Lamivudine	100	100	100	100	100	100	100	100
$NaHCO_3$	50	50	50	50	50	50	50	50
$CaCO_3$	25	25	25	25	25	25	25	25
Lactose monohydrate	115	105	95	85	140	130	120	110
MCC	50	50	50	50	50	50	50	50
Mg stearate	5	5	5	5	5	5	5	5
Talc	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
HPMC K100M	50	60	70	80	50	60	70	80
Sodium alginate	100	100	100	100	-	-	-	-
Carbopol	-	-	-	-	75.0	75.0	75.0	75.0

Table II: Lamivudine tablets with combination of luctoman, sodium alginate, carbopol (mg).

Ingredients	FLC1	FLC2	FLC3	FLS1	FLS2	FLS3
Lamivudine	100	100	100	100	100	100
$NaHCO_3$	50	50	50	50	50	50
$CaCO_3$	25	25	25	25	25	25
Lactose monohydrate	140	115	90	115	90	65
MCC	50	50	50	50	50	50
Mg stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Luctoman	50	75	100	50	75	100
Sodium alginate	-	-	-	100	100	100
Carbopol	75	75	75	-	-	-

Pre compression evaluation studies

Angle of repose

It is defined as the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. It is used to compute the frictional forces between the voluminous powder and granules.

$$\Theta = Tan^{-1} (h/r)$$

Where Θ = angle of repose, h = height of pile, r = radius of pile

A funnel was filled with the powdered blend of drug excipient mixture. The mixture was allowed to slip away gradually and smoothly through the orifice of the funnel, which formed a pile/heap on the graph sheet positioned below it. The radius and the height of the pile were measured using a scale and angle of repose was calculated.

Bulk density

A precisely weighed quantity of the powder was gently poured into a graduated measuring cylinder and the volume was noted as V_i (bulk volume).

Bulk density= mass of powder/bulk volume

Tapped density

The graduated cylinder filled with powder was clogged with a lid and was sited into the tap density tester for 100 tabs. The volume was noted when two consecutive readings were found to be the same.

Tapped density = mass of powder/tapped volume

Hausner's ratio and carr's index are calculated by the following formula

Hausner's ratio = Td/Bd

Carr's index = TD-BD/TD×100

Drug excipient interaction studies

Fourier transform infrared (FTIR) spectroscopy

FTIR spectra of the pure drug (lamivudine) and the drug – excipient mixture were obtained by using KBr mixing method on transform infrared spectrophotometer. Samples were prepared by using KBr discs by means of hydraulic pellet press at a pressure of 7- 10 tons.

Differential scanning calorimetry

Temperature calibrations were carried out using indium as standard. A sealed empty pan analogous to sample pan was used as reference.DSC spectra of pure drug and drug – excipient composite mixture was recorded. The samples were heated in a hermetically sealed aluminium pans from 30 – 400^0c at a heating rate of 10^0c/min using nitrogen as blank gas.[6]

Post compression evaluation studies

Weight variation

This test is carried out to ensure equivalency of weight in a batch of tablets. The individual weight of 10 tablets from each formulation was determined precisely and the average weight was calculated. The weight variation was calculated using the following formula:

% Wt variation = Average wt- Individual wt/Average wt ×100

Tablet thickness

Thickness is a key factor for uniformity of tablet size. Digital vernier caliper was used to compute the thickness of three deliberately selected tablets from each formulation.

Tablet hardness: Monsanto and Pfizer hardness tester were used to determine the hardness.

Tablet friability

Initially twenty tablets were accurately weighed (W_o) and placed in the Roche's friabilator, which revolves at 25rpm, tumbling the tablets from a height of 6 inches. After 4 minutes the tablets were withdrawn, dusted and reweighed (w_1).

$$\%F = (W_O - W_1/W_O) \times 100$$

Where W_o = wt of tablet before test, w_1 = wt of tablet after test

Drug content estimation

The drug content in each formulation was determined by taking a 500 mg tablet and triturating it in a mortar and pestle. Powder equivalent to 100mg of drug was taken and added in a 100ml volumetric flask containing 0.1N HCL. The volume was made up to 100ml with 0.1N buffer. It was stirred for 30 minutes on a magnetic stirrrer and filtered to remove the excipients. 1ml of the above solution was taken and absorbance was measured at λ_{max} 270nm and the content of lamivudine was calculated from the standard graph.

***In-vitro* buoyancy studies**

Floating lag time

Time taken by the dosage form to ascend to the surface and float on top of the dissolution media was determined**.**

Total floating time

The time period for which the tablet remains floating/buoyant was measured.

Raft strength measurement

A 500mg tablet was powdered in a mortar and pestle. The powder was added to a 250ml beaker containing 150ml of 0.1N HCL kept at 37^0c. Each raft was allowed to form all-around an L shaped wire probe (diameter-1.2mm) held erect in the beaker throughout the whole period of 30 minutes of raft formation. Raft strength was determined using modified balance method. Water was added drop wise to the pan and the mass of water required to break down the raft was noted.[7]

Figure II: modified dispensing balance for raft strength measurement

***In-vitro* drug release studies**

Dissolution study was performed in USP type-II dissolution apparatus using 900ml of 0.1N HCL as dissolution media. The paddles were operated at 50rpm to stimulate gastric peristaltic movements and the temperature was maintained at 37± 0.5^0c. 1ml of sample was withdrawn at specified time intervals (1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, and 8) for 8hrs and replenished with equal volume of fresh dissolution media to maintain constant volume and sink conditions throughout the experiment. Each sample was diluted to 10ml with buffer and analyzed at 270nm using UV-Visible spectrophotometer.

Drug Release Kinetics

Following the drug release model approach, the drug release values of the optimized formulation were substituted in 5 popular models namely zero order, first order, Higuchi, Hixson Crowell and korsmeyer-peppas equation.[8]

Stability studies

To examine the drug and formulation stability, the studies were carried out according to ICH guidelines. The optimized formulation was stored in the

conditioning chamber, maintained at 75±5% RH, 40 ± 2^0C temperature for a period of 3 months. At periodic time intervals the samples were evaluated for the physical characteristics like hardness, friability, weight uniformity, drug content, *in-vitro* buoyancy and drug release at 1, 2 and 3 months respectively.

RESULTS AND DISCUSSION

Fourier Transform Infrared (FTIR) Spectroscopy

The FT-IR spectrum of pure drug, drug-excipient mixture was recorded. It was concluded that there was no significant shift in the spectral peaks of drug-excipient spectra in comparision with the pure drug spectra.

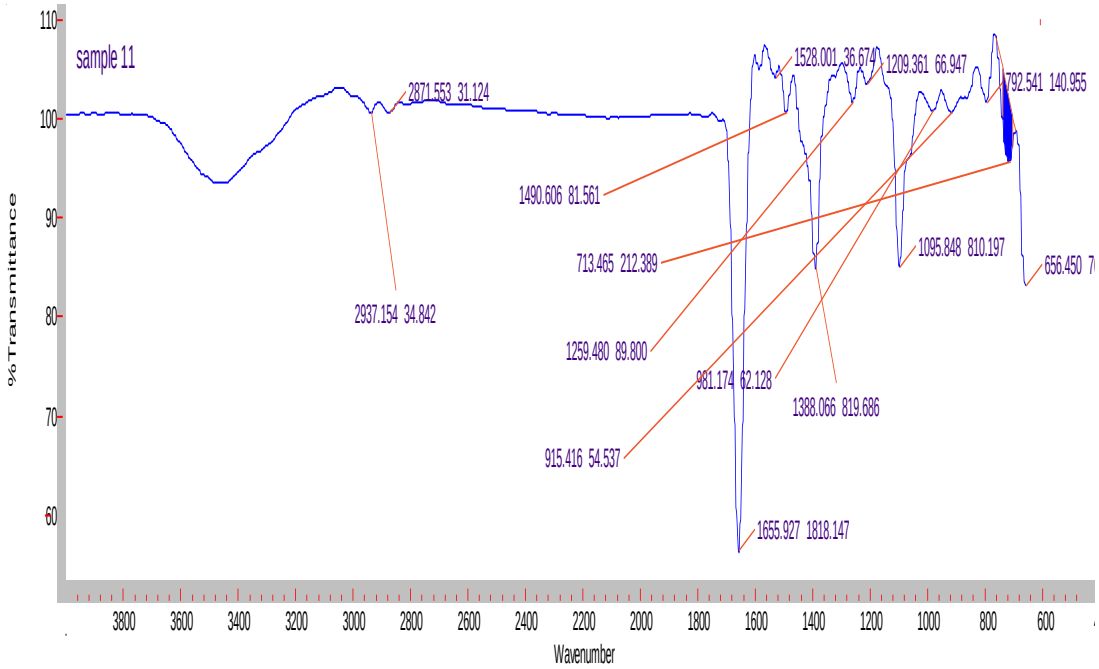

Fig. III: FTIR spectra of pure drug.

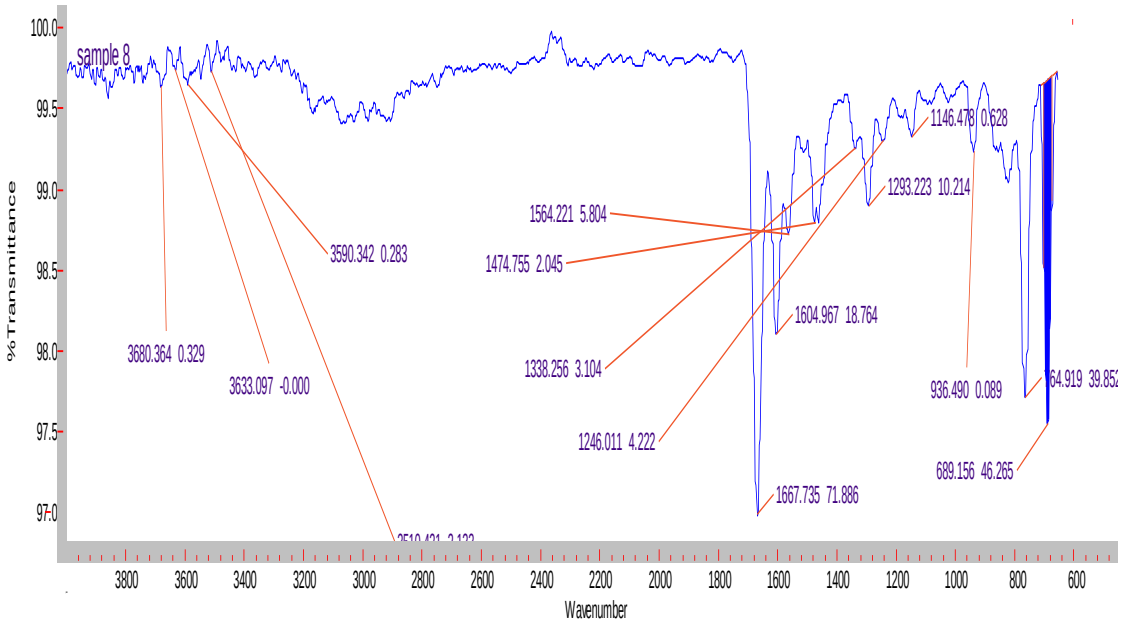

Fig. IV: FTIR spectra of physical mixture of Drug and Excipients.

Differential scanning calorimetry (DSC)

DSC thermogram of pure drug (lamivudine) exhibited an endothermic peak at 163.48^0c, corresponding to the melting point of drug. No varying endothermic peaks were detected in the pure drug, and drug-excipient mixture thermograms, thus ruling out the possibility of drug-excipient interaction and complexation.

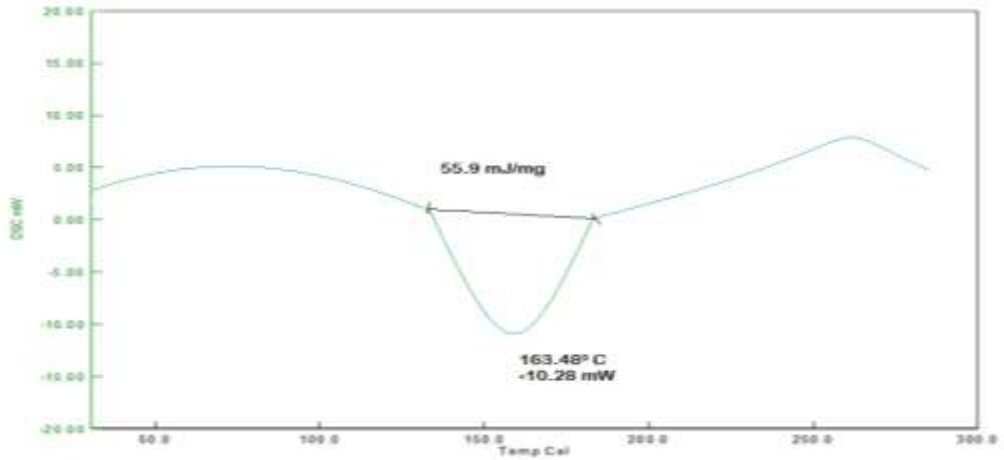

Fig. V: DSC Thermogram of pure lamivudine.

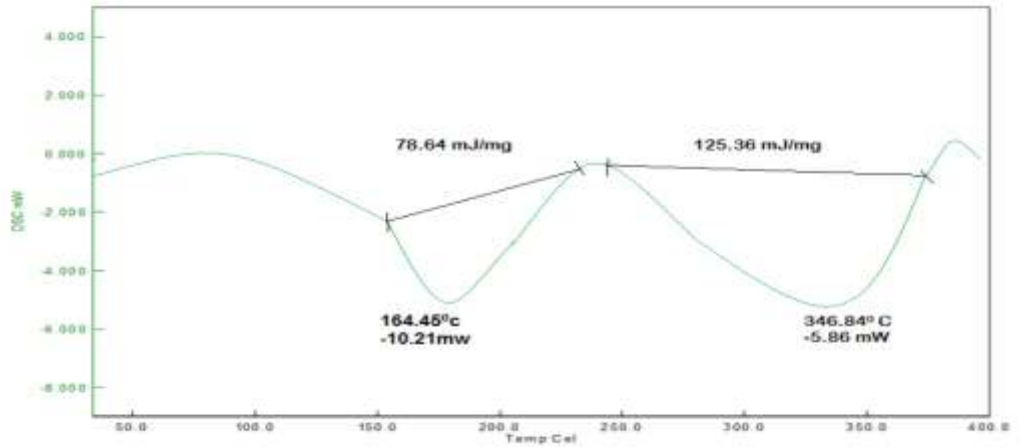

Fig. VI: DSC Thermogram of Drug Excipient mixture.

Pre compression evaluation results

Table III: a) Physico chemical properties of powdered blend with HPMC.

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio (kg/cm^2)	Carr's index (%)	Angle of repose (^{0})
FHS1	0.410±0.02	0.461±0.02	1.113±0.03	14.13±0.15	24.21±0.31
FHS2	0.422±0.01	0.512±0.02	1.106±0.01	12.43±0.28	25.12±0.60
FHS3	0.441±0.02	0.481±0.04	1.148±0.04	10.15±0.10	25.58±0.54
FHS4	0.432±0.03	0.522±0.03	1.201±0.04	9.98±0.62	22.11±1.04
FHC1	0.420±0.02	0.436±0.01	1.199±0.05	10.11±0.55	24.16±0.43
FHC2	0.425±0.05	0.444±0.03	1.011±0.02	14.63±0.42	23.58±1.08
FHC3	0.390±0.01	0.440±0.03	1.001±0.01	10.54±0.33	23.11±0.78
FHC4	0.399±0.03	0.481±0.01	1.21±0.03	9.19±0.45	21.14±0.65
±S.D = standard deviation (n=3)					

Physico chemical properties of powdered blend with Luctoman

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio (kg/cm^2)	Carr's index(%)	Angle of repose (^{0})
FLC1	0.391±0.01	0.478±0.02	1.280±0.03	16.32±0.18	19.64±0.14
FLC2	0.428±0.02	0.462±0.01	1.134±0.01	13.11±0.42	20.11±0.51
FLC3	0.395±0.01	0.514±0.03	1.190±0.02	14.93±0.34	23.81±0.65
FLS1	0.390±0.04	0.485±0.04	1.003±0.04	15.82±0.78	21.41±0.76
FLS2	0.411±0.04	0.479±0.03	1.196±0.01	10.20±0.61	16.78±0.42
FLS3	0.402±0.05	0.511±0.01	1.012±0.03	11.11±0.33	24.15±0.34
±S.D = standard deviation (n=3)					

Post compression evaluation results

- The thickness of the tablets was found to be nearly uniform in all the formulations ranging between 4.9 ±0.03 – 5.1±0.08mm.
- The hardness was measured and the strength was satisfactory ranging between 3.1±0.06 – 4.9±0.01 kg/cm^2.
- The values of weight variation ranged from 498±1.42 - 502±0.54 mg within pharmacopoeia limits.
- The friability test was performed and all the values were below 1%.

Table IV: Post compression evaluation results of formulations containing HPMC.

Formulation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation(mg)	Drug content (%)
FHS1	5.0±0.03	3.1±0.06	0.23±0.06	499±1.04	99.23±0.56
FHS2	5.1±0.08	3.2±0.03	0.26±0.01	501±1.24	98.99±0.67
FHS3	5.0±0.05	3.4±0.03	0.29±0.01	498±1.42	97..89±0.98
FHS4	4.9±0.06	3.3±0.01	0.30±0.04	500±0.45	99.56±0.56
FHC1	4.9±0.02	4.2±0.01	0.41±0.03	502±0.54	98.45±0.54
FHC2	5.1±0.01	4.6±0.04	0.38±0.02	499±1.35	99.87±0.34
FHC3	5.0±0.06	4.5±0.06	0.23±0.03	500±1.28	99.89±0.89
FHC4	5.1±0.08	4.9±0.01	0.35±0.02	499±0.42	99.64±0.45
±S.D = standard deviation (n=3)					

Table V: Post compression evaluation results of formulations containing luctoman.

Formulation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation(mg)	Drug content(%)
FLC1	5.1±0.01	4.8±0.03	0.25±0.06	498±1.76	98.01±0.12
FLC2	5.0±0.03	3.8±0.02	0.30±0.02	500±1.21	98.99±0.40
FLC3	5.1±0.04	4.4±0.07	0.38±0.01	501±1.56	99.01±0.22
FLS1	5.0±0.05	4.6±0.09	0.44±0.03	500±0.54	99.99±0.31
FLS2	4.9±0.07	3.9±0.06	0.39±0.08	499±0.64	99.02±0.17
FLS3	5.1±0.01	4.9±0.01	0.29±0.06	501±1.28	99.02±0.61
±S.D = standard deviation (n=3)					

***In-vitro* buoyancy studies**

The floating duration of all the formulations was found to be 8h except for FHS1- FHS4. FHS1 and FHS2 underwent disintegration in appx 1hr, whereas FHS3, FHS4 disintegrated in 3h. While the formulations with carbopol combination showed better buoyancy with a floating time of about 8h sustaining the release for prolonged time, which can be due to more swelling property of carbopol when compared to sodium alginate in HPMC combination. Further studies were carried out on FHC1-4.

While luctoman has more floating time with carbopol as well as sodium alginate. As luctoman is a spray dried product its surface area is increased making it more swellable on absorbing water, thus showing a floating time of 8h.

Table VI: Floating studies of tablets containing HPMC.

Batch no.	Floating lag time(min)	Total floating time(h)
FHS1	1.04±0.64	Disintegrated in 1h
FHS2	3.11±0.52	Disintegrated in 1h
FHS3	2.00±0.12	Disintegrated in 3h
FHS4	1.20±0.32	Disintegrated in 3h
FHC1	4.11±0.55	8
FHC2	6.49±0.42	8
FHC3	3.12±0.86	8
FHC4	4.28±0.54	8
±S.D = standard deviation (n=3)		

Table VII: Floating studies of tablets containing Luctoman.

Batch no.	Floating lag time(min)	Total floating time(hrs)
FLC1	3.11±0.22	8
FLC2	4.12±0.70	8
FLC3	2.35±0.45	8
FLS1	4.30±0.08	8
FLS2	3.32±0.64	8
FLS3	6.59±0.54	8
±S.D = standard deviation (n=3)		

Raft Strength

Raft strength was determined after completion of raft forming process (30 min). The raft strength of HPMC formulations was in the range of 4.7±0.34- 8.0±0.16. It was observed with the increase in HPMC concentration the raft strength decreased as it becomes more gelly mass. While luctoman showed highest raft strength at its lower concentration in combination with sodium alginate which forms a stronger raft system.

Table VIII: Raft strength of formulations containing HPMC.

Formulation	Raft strength (gm)
FHC1	8.0±0.16
FHC2	6.8±1.05
FHC3	7.1±0.23
FHC4	4.7±0.34
±S.D = standard deviation (n=3)	

Table IX: Raft strength of formulations containing luctoman

Formulation	Raft strength(gm)
FLC1	5.6±0.10
FLC2	7.1±0.96
FLC3	4.9±0.34
FLS1	8.2±0.76
FLS2	7.1±0.56
FLS3	6.2±0.45
±S.D = standard deviation (n=3)	

***In-vitro* drug release studies**

Cumulative percentage drug release was calculated at different time intervals (1, 1.5, 2, 2.5, 3, 4, 5, 6, 7 and 8 h). It was observed that the polymers had an effect on drug release. As the quantity of retardant is increased, the release of the drug decreased. The formulations FHC1-FHC4 showed percentage drug release in the range of 81.92±0.33- 96.14±0.67 by 8th hour, FLC1-FLS3 showed drug release 81.13±0.99- 85.86±1.34 while FLS1-FLS3 showed 86.26 ±0.98- 99.25±0.98. When compared to HPMC the drug release was maximum with Luctoman FLS1 which may be due to higher raft strength and better matrix formation of sodium alginate with guargum. Also the presence of luctoman (modified guar gum) and sodium alginate combination may have triggered tablet erosion in a controlled manner and thus resulting in maximum release by the end of 8 hrs. Hence FLS1 was considered as the optimized formulation.

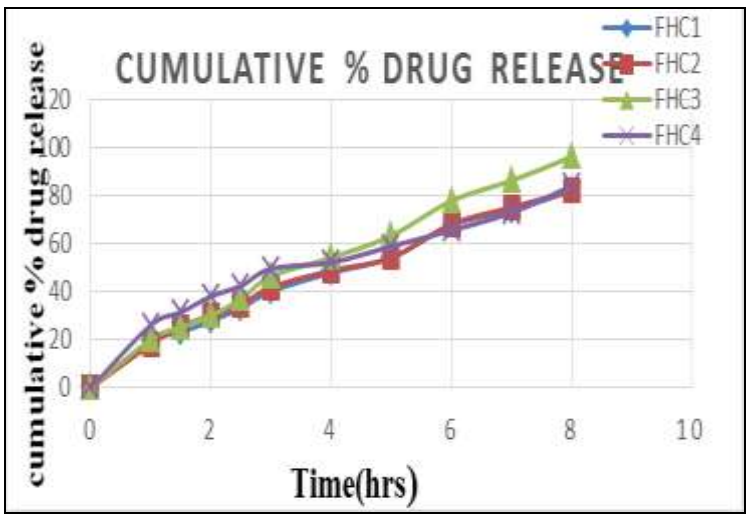

Fig. VII: *in-vitro* drug release of FHC1 – FHC4.

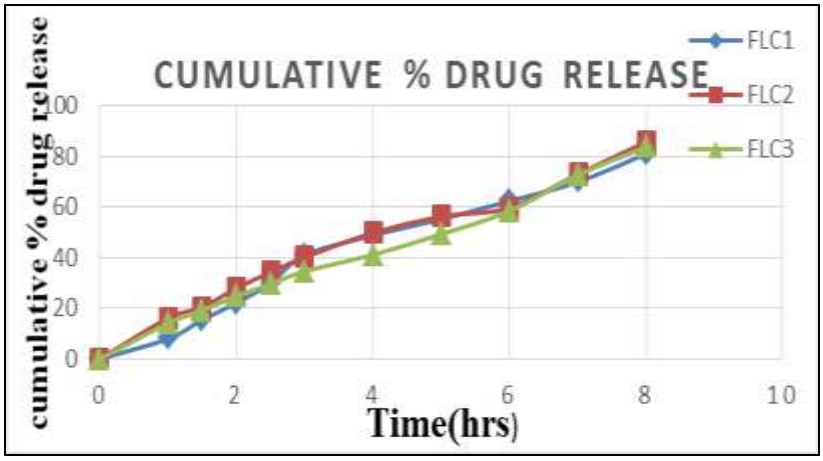

Fig VIII: *in-vitro* drug release of FLC1 – FLC3

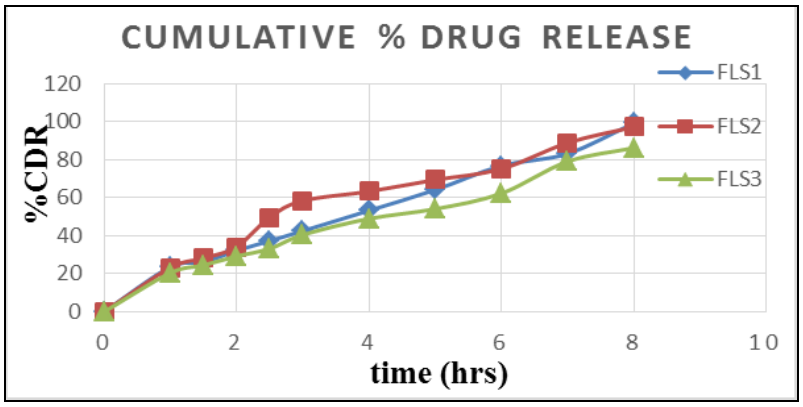

Fig IX: *In-vitro* drug release of FLS1 – FLS3

Drug release kinetics

The Drug Release data of optimized formulation FLS1 when subjected to fitting into kinetic models, fitted best in zero order with R^2 value of 0.988. The n value for the korsmeyer-peppas model was found to be >0.89 indicating super case II transport.

Table X: Optimized formulation FLS1 ($R^{2)}$ values of different models

Formulation	R^2				
	Zero order	First order	Higuchi	Hixson- Crowell	Korsmeyer-peppas
FLS1	**0.988**	**0.697**	**0.946**	**0.878**	**-8.67**

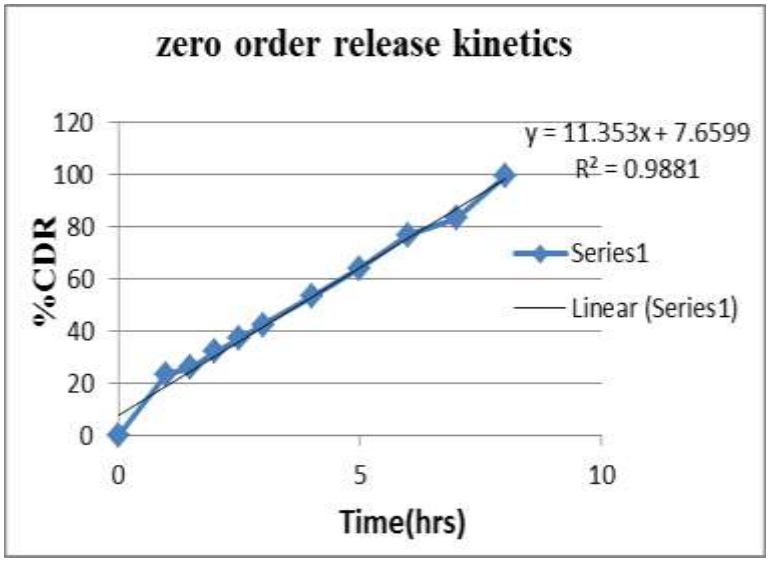

Fig X: Zero order release kinetics of FLS1.

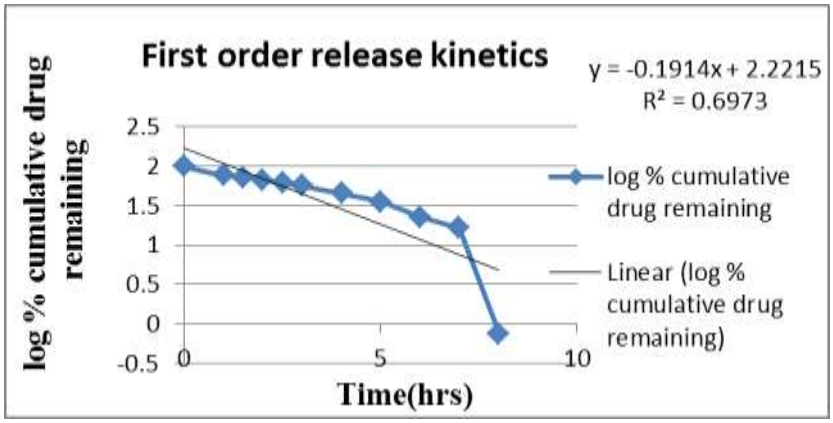

Fig XI: First order release kinetics of FLS1.

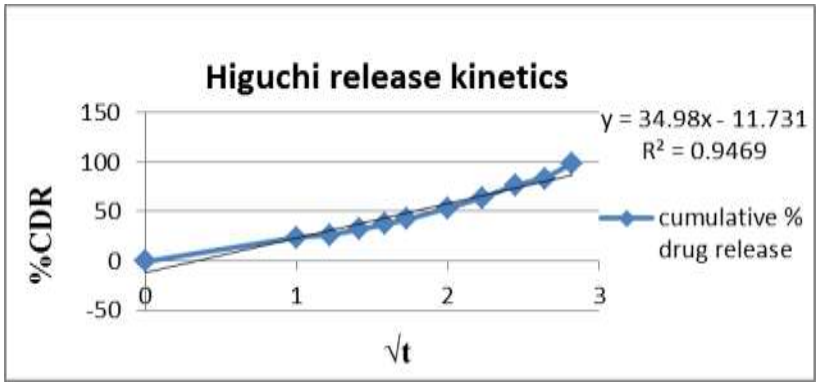

Fig XII: Release kinetics of FLS1 fitted in Higuchi model.

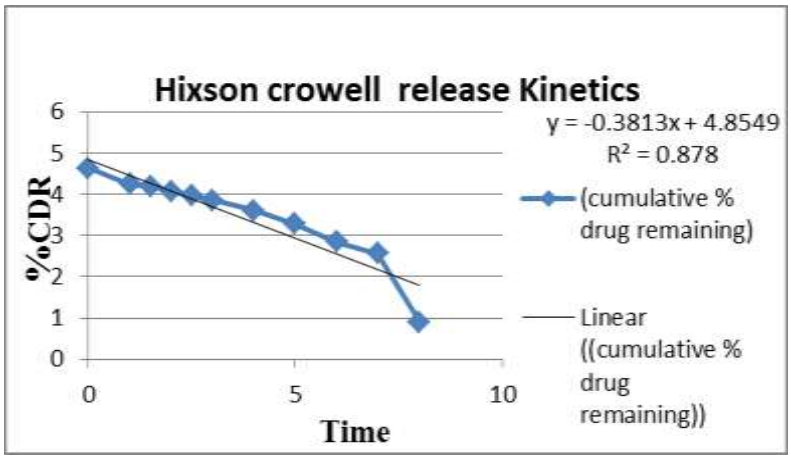

Fig XIII: Release kinetics of FLS1 fitted in Hixson Crowell model.

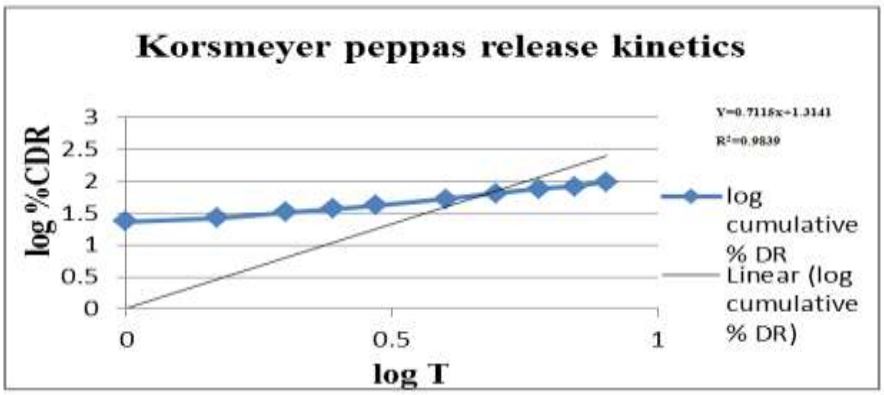

Fig XIV: Release kinetics of FLS1 fitted in korsmeyer- peppas model.

Stability Studies: Stability studies results are shown in the table below. Lamivudine percentage release was found to be 98.88±0.67 at the end of the investigation. From the results acquired, it was concluded that the optimized formulation FLS1 was stable as there was no significant change in the physical characteristics and *in vitro* drug release.

Table XI: Physico- chemical data of stability study.

Formulation	Storage condition		Hardness (kg/cm^2)	Friability (%)	Weight uniformity (mg)	Drug content (%)
FLS1	Before storage		4.6±0.09	0.44±0.03	500±0.54	99.99±0.31
	75±5% RH, 40±2^{0}c	1month	4.5±0.02	0.44±0.08	500±0.66	99.99±0.43
		2month	4.4±0.45	0.46±0.06	500±0.98	99.40±0.45
		3month	4.6±0.08	0.46±0.09	499±0.98	98.91±0.89
±S.D = standard deviation (n=3)						

Table XII: FLT and drug release data of stability study

Formulation	Storage condition		FLT (mins)	Drug release (%)
FLS1	Before storage		4.30±0.08	99.25±0.98
	75±5% RH,40±2^{0}c	1month	4.30±0.12	99.25±0.98
		2month	4.54±0.34	99.10±0.78
		3month	5.02±0.45	98.88±0.67
±S.D = standard deviation (n=3)				

CONCLUSION

It can be concluded that the gastro retentive raft forming tablets of lamivudine were formed using various polymers such as luctoman – modified guar gum, HPMC, carbopol and sodium alginate by direct compression method. Pre compression evaluations showed that they have excellent free flowing tendency. *In vitro* dissolution studies conducted in pH- 0.1N HCL buffer showed that FLS1 showed highest drug release and raft strength of 99.25%, 8.2±0.76gms respectively, hence it can be said that luctoman with sodium alginate had a better sustainability and drug release capacity so was optimized. The drug was also compatible with the excipients used in the formulation. The drug release profile of the optimized formulation was best fitted in zero-order model with super case II transport. The optimized formulation was stable at accelerated temperature and humidity.

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