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Formulation and *in vitro* Evaluation of Gastroretentive Oral Matrix Tablets of Potential Anti- HIV Agent

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ABSTRACT

The purpose of this research was to prepare and evaluate floating drug delivery system of Lamivudine. Floating matrix tablets of Lamivudine were developed to prolong gastric residence time and increase its bioavailability. Rapid gastrointestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of the administered dose. The tablets were prepared by direct compression technique, using polymers such as hydroxyl propyl methyl cellulose (HPMC E15), Ethyl cellulose and Xanthan gum combination and other standard excipients. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of different concentrations of HPMC, EC and Xanthan gum on drug release profile and floating properties were investigated. Comparable release profiles between the commercial product and the designed system were obtained. The model fitting showed that the optimized formulation F2 formulations followed Korsmeyer and Peppas model, which had a higher value of correlation coefficient (r). While tablet hardness had little or no effect on the release kinetics and was found to be a determining factor with regards to the buoyancy of the tablets.

KEYWORDS: *Gastroretentive, anti HIV agent, oral Matrix Tablets, Lamivudine.*

INTRODUCTION

Retention of drug delivery systems in the stomach prolongs overall gastrointestinal transit time and improves the oral bioavailability of the drugs that are having site-specific absorption from the stomach or upper part of the small intestine. Therefore different approaches have been proposed to retain the dosage form in the stomach including bioadhesive systems[1] swelling and expanding systems[2,3] floating systems[4,5] and delayed gastric emptying devices.[6] The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release. Lamivudine is a potential anti- HIV agent, used for the long term treatment of HIV-1 infection as well as for the treatment of chronic Hepatitis B. It is approved by the US food and drug administration (USFDA). It has an elimination half-life of around 5 hours and has an absorption zone from the upper intestinal tract. Efficacy of the administered dose may get diminished due to incomplete drug release from the device above the absorption zone.[11] Lamivudine requires multiple daily drug dosage in order to maintain adequate plasma concentrations. Therefore, it is a suitable model candidate for gastroretentive formulation. The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability.[12] High solubility of Lamivudine was a major challenge in designing its controlled drug delivery system. In this study, HPMC E 15 was used as a matrix-forming controlled release polymer. Ethyl cellulose and Xanthan gum are used as floating enhancers and also as release ratardants. Because high water soluability of the Lamivudine results in hydration of matrix prepared with HPMC E 15 alone, thereby resulting in variability in the release profiles of Lamivudine. To minimize the hydration rate of the matrix and variability in the release profiles, Ethyl Cellulose and Xanthan gum were tried in combination with HPMC E 15. The formulations were optimized for desired acceptance criteria (ie, floating lag time is of less than 3 minutes; floating

duration of 12 hours ;). In context of the above principles, a strong need was recognized for the development of a dosage form to deliver Lamivudine in the stomach and to increase the efficiency of the drug, providing controlled release action. The present investigation applied a systematic balance between floating lag time, floating duration, and in vitro drug release for the development of gastroretentive dosage forms of Lamivudine suitable for once daily formulation with improved bioavailability.

MATERIALS AND METHODS

Materials

HPMC E 15, Ethyl Cellulose and Xanthan gum were kindly supplied by Rankem Pvt ltd. Delhi. Lamivudine was a gift sample from Cipla Ltd (Mumbai, India). Sodium bicarbonate, talc, and magnesium stearate were purchased from S. D. Fine Chemicals Ltd (Mumbai, India). All other ingredients were of analytical grade.

METHODS

Preparation of Lamivudine Floating Tablets

Lamivudine, HPMC E 15,Xanthan gum and Ethyl Cellulose were passed through sieve No. 60 separately. The drug was mixed with the polymers and other ingredients in weight proportion as mentioned in **Table 1**. The powder blend was then lubricated with magnesium stearate (2% w/w) and talc (2% w/w), and this lubricated blend was compressed into tablets using 8-mm flat-face round tooling on a single punch tablet machine (Rimek). The compression force was adjusted to obtain tablets with hardness in range of 7 to 8 kg/cm^2.

Table 1 Composition of LAMIVUDINE FLOATING TABLETS (all quantities in mg)

FORMULATION	F1	F2	F3	F4	F5	F6	F7	F8
Drug polymer ratio	1:1	1:0.9	1:0.8	1:0.6	1:1	1:0.9	1:0.8	**1:0.6**
Lamivudine	100	100	100	100	100	100	100	**100**
Hpmc e15	100	90	80	60	100	90	80	**60**
Ethyl cellulose	20	30	40	60	-	-	-	**-**
Xanthane gum	-	-	-	-	20	30	40	**60**
Sodium bicarbonate	30	30	30	30	30	30	30	**30**
Pvp k30	45	45	45	45	45	45	45	**45**
Talc	q.s	q.s	q.s	q.s	q.s	q.s	q.s	**q.s**
Magnesium stearate	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**

In Vitro Buoyancy Studies

The in vitro buoyancy was determined by floating lag time, as per the method described by Rosa et al. The tablets were placed in a 100-mL beaker containing 0.1 N HCl and the time required for the tablet to rise to the surface and float was determined as floating lag time.

In Vitro Dissolution Studies

The release rate of Lamivudine from floating tablets (n = 3) was determined. The dissolution test was performed using United States Pharmacopeia (USP) type II (paddle) apparatus, 900 mL of 0.1 N HCl, at 37-C ± 0.5-C and 50 rpm. A sample (1 mL) of the solution was withdrawn from the dissolution apparatus at the appropriate time for 12 hours, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45-µm membrane filter and diluted to a suitable concentration with 0.1 N HCl. Absorbance of these solutions was measured at 280 nm using a Shimadzu UV- 1601 UV/Visible double-beam spectrophotometer (Shimadzu Corp, Kyoto, Japan). Cumulative percentage drug release was calculated using a PCP Disso Version 2.08 software, the time required for 50% and 85% drug release was calculated based on the Korsmeyer and Peppas model.[17]

Table -2 *In vitro* release study of Lamivudine floating tablets for different formulations

Time in hrs	% cumulative drug release±SD		
	F1	F2	F3
0.25	12.47±0.05	8.21±0.11	9.20±0.08
0.5	14.77±0.03	11.82±0.14	13.14±0.09
1	22.32±0.14	16.09±0.09	16.10±0.11
2	26.26±0.11	22.33±0.32	19.72±0.14
3	34.47±0.36	31.53±0.22	30.57±0.34
4	43.01±0.25	40.39±0.28	41.08±0.32
5	47.27±0.23	45.65±0.37	51.93±0.27
6	55.48±0.34	56.21±0.26	54.23±0.46
7	65.66±0.47	65.74±0.34	65.74±0.47
8	97.51±0.35	71.98±0.31	67.38±0.29
12	87.20±0.33	98.94±0.39	90.06±0.40

n=3, SD-Standard deviation

Table 3 *In vitro* release study of Lamivudine floating tablets for different formulations

Time in hrs	% cumulative drug release±SD		
	F4	F5	F6
0.25	6.59±0.10	13.47±0.06	12.18±0.09
0.5	10.55±0.24	14.78±0.10	15.74±0.05
1	14.84±0.16	20.04±0.25	21.29±0.10
2	18.13±0.37	25.62±0.19	29.86±0.14
3	26.05±0.24	35.81±0.34	33.47±0.13
4	30.66±0.31	42.71±0.25	41.01±0.26
5	37.59±0.28	46.33±0.21	45.28±0.24
6	46.16±0.36	50.93±0.36	51.19±0.34
7	52.10±0.45	60.13±0.47	61.69±0.41
8	59.69±0.39	97.26±0.55	67.27±0.40
12	71.23±0.54	97.66±0.56	91.89±0.46

n=3, SD-Standard deviation

Table 4 *In vitro* release study of Lamivudine floating tablets for different formulations

Time in hrs	% cumulative drug release±SD	
	F7	F8
0.25	10.19±0.06	10.86±0.18
0.5	13.14±0.05	16.79±0.12
1	16.76±0.09	20.08±0.25
2	22.35±0.16	24.69±0.29
3	28.59±0.11	29.63±0.14
4	37.80±0.31	31.93±0.19
5	45.03±0.29	36.54±0.36
6	53.58±0.39	37.40±0.48
7	61.47±0.26	43.79±0.26
8	67.71±0.41	46.42±0.64
12	85.13±0.26	66.83±0.76

n=3, SD-Standard deviation

Fig.1Comparision of dissolution profiles

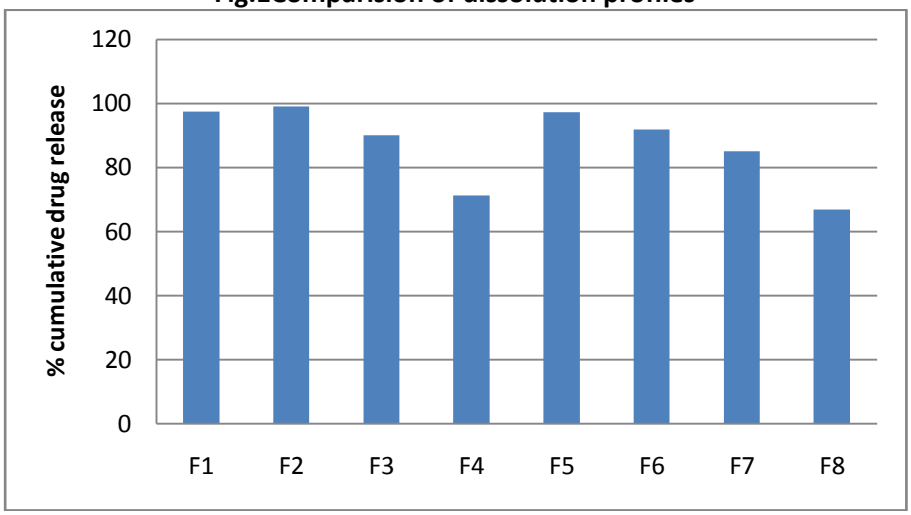
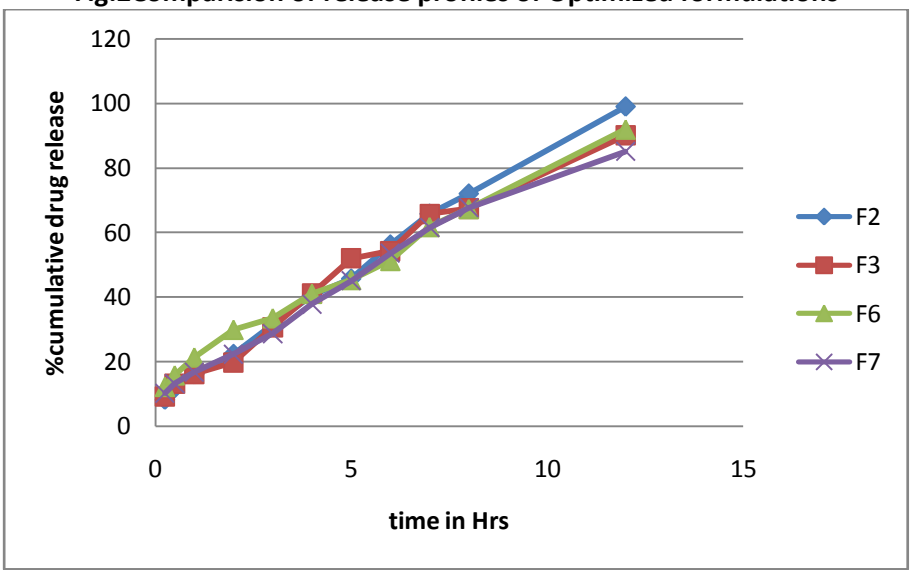


Fig.2Comparision of release profiles of Optimized formulations



Kinetic Modeling of Drug Release

The dissolution profile of all the batches was fitted to zero order, first order, [18, 19] Higuchi, [20-22] Hixon-Crowell, Korsmeyer and Peppas, [17] to ascertain the kinetic modeling of drug release by using PCP Disso Version 2.08 software, and the model with the highest correlation coefficient was considered to be the best model

Table 5: Results of Correlation coefficient for best formulation F2

Formulation	Correlation coefficient R^2				
Order of release	Zero order	First order	Higuchi matrix	Korsmeyer-peppas	**Hixson-crowell**
F2	**0.996**	**0.768**	**0.994**	**0.997**	**0.990**

Fig.3 Zero order release kinetics

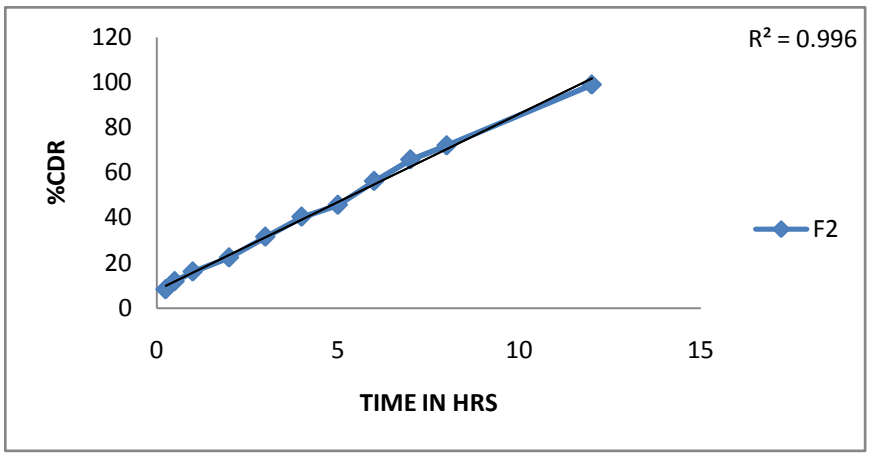


Fig. 4 First order release kinetics

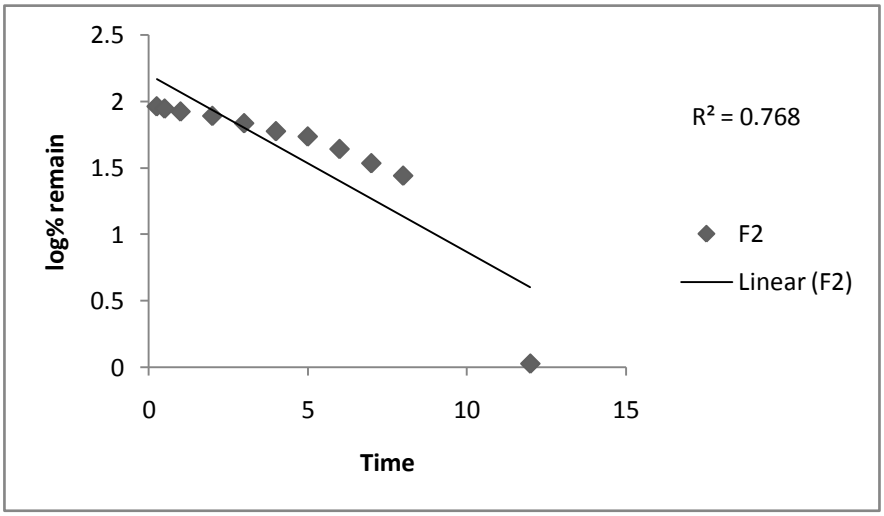


Fig. 5 Higuchi matrix release kinetics

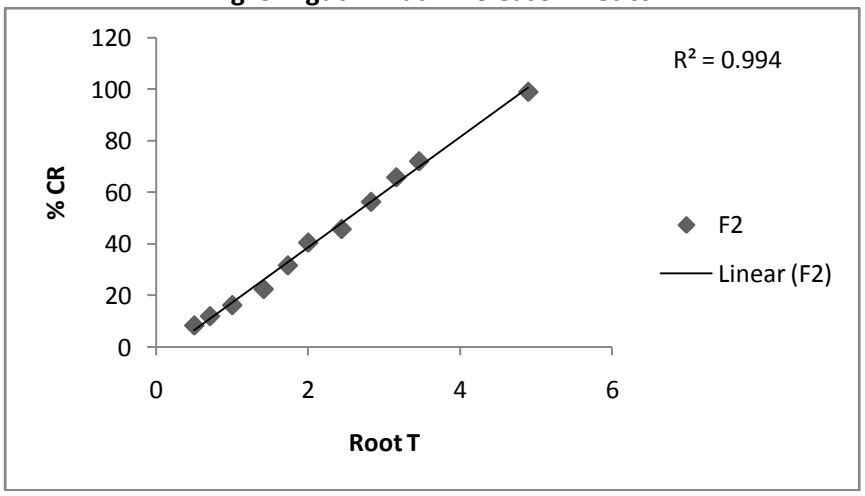


Fig. 6 Korsmeyer peppas equation

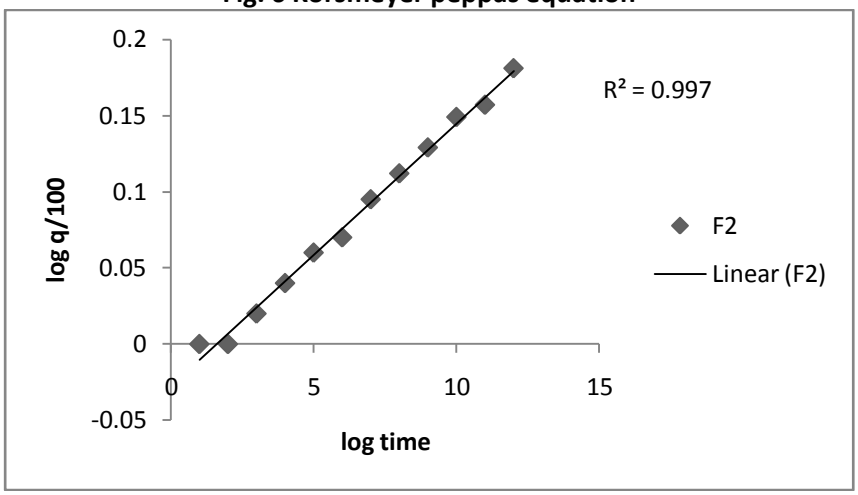
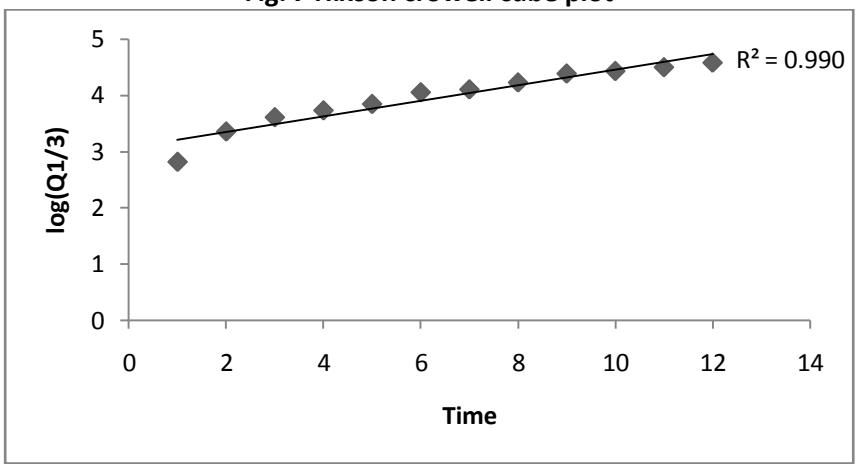


Fig. 7 Hixson crowell cube plot



RESULTS AND DISCUSSION

In Vitro Buoyancy Studies

The initial batches prepared without sodium bicarbonate did not show any sign of floating. Therefore, sodium bicarbonate was used as a gas-generating agent in order to float the tablet. The sodium bicarbonate induces CO2 generation in the presence of dissolution medium (0.1 N HCl). The gas generated is trapped and protected within the gel formed by hydration of the polymer, thus decreasing the density of the tablet below 1 gm/mL, and the tablet becomes buoyant.. As the amount of sodium bicarbonate increases, the floating lag time decreases. Thus, sodium bicarbonate 10% was essential to achieve optimum in vitro buoyancy (ie, floating lag time of 2-3 minutes and floating duration of 12 hours). Further increase in concentration of bicarbonate does not show any significant effect on floating behaviour. Moreover, the increased amount of sodium bicarbonate caused a large amount of effervescence, which in turn resulted in pore formation, which led to rapid hydration of the polymer matrix and thereby to rapid drug release. Thus 10% concentration of sodium bicarbonate was kept constant for batches F1-F8, which showed floating lag time between 1and 3 minutes and remained floating for 12 hours.

In Vitro Dissolution Studies

The results of In Vitro dissolution studies showed that as the concentrations of Ethyl Cellulose and Xanthan gum were increased, the release rate has been retarded and baced on this HPMC:EC and HPMC:Xanthan gum was optimised as (3:1) which

showed maximum drug release along with good floating properties.As the concentration of EC increased from F1-F4 ,the release rate is substantially decreased and same is the case with Xanthan gum.

MODEL FITTING

The *in-vitro* release data of selected formulation thus obtained was subjected to different kinetic treatments (Zero order, First order, Higuchi, Hixson-Crowell and Korsmeyer's Peppas). The results are shown in Figures 13-17 .The coefficient of determination (R^2) was considered as main parameter for interpreting the release kinetics. For Zero order treatment the R^2 values was 0.996. Zero order kinetics show the drug releases rate is independent of its concentration. The R^2 values of first order treatment were 0.768 which indicate that, the formulations do not follow first order kinetics.

When the data was subjected to Higuchi treatment the R^2 values was 0.994. Which describe release of drug from an insoluble matrix as a square root of a time dependent process based on Fickian diffusion. The data was also given Hixson-Crowell treatment where in R^2 value was 0.990. In order to predict the release mechanism, the data was subjected to Korsmeyer's treatment. The R^2 value was 0.997 and which is maximum as compared to other release kinetics. For the formulation (F2) containing HPMC E15 and EC indicating that the dominant mechanism for drug release through matrix systems is anomalous diffusion which is coupling of diffusion and erosion mechanism. The formulations F2 indicating the drug transport mechanism is Fickian diffusion and follows Korsmeyer-peppas order of kinetics.

CONCLUSION

From the evaluation studies of all the formulations, the formulation F2 containing HPMC and EC in the ratio 1:3 showed the best results regarding buoyancy lag time as well as total buoyancy time and also showed the best drug release profile. Hence it can be concluded that floating tablets show the best results when the polymer ratio of HPMC and EC is maintained as 3:1 and the gas generating agent is used at 10% of the formulation. Hence the floating tablet of Lamivudine is a novel approach so as to avoid the disadvantages of anti-viral conventional dosage forms.

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