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Formulation and evaluation of floating tablets of antiretroviral drug lamivudine

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ABSTRACT

The purpose of this research was to prepare and evaluate floating drug delivery system of Lamivudine. Floating 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 K15M and HPMC K4M), Ethyl cellulose combination and other standard excipients. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of different concentrations of hydroxyl propyl methyl cellulose (HPMC K15M and HPMC K4M) and EC 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 F5 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: Gastro retentive, Controlled Release Formulation, Anti HIV agent, Oral Floating Tablets, Lamivudine.

INTRODUCTION

Novel Drug Delivery System

The design of oral controlled DDS should be primarily aimed to achieve more predictable and increased bioavailability. Now a day's most of the pharmaceutical scientist is involved in developing the ideal DDS. This ideal system should have advantage of single dose for the whole duration of treatment and it should deliver the active drug directly at the specific site. Scientists have succeeded to develop a system and it encourages the scientists to develop control release systems. Controlled release implies the predictability and reproducibility to control the drug release, drug concentration in target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose. [1] However, this approach is be filled with several physiological difficulties such as in ability to restrain and locate the controlled drug delivery system within the desired region of the GIT due to variable gastric emptying and motility. Furthermore, the relatively brief GET in humans which normally average 2-3 hrs through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy

of the administered dose. Therefore, control of placement of a DDS in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem. [2]

Anatomy and physiology of stomach [3]

The stomach is the most dilated part of the GIT and is situated between the lower end of the esophagus and the small intestine .Its opening to the duodenum is controlled by the pyloric sphincter .The stomach can be divided into four anatomical regions, namely the fundus, the body, the antrum and the pylorus.

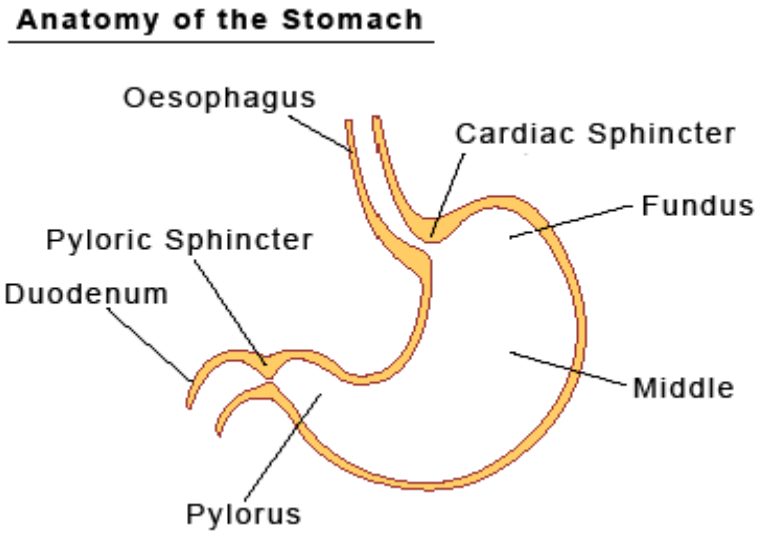

Fig 1 Anatomy of stomach

The two major functions of the stomach are

To act as a temporary reservoir for ingested food and to deliver it to the duodenum at a controlled rate. to reduce the ingested solids to uniform creamy consistency, known as chime, by the action of acid and enzymatic digestion. This enables better contact of the ingested material with the mucous membrane of the intestines and their by facilitates absorption.Another perhaps less obvious, function of stomach is its role in reducing the risk of noxious agents reaching intestine.

Approaches to Gastric Retention

A number of approaches have been used to increase the GRT of a dosage form in stomach by employing a variety of concepts. These include

Floating systems [4]

FDDS have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the GER. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. These results in an increase in the GRT and a better control of fluctuationsin the plasma drug concentration. Floating systems can be classified into two distinct categories, effervescent and non-effervescent systems.

Bio/Muco-adhesive systems [5]

Bio adhesive or mucoadhesive systems are used to localize a delivery device within the lumen and cavity of the body to enhance the drug absorption process in a site-specific manner. The approaches involve the use of bio adhesive polymers that can be adhering to the epithelial surface of the GIT. The proposed mechanism of bio adhesive is the formation of hydrogen and electrostatic bonding at the mucus polymer boundary.

Swelling and expanding systems [6, 7]

These are the dosage forms, which after swallowing; swell to an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a longer. These systems may be named as "plug type system" since they exhibit the tendency to remain logged at the pyloric sphincter if that exceed a diameter of approximately 12-18 mm in their expanded state. Such polymeric matrices remain in the gastric cavity for several hrs even in the fed state.

A balance between the extent and duration of swelling is maintained by the degree of cross-linking between the polymeric chains. A high degree of cross-linking retards the swelling ability and maintains its physical integrity for prolonged period.

High density systems [8]

These systems with a density of about 3 g/cm3 are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. A density of 2.6-2.8 g/cm3 acts as a threshold value after which systems can be retained in the lower part of the stomach. High-density formulations include coated pellets. Coating is doneby heavy inert materials such as barium sulphate, zinc oxide, titanium dioxide, and iron powder.

Incorporation of passage delaying food agents [9]

Food excipients like fatty acids eg. Salts of myristic acid change and modify the pattern of the stomach to a fed state, thereby decreasing GER and permitting considerable prolongation of release. The delay in the gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain length of C10-C14.

Ion exchange resins [10]

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin. The resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach, an exchange of chloride and bicarbonate ions take place, as a result of this reaction carbon dioxide was released and trapped in the membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast to the uncoated beads, which will sink quickly.

Osmotic regulated systems [11]

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bio erodible capsule. In the stomach the capsule quickly disintegrates to release the Intragastricosmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic controlled drug delivery device consists of two components, drug reservoir compartment and osmotically active compartment.

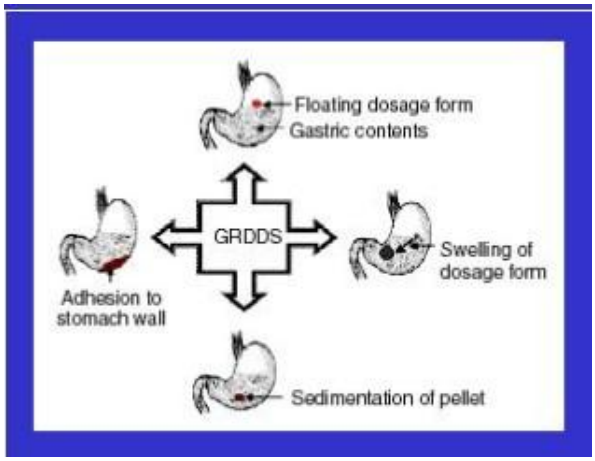

Fig 2 Classification of gastro retentive drug delivery

Floating Drug Delivery Systems (FDDS)

Based on the mechanism of buoyancy, two distinctly different technologies have been utilized in the development of FDDS, which are effervescent system and non- effervescent system.

Effervescent system [12, 13, 14]

Effervescent systems include use of gas generating agents, carbonates (Sodium bicarbonate) and other organic acid (Citric acid and Tartaric acid) to produce carbon dioxide (CO2) gas, thus reducing the density of the system and making it to float on the gastric fluid. These effervescent systems further classified into two types Gas generating systems Intra gastric single layer floating tablet or Hydro dynamically balanced system (HBS)

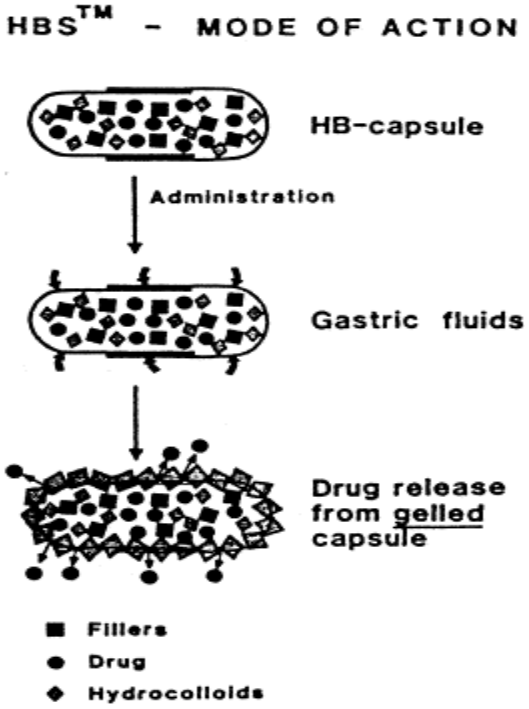

Fig 3 Hydro dynamically balanced system

These are formulated by mixing the CO2 generating agents and the drug within the matrix tablet (Fig 3). These have a bulk density lower than gastric fluids and therefore remain floating in the stomach unflattering the GER for a prolonged period. The drug is slowly released at a desired rate from the floating system and after the complete release the residual system is expelled from the stomach. This leads to an increase in the GRT and a better control over fluctuations in plasma drug concentration.

MATERIALS AND METHODS

Materials

The following materials of Pharma grade or the best possible Laboratory Reagent (LR) were used as supplied by the manufacturer. The double distilled water was used in all experiments.

1. Formulation of Lamivudine floating tablets using different polymers: HPMC K15M, HPMC K4M, Sodium bi carbonate, ethyl cellulose, PVP K30, and excipients like Magnesium. Stearate and talc in different rations.
2. Compression of the powders into floating tablets of Lamivudine. Evaluation of floating tablets of Lamivudine for physical appearance,

hardness, thickness, friability, weight variation, content uniformity test, and in-vitro buoyancy studies.

3. In vitro dissolution studies for all the formulations of Lamivudine floating tablets.

Drug excipient Compatibility studies

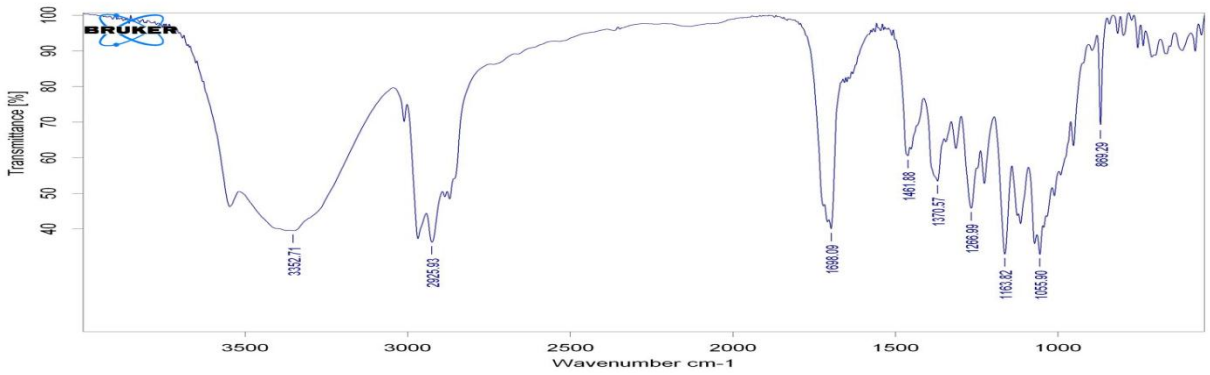

Fig No: 4 The Drug excipient Compatibility studies was performed under two graphs of IFTR using FTIR

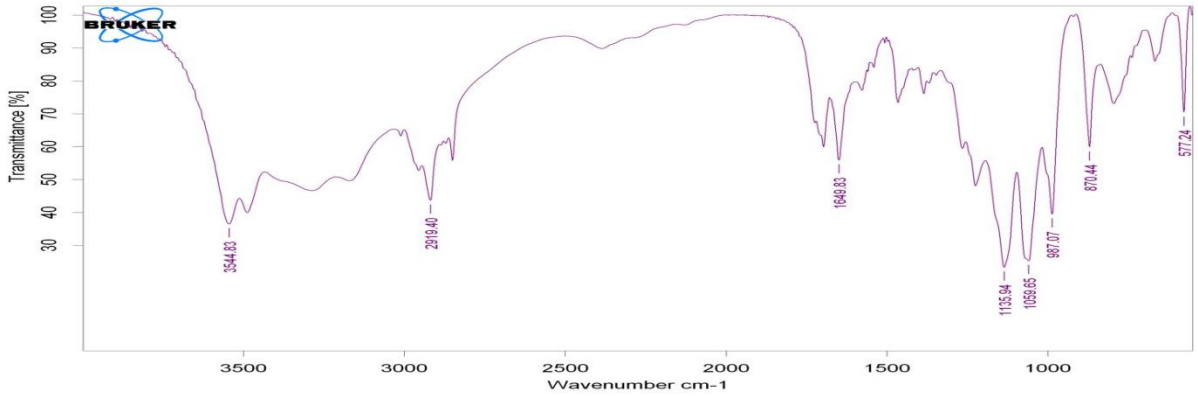

Fig No: 5 The Drug excipient Compatibility studies was performed under two graphs of IFTR using FTIR

Analytical Methods

Method used for the Estimation of Lamivudine

A spectrophotometric method based on the measurement of absorbance at 270nm in 0.1N Hydrochloric acid was used in the present study for the estimation of Lamivudine.

Table 1: Calibration curve for the Estimation of Lamivudine

Sl.no	Concentrations(µg/ml)	Absorbance
1.	2	0.1
2.	4	0.197
3.	6	0.284
4.	8	0.386
5.	10	0.479

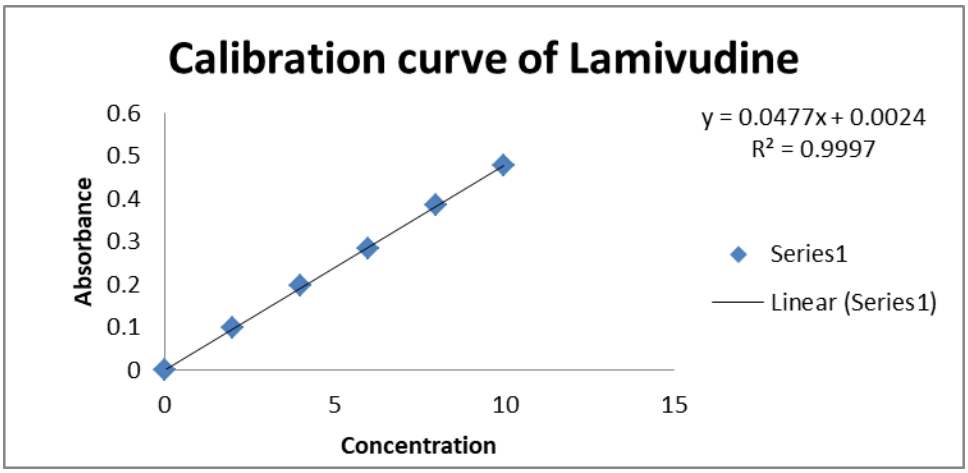

Fig no: 6 Calibration curve of lamivudine

Table 2: Composition of Lamivudine Floating Tablets (all quantities in mg)

	F1	F2	F3	F4	F5	F6	F7	F8
Lamivudine	100	100	100	100	100	100	100	100
HPMC K15M	100	90	80	60	100	90	80	60
HPMC K4M	20	30	40	60	-	-	-	-
Ethyl cellulose	-	-	-	-	20	30	40	60
Sodium bi carbonate	30	30	30	30	30	30	30	30
Pvpk30	38	38	38	38	38	38	38	38
Talc	6	6	6	6	6	6	6	6
Magnesium Sterate	6	6	6	6	6	6	6	6

Formulation and Preparation of Lamivudine Floating Tablets

All the formulations were prepared by direct compression method using different polymers in various ratios (designated as F-1 to F-8).

Procedure

Lamivudine and all other ingredients were individually passed through sieve ≠ 60. All the ingredients were mixed thoroughly for 15 min. The powder mixture was lubricated with talc. The tablets were prepared by using direct compression method.

Evaluation of Lamivudine Floating Tablets

Weight Variation Test

Weigh 20 tablets selected at random and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage limits. As per Indian Pharmacopoeial Specification.

Table 3: Weight Variation Limits

Average weight of tablets(mg)	Maximum % difference allowed
Less than 80	10
80- 250	7.5
Above 250	5

$$\% \text{ Deviation} = \frac{\text{Tablet weight-Average weight}}{\text{Tablet weight}} \times 100$$

Friability Test

20 tablets were weighed and subjected to rotate on friability test apparatus. The drum rotated at a speed of 25 rpm for 4 minutes, then dedusted and reweighed the tablets. Percentage friability was calculated by the following formula.

$$\text{Percentage of Friability (\% F)} = 100\ (1\text{-}w/w_0)$$

Where, Wo = Initial weight, W = Final weight, Percentage friability of tablets less than 1% is considered acceptable.

Hardness Test

The hardness of tablet was carried out by using Monsanto type hardness tester. The hardness of the tablet kg / cm^2 was measured.

Thickness Test

Control of physical dimension of the tablets such as sizes and thickness is essential for consumer acceptance and to maintain tablet to tablet uniformity. The dimensional specifications were measured using verniar calipers. Six tablets from each batch were tested and average values were calculated. The thickness of the tablet is mostly related to the tablet hardness can be uses as initial control parameter.

Buoyancy lag time (BLT)

The time taken for dosage form to emerge on surface of medium called floating lag time (FLT) or buoyancy lag time (BLT).

Buoyancy time

The time during which the dosage form remains buoyant were measured.

Dissolution Study

Preparation of Buffer 0.1N HCL

Measure 8.5ml of conc. HCL in a 1000ml volumetric flask and make up the volume up to 1000 ml using distilled water.

Assay

Crushed 20 tablets and weighed equivalent to 20 mg of Rosiglitazone maleate and dissolved in 0.1M HCl and made the volume with0.1M HCl. 10 ml of the above solution was further diluted to 100 ml with 0.1M HCl and read the absorbance at 318 nm with the help of UV spectrophotometer.

Kinetics of drug release

The invitro dissolution profile of all batches were fitted to Zero order, first order, Higuchi model and Koresmeyer-Peppas model to ascertain the kinetic modeling of drug release.

- **Zero-order kinetic model** – Cumulative % drug released Vs time.
- **First-order kinetic model** – log cumulative % drug remaining Vs time.
- **Higuchi model** - Cumulative % drug released Vs square root of time.
- **Korsmeyer-Peppas model** - log cumulative % drug released Vs log time.

Mechanism of drug release as per Korsmeyer-Peppas equation / Peppas model

Table 4: Mechanism of drug release

S.No	n value	Drug release
1	0 – 0.5	Fickian release
2	0.5 – 1.0	Non-Fickian release
3	> 1.0	Class II transport

RESULTS AND DISCUSSIONS

Table 5: Physical Properties of Pre-Compression Blend:

Batch. No	Angle of Repose(^{0})	Bulk Density(g/ml)	Tapped bulk density(g/ml)	Carr's index (%)	Huasner Ratio
F1	20.85±0.34	0.499±0.56	0.75±0.45	33.46	1.50
F2	21.34±1.23	0.48±1.09	0.803±1.01	40.22	1.60
F3	22.54±0.98	0.53±0.98	0.785±0.89	32.48	1.47
F4	21.12±1.34	0.520±0.54	0.736±0.62	29.34	1.40
F5	20.23±1.1	0.524±0.67	0.76±0.92	31.05	1.46
F6	22.67±0.56	0.526±0.49	0.73±0.69	27.94	1.40
F7	20.89±1.56	0.405±0.13	0.685±0.57	40.87	1.68
F8	20.13±0.98	0.409±0.23	0.71±0.27	42.39	1.73

The angle of repose for the formulated blend F1-F8 was found to be in the range 20.13 to 22.67 shows good flow property. Compressibility index for the formulations F1-F8 found between 42.39 % to 27.94% indicating the powder blend has the required flow property for compression.

Evaluation of Lamivudine Floating Tablets

Table 6: Weight Variation and Friability

Batch. No	Weight Variation (%)	Friability (%)
F1	±1.52	0.21
F2	±2.37	0.24
F3	±1.44	0.20
F4	±1.86	0.18
F5	±2.56	0.28
F6	±2.13	0.27
F7	±2.25	0.23
F8	±1.93	0.19

The weight variation of the tablet in the range of ± 1.44 % to ± 2.56 %(below 7.5%) complying with pharmacopoeial specification. The friability of the tablet in the range of 0.18 % to 0.28% **(**below 1%) complying with pharmacopoeial specifications

Table 7: Thickness and Hardness:

Batch.No	Thickness(mm)	Hardness(Kg/cm^2)
F1	3.53±0.02	3.7±0.20
F2	3.44±0.03	3.6±0.10
F3	3.56±0.01	3.5±0.15
F4	3.54±0.02	3.6±0.05
F5	3.49±0.03	3.9±0.20
F6	3.52±0.02	3.8±0.15
F7	3.45±0.01	3.6±0.15
F8	3.42±0.02	3.7±0.20

The thickness of the formulations from F1- F8 was found to be in the range of 3.42±0.01 to 3.54±0.02 the hardness of the formulated tablets was found to be 3.5±0.05 to 3.9±0.20 indicating a satisfactory mechanical strength.

In vitro Buoyancy studies

In Vitro buoyancy studies was performed for all the eight formulations as per the method described by Rosa *et al* [15] The randomly selected tablets from each formulation was kept in a 100ml beaker containing simulated gastric fluid, pH 1.2 as per USP. The time taken for the tablet to rise to the surface and float was taken as floating lag time. The overall floating time was calculated during the dissolution studies.

Table 8: *In vitro* Buoyancy studies

F. CODE	FLOATING LAG TIME(Min)	FLOATING TIME(HRS)
F1	1:46	24
F2	1:56	24
F3	1:54	24
F4	1:43	24
F5	1:48	24
F6	1:59	24
F7	2:29	24
F8	1:58	24

In-vitro Dissolution Study

In-vitro release studies were carried out using USP type II (paddle) dissolution test apparatus. 900ml of 0.1N HCl was filled in dissolution vessel and the temperature of the medium was set at 37^0c±0.5^0c. Sink condition was maintained for the whole experiment. The speed was set at 50 rpm. 5ml of sample was withdrawn at predetermined time intervals for 24 hours and same volume of fresh medium was replaced. The samples were analyzed for drug content against 0.1N HCl as a blank at max 280nm using U.V. spectrophotometer.

Table 9: Dissolution profiles of lamivudine F1 to F8 formulations

Time	Formulation							
(hrs)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0.00	0	0	0	0	0	0
0.5	12.89	18.63	15.21	22.82	15.59	15.78	17.87	56.09
1	23.01	26.24	19.01	23.77	22.25	21.49	25.29	62.75

2	27.95	32.13	29.47	35.18	31.56	32.32	32.70	71.68
3	37.27	41.07	42.02	46.20	35.75	45.25	43.92	75.87
4	43.92	47.34	53.05	52.67	51.34	51.53	49.63	80.24
5	48.68	50.39	60.84	57.61	60.65	61.80	56.47	84.80
6	57.04	56.66	66.36	63.51	62.37	68.07	63.51	88.99
7	61.20	57.23	71.68	67.31	64.46	74.34	71.11	90.13
8	65.22	62.75	75.87	69.02	72.06	78.15	73.20	90.89
9	69.02	71.68	79.48	73.96	73.39	87.27	80.24	91.46
10	72.44	72.25	81.95	80.24	79.48	87.84	82.71	92.41
11	74.54	74.34	83.85	81.19	84.23	90.51	83.85	91.65
12	77.01	74.73	84.80	85.56	88.42	95.26	88.03	91.65
14	78.72	75.49	87.46	89.56	89.56	96.59	89.56	92.22
16	80.24	79.86	88.22	91.46	90.51	97.16	90.13	94.88
18	81.38	80.05	88.80	91.84	95.26	98.49	90.51	96.21
20	81.57	80.05	89.56	92.60	95.26	98.49	91.08	97.73
22	81.76	80.43	90.13	92.98	97.35	99.25	91.46	98.87
24	82.33	80.81	90.89	97.92	98.49	99.63	92.22	98.87

Table 10: Drug release kinetic models for Formulations F1- F8

				Peppas model	
Formulation	**Zero order**	**First order**	**Higuchis matrix**	**R^2 value**	**n valuve**
F1	0.286	0.785	0.937	0.951	0.502
F2	0.102	0.716	0.925	0.960	0.514
F3	0.207	0.822	0.908	0.909	0.533
F4	0.262	0.966	0.953	0.967	0.464
F5	0.432	0.718	0.961	0.960	0.539
F6	0.318	0.990	0.931	0.936	0.545
F7	0.213	0.859	0.926	0.946	0.484
F8	-2.398	0.700	0.387	0.939	0.154

CONCLUSION

The concept of formulating floating tablets containing Lamivudine offers a suitable and practical approach to achieve a prolonged therapeutic effect by continuously releasing the medication over extended period of time. In the present work, floating tablets of Lamivudine were prepared successfully by direct compression method using the different concentration & combination of polymers like HPMC K15 M, HPMC K4M and EC and subjected to pre-formulation and post-formulation studies. From the experimental results it can be concluded that the drug release data was best fitted with zero order kinetics. The Higuchi equation explains the diffusion controlled release mechanism. The diffusion exponent 'n' values of Korsemeyer-Peppas model was found to be in the range of 0.5 to 0.1 indicating Non-fickin diffusion of drug through Lamivudine floating tablets. The study also indicated that the amount of drug release decreases with an increase in the polymer concentration. The in vitro performance of Lamivudine floating tablets showed prolonged and controlled release of drug. it was concluded that the formulation F2 containing 10% of HPMC K4M & 30% of HPMC K15M was the best formulation showing only 80.8% drug release up to 24 hrs. From the study it is evident that promising controlled release floating tablets of Lamivudine may be developed by Direct compression technique

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