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Research Article

Formulation, Development and Evaluation of Gastroretentive Floating Tablets of Lovastatin Using Natural Polymer

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Abstract: Lovastatin a 3-hydroxy-3-methyl glutyryl coenzymeA (HMG coA) reductase inhibitor is a statin with well-known lipid lowering effects that decreases cardiovascular morbidity and mortality in patients with and without coronary artery diseases. Floating drug delivery systems are the gastroretentive forms that precisely control the release rate of target drug to a specific site which facilitate an enormous impact on health care. This can be achieved by use of various polymeric substances including natural polymers. These polymers are inexpensive, safe and available in a variety of structures with versatile characteristics. The purpose of this research was to develop a novel gastro retentive drug delivery system based on direct compression method for sustained delivery of active agent to improve the bioavailability, reduce the number of doses and to increase patient compliance. Gastro retentive floating tablets of lovastatin were prepared by direct compression method using altered concentrations of HPMC K4, HPMC K15 and gaur gum as polymers. The prepared tablets of lovastatin were evaluated for hardness, thickness, friability, weight variation, drug content uniformity, buoyancy lag time, total floating time, *in-vitro* dissolution study, etc. All the compositions were resulted in adequate Pharmacopoeial limits. Compatibility studies was execution during FTIR shown that there was absence of probable chemical interaction between pure drug and excipients. The varying concentration of gas generating agent and polymers was found to effect on *in-vitro* drug release and floating lag time. *In vitro* drug release of floating gastro retentive tablet of lovastatin shown that the formulation F8 was found to be the best formulation as it releases 99.45% lovastatin in a controlled manner for an extended period of time (up to 12 hrs). The release data was fitted to various mathematical models such as higuchi, korsmeyer-peppas, first order and zero order to evaluate the kinetics and mechanism of the drug release. The Optimized formulation (F8) showed no significant change in physical appearance, drug content, floating lag time, *in vitro* dissolution studies after 75%±5% RH at 40±20C relative humidity for 6 months. Prepared floating tablets of lovastatin may prove to be a potential candidate for safe and effective controlled drug delivery over an extended period of time for gastro retentive drug delivery system.

Keywords: Lovastatin, Statin, Gastro retentive, Floating tablet, Total floating time.

INTRODUCTION

The oral route is considered as the most promising route of drug delivery. Drugs with narrow absorption window in the GIT have poor absorption (Praveen, N. *et al.*, 2010). Therefore, GRDDS have been developed, which prolong gastric emptying time of drug and offers numerous advantages; improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment of small intestine (Gendle, R. *et al.*, 2010). To formulate a successful stomach specific or gastroretentive drug delivery system, several techniques are currently used such as HBS or floating drug delivery systems, low density systems, raft systems, incorporating alginate gels, bioadhesive or mucoadhesive systems, super porous hydrogels and magnetic systems. Swellable, floating and SR tablets are developed by using a combination of hydrophilic polymers (HPMC), swelling agents (crosspovidone and crosscarmellose sodium) and effervescent substances ($NaHCO_3$ and citric acid) (Praveen, N. *et al.*, 2010). Lovastatin a 3-hydroxy-3-methyl glutyryl coenzymeA (HMG coA) reductase inhibitor is a statin with well-known lipid lowering effects that decreases

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cardiovascular morbidity and mortality in patients with and without coronary artery diseases (Ganesh, S.K. *et al.,* 2003; LaRosa, J.C. 2000). Lovastatin is extensively excreted after oral administration; 83% is eliminated in bile and 10% is excreted in urine. It undergoes extensive first pass hydrolysis in liver in to active metabolites like beta-hydroxyacid and 6- hydroxy derivative and hence, the absolute bioavailability of drug in general circulation is very less (<5%).GRDDS might be suitable for lovastatin. Statins are suitable drug candidates for GRDDs. various works have been reported on GRDDS employing statins to overcome the problems associated with oral administration. Floating tablet of fluvastatin was prepared by Asif *et al.,* (2010). Lovastatin and atenolol were combined in floating tablet by Kulkarni and Bhatia (2009) and Sharman *et al.,* (2011) reported GRDDS of atorvastatin calcium. Floating tablet of simvastatin using HPMCK4M was reported by Hussain *et al.,* (2012). With an aim to improve the absorption and oral bioavailability we took an attempt to formulate floating drug delivery systems using lovastatin as the drug candidate employing methocel of various grades like K4, K15 and natural polymers like guar gum.

MATERIALS AND METHODS

Materials

Hydroxypropyl methylcellulose (HPMC K4M, HPMC K15M) was procured from Meditab Specialities Pvt. Ltd., Satara. Guar gum was purchased from S.D fine chemicals, Mumbai. Sodium bicarbonate, citric acid, magnesium stearate, talc were purchased from Mapromax, Life sciences Pvt. Ltd., Dehradun. Other solvents and chemicals used in the research were of LR grade. All the studies were carried in distilled water.

METHODS

Procedure for the determination of λ_{max}

Accurately weighed 10 mg of drug was dissolved in 10 ml of 0.1 N HCl solutions in 10 ml of volumetric flask, to make (1000 µg/ml) standard stock solution (1). Then 1 ml stock solution (1) was taken in another 10 ml volumetric flask to make (100 µg/ml) standard stock solution (2), then again 1 ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 5, 10, 15, 20, and 25 µg/ml with 0.1N HCl. This solution was scan at wavelength 400-200 nm on UV spectrophotometer (Labindia UV 3000 +). The higher absorption peak was obtained at 228 nm which was the λmax of drug.

Fourier transforms infrared (FTIR) spectroscopy

The physical properties of the physical assortment were comparing with those of lovastatin pure drug. Samples was assorted comprehensively through 100mg potassium bromide IR powder as well as compacted under vacuum at a pressure of concerning 12 psi for 3 minutes. The ensuing disc was mounted in an appropriate holder in Brukers Alpha IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Pre Compression Evaluation

Flow properties and compressibility properties of powder mixture were evaluated by measurement of angle of repose, bulk density, tapped density, carr's index and hausner's ratio.

Angle of repose (θ)

The angle of repose was determined by using fixed funnel method. The physical mixtures of drug with different excipients were prepared and the accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The angle of repose was calculated using the following equation**.**

$$\theta = \tan\text{-}1(h/r)$$

Where, h and r are the height and radius of the powder cone respectively.

Bulk density

Both loose bulk density (LBD) and tapped density (TBD) were determined were calculated using the following formulas.

LBD = Powder weight/volume of the packing

TBD = Powder weight /tapped volume of the packing

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index**.**

$$\text{Carr's index (\%)} = [(TBD - LBD)/TBD] \times 100.$$

Hausner's Ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula (Sinko, P.J. 2006; Chein, Y.W. 1992; Liberman, H.A. *et al.,* 1990).

$$\text{Hausner's ratio} = \text{Tapped density/Bulk density.}$$

FORMULATION DEVELOPMENT OF TABLETS

Direct Compression Method

Different tablets formulations (F1-F9) were prepared by direct compression technique. All powders were passed through 40 meshes. Required quantities of drug and polymers were mixed thoroughly Magnesium stearate was added as lubricant. Talc was used as glidant. Lactose was used as diluents. Finally the powder mix was subjected to compression after mixing uniformly in a polybag. Prior to compression, the blends were evaluated for several tests (Ambati, B.R. *et al.,* 2011). The composition of lovastatin floating tablets was shown in Table 1.

Table 1 Formulation composition of lovastatin gastro retentive tablets

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lovastatin	20	20	20	20	20	20	20	20	20
HPMC K 15	100	120	140	-	-	-	50	60	70
HPMC K 4	-	-	-	100	120	140	50	60	70
Gaur gum	15	15	15	15	15	15	15	15	15
Citric acid	5	5	5	5	5	5	5	5	5
$NaHCO_3$	20	20	20	20	20	20	20	20	20
$Mg(C_{18}H_{35}O_2)_2$	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Lactose	80	60	40	80	60	40	80	60	40
Total Weight	250	250	250	250	250	250	250	250	250

Evaluation of tablets

All the tablets were evaluated for following different parameters which includes;

General Appearance

Five tablets from various batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. Appearance was judged visually. Very good (+++), good (++), fair (+) poor (-), very poor (- -).

Thickness and Diameter

Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

Friability

The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab).Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of Weight

Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

Drug Content

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and analyzed for drug content by UV spectrophotometer at a λmax of 228 nm using of 0.1 N HCl as blank.

In Vitro Buoyancy Studies

In vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al.*, (1994). The tablets were separately in a 100 ml glass beaker containing simulated gastric fluid (SGF), pH 1.2 as per USP. The time necessary for the tablet to increase to the outside and float was determined as floating lag time. The experiments were conducted in triplicate. Total floating times were measured during *in vitro* dissolution studies.

Dissolution Rate Studies

In vitro drug release of the sample was done using USP-type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was set into the dissolution flask maintaining the temperature of 37 ± 0.5^0c and rpm of 75. One Betahistine hydrochloride tablet was set in every container of dissolution apparatus. The mechanical assembly was permitted to keep running for 10 hours. Sample measuring 5 ml were pulled back after each 1 hour up to 10 hours using 10ml pipette. The new disintegration medium (37^0C) was supplanted each time with a similar amount of the sample and takes the absorbance at 228nm using spectroscopy (Rajesh, K. *et al.*, 2009; Patil, J.M. *et al.*, 2006; Ritger, P.L., & Peppas, N. A. 1987).

Mathematical Treatment of *In-Vitro* Release Data

The quantitative analysis of the qualities got in dissolution/release tests is simpler when mathematical formulas that express the dissolution comes about as an element of a portion of the measurement frames attributes are utilized.

Zero-Order Kinetics

The pharmaceutical dosage frames following this profile release a similar measure of medication by unit of time and it is the ideal method of medication release keeping in mind the end goal to accomplish a pharmacological prolonged action. The following relation can, in a simple way, express this model:

$$\mathbf{Q_t = Q_o + K_o t}$$

Where Q_t is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution (most times, Q_o=0) and K_o is the zero order release constant.

First-Order Kinetics

The following relation expresses this model:

$$\log Q_t = \log Q_o + \frac{K_1 t}{2.303}$$

Where Q_t is the amount of drug dissolved in time t, Q_o is the initial amount of drug in the solution and K_1 is the zero order release constant.

Along these lines a graphic of the decimal logarithm of the released measure of drug versus time will be linear. The pharmaceutical dosage shapes following this dissolution profile, for example, those containing water-solvent drugs in permeable frameworks, discharge drug in a way that is corresponding to the measure of drug staying in its inside, in such way, that the measure of drug released by unit of time reduce.

Higuchi Model

Higuchi built up a few theoretical models to ponder the arrival of water-solvent and low dissolvable medications in semi-strong or potentially strong grids. Mathematical expressions were acquired for sedate particles scattered in a uniform grid acting as the diffusion media. The simplified Higuchi model is expressed as:

$$Q = K_H \cdot t^{1/2}$$

Where Q is the amount of drug released in time t and K_H is the Higuchi dissolution constant. Higuchi model describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be utilized to portray the drug dissolution from a few kinds of modified release pharmaceutical dosage structures, for example, transdermal systems and matrix tablets with water-dissolvable drugs.

Korsmeyer-Peppas model

Korsmeyer *et al.*, used a simple empirical equation to describe general solute release behaviour from controlled release polymer matrices:

$$\frac{M_t}{M_\infty} = a\, t^n$$

Where M_t/M_∞ is fraction of drug released, is kinetic constant, t is release time and n is the diffusional exponent for drug release. 'n' is the slope value of log M_t/M_∞ versus log time curve. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. Peppas used this n value in order to characterize different release mechanisms, concluding for values for a slab, of *n* =0.5 for fickian diffusion and higher values of *n*, between 0.5 and 1.0, or *n* =1.0, for mass transfer following a non-fickian model. In case of a cylinder *n* =0.45 instead of 0.5, and 0.89 instead of 1.0. This equation can only be used in systems with a drug diffusion coefficient fairly concentration independent. To the determination of the exponent *n* the portion of the release curve where $M_t/M_\infty < 0.6$ should only be used. To use this equation it is also necessary that release occurs in a one-dimensional way and that the system width-thickness or length-thickness relation be at least 10. A modified form of this equation was developed to accommodate the lag time (*l*) in the beginning of the drug release from the pharmaceutical dosage form:

$$\frac{M_{t-l}}{M_\infty} = a\,(t-l)^n$$

When there is the possibility of a burst effect, b, this equation becomes:

$$\frac{M_t}{M_\infty} = at^n + b$$

In the absence of lag time or burst effect, l and b value would be zero and only at^n is used. This mathematical model, also known as *Power Law*, has been used very frequently to describe release from several different pharmaceutical modified release dosage forms (Brahamankar, D.M., & Jaiswal, S.B. 2009; Higuchi, T. 1963; Korsmeyer, R.W. *et al.*, 1983).

Stability studies

The optimized formulation of lovastatin were packed in strips of 0.04 mm thick aluminum foil laminated with poly vinyl chloride by strip packing and these packed formulations were stored in ICH certified stability chambers (Thermo labs, Mumbai) maintained at 40^0C and 75% RH for 6 months. The samples were withdrawn periodically and evaluated for their floating lag time, content uniformity and for in vitro drug release.

RESULTS AND DISCUSSION

Solubility of lovastatin was soluble in distilled water, 0.1 N HCl, 0.1 N NaOH and chloroform, 6.8 pH phosphate buffer and freely soluble in ethanol and methanol. The melting point of lovastatin was 183°C and λ_{max} of lovastatin HCl was found to be 228 nm by using UV spectrophotometer (Labindia-3000+) in linearity range 5-25µg/ml Fig.1. Identification of betahistine was done by FTIR spectroscopy with respect to marker compound. It was identified from the result of IR spectrum as per specification. Tablet powder blend was subjected to various pre-formulation parameters Table 2. The angle of repose values indicates that the powder blend has good flow properties. The bulk density and tapped density of all the formulations was found to be in the range of 0.456 to 0.469 (gm/ml) and 0.573 to 0.589 showing the powder has good flow properties. The compressibility

index and hauser's ratio of all the formulations was found to be ranging between 19.546 to 21.934 and 1.243 to1.281 which shows that the powder has good flow properties. Lovastatin tablet quality control tests such as weight variation, hardness and friability, thickness, drug content and drug release studies in different media were performed on the compression tablet. All the parameters such as weight variation, hardness, friability, thickness and drug content were found to be within limits Table 3.

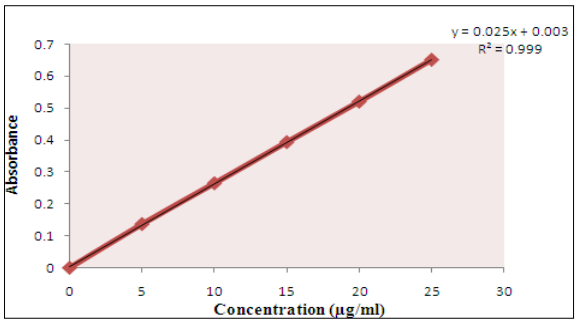

Fig. 1Calibration curve of lovastatin in 0.1 HCL at 228nm

Table 2 Result of pre-compression properties of lovastatin GRF tablets

Material	Bulk density(gm/ml)	Tapped density(gm/ml)	Carr's index	Hauser's ratio
F1	0.456	0.585	22.051	1.283
F2	0.459	0.581	20.998	1.266
F3	0.462	0.587	21.295	1.271
F4	0.461	0.590	21.864	1.280
F5	0.465	0.585	20.513	1.258
F6	0.469	0.589	20.374	1.256
F7	0.468	0.587	20.273	1.254
F8	0.452	0.579	21.934	1.281
F9	0.461	0.573	19.546	1.243

Table 3 Results of post compression properties of lovastatin GRF tablets

F. code	Thickness (mm)	Hardness (kg/cm^2) n=3	Weight variation (mg) n=3	Friability (%) n=3	Drug content (%) n=3
F1	3.22	5.1	248	0.458	98.98
F2	3.25	5.2	256	0.498	99.12
F3	3.26	5.1	250	0.463	98.65
F4	3.21	5.3	255	0.412	99.45
F5	3.20	5.2	248	0.542	97.65
F6	3.25	5.4	247	0.621	98.25
F7	3.24	5.2	253	0.458	99.23
F8	3.25	5.1	251	0.569	97.65
F9	3.26	5.2	250	0.541	98.89

In the present study 9 formulations with variable concentration of polymers (HPMC K4, K 15 and Guar gum) were prepared by direct compression method and evaluated for physicochemical properties. The results of buoyancy lag time, total floating time and *in vitro* drug release was given in Table 4, 5 & Fig.2. The results indicated that optimizes formulation F8 on immersion in 0.1N HCl at 37±0.5^{0}C tablets immediately and remain buoyant upto 12hr without disintegration. These 2 factors are essential for tablets to acquire density< 1, so that it remains buoyant on the gastric fluids. The *in vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, higuchi's and korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of first order was maximum i.e. 0.986 hence indicating drug release from formulations was found to follow first order release kinetics, Table 6, 7 & fig. 5-9.

Table 4 Results of *in-vitro* buoyancy study of lovastatin

F. Code	Floating lag times (sec)	Total floating time (hrs)
F1	110	>12
F2	120	>12
F3	115	>12
F4	123	>12
F5	113	>12
F6	112	>12
F7	110	>12
F8	129	>12
F9	110	>12

Table 5 *In-vitro* drug release study of GRF tablets

Time	% Cumulative Drug Release								
(hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	45.85	42.54	39.98	35.45	30.25	28.74	25.74	22.69	19.89
1	69.98	69.98	65.84	45.85	42.25	33.56	30.12	29.78	29.85
1.5	88.98	85.65	78.85	63.12	55.45	49.98	45.71	39.84	35.78
2	99.12	98.85	89.98	76.45	69.98	59.98	63.78	45.65	42.12
3	-	-	98.22	88.98	85.45	73.12	71.56	65.74	54.65
4	-	-	-	98.81	90.45	88.98	85.69	73.45	65.85
6	-	-	-	-	98.85	92.45	93.47	88.98	72.32
8	-	-	-	-	-	98.85	99.87	94.85	85.45
12	-	-	-	-	-	-	-	99.45	90.12

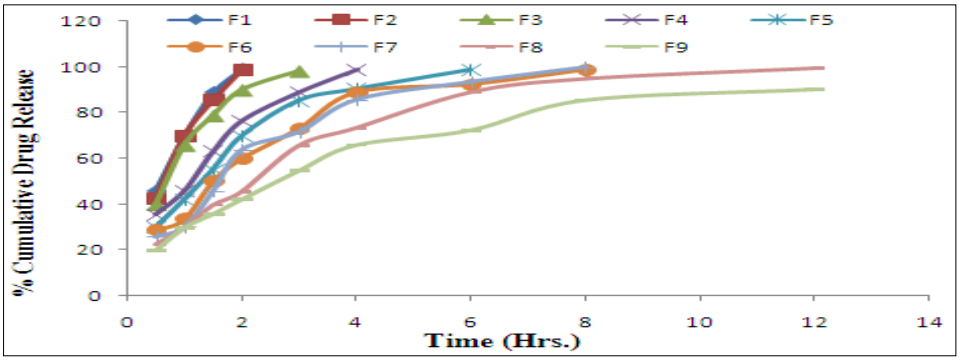

Fig.3 *In-vitro* drug release study of GRF tablets

Table 6 *In-vitro* drug release data for optimized formulation F8

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative*% Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	22.69	1.356	77.31	1.888
1	1	0	29.78	1.474	70.22	1.846
1.5	1.225	0.176	39.84	1.600	60.16	1.779
2	1.414	0.301	45.65	1.659	54.35	1.735
3	1.732	0.477	65.74	1.818	34.26	1.535
4	2	0.602	73.45	1.866	26.55	1.424
6	2.449	0.778	88.98	1.949	11.02	1.042
8	2.828	0.903	94.85	1.977	5.15	0.712
12	3.464	1.079	99.45	1.998	0.55	-0.260

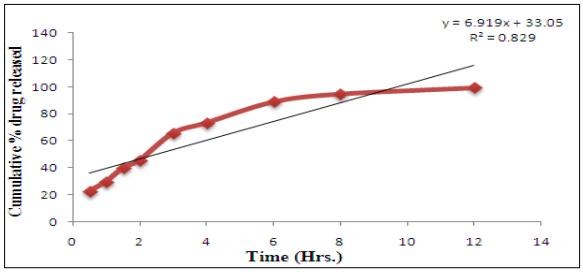

Fig. 4 Zero order release Kinetics

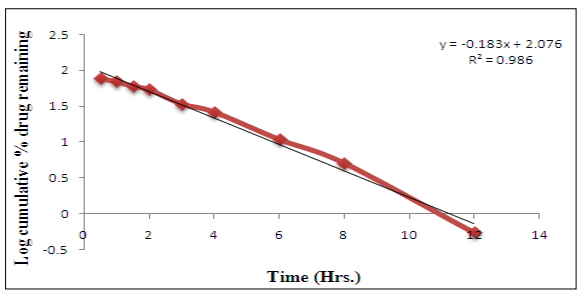

Fig. 5 First order release kinetics

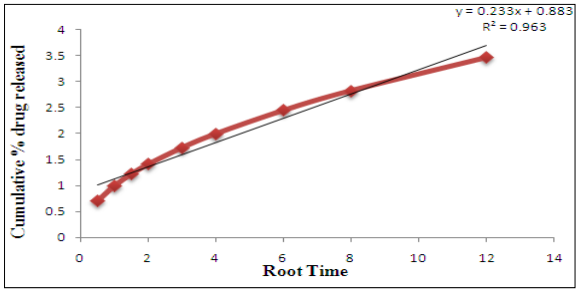

Fig. 6 Higuchi release Kinetics

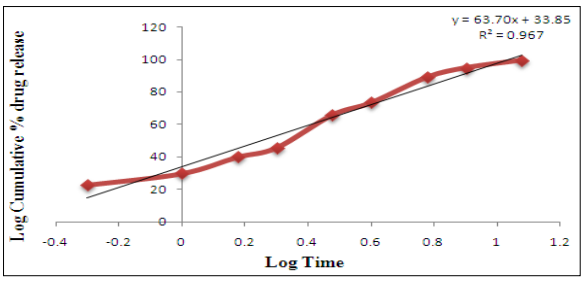

Fig. 7 Korsmeyer-Peppas release Kinetics

Table 7 Regression analysis data of betahistine floating tablets

Batch	Zero Order	First Order	Higuchi	Korsmeyer-Peppas
	R^2	R^2	R^2	R^2
F8	0.829	0.986	0.963	0.967

CONCLUSION

Lovastatin floating tablets were successfully formulated by floating technique. The optimized formulation (F8) was selected on the basis of *in vitro* buoyancy and *in vitro* drug release. The addition of gel forming agent and gas generating agent was essential to achieve *in vitro* buoyancy. The results of the *in vitro* drug release and *in vitro* buoyancy study showed that the optimized formulation (F8) sustained the drug release (99.45) up to 12 hrs and remained buoyant for >12 hrs. Optimized formulation (F8) does not show any significant change in physical appearance, floating properties and drug release after storage at 40°C/75% RH and stable for 3 months.

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