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ORIGINAL RESEARCH ARTICLE

Formulation and Evaluation of Gastroretentive Tablets of Lovastatin using Hydrophilic Rate Retarding Polymers

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ABSTRACT

Gastro retentive floating tablet of Lovastatin was prepared by direct compression technique using various hydrophilic polymers of natural and synthetic grades. The tablets from all formulations were evaluated for thickness, density, weight variation and friability. The tablets were also tested for in-vitro buoyancy, dissolution studies and in-vivo gastric retention test. The drug release study was evaluated for 24hrs using USPXXII paddle dissolution apparatus using 0.1N Hcl as dissolution medium

The optimized formulation (F6) developed were fitted to various kinetic models revealed first order (r^2=0.986) with higuchi kinetics. The drug release was influenced by the amount of polymer incorporation in the formulation

Key words: Lovastatin, Gastroretentive, Floating tablets, Natural polymers.

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.[1] 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.[2]

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, raftsystems, 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).[1]

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.[3,4]

Lovastating is extensively excreted after oral admnstation; 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 bioavailabily 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).[5] Lovastatin and atenolol were combined in floating tablet by Kulkarni and Bhatia (2009) and Sharman et al.,(2011)[6,7] reported GRDDS of atorvastatin calcium. Floating tablet of Simvastatin using HPMCK_4M was reported by Hussain *et al*., (2012). [8]With an aim to improve the absorption and oral bioavailability we took an attempt to formulate floating drug delivery systems using

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lovastatin as the drug candidate employing Methocel of various grades like K4 ,K5, K100M and natural polymers like guargum and xanthum gum.

MATERIALS AND METHODS

Materials:

Lovastatin was received as a gift sample from Natco Pharma ltd, Hyderabad. HPMC K4M, HPMCK15M, HPMCK100M, xanthan gum, guargum was gift samples from Signet chemical corporation Pvt ltd, Mumbai. MCC and PVPK30 were procured from Zydus Cadila ltd, Ahmedabad. Aerosil, Mg stearate was procured from S.D fine chemicals, Mumbai. $NaHCO_3$ was purchased from Merck Specialities Pvt ltd, Mumbai. Hydrochloric acid LR was obtained from Universal chemicals. All other ingredients used were of analytical grade.

Preparation of floating tablets of Lovastatin:

Floating tablet containing lovastatin were prepared by direct compression using variable concentrations of HPMC (K4, K15, K100M) and guargum, xanthan gum by geometric mixing. All the formulation powder blends were passed through 60 mesh sieve to ensure proper mixing. Required quantity of drug and other ingredients were mixed thoroughly. Aerosil (2% w/v) and Mg stearate (1%w/v) were finally added as glidant and lubricant respectively. The blend was directly compressed on 16 station rotary compression machine using 7mm punch. Composition of different formulations of Lovastatin floating tablet (in mg) is shown in (**Table 1 & 2**).

Table 1: Formulae of different floating tablet formulations of Lovastatin formulations F1-F6

Ingredients (mg)	Formulation code					
	F1	F2	F3	F4	F5	F6
Lovasattin	80	80	80	80	80	80
HPMCK15M	25	50				
HPMCK100M			25	50		
HPMCK4M					25	50
Guar gum	-	-	-	-	-	-
Xanthan gum	-	-	-	-	-	-
PVPK30	7	7	7	7	7	7
Sodium bicarbonate	30	30	30	30	30	30
MCC	55.6	30.6	55.6	30.6	55.6	30.6
Aerosil	1.2	1.2	1.2	1.2	1.2	1.2
Magnesium stearate	1.2	1.2	1.2	1.2	1.2	1.2
Total	200	200	200	200	200	200

HPMC= Hydroxy Propyl Methyl Cellulose, PVP= Poly Vinyl Pyrrolidine, MCC= Micro crystalline cellulose

Table 2: Formulae of different floating tablet formulations of Lovastatin formulations F7-F12

Ingredients [mg]	Formulation code					
	F7	F8	F9	F10	F11	F12
Lovasattin	80	80	80	80	80	80
HPMCK15M	-	-	-	-	-	-
HPMCK100M	-	-	-	-	-	-
HPMCK4M	-	-	-	-	-	-
Guar gum	10	20	30	-	-	-
Xanthan gum	-	-	-	10	20	30
PVPK30	7	7	7	7	7	7
Sodium bicarbonate	30	30	30	30	30	30
MCC	70.6	60.6	50.6	70.6	60.6	50.6
Aerosil	1.2	1.2	1.2	1.2	1.2	1.2
Magnesium stearate	1.2	1.2	1.2	1.2	1.2	1.2
Total	200	200	200	200	200	200

HPMC= HydroxyPropylMethylCellulose, PVP= PolyVinylPyrrolidine, MCC= Micro crystalline cellulose

Evaluation of Tablets:

Drug Polymer Interaction Study by IR:

The IR spectra of lovastatin pure drug excipients, physical mixture of drug and excipients were recorded between400-4000cm^{-1}. The IR spectra were obtained using KBr disk method using an FTIR spectrophotometer.

Tablet Thickness:

Thickness of the tablet was measure by using vernier calipers in mm

Hardness Test:

Hardness was carried out by using Monsanto hardness tester.

Friability Test:

Friability of the tablets was tested using Roche Friabilator. Loss of less than 1% in weight is considered to be acceptable. Twenty tablets were weighed and placed in the Electrolab friabilator

and the apparatus was rotated at 25RPM for 4 minutes. After revolutions the tablets were dedusted and weighed again.

The difference in the weight is noted and expressed as %

Percentage friability = $(w_1-w_2)/w_1 x100$

W_1= initial weight of tablets; W_2=weight of tablets after revolution.

Weight Variation Test:

20 tablets were selected at random and the average weight was determined. Not more than 2 of the individual weights deviate from the average weight.

Table 3: IP Standard for Uniformity of weight

S. No	Average Wt of tablet	% of deviation
1	80mg or <80	10
2	>80 to < 250	7.5
3	>250 or more	5

Drug content:

This test is performed by taking 20 tablets randomly, weighed and powdered. The tablet powder equivalent to 200mg of lovastatin was dissolved in 0.1N Hcl in 100ml volumetric flask.

The so formed sample was diluted and the absorbance was measured at 245nm using 0.1N Hcl as blank and the % drug content was estimated using the following formula.

%drug content =Drug content (mg)/label claim (mg) x100

Determination of In-vitro Buoyancy studies:

The in- vitro buoyancy was determined by floating lag time and total floating time. It was determined by using beaker containing 100ml of 0.1N Hcl maintained at 37^{o}C.The time taken by a tablet to rise to the surface of the medium was determined as buoyancy lag time and the duration of which the tablet floats on the surface of the medium was noted as the buoyancy floating time.

Determination of swelling index:

The swelling index of tables was determined in 0.1N Hcl (pH 1.2) at 37^{0}C temperature. The swollen weight of the tablet was determined at predefined time intervals over a period of 5hrs.The swelling index (SI) is expressed as a % and was calculated from the following equation.

S.I=Wt.of tablet at time (t)-Initial wt of tablet/initial wt of tabletx100

In- vitro dissolution studies:

In-vitro dissolution studies of lovastatin floating tablets were carried out using USP type II tablet dissolution apparatus employing a paddle stirrer at 50rpm using 900ml of 0.1N Hcl at 37$\pm$0.5^{0}C as dissolution medium. One tablet was used in each test. At predetermined time intervals 5ml of the samples were withdrawn by means of a syringe fitted with a pre filter. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at 37$\pm$0.5^{0}C .The samples were analysed for drug release by measuring the absorbance at 245nm using UV-visible spectrophotometer after suitable dilutions. All the studies were conducted in triplicate.

In- vitro drug release study:

The results of in-vitro profiles obtained for all the formulations were fitted into four models of data treatment as follows

1. Cumulative percent drug release versus time(Zero order kinetic model)
2. Log cumulative% drug remaining versus time (1st order kinetic model)
3. Cumulative % drug released versus square root of time (Higuchis model)
4. Log cumulative % drug released versus log time (Korsemeyer & Peppas model)

RESULTS AND DISCUSSION

Floating tablets of Lovastatin were prepared by direct compression method. The tablets were evaluated for weight variation test, friability, hardness and thickness for all formulations (F1 to F12). No significant difference was observed in the weight of individual tablets from the average weight.

The hardness of tablets of the all formulations was in acceptable limits (5.2-6.2kg/cm^2).All the formulations showed % friability less than1%, which indicates the ability of tablets to with stand shock. No significant difference was observed in the thickness of individual tablets from the average.

The% drug content of all the tablets was found to be in the range of 98.64% - 100.38%.

Table 4: Physical characterization of prepared tablets

Formulation code	Weight Variation	Hardness (kp)	Friability (%)	Drug Content	Thickness (mm)
F1	198.12±0.87	5.1±0.75	0.16	98.65	3.55±0.01
F2	201.75±1.67	6.0±0.77	0.24	99.24	3.56±0.01
F3	208.26±1.41	5.8±0.73	0.58	98.64	3.54±0.03
F4	205.56±2.13	5.2±0.76	0.13	99.29	3.57±0.02

F5	199.18±1.12	5.9±0.77	0.24	100.38	3.57±0.01
F6	201.62±1.56	5.8±0.74	0.22	99.98	3.56±0.04
F7	204.56±1.11	5.3±0.79	0.11	99.27	3.25±0.01
F8	103.65±1.12	5.2±0.99	0.28	98.89	3.56±0.12
F9	106.78±2.14	6.1±0.32	0.29	99.27	3.55±0.18
F10	209.12±2.13	5.3±0.65	0.26	99.18	3.65±0.01
F11	198.06±2.19	5.5±0.98	0.32	98.82	3.58±0.112
F12	2060.98±1.19	6.4±0.55	0.24	99.16	3.57±0.18

IR spectra of pure Lovastatin (**Fig 1**) and the formulation F6 (**Fig 2**) were found to be identical which indicated no interaction between Lovastatin and used excipients at the incorporated ratio.

The spectra of formulation F6 was clearly composed of identical peaks of Lovastatin and its characteristic peaks were not affected by the presence of excipients used in the formulation. In addition no degradation during manufacturing process was found from IR spectra.

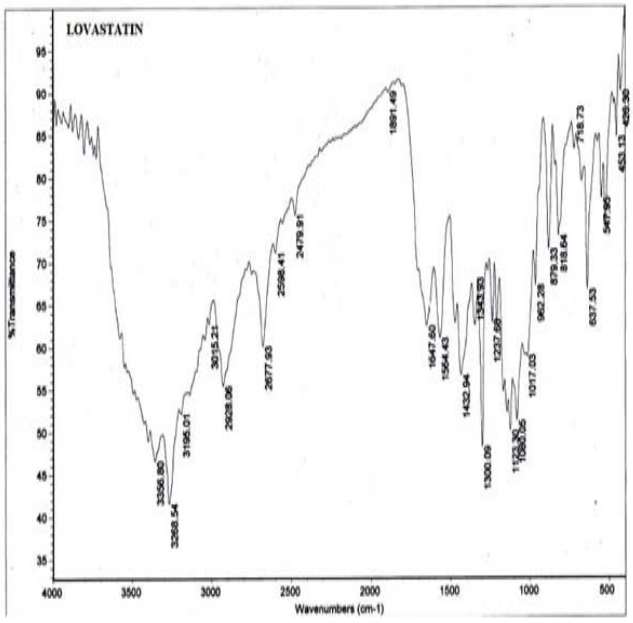

Fig 1: FTIR spectrum of lovastatin

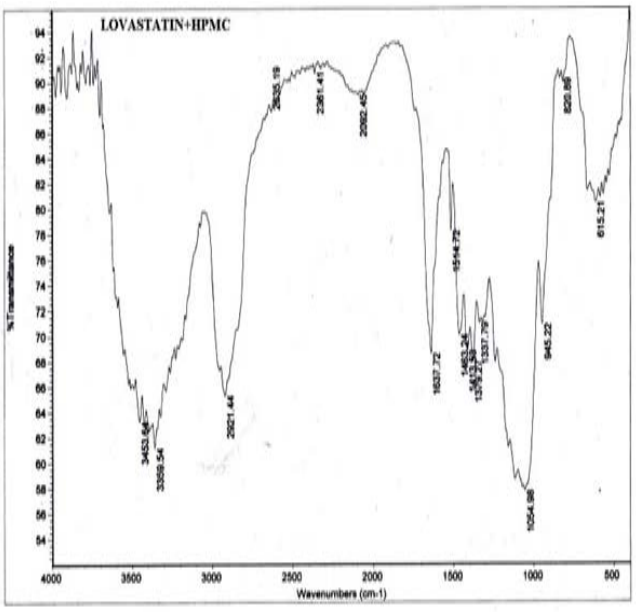

Fig 2: FTIR spectrum of lovastatin+HPMCK4M

Floating lag time and total floating time were determined and the results are shown in (**Table 5**). All the twelve formulations showed the floating lag time within 6-12min.These values were found to be within the limits acceptable to I.P., thus ensuring sustained floating of the formulations, the total floating time of all the formulations were found to be >12hrs and upto24hrs.Based upon the floatation time, the formulation F6 was selected as the best formulation.

Table 5: *In-vitro* Buoyancy studies

Batch	Floating lag time	Total floating time
F1	7 min	>12 hours
F2	8 min	>14 hours
F3	11 min	>14 hours
F4	12 min	>16 hours
F5	11 min	>20 hours
F6	6 min	>24 hours
F7	8 min	>16 hours
F8	10 min	>18 hours
F9	12 min	>22 hours
F10	9 min	>20hours
F11	7 min	>20hours
F12	9 min	>24hours

The swelling index for these formulations from synthetic polymer HPMCK4M (F6); Guargum(F9) and Xanthan gum (F12) was shown in (**Table 6**). Swelling indexes have a direct relationship on tablet floating. Initially the index had found to rise quickly due to rapid water intake of the water soluble matrix. This water intake made the matrix swell and thus reduced the bulk density that is responsible for buoyancy. The total floating time hence, depends on the decrease of bulk density.

Table 6: Determination of swelling index

Time	% SI of F6	% SI of F9	% SI of F12
0	0	0	0
1	27.09	10.7	13.8
2	60.59	29.5	33.2
3	81.28	44.6	60.3
4	94.46	65.6	82.4
5	95.27	86.2	94.0

The cumulative % drug release data obtained for formulations F1 to F6 is plotted in (**Fig 3**).

Formulation F1 and F2 were designed using the polymer Methocel K15M at concentration 12.5% and 25% which were found to be retard the drug release as a function of polymer loading. F1 and

F2 were found to release 98.2% at 12th hr and 98.7% at 14th hr of dissolution in acidic medium.

Formulations F3 F4 were designed using the polymer Methocel K100M at a concentration of 12.5% and 25%, F3 formulation found to release 98.1% at14th hr and 98.1%at 16th hr of dissolution in acidic medium.

Formulation F5 and F6 were designed using the polymer Methocel K4M at a concentration of12.5% and 25%. F5 formulation found to release 95.2% at 18th hr and 99.1 at 24th hr of dissolution in acidic medium

The rate retarding ability of Methocel K4M was reported by Mishra *et al.*,(2006)[9] who claimed that higher viscosity, high molecular weight, slower rate erosion and higher swelling ability render the polymer the ability to retard the rate of drug release.

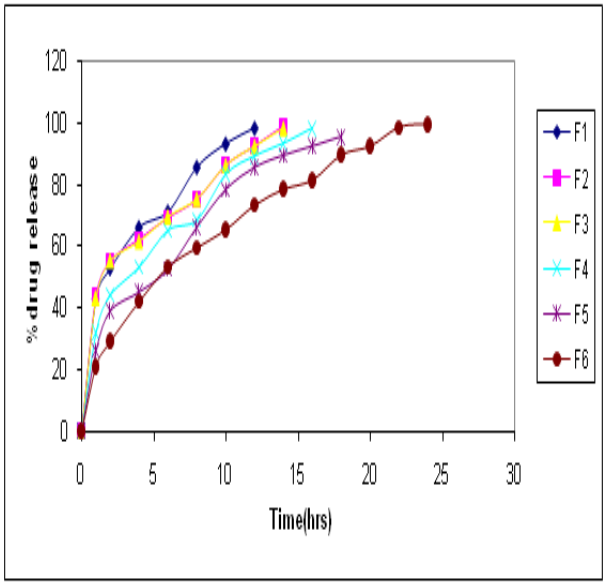

Fig 3: In-vitro drug release profile of lovastatin floating formulations F1 to F6

Formulation F7-F9 were designed using the natural polymer Guargum in the concentration of 5%, 10%, 15%. Formulation F7 released 98.5% at 16th hr and F8 about 97.1% at 16th hr and F9 about 99.1% at 24th hr of dissolution in acidic medium. Formulation F10-F12 was designed using the natural polymer Xanthum gum in the concentration of 5%, 10%, 15%.

Formulation F10, F11, F12 released 96.2% at 14th hr, 97.1% at 18th hr and 98.2% at 22th hr. Though F6 and F9 found to release same amount of drug that is 99.1% at 24th hr, F6 containing Methocel K4M was the optimized formulation based on in-vitro buoyancy studies (Floating lag time and floating time).

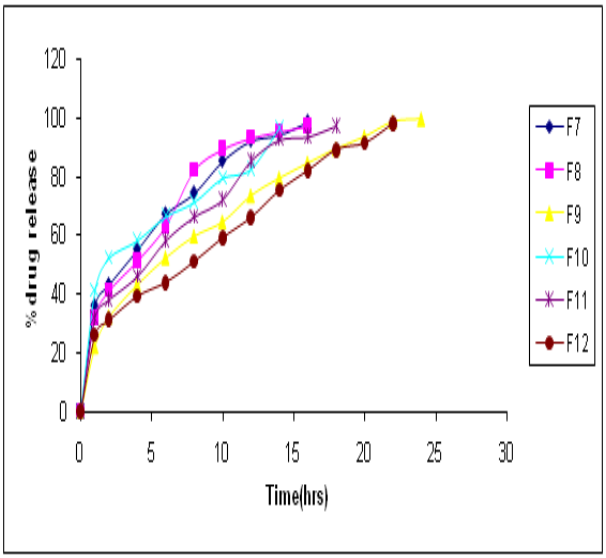

Fig 4: In-vitro drug release profile of lovastatin floating formulations F7 to F12

Methocel K4M has been well known to retard the drug release swelling in aqueous media A polymers ability to retard the drug release rate is related to viscosity. Processing factors including particle size, hardness, porosity and compressibility index etc. can also affect the release rate of drug from tablets (Ebube *et al.*, 1997).[10]

The hydration rate of HPMC depends on the nature of the substituents like Hydroxy propyl group content. Hence, MethocelK4M was used because it forms a viscous gel in contact with aqueous media which may be useful in controlled drug delivery (Gao *et al.*, 1996). [11]

Thus from the cumulative data, it can be concluded that rate controlling ability of MethocelK4M depends on its capacity of forming viscous gel and hence rate retardation is achieved by using the polymer at the higher quantity in the matrix.

In–vitro drug release data of formulation(F6) obtained were fitted to kinetic models Zero order,1st order, Higuchi and Korsemayer-Peppas to know the pattern of drug release and mechanism of drug release from the Matrix tablets.

Formulation F6 followed 1st order with a good coefficient (r^2=0.986) showed good linearity. This indicates that the amount of drug released is dependent on the matrix drug loading.

In-vitro drug dissolution data of F6 formulation showed good linearity to Higuchi model with an r^2 value of 0.999. Incorporation of more the

polymer in the matrix made the drug release profile linear to Higuchi plot.

To confirm the release mechanism of lovastatin from the floating matrix, the data were fitted to Korsemeyer-Peppas equation. Formulation F6 showed r^2 value of 0.998 with slope' n' value of 0.5 indicating that the release mechanism was Fickian diffusion.

Therefore, it can be concluded that the release from the hydrophilic matrix was dependent on drug diffusion from the polymer matrix.

From the kinetic data analysis it was found that the release of the drug from the formulation follows the 1st order and Fickian transport of diffusion.

CONCLUSION

Gastroretentive floating tablets of lovastatin were prepared using various grades of hydrophilic cellulose derivative methocel and natural polymers like guargum and xanthan gum. All the formulations were able to float instantaneously and kept floating for more than 12hrs to more than 24hrs with controlling the release rate throughout the time.

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