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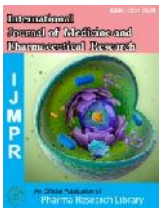

Research Article Open Access

Formulation and Evaluation of Atorvastatin Floating Tablets

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A B S T R A C T

The aim of present study is to formulate and evaluate atorvastatin floating tablets using three different polymers such as HPMC, microcristaline cellulose, magnesium stearate, Atorvastatin is an histamine H2-receptor antagonist drug used against peptic ulcer disease and gastroesophagal reflux To development analytical method for the estimation of selected drug by UV double beam spectrophotometer. Success of the invitro drug release studies recommends the product for further in vivo studies, which may improve patient compliance. From the results, formulation F9 containing Atorvastatin40 mg, Guar gum 60 mg and $NaHCO_3$ 35 mg evolved as the optimized formulation and it releases more than 90% drug in 12hrs.Short-term stability studies of optimized formulation F9 indicate, that there are no significant changes in drug content and dissolution parameter values after 3 weeks storage at 45±1ºC. IR spectroscopic studies indicated that there is no drug-excipient interaction in the optimized formulation. The optimized formulation F9 can be considered as a promising gastro-retentive drug delivery system of Atorvastatin providing nearly zero order drug release over a period of 12 hrs.

Keywords: Atorvastatin, HPMC, H2 Receptor, magnesium stearate, microcristalline cellulose

A R T I C L E I N F O

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1. Introduction

Oral administration is the most convenient and preferred means of any drug delivery. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic

advantages, such as ease of dosing administration, patient compliance and flexibility in formulation.

Progress in Controlled Gastroretentive Delivery Systems

Oral controlled release dosage forms (CRDFs) have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is bedilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract due to variable gastric emptying and motility. Control of placement of a drug delivery system in a specific region of the GItract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem.

- Low density form of the DF that causes buoyancy in gastric fluid.
- High density DF that is retained in the bottom of the stomach.
- Bioadhesion to stomach mucosa.

Suitable Drug Candidates for Gastroretention

Appropriate candidates for CRGRD Fare molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT;

- Drugs those are locally active in the stomach e.g. misroprostol, antacids etc.
- Drugs that disturb normal colonic microbes e.g. antibiotics against H.pylori.

Disadvantages of Gastroretentive Drug Delivery Systems: These drug delivery systems suffer from mainly two adversities:

- The short gastric retention time (GRT).
- Unpredictable short gastric emptying time (GET).

Drug Profile of Atorvastatin

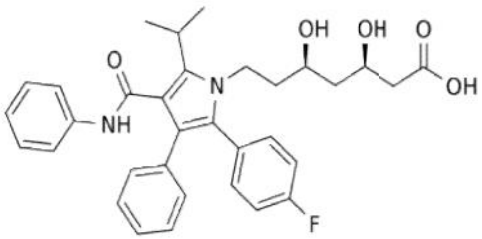

Figure 1: structure of atorvastatin

The molecular formula formuala of atorvastatin C_{33} H_{35} FN_2O_5, Molecular weight was 558.649 g/mol with Half life 14 hrs and Bioavaliability of Drug was 12%. The recomended dose were 10,40 and 80 mg.

Mechanism of Action:

Atorvastatin selectively and competitively inhibits the hepatic enzyme HMG-CoA reductase. As HMG-CoA reductase is responsible for converting HMG-CoA to mevalonate in the cholesterol biosynthesis pathway.

Pharmacokinetics:

Absorption: taken orally, with a maximum plasma concentration (T_{max}) of 1–2 h. Administration of atorvastatin with food produces a 25% reduction in C_{max} (rate of absorption) and a 9% reduction in AUC (extent of absorption),

Distribution:

The mean volume of distribution of atorvastatin is approximately 381 L. It is highly protein bound (≥98%), and studies have shown it is likely secreted into human breast milk.

Metabolism:

Atorvastatin metabolism is primarily through cytochrome P450 3A4 hydroxylation to form active ortho- and parahydroxylated metabolites, the ortho-hydroxy metabolite undergoes further metabolism via glucuronidation. As a substrate for the CYP3A4 isozyme.

Excretion:

Atorvastatin is primarily eliminated via hepatic biliary excretion, with less than 2% recovered in the urine. Bile elimination follows hepatic and/or extra hepatic metabolism.

Pharmacodynamics:

The liver is the primary site of action of atorvastatin, as this is the principal site of both cholesterol synthesis and LDL clearance. It is the dosage of atorvastatin, rather than systemic drug concentration, which correlates with extent of LDL-C reduction.

Medical Uses:

The primary uses of atorvastatin are for the treatment of dyslipidemia and the prevention of cardiovascular disease.

2. Materials and Methods

Materials:

Atorvastatin HCL, HPMC K4M, Xantham gum, Guar gum, Sodium bicarbonate, Mg.stearate, Talk and MCC.

Preformulation Studies:

Drug-Excipient Compatability Studies:

Fourier Transform-Infrared spectroscopic studies

A Fourier Transform – Infra Red spectrophotometer was used to study the non-thermal analysis of drug- excipients (binary mixture of drug: excipients ratio 1:1) compatibility. The spectrum of each sample was recorded over the 450-4000cm^{-1}. Pure drug of Atorvastatin, Atorvastatin with physical mixture (excipients) compatibility studies were performed.

Analytical Method Used in the Determination of Atorvastatin HCL

Preparation of Buffer Solution

Before preparation of floating Tablets, standard curve of Atorvastatin in 0.1HCl was constructed.

Preparation of 0.1N HCl

A 8.65 ml of Conc. HCL was placed in a 1000 ml volumetric flask and the volume was made up with water and pH was adjusted to 1.2.

Preparation of Standard Solution Atorvastatin HCL

Accurately weighed 100mg of Atorvastatin was placed in a 100mL volumetric flask and 50mL of 0.1 N HCl was added to dissolve the drug. The volume was made up to 100mL HCL to give 1000 µg/ml of solution (stock solution -I). A 10mL aliquot from stock solution -I was taken and diluted to 100mL with in a volumetric flask to get 100µg/ml (stock solution -II).

Determination of absorption maxima (λ_{max}) for Atorvastatin HCL

A 1mL aliquot of standard solution standard solution stock solution-II was diluted to 10mL to give 10 µg/ml standard solutions of Atorvastatin in 0.1 N HCL. These solutions were scanned on a UV-Visible spectrophotometer against respective media blank. An absorption maxima (λ_{max}) of 246nm was obtained for all solutions and was selected to prepare standard curve.

Preparation of Standard Curves for Atorvastatin HCL

Aliquots of 0.5, 1, 1.5, 2, 2.5, and 3mL of Atorvastatin standard solution of 100mcg/ml (stock solution-II) was taken and diluted to 10ml to obtain concentrations from 5 to 30µg/ml with 0.1 N HCL. The absorbances of solutions were determined at 246nm against respective media solutions as blank and a standard curve was plotted.

Evaluation of Tablets

1. Angle of Repose (ɵ):

The friction forces in a loose powder can be measured by the angle of repose (ɵ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

$\text{Tan } ɵ = h / r$

$ɵ = \tan^{-1}(h / r)$

Where, ɵ is the angle of repose.

h is the height in cm

r is the radius in cm.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel.

2. Bulk Density (D_b):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by

$Db = M / Vb$

Where,

M is the mass of powder

Vb is the bulk volume of the powder.

3. Tapped Density (D_t):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

$Dt = M / Vt$

Where,

M is the mass of powder

Vt is the tapped volume of the powder.

4. Carr's index (or) % compressibility:

It indicates powder flow properties. It is expressed in percentage and is given by $I = Dt – Db / Dt \text{ X } 100$

Where,

Dt is the tapped density of the powder and Db is the bulk density of the powder.

5. Hausner's ratio: Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

Hausner's ratio = Dt / Db

Where,

Dt is the tapped density

Db is the bulk density.

Lower hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

6. Weight variation: 20 tablets were selected randomly from the batch and weighed individually to check for weight variation. Table -2 Weight Variation Specification as per IP Average Weight Of Tablet % Deviation 80 mg or less ±10. More than 80 mg but less than 250 mg ±7.5. 250 mg or more ±5

7. Hardness (or) tablet crushing strength (fc): Hardness or tablet crushing strength (fc) (the force required to break a tablet in a diametric compression) was measured using Monsanto tablet hardness tester . It is expressed in kg/cm2.

8. Thickness: The thickness of the tablets was measured using vernier caliber. It is expressed in mm.

9. Friability (F): Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at I height of 6 inches in each revolution. Preweighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed.

The friability (F) is given by the formula.

$$F = W_{initial} - W_{final} / W_{initial} \text{ x } 100$$

10. Floating Test: The time between introduction of dosage form and its buoyancy on simulated gastric fluid and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time (TFT).

11. Swelling Index: The individual tablets were weighted accurately and kept in 50 ml of water. Tablets were taken out carefully after 60 minutes, blotted with filter paper to remove the water present on the surface and weighed accurately. Percentage swelling (swelling index) was calculated by using the formula:

$$\text{Swelling index} = W_{wet} – W_{dry} / W_{dry} \text{ x } 100$$

12. *In-vitro* Dissolution Study: The test for buoyancy and *in vitro* drug release studies are usually carried out in simulated gastric and intestinal fluids maintained at 37°C. In practice, floating time is determined by using the USP dissolution apparatus containing 900ml of 0.1 HCL as a testing medium maintained at 37°C. The time required to float the HBS dosage form is noted as floating (or floatation) time. Dissolution tests are performed using the USP dissolution apparatus. Samples are withdrawn

periodically from the dissolution medium, replenished with the same volume of fresh medium each time, and then analyzed for their drug contents after an appropriate dilution. Recent methodology as described in USP XXIII states that the dosage unit is allowed to sink to the bottom of the vessel before rotation of blade is started. A small, loose piece of non reactive material such as not more than a few turns of wire helix may be attached to the dosage units that would otherwise float. However, standard dissolution methods based on the USP or British Pharmacopoeia (BP) have been shown to be poor predictors of *in vitro* performance for floating dosage forms.

Kinetic Analysis of Dissolution Data:

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics.

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.
3. Higuchi's model – Cumulative percent drug released versus square root of time.
4. Korsemeyer Peppa's model – Log cumulative % drug released versus log time.
5. Hixson-Crowell model - cubic root of unreleased fraction of drug versus time.

Zero order kinetics: Zero order release would be predicted by the following equation:

$$\mathbf{A_t = A_0 - K_0 t}$$

Where,

A_t = Drug release at time't'.

A_0 = Initial drug concentration

K_0 = Zero – order rate constant (hr^{-1}).

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys Zero – order release kinetics, with a slope equal to K_0.

First Order Kinetics: First – order release would be predicted by the following equation:

$$\mathbf{Log\ C = log\ C_0 - K_t / 2.303}$$

Where,

C = Amount of drug remained at time't'.

C_0 = Initial amount of drug.

K = First – order rate constant (hr^{-1}).

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line, indicating that the release follow first order kinetics. The constant 'K' can be obtained by multiplying 2.303 with the slope values.

Higuchi's model:

Drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$$\mathbf{Q = [D£ / {}^{2}\ (2\ A - £Cs)\ Cst]^{1/2}}$$

Where,

Q = Amount of drug released at time't'.

D = Diffusion coefficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

Cs = the solubility of the drug in the matrix.

ε = Porosity of the matrix.

τ = Tortuosity.

t = Time (hrs) at which 'q' amount of drug is released.

Above equation may be simplified if one assumes that 'D', 'Cs', and 'A', are constant. Then equation becomes:

$$\mathbf{Q = Kt^{1/2}}$$

When the data is plotted according to equation i.e. cumulative drug release versus square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

Korsmeyer equation / Peppa's model:

To study the mechanism of drug release from the floating tablets of Atorvastatin HCl, the release data were also fitted to the well – known exponential equation (Korsmeyer equation / Peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

$$\mathbf{M_t / M_a = Kt^n}$$

Where

M_t / M_a = the fraction of drug released at time't'.

K = Constant incorporating the structural and geometrical characteristics of the drug / polymer system.

n = Diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying log on both sides,

And we get:

$$\mathbf{Log\ M_t / M_a = LogK + n\ Logt}$$

When the data is plotted as log of drug released versus log time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y – intercept. For Fickian release 'n' = 0.5 while for anomalous (non – Fickian) transport 'n' ranges between 0.5 and 1.0.

Table 1: Mechanism of Drug Release as per Korsemeyer Equation / Peppa's Model

S. No	n value	Drug Release
1	n <0.5	Fickian release
2	0.5<n<1	Non-Fickian release
3	n>1	Case II transport

Stability studies:

Short-term stability studies were performed at a temperature of 45°±1°Cover a period of three weeks (21 days) on the promising HBS tablet formulationF9. Sufficient number of tablets (15) were packed in amber colored screw capped bottles and kept in hot air-oven maintained at 45°±1°C. Samples were taken at weekly intervals for drug content estimation. At the end of three weeks period, dissolution test and *in vitro* floating studies were performed to determine the drug release profiles, *in vitro* floating lag time and floating time.

3. Results and Discussion

The present investigation was under taken to formulate and evaluate floating tablets of Atorvastatin that retain in stomach for longer period using various polymers like HPMC K15M, Xanthan gum and guar gum tablets were prepared along with other additives. Direct compression method was used for the preparation of tablets. A total number of 9formulations were prepared and evaluated. To retain tablet in stomach for long period, most of the excipients selected must be water soluble by nature. This excipient was used a bulking agent to achieve the desired

tablet weight. To impart buoyancy nature sodium bi carbonate included as effervescent agent. Aerosol was employed as a lubricant and magnesium stearate used as glidant. The results obtained by evaluating the powder blends of drug and excipients are shown in (table 4 and 8) .Bulk density and tapped density were found in the range 0.48-0.52 g/cc and 0.57-0.64 g/cc respectively. The value of hausner's ratio was in between 1.17-1.25 (< 1.3) indicating that all batches of powder blends were having good compressibility. Values of angle of repose (θ) was found in the range of 24.05-29.02 showing that blend of powder mass was Good flowing and can be used for direct compression.

The average weight in all the formulations was found to be 248±0.99 mg to 251±0.23 mg. In all formulations no tablets were outside the ±10%of tablet weight in weight variation test. The thickness varies between 1.96 ± 0.7 to 2.02 ± 0.01mm. In all formulations tablet thickness of all formulations was within ±5% of standard value. Friability values were less than 1% in all cases. Hardness of all the tablets was maintained at 3.5 to 4.5 kg/cm^2 for all the formulations. Assay was performed and percent drug content of all the tablets were found to be between 94.41 % and 98.56% of Atorvastatin HCl, which was within the acceptable limits. The swelling index of the tablets increases with an increase in the polymer content and the content of gas generating agent (NaHCO3), as can be seen from the data given in tables 11.

In-vitro dissolution studies are performed for optimized floating tablets of Atorvastatin mixture of solvent 0.1N HCl using USP dissolution apparatus type 2. The dissolution rate was found to increase linearly with increasing concentration of polymer. The optimized formulations are Guar gum containing tablets (F7-F9).Formulations F7, F8, andF9which contained increasing concentrations of Guar gum have recorded drug release 85.32±0.17, 90.38±0.56 and 96.25±0.28 respectively in 12hrs and buoyancy of tablets were maintained up to 24 hrs.

Drug Release Kinetics:

In-vitro drug release data of all the HBS formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer–Peppas models to ascertain the mechanism of drug release. From the above data, it can be seen that all the formulations have displayed first order release kinetics ('r^2' values in the range of 0.81 to 0.97). From Higuchi and Peppas data, it is evident that the drug is released by fickian diffusion mechanism (n=0.91 to 0.98). From the kinetic data of factorial formulations (table-16), it is evident that all the 9 formulations have shown drug release by first order kinetics. Formulation F9 releases drug by first order kinetics with maximum r^2 value (r^2=0.9671).

The values of 'r^2' for Higuchi's equation of formulations range from 0.91 to 0.98 and those of 'n' values of Peppas equation range from 0.42 to 0.51. This data reveals that drug release follows Fickian diffusion mechanism. Short-term stability study was performed on the promising formulation F9 by storing the samples at 45±1ºC for 3 weeks (21 days). The samples were tested for any changes in physical appearance and drug content at weekly intervals. Invitro floating ability and in vitro drug release studies were performed at the end of 3 weeks storage. These results indicate that there were no significant changes in drug content and dissolution profile of the formulation F9 during storage at 45ºC for 3 weeks.

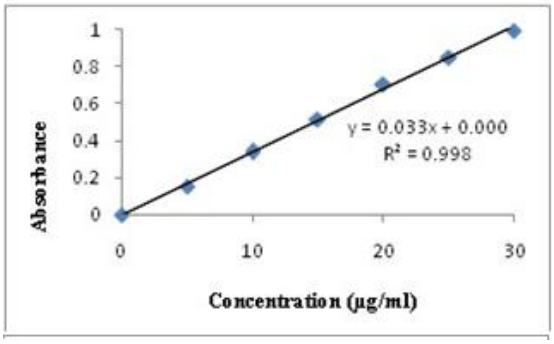

Figure 1: Calibration curve

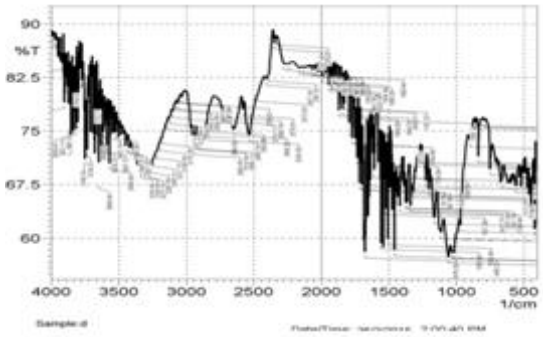

Figure 2: IR spectrum of Atorvastatin

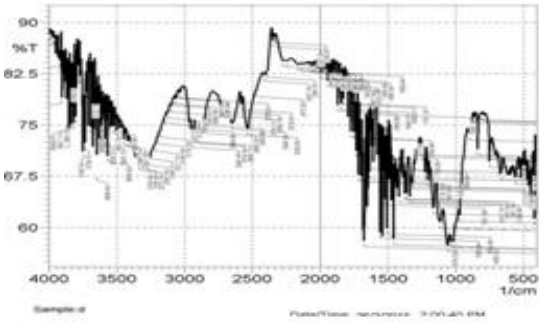

Figure 3: FT-IR spectra of HPMC K4M

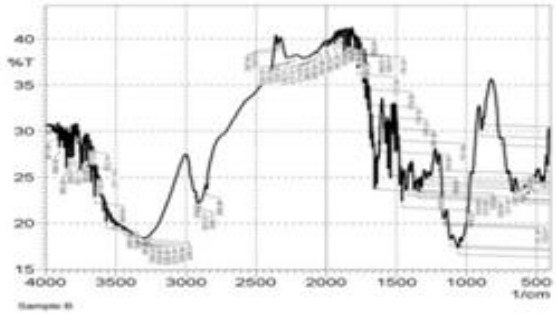

Figure 4: FT-IR spectra of Xanthum gum

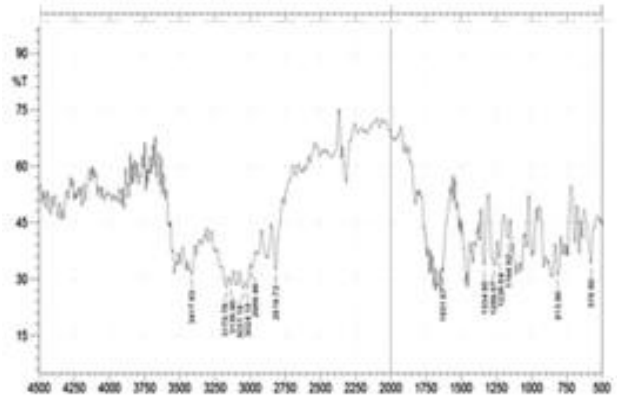

Figure 5: FT-IR spectra of drug and Guar gum

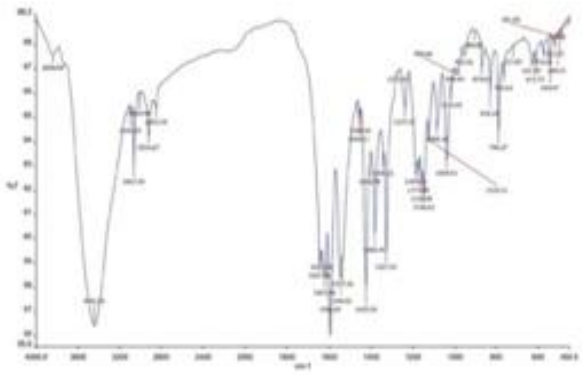

Figure 6: FT-IR Spectra of Drug and excipients profile

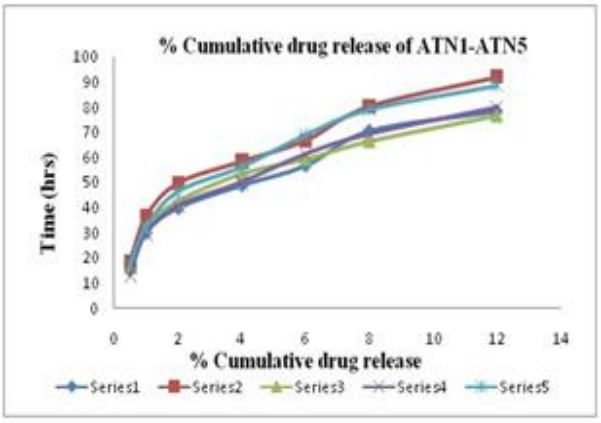

Figure 7: Cumulative drug release for 1-5

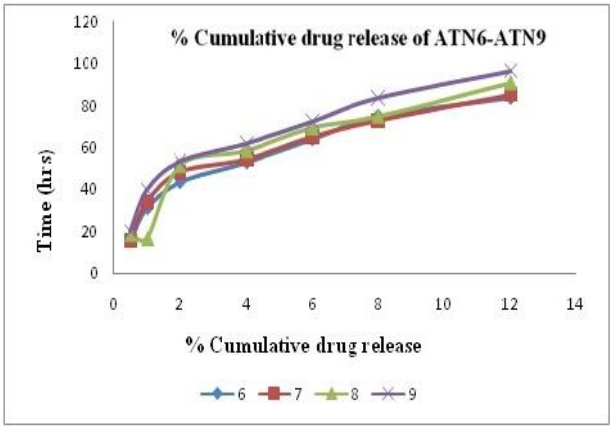

Figure 8: Cumulative drug release for 6-9

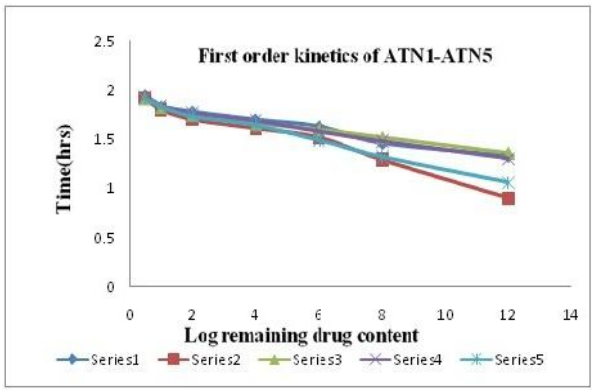

Figure 9: First order plots of 1-5

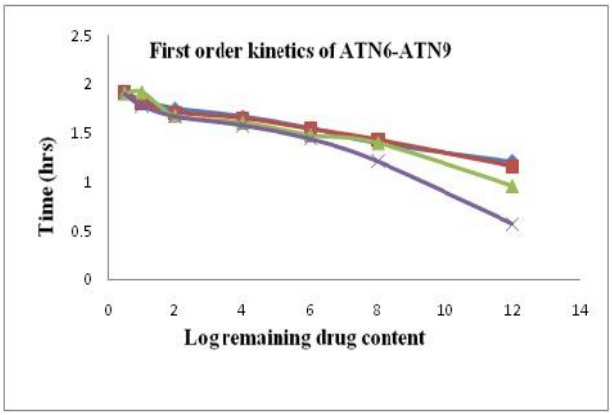

Figure 10: First order plots of 6-9

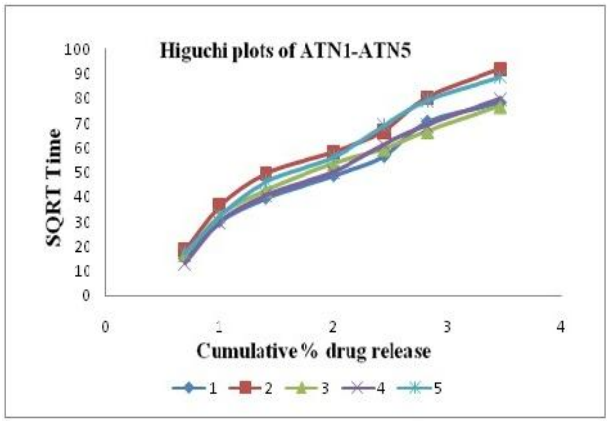

Figure 11: Higuchi plots of 1-5

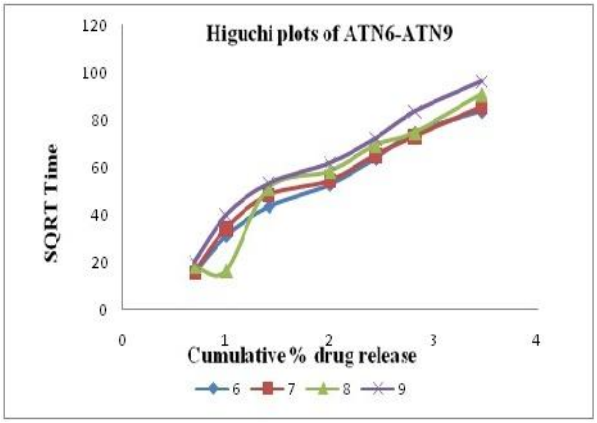

Figure 12: Higuchi plots of 6-9

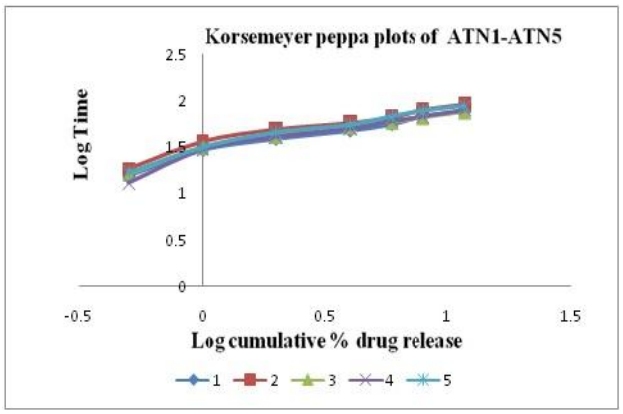

Figure 13: Korsemeyer peppas plots of 1-5

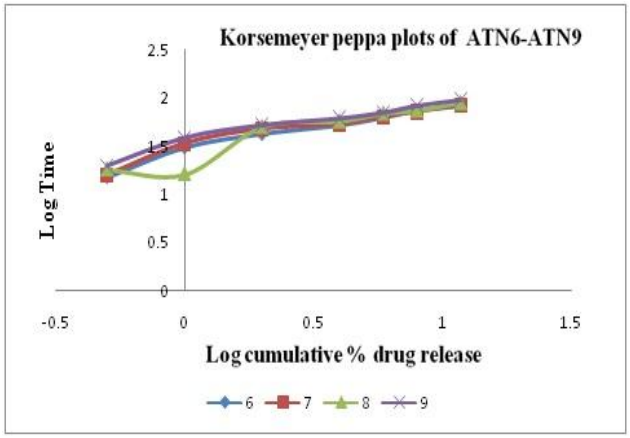

Figure 14: Korsemeyer peppas plots of 6-9

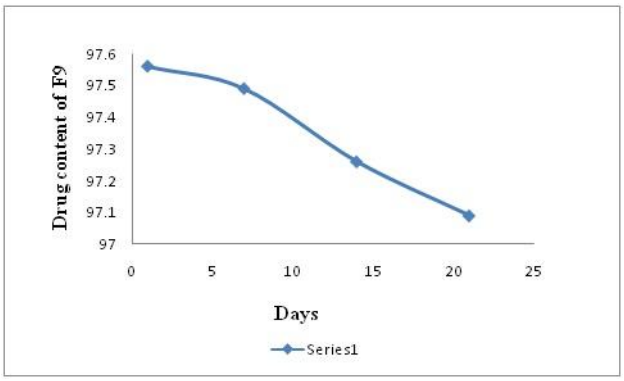

Figure 15: Stability studies of in vitro dissolution profile of F9

4. Conclusion

Success of the i*n-vitro* drug release studies recommends the product for further *in vivo* studies, which may improve patient compliance. From the results, formulation F9 containing Atorvastatin40 mg, Guar gum 60 mg and $NaHCO_3$ 35 mg evolved as the optimized formulation and it releases more than 90% drug in 12hrs.Short-term stability studies of optimized formulation F9 indicate, that there are no significant changes in drug content and dissolution parameter values after 3 weeks storage at 45±1ºC. IR spectroscopic studies indicated that there is no drug-excipient interaction in the optimized formulation. The optimized formulation F9 can be considered as a promising gastro-retentive drug delivery system of Atorvastatin providing nearly zero order drug release over a period of 12 hrs.

Table 2: Calibration curve values

S.no	Concentration (mcg/ml)	Absorbance
1	0	0
2	5	0.155
3	10	0.339
4	15	0.515
5	20	0.707
6	25	0.852
7	30	0.994

Table 3: Interpretation data of Atorvastatin

IR Absorption bands(cm^{-1})		Bond	Functional group
Observed peak	**Characteristic peak**		
1262,1317	1320-1290	C-N stretch C-O stretch	Aromatic amines, esters, alkanes
2531, 2578 2644, 2692 2716, 2765	3300-2500 2830-2695 3000-2850	c-c stretch	Carboxylic acids, alkanes
1153, 1113 1216, 1242	1320-1000 1300-1150 1250-1020 1360-1290 1370-1350	N-O symmetric stretch	Nitro compounds, aromatic compounds
1432, 1465	1500-1400 1470-1450	(m) C-C stretch (in ring)	Aromatic

Table 4: Interpretation data of HPMCK4M

IR Absorption bands(cm^{-1})		Bond	Functional group
Observed peak	**Characteristic peak**		
1318, 1329	1360-1290	N-O symmetric stretch	Nitro compound
1339, 1365	1335-1250	C-N stretch	Aromatic amines
	1320-1000	C-O stretch	Alcohol, carboxylic acids, esters, ethers
	1370-1350	C-H rock	Alkanes
1415, 1457	1500-1400	C-C stretch	Aromatics
1505, 1520	1470-1450	C-H bend	Alkanes
	1550-1475	N-O asymmetric stretch	Nitro compound
1605, 1637	1650-1580	N-H bend	1^{*} amines
1679, 1698	1760-1665	C=O stretch	Carbonyls (general)
1715, 1733	1710-1665	C=O stretch	α,β- unsaturated aldehydes, ketones
1748,	1680-1640	C=C stretch	alkenes
	1760-1690	C=O stretch	carbonyls (general)
	1730-1715	C=O stretch	α,β- unsaturated esters
	1740-1720	C=O stretch	aldehydes, saturated aliphatic
	1750-1735	C=O stretch	esters, saturated aliphatic
2134, 2062	2260-2100	C≠C stretch	Alkanes
2247,	2260-2210	C≠N stretch	Nitriles
2530, 2579	3300-2500	O-H stretch	Carboxylic acid
2645, 2694	2830-2695	H-C=O:C-H stretch	Aldehydes
2717, 2766	3000-2850	C-H stretch	Alkanes

Table 5: Interpretation data of xanthum gum

IR Absorption bands(cm^{-1})		Bond	Functional group
Observed peak	**Characteristic peak**		
1154, 1112	1320-1000	C-O stretch	Alcohol, carboxylic acids,
1206, 1252			Esters, ethers
1283, 1318	1300-1150	C-N stretch	Aliphatic amines
1337, 1357	1250-1020	C-H wag	Alkyl halides
	1335-1250	N-O symmetric	Nitro compound
	1360-1290	C-N stretch	Aromatic compound
	1370-1350	C-H rock	alkanes
1418, 1457	1500-1400	C-C stretch	Aromatics
1522	1470-1450	C-H bend	Alkanes
	1550-1475	N-O asymmetric stretch	Nitro compound
1615, 1634	1650-1580	N-H bend	1^{*} amine
1682, 1696	1760-1665	C=O stretch	Carbonyls (general)
1715, 1735	1710-1665	C=O stretch	α,β- unsaturated aldehydes, ketones
	1760-1690	C=O stretch	Carbonyls (general)
	1740-1720	C=O stretch	Aldehydes, saturated aliphatic
2115, 2137	2260-2100	C≠C stretch	Alkanes
2163, 2228	2260-2210	C≠N stretch	Nitriles

Table 6: Interpretation data of of drug and excipients profile

IR Absorption bands(cm^{-1})		Bond	Functional group
Observed peak	**Characteristic peak**		
1605, 1637	1650-1580	N-Osymmetric stretch	Nitro compounds
1679, 1698	1760-1665	N-H bend	1^{*} amines
1715, 1733	1710-1665	C=O stretch	Carbonyls (general)
1748,	1680-1640	C=O stretch	α,β- unsaturated aldehydes, ketones
	1760-1690	C=C stretch	alkenes
	1730-1715	C=O stretch	carbonyls (general)
	1740-1720	C=O stretch	α,β- unsaturated esters
	1750-1735	C=O stretch	aldehydes, saturated
		C=O stretch	aliphatic

			esters, saturated aliphatic
1670	1670-1665	(s) C=O stretch	Carbonyls (general)
	1710-1665	(s) C=O stretch	a , ß unsaturated aldehydes, ketones
1154, 1112 1206, 1252 1283, 1318 1337, 1357	1320-1000 1300-1150 1250-1020 1335-1250 1360-1290 1370-1350	C-O stretch C-N stretch C-H wag N-O symmetric C-N stretch C-H rock	Alcohol, carboxylic acids, Esters, ethers Aliphatic amines Alkyl halides Nitro compound Aromatic compound alkanes
1332, 1363	1360-1290 1335-1250 1370-1350	(m) N-O symmetric stretch (s) C-N stretch (m) C-H rock	Nitro compounds Aromatic amines alkanes

Table 7: Interpretation data Guar gum

IR Absorption bands(cm^{-1})		**Bond**	**Functional group**
Observed peak	**Characteristic peak**		
749, 812, 834	1000-650	(s) =C-H bend	Alkenes
	900-675	(s, b) N-H wag	1^o, 2^o amines
	910-665	(s) C-H “oop”	Aromatics
	850-550	(m) C-Cl stretch	Alkyl halides
1332, 1363	1360-1290	(m) N-O symmetric stretch	Nitro compounds
	1335-1250	(s) C-N stretch	Aromatic amines
	1370-1350	(m) C-H rock	alkanes
1432, 1465	1500-1400	(m) C-C stretch (in ring)	Aromatic
	1470-1450	(m) C-H bend	Alkanes
1509	1550-1475	(s) N-O asymmetric stretch	Nitro compounds
1602, 1628	1650-1580	(m) N-H bend	1^0 amines
1670	1670-1665	(s) C=O stretch	Carbonyls (general)
	1710-1665	(s) C=O stretch	a , ß unsaturated aldehydes, ketones
	1680-1640	(m) –C=C- stretch	alkenes
3055	3300-2500	(m) O-H stretch	Carboxylic acid
	3100-3000	(s) C-H stretch	Aromatics
	3100-3000	(m) =C-H stretch	alkenes

Table 8: Pre compression parameters

S. no	**Formulation**	**Angle of repose**	**Bulk density**	**Tapped density**	**Carrr’s index**	**Hausners ratio**
1	F1	29.05±0.06	0.49±0.03	0.64±0.05	20.26±0.07	1.17±0.06
2	F2	27.02±0.03	0.53±0.07	0.62±0.04	15.15±0.02	1.18±0.03
3	F3	25.04±0.12	0.54±0.05	0.61±0.06	18.39±0.07	1.18±0.03
4	F4	28.06±0.09	0.51±0.02	0.65±0.07	14.16±0.03	1.23±0.07
5	F5	27.02±0.02	0.49±0.03	0.63±0.03	17.18±0.05	1.25±0.05
6	F6	26.03±0.05	0.52±0.05	0.61±0.03	21.85±0.05	1.27±0.04
7	F7	26.06±0.03	0.48±0.02	0.59±0.05	19.25±0.01	1.19±0.08
8	F8	25.09±0.07	0.52±0.07	0.58±0.04	15.21±0.06	1.21±0.03
9	F9	24.05±0.08	0.51±0.02	0.57±0.02	12.35±0.08	1.15±0.05

Table 9: Post compression parameters

Formulation Code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability	Floating lag time (sec)	Floating Duration (hrs)
F1	250.2±0.86	2.01±0.03	3.5	0.54	118	>24
F2	251.8±0.67	1.95±0.07	3.5	0.51	58	>24
F3	249±0.48	1.98±0.03	3.5	0.49	55	>24
F4	250.6±0.99	2.02±0.01	4.5	0.52	105	>24
F5	251.6±0.69	1.96±0.07	4	0.51	300	>24
F6	249.9±0.76	2.01±0.02	4.5	0.48	250	>24
F7	248.4±0.99	1.99±0.06	3.5	0.53	50	>24
F8	250.8±0.76	1.98±0.05	4.5	0.52	150	>24
F9	250.6±0.86	2.01±0.02	4.5	0.51	200	>24

Table 10: Swelling index data

Formulation Code	Swelling Index ±SD
F1	22.4±1.79
F2	20.07±2.14
F3	23.67±1.20
F4	218.63±1.53
F5	19.76±1.42
F6	21.80±1.75
F7	28.69±1.61
F8	29.45±1.21
F9	30.12±1.53

Table 11: Dissolution profile of all formulations

Time (hrs)	% Cumulative drug release								
	1	2	3	4	5	6	7	8	9
0.5	15.72	18.65	16.39	13.16	17.35	15.35	15.86	18.35	20.04
1	29.94	36.32	32.3	29.81	32.15	30.96	34.15	16.38	39.69
2	39.70	49.65	42.6	40.75	46.25	43.35	48.34	51.26	53.14
4	48.82	58.34	53.5	50.18	56.12	52.75	54.36	58.34	61.75
6	56.63	66.7	59.4	61.26	68.86	63.78	65.18	69.35	72.16
8	70.50	80.24	66.54	69.15	78.96	74.72	72.98	74.75	83.45
12	78.34	91.89	76.8	79.76	88.5	83.62	85.32	90.8	96.25

Table 12: Dissolution profile of First order

Time (hrs)	Log Remaining drug content								
	1	2	3	4	5	6	7	8	9
0.5	1.95	1.91	1.92	1.93	1.91	1.92	1.92	1.91	1.9
1	1.84	1.8	1.83	1.84	1.83	1.83	1.81	1.92	1.78
2	1.78	1.7	1.75	1.77	1.73	1.75	1.71	1.68	1.67
4	1.7	1.61	1.66	1.69	1.64	1.67	1.65	1.61	1.58
6	1.63	1.52	1.6	1.58	1.49	1.55	1.54	1.48	1.44
8	1.46	1.29	1.52	1.48	1.32	1.4	1.43	1.4	1.21
12	1.33	0.9	1.36	1.3	1.06	1.21	1.16	0.96	0.57

Table 13: Dissolution profile of all formulations

SQRT Time	Cumulative % drug release								
	1	2	3	4	5	6	7	8	9
0.70	15.72	18.65	16.39	13.16	17.35	15.35	15.86	18.35	20.04
1	29.94	36.32	32.3	29.81	32.15	30.96	34.15	16.38	39.69
1.41	39.70	49.65	42.6	40.75	46.25	43.35	48.34	51.26	53.14
2	48.82	58.34	53.5	50.18	56.12	52.75	54.36	58.34	61.75
2.44	56.63	66.7	59.4	61.26	68.86	63.78	65.18	69.35	72.16
2.82	70.50	80.24	66.54	69.15	78.96	74.72	72.98	74.75	83.45
3.46	78.34	91.89	76.8	79.76	88.5	83.62	85.32	90.8	96.25

Table 14: Dissolution profile of all formulations

Log Time	Log cumulative % drug release								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
-0.30	1.19	1.27	1.21	1.11	1.23	1.18	1.20	1.26	1.30
0	1.47	1.56	1.50	1.47	1.50	1.49	1.53	1.21	1.59
0.30	1.59	1.69	1.62	1.61	1.66	1.63	1.68	1.70	1.72
0.60	1.68	1.76	1.72	1.70	1.74	1.72	1.73	1.76	1.79
0.77	1.75	1.82	1.77	1.78	1.83	1.80	1.81	1.84	1.85
0.90	1.84	1.90	1.82	1.83	1.89	1.87	1.86	1.87	1.92
1.07	1.89	1.96	1.88	1.90	1.94	1.92	1.93	1.95	1.98

Table 15: Order of kinetics

Formulation Code	Zero Order	First Order	Higuchi	Korsmeyer Peppas	
	R^2	R^2	R^2	R^2	N
F1	0.9229	0.9273	0.9842	0.9671	0.4992
F2	0.7242	0.8152	0.9192	0.9140	0.4271
F3	0.8689	0.9697	0.9750	0.9362	0.4688
F4	0.8473	0.9649	0.97850	0.9359	0.5148
F5	0.8288	0.9575	0.9731	0.9587	0.4753
F6	0.8319	0.9521	0.9737	0.9488	0.4896
F7	0.8571	0.9689	0.9774	0.9411	0.4918
F8	0.7957	0.9593	0.9582	0.9288	0.4414
F9	0.7998	0.9738	0.9605	0.9343	0.4361

Table 16: Stability data of optimized formulation

S.NO	Formulation no.	1st day (%)	7thday	14thday	21st day
1	F9	97.56	97.49	97.26	97.09

Table 17: *In-vitro* release data of the optimized formulation (F9)

S. no	Time (hr)	Cumulative Percent Drug Released ± SD at 45±1ºC	
		1st day	21st day
1	0.5	20.04±0.28	18.56±0.52
2	1	39.69±0.98	37.12±0.86
3	2	53.14±0.56	50.29±0.15
4	4	61.75±0.18	59.01±0.29
5	6	72.16±0.46	69.92±1.01
6	8	83.45±1.04	81.15±0.76
7	12	96.25±0.28	94.12±0.12

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