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In vitro - in vivo evaluation of E/R trilayer matrix tablets containing solid dispersion of atorvastatin

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Abstract

Investigation of in vitro/in vivo behavior of extended release tablets containing solid dispersions of Atorvastatin is the focus of the present research work. Atorvastatin trilayer matrix tablets were prepared by direct compression method and consisted of middle active layer with different grades of hydroxypropylmethylcellulose (HPMC), ethyl cellulose and Carbopol 934P. Barrier layers are prepared with hydrophobic polymers carnauba wax and xanthan gum. Based on the evaluation parameters, drug dissolution profile and release order kinetics HF16 was found to be optimized formulation. The developed drug delivery system provided prolonged drug release rates over a period of 24 h. The release profile of the optimized formulation (HF16) was described by the Zero-order and best fitted to Higuchi model. FTIR confirmed that there was no chemical interaction between drug and excipients used in the formulation. . In vivo bioavailability studies were conducted for optimized formulation HF16 and reference standard. The optimized formulation of Atorvastatin trilayer matrix tablet was shown significant plasma concentration with extended release and maintained for 24 hrs with patient compliance by reducing the dosage frequency, when compared with reference standard.

Keywords: Atorvastatin, Carbopol 934P, Geometric, Trilayer matrix tablet, In-vivo bioavailability studies.

Introduction

Solid dispersions refer to a system in which hydrophobic drug is dispersed in hydrophilic matrix, in order to improve its dissolution properties and bioavailability. In solid dispersion, a drug can exist in an amorphous or crystalline form in hydrophilic polymeric carriers, which results in improved solubility and dissolution rates [1].

Many problems are associated with conventional multiple dosing regimen of long acting therapy, such as systemic accumulation of the drug leading to side effects or toxicities, irregular profile of the plasma drug level, and poor patient compliance. Controlled release drug delivery systems have the potential of solving these problems. Controlled release systems are the methods that can achieve therapeutically effective concentration of drug in the systemic circulation over an extended period of time with better patient compliance [2].

There are many ways to design modified release dosage forms for oral administration and one of them is multi layered matrix tablet. One to three layer matrix tablets is a drug delivery device, which comprises a matrix core containing the active solute and one or more barriers incorporated during tab letting process [2]. The presence of the barriers-layers modifies the hydration/swelling rate of the core and reduces the surface area available for drug release [3]. The barrier layers delay the interaction of active solute with dissolution medium, by limiting the surface available for the solute release and at the same time controlling solvent penetration rate [4,5]. Hydrophilic polymers have been given considerable attention in the formulation of controlled release drug delivery systems for various drugs. HPC, HPMC and sodium CMC & Carbopol are a few representative examples of the hydrophilic polymers that have been extensively used in the formulation of controlled release systems [6]. Guar gum is soluble in water, it swells in gastric fluid to produce a highly viscous layer around the tablet through which the drug can slowly diffuse [7], and is used for the fabrication of matrices with uniform drug release characteristics [8,9].

Geometric technology: There have been different approaches to achieve zero-order drug release from dosage forms for sustained plasma concentration. Among different approaches to achieve zero-order release from hydrophilic matrix technologies, multilayer matrices have been widely evaluated and developed for commercial products under the trade name of Geometric. The technology makes use of belayed or trilayer tablets to modulate the release and to achieve constant release [10].

Atorvastatin is a white crystalline powder, molecular formula: $(C_{33}H_{34}FN_2O_5)_2$ $Ca.3H_2O$, molecular weight: 1209.12, bioavalability-12%, and half life: 14hrs. It is a selective competitive HMG-COA reductase inhibitor drug that lowers the level of cholesterol in the blood and triglycerides in patients with hypercholesterolemia [11].

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The objective of the present study was to develop a trilayered controlled release matrix tablet containing Atorvastatin solid dispersion with different hydrophobic and hydrophilic polymers to achieve zero-order drug release for sustained plasma concentration.

Materials and methods

Materials

Atorvastatin calcium pure drug was generous gift from Aurobindo Pharma Ltd, Hyderabad, India Carbopol 934P, Ethyl cellulose, HPMC K 15 M & HPMC K 100 M was obtained from Rubicon labs, Mumbai. Xanthan gum was gifted from MSN Labs Ltd. Hyderabad. All other chemicals used were of analytical grade.

Methods

Micromeretic Studies of Atorvastatin

Angle of Repose: In powder frictional forces can be measured with the help of angle of repose. Angle of repose is the maximum angle which is possible between surface of pile of powder and horizontal plane i.e. height.

tan= h/r

$=\tan^{-1}h/r$

Where = Angle of repose

h= height of pile

r = radius of pile[13]

Carr's compressibility Index: The propensity of the powder to be compressed is measured by compressibility index and it also helps in measurement of settling property and inter particulate interaction.

Carr's index (%) = $\rho t - \rho o^* 100 / \rho t$

Where ρt = Tapped density gram/ml

ρo = Bulk density gram/ml

Bulk Dentistry: It is denoted by ρb and is defined as mass of powder divided by bulk volume (The United States Pharmacopeial Convention Stage 6 Harmonization Official December 1, 2012, 616.).

Tapped Density: An increase in bulk density which is attained after mechanical tapping in measuring cylinder is called as tapped density

Tapped density= Weight of powder taken/ Tapped Volume.

Hausner Ratio: The propensity of the powder to be compressed is measured by Hausner ratio. Interparticulate interaction and settling property can be measured by Hausner ratio.

Hausner ratio= Tapped density/ Bulk density

Hausner ratio= Vo/Vf

Where, Vo= Unsettled apparent volume

Vf= Final tapped volume[14]

Formulation of controlled release Atorvastatin trilayer matrix tablets

The trilayered matrix tablets of Atorvastatin were prepared by direct compression method. The first step in the formulation was to develop the middle active layer so as to give at least 90%drug release during 12hours. The release profile of this layer might not be of constant rate type but would be preferably of constantly falling rate type. This layer would then be sandwiched between barrier layers (Upper & Lower layers) so as to continue the drug release for 24hours.

Preparation of middle active layer

Sixteen formulations (F1-F16) for active layer were prepared by direct compression method using polymers like different HPMC grades, Carbobopol 934P and Ethyl Cellulose. All the formulations were varied in concentration of polymers, talc (1.5mg) & magnesium stearate (1.5mg) constituted in all the formulations. These materials were screened through 60 and mixed together in motor by using pestle. Final mixtures were compressed by using 12mm diameter flat punches on a sixteen station rotary tablet press. Formulation of active layer was depicted in Table 1. The prepared tablets were subjected to dissolution studies.

Formulation of controlled release Atorvastatin trilayer matrix tablets

The trilayered matrix tablets of Atorvastatin were prepared by direct compression method. The first step in the formulation was to develop the middle active layer so as to give at least 90%drug release during 12hours. The release profile of this layer might not be of constant rate type but would be preferably of constantly falling rate type. This layer would then be sandwiched between barrier layers (Upper & Lower layers) to achieve the drug release for 24hours.

Formulation trails for active layer

Sixteen formulations (F1-F16) for active layer were formulated using polymers like different grades of HPMC (HPMC K15M & HPMC K100M) and xanthan gum. All the formulations were varied in concentration of release retardant polymers and the solid dispersion of Atorvastatin [12], talc (1.5mg) & magnesium stearate (1.5mg) constituted in all the formulations. These materials were screened through 60 and mixed together in motor by using pestle. Final mixtures were compressed by using 12mm diameter flat punches on a sixteen station rotary tablet press where only one station was operative and other station were nullified Formulation F1-F16 containing drug and other polymers prepared under condition as showed in table.

Table 1: Formulation trails for active layer (F1-F8)

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Atorvastatin (Solid dispersion equivalent to 20mg of Atorvastatin)	80	80	80	80	80	80	80	80
HPMC K 15M	18	21	25	28	30	33	35	38
HPMC K 100M	---	---	---	----	---	----	----	----
Ethyl cellulose	14	11	12	11	10	9	8	8
Xanthan gum	12	13	10	10	12	9	9	9
Carbopol 934P	11	10	10	9	8	8	8	6
Dibasic calcium phosphate	12	12	10	9	7	8	7	6
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Table 2: Formulation trails for active layer (F9-F16)

INGREDIENTS (mg)	F9	F10	F11	F12	F13	F14	F15	F16
Atorvastatin (Solid dispersion equivalent to 20mg of Atorvastatin)	80	80	80	80	80	80	80	80
HPMC K 15M	---	---	---	----	---	----	----	----
HPMC K 100M	18	21	25	28	30	33	35	38
Ethyl cellulose	14	11	12	11	10	9	8	8
Xanthan gum	12	13	10	10	12	9	9	9
Carbopol 934P	11	10	10	9	8	8	8	6
Dibasic calcium phosphate	12	12	10	9	7	8	7	6
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Preparation of barrier layers

The barrier layers (Upper & Lower layers) was formulated employing hydrophobic polymers Carnauba wax and Xanthan gum, which include water soluble DCP & EC. Composition of barrier layers was depicted in Table 3.

The procedure tried to make the compacts was via direct compressions. For the first procedure the carnauba wax, xanthan gum and the filler was mixed in mortar and lubricated with magnesium stearate. The mix is then compressed using rotary press having 12mm flat tooling.

Table 2: Formulation trails for barrier layer

Ingredients (mg)	A	B	C	D	E	F	G	H
Carnauba wax	5	10	15	20	25	30	35	40
Xanthan gum	22	24	22	18	20	22	20	20
Ethyl cellulose	20	16	20	17	18	10	12	12
Dibasic calcium Phosphate	50	47	40	42	34	35	30	25
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Formulation of Atorvastatin tryilayer tablets

The powder mixtures required for active and barrier layers were weighed accurately and thoroughly mixed using mortar and pestle for about 20minutes. Initially, the volume of die cavity (12mm, round) was adjusted equivalence to the weight of trilayered matrix tablets (350mg). Then the pre weighed amount of powder equivalent to bottom layer (100mg) was taken and placed in the die cavity and slightly compressed for uniform spreading. The upper punch was lifted up and 150mg of the drug containing middle active layer optimized formulation (F15) was placed over the bottom layer in the die cavity and again slightly compressed. The remaining volume of the die cavity was filled with pre weighed (100mg) amount of powder equivalent to top layer and compressed with the full force of compression on rotary tablets press to obtain tri-layered tablets. Tri-layered matrix tablets of each composition were compressed and tested for their friability, Hardness, drug content and drug release characteristics with a suitable number of tablets for each test.

Table 3: Trilayer tablet composition

Ingredients (mg)	AF16	BF16	CF16	DF16	EF16	FF16	GF16	HF16
MIDDILE LAYAER (F16)								
Atorvastatin (SD equivalent to 20mg)	80	80	80	80	80	80	80	80
HPMC K 100M	38	38	38	38	38	38	38	38
Ethyl cellulose	8	8	8	8	8	8	8	8
Xanthan gum	9	9	9	9	9	9	9	9
Carbopol 934P	6	6	6	6	6	6	6	6
Dibasic calcium phosphate	6	6	6	6	6	6	6	6
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
BARRIER LAYER (on each side)								
Carnauba wax	5	10	15	20	25	30	35	40
Xanthan gum	22	24	22	18	20	22	20	20
Ethyl cellulose	20	16	20	17	18	10	12	12
Dibasic calcium phosphate	50	47	40	42	34	35	30	25
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Ingredients(mg)	AF15	BF15	CF15	DF15	EF15	FF15	GF15	HF15
MIDDILE LAYAER (F15)								
Atorvastatin SD	320	320	320	320	320	320	320	320
HPMC K 100M	45	45	45	45	45	45	45	45
Ethyl cellulose	09	09	09	09	09	09	09	09
Xanthan gum	08	08	08	08	08	08	08	08
Sodium CMC	08	08	08	08	08	08	08	08
Dibasic calcium phosphate	07	07	07	07	07	07	07	07
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
BARRIER LAYER (on each side)								
Carnauba wax	5	10	15	20	25	30	35	40
Xanthan gum	22	24	22	18	20	22	20	20
Ethyl cellulose	20	16	20	17	18	10	12	12
Dibasic calcium phosphate	50	47	40	42	34	35	30	25
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Evaluation of Matrix and Tri-Layered Tablets

Weight variation

The weight variation test was performed as per the I.P. guidelines. Twenty randomly taken tablets were weighed together and the average weight was determined. Each tablet was then weighed individually and deviation from average weight was calculated.

Hardness

Hardness of ten randomly picked tablets was determined using Monsanto hardness tester.

Friability

A sample of twenty randomly selected tablets were accurately weighed and placed in a Roche Friabilator. The Friabilator was operated for 4 min at a speed of 25 rpm. The tablets were removed

from the Friabilator, de-dusted and reweighed. The percent loss in weight due to abrasion and impact was calculated as,
%Friability= (Loss in weight/ Initial weight) X 100.

Drug content / Assay

20 tablets were accurately weighed and powdered.10mg equivalent powder was dissolved in 50ml distilled water and sonicated for 15 minutes. It was filtered and washed with distilled water. Filtrate and washings were combined. Final volume was made up to 100ml with distilled water. Absorbance of this solution was determined in a UV spectrophotometer at 247nm. Amount of Atorvastatin in tablets was calculated by using regression equation.

In-vitro drug release profile

In vitro drug release studies for developed trilayer matrix tablets were carried out by using dissolution apparatus II paddle type (Electro lab TDL-08L). The drug release profile was studied in 900ml Phosphate buffer pH 6.8 at 37± 0.5^0C temperature. The amount of drug release was determined by UV visible spectrophotometer (Shimadzu UV 1800) at 247nm.

Drug release kinetics

To describe the kinetics of the drug release from matrix tablet, mathematical models such as Zero-order, First order and Higuchi, models were used. The criterion for selecting the most appropriate model was chosen on the basis of the goodness-or fit test.

Pharmacokinetic studies of Atorvastatin
Animal Preparation

Male rabbits were (weighing 2-3kg) selected for this study, all the animals were healthy during the period of the experiment. Animals were maintained at room temperature 25^0C, Relative Humidity 45% and 12h alternate light and dark cycle with 100 % fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water ad libitum. The protocol of animal study was approved by the institutional animal ethics committee, CMR College of Pharmacy, Medchel. (IAEC NO: CPCSEA/1657/IAEC/CMRCP/Ph.D-15/48).

In vivo study design

The rabbits were randomly divided into two groups each group contains six animals. The group A was received prepared Atorvastatin matrix tablets (20mg), standard conventional tablets (20mg) was administered group B with equivalent dose of animal body weight. Blood samples (approximately 0.5ml) were obtained with syringes by marginal ear vein at 0, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 20 and 24h post dose. During collection, blood sample has been mixed thoroughly with heparin in order to prevent blood clotting. Plasma was separated by centrifugation of the blood at 5000rpm in cooling centrifuge for 5min to 10min and stored frozen at 20 C until analysis.

Preparation of Plasma Samples for HPLC Analysis

Rabbit plasma (0.5ml) samples were prepared for chromatography by precipitating proteins with 2.5ml of ice-cold absolute ethanol for each 0.5ml of plasma. After centrifugation the ethanol was transferred into a clean tube. The precipitate was re suspended with 1ml of Acetonitrile by vortexing for 1 min. After centrifugation (5000 – 6000 rpm for 10min), the Acetonitrile was added to the ethanol and the organic mixture was taken to near dryness by a steam of nitrogen at room temperature.

HPLC method

Atorvastatin was analyzed on a BDS hypersil C18 column (250 mm 4.6 mm, 5µm), applying methanol: water (68:32, v/v) in isocratic mode as a mobile phase. Its pH was adjusted to 3.0 with trifluroacetic acid at a flow rate of 1ml/min. The peak response was monitored at 241nm after injecting a 100µl sample into HPLC system. The different HPLC experimental parameters were optimized and the method was validated according to standard guidelines. A peak area was obtained for Atorvastatin and internal standard (naproxen sodium) with 7.41 and 9.64 min retention time, respectively [13].

Pharmacokinetic analysis

The pharmacokinetic parameters employed to evaluate were maximum plasma concentration (C_{max}), time to attain C_{max}i.e., T_{max} and t ½ values, area under plasma concentration–time curve from zero to the last sampling time (AUC_{0-t}), area under plasma concentration–time curve from zero to infinity ($AUC_{0-\infty}$). $AUC_{0-t}$was calculated by the linear trapezoidal rule and $AUC_{0-\infty}$ from the following formula.

$$AUC_{0-\infty} = AUC_{0-t} + C_t / K_E$$

Results and discussion

Matrix Tablets

The matrix tablets of Atorvastatin were prepared without the barrier layers. All the formulation trails were subjected to *in vitro* dissolution to determine the release profile of the drug.

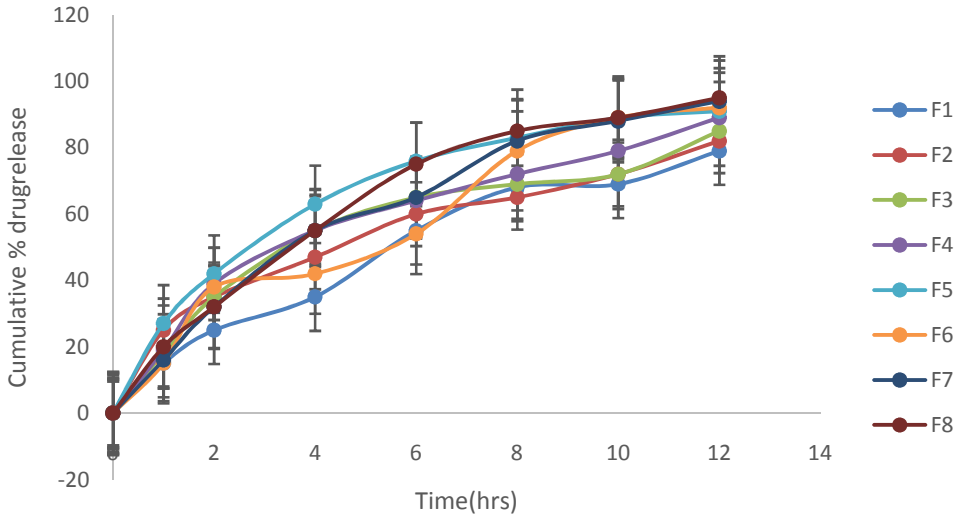

Figure 1: In vitro Dissolution profile of F1-F8 Atorvastatin active layer formulations

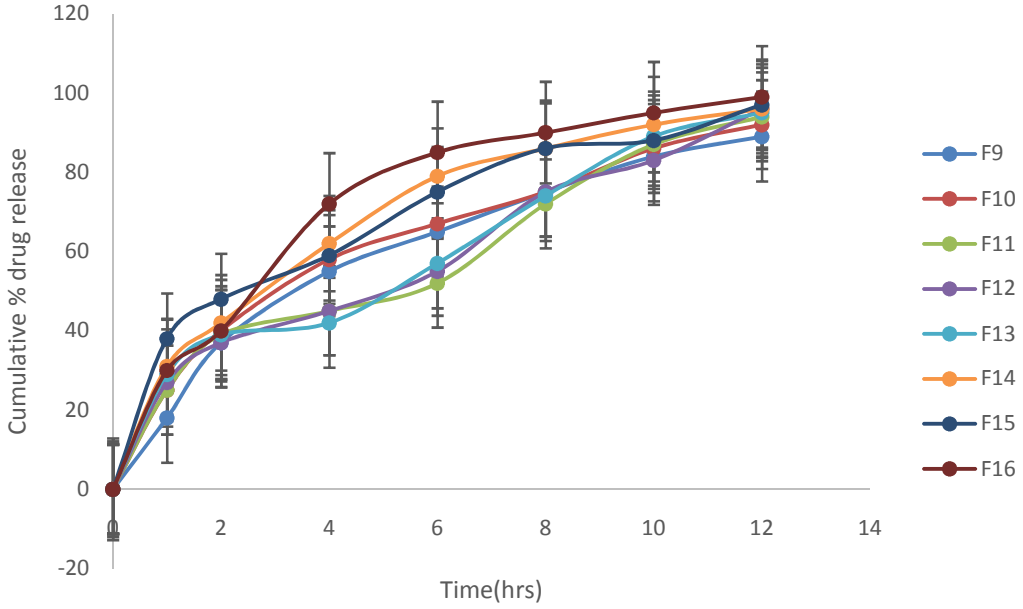

Figure 2: *In vitro* Dissolution profile of F9-F16 Atorvastatin active layer formulations

From the above results, the formulation F16 was decided as optimized formulation based on the highest drug release i.e. 99.8±0.15 up to 12h when compare with other formulations as active layer of the trilayer tablets.

Micromeretic studies of Atorvastatin

All the powder mixture belonging to different formulations of Atorvastatin trilayer tablets was tested for micrometrics studies like bulk density, tapped density, angle of repose and Carr's index in order to determine the flow properties. All the formulations AF16 to HF16 showed good flow properties and the results are summarized in Table 4.

Table 4: Powder flow properties of Atorvastatin trilayer tablets

Powder properties	AF16	BF16	CF16	DF16	EF16	FF16	GF16	HF16
Bulk density (g/cc)	0.647±0.04	0.6882±0.46	0.515±0.02	0.701±0.14	0.599±0.56	0.684±0.78	0.695±0.02	0.714±0.56
Tapped density(g/cc)	0.581±0.10	0.613±0.93	0.649±0.17	0.667±0.2	0.695±0.53	0.702±0.82	0.733±0.048	0.795±0.93
Angle of repose (o)	29.69±0.63	34.93±0.66	33.12±0.63	31.89±0.43	30.39±0.66	33.09±0.27	31.15±0.02	27.39±0.66
Carr's index	12.01±0.22	11.13±0.93	13.11±0.41	12.29±0.91	13.35±0.94	8.62±0.58	11.28±0.33	13.15±0.94

All the powder mixture belonging to different formulations was tested for micrometrics studies in order to determine the flow properties. All the formulations AF16 to HF16 showed good flow properties.

Table 5: Evaluation parameters of Atorvastatin trilayer matrix tablets

Formulation code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight variation(mg)	%Drug content
AF16	4.10	6.3±0.23	0.34	349±±6.5	98.4
BF16	4.01	7.6±0.42	0.23	348±4.5	97.3
CF16	4.14	7.4±0.41	0.35	346±8.5	97.2
DF16	4.23	7.1±0.32	0.26	349±3.5	98.8
EF16	4.11	7.2±0.59	0.28	349±1.5	97.5
FF16	4.02	6.8±0.22	0.26	348±2.5	97.4
GF16	4.104	7.6±0.55	0.27	347±1.5	97.6
HF16	4.00	7.3±0.15	0.22	350±0.5	99.3

The evaluation parameters of all the tablets are within the limits and the hardness ranges in between 6-7kg/cm^2. The percentage drug content was between 96-99. The Friability, weight variation and thickness was found to be within the limits. Hence all the tablets were subjected to in vitro dissolution test to determine the release profiles.

Table 6: In-vitro dissolution studies of Atorvastatin Trilayer tablets

Time (h)	AF16	BF16	CF16	DF16	EF16	FF16	GF16	HF16	Marketed product
1	9.34±0.11	11.26±0.21	13.21±0.04	14.22±0.04	16.32±0.04	18.85±0.04	19.47±0.05	21.02±0.04	96.11±0.02
2	20.11±0.12	22.28±0.22	23.23±0.05	24.21±0.05	25.32±0.02	26.25±0.05	27.54±0.05	29.12±0.04	
4	31.15±0.03	33.38±0.02	32.28±0.05	36.32±0.04	36.35±0.03	35.23±0.05	36.43±0.05	38.23±0.03	
6	40.25±0.05	42.45±0.03	43.79±0.05	44.15±0.04	45.62±0.04	48.54±0.05	47.25±0.04	49.55±0.05	
8	54.16±0.09	58.98±0.04	48.53±0.05	56.42±0.08	63.32±0.05	48.15±0.04	69.45±0.02	59.99±0.07	
12	60.34±0.05	69.99±0.05	56.75±0.06	74.12±0.05	74.46±0.05	50.75±0.05	70.74±0.03	68.97±0.05	
16	69.75±0.03	75.55±0.04	74.68±0.06	82.24±0.04	84.53±0.04	72.32±0.01	81.65±0.03	79.67±0.05	
20	80.24±0.05	80.20±0.05	82.95±0.07	90.21±0.05	89.15±0.06	87.22±0.05	90.85±0.02	87.88±0.06	
24	86.12±0.04	90.24±0.03	93.45±0.01	91.22±0.02	96.55±0.04	94.24±0.04	95.25±0.02	99.11±0.09	

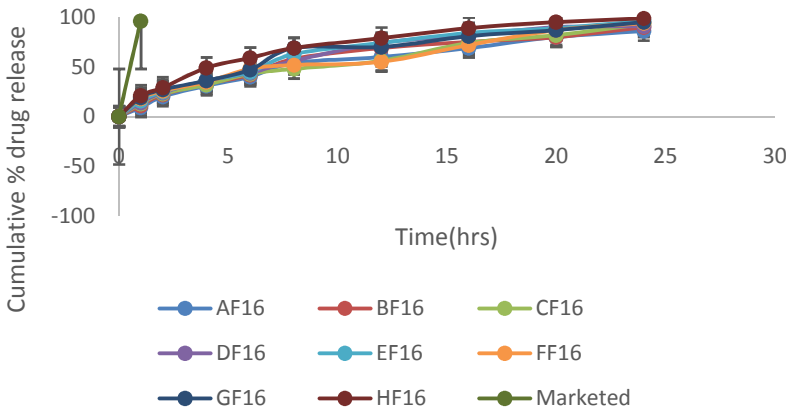

Figure 3: Comparison of Cumulative percentage drug release of Atorvastatin trilayered matrix tablets and reference standard

The In vitro drug profile of Atorvastatin from different formulations was carried and the results are depicted in Table 6 & Figure 3. The trilayer tablets extended the drug release up to 24 hrs. The highest drug release was found in the formulation HF16 i.e. 99.11±0.09% within 24 hrs. HF16 was found to be optimized formulation based on the dissolution and other evaluation parameters. The in vitro drug release profile from reference standard conventional tablet was found to be 96.11±0.02% within 60min.

Release order kinetics of optimized Atorvastatin HF16 trilayer matrix tablets with reference standard

In the present study drug release mechanism of optimized trilayer matrix tablets HF 16 are best fitting to zero order and Higuchi model because regression coefficient was seen closest to 1 in these models which conforms diffusion assisted mechanism of release. The reference standard release was explained by first order kinetics as the plot showed highest linearity as the drug release was best fitted in first order kinetics. The results are summarized in Table 7.

Table 7: Release order kinetics different formulations of Atorvastatin trilayer tablets

Formulation code	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyer Peppas R^2	Korsmeyer Peppas n value
AF16	0.983	0.865	0.944	0.966	0.578
BF16	0.985	0.867	0.946	0.968	0.604
CF16	0.986	0.869	0.947	0.970	0.570
DF16	0.987	0.870	0.949	0.971	0.634
EF16	0.988	0.872	0.951	0.973	0.598
FF16	0.989	0.874	0.952	0.975	0.612
GF16	0.993	0.875	0.953	0.976	0.635
HF16	0.994	0.876	0.954	0.977	0.697
Marketed product	0.958	0.988	0.928	0.905	0.665

Pharmacokinetic studies

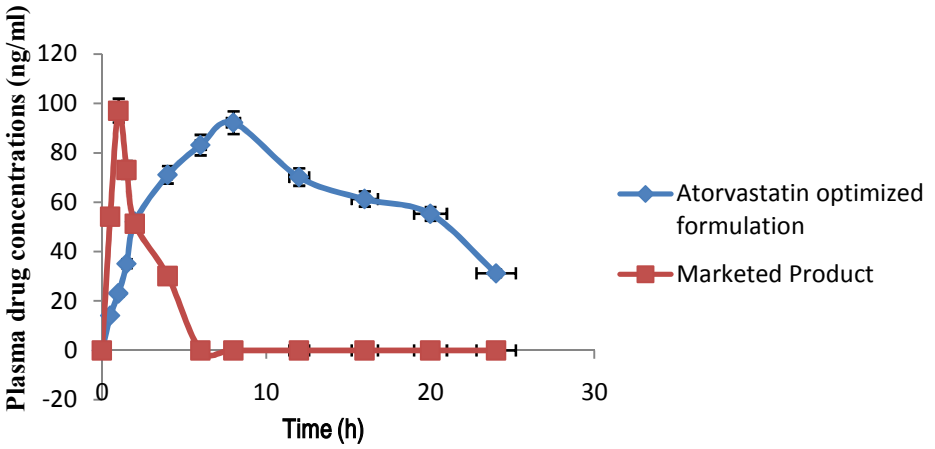

Figure 4: Plasma Concentrations of Atorvastatin Optimized formulation and Innovator at different time intervals

Table 8: Comparison of pharmacokinetic parameters of Atorvastatin Optimized formulation and Innovator

Parameters	Atorvastatin Optimized formulation	innovator
C_{max} (ng/ml)	92.22±0.05	97.11±0.01
AUC_{0-t} (ng h/ml)	1213.65±0.12	842.25±0.12
$AUC_{0-\infty}$ (ng h/ml)	1516.75±0.14	1045.14±0.22
T_{max} (h)	8.00±0.14	1.02±0.12
$t_{1/2}$ (h)	10.5±0.014	2.50±0.05

Bioavailability Parameters

Mean plasma concentration profiles of prepared Atorvastatin optimized formulation and marketed product are presented in Figure 4. Atorvastatin optimized formulation exhibited as sustained release in vivo when compared with marketed tablet. All the pharmacokinetics parameters displayed in Table 8. In this study the prolonged drug absorption was achieved with the test formulation. The average peak concentration of the reference formulation was higher than that of the test (92.22±0.05ng/ml for the test formulation versus 97.11±0.01ng/ml for the reference). AUC is an important parameter in evaluating bioavailability of drug from dosage form, as it represents the total integrated area under the blood concentration time profile and represents the total amount of drug reaching the systemic circulation after oral administration. $AUC_{0\text{-}inf}$ for optimized formulation was higher (1516.75±0.14ng h/ml) than the innovator product 1045.14±0.22ng h/ml. Statistically, $AUC_{0\text{-}t}$ of the optimized preparation was significantly higher ($p<0.05$) as compared to innovator product. The results indicated that the test formulation could increase the bioavailability of Atorvastatin in vivo effectively. In this study, the Atorvastatin matrix tablets produce higher bioavailability than that of a marketed product.

Summary and conclusion

In the present study, the proposed solid dispersions of Atorvastatin containing trilayer tablets were confirmed to be a successful tool for prolonged period of time up to 24 h. The study proves that the potential use of controlled release trilayer matrix tablets as an efficient strategy for the oral delivery of Atorvastatin prepared by direct compression technique using different polymers combination. Based on the evaluation parameters, drug dissolution profile and release drug kinetics HF16 was found to be optimized formulation. The drug release from HF16 was found to fit Zero order and best fitted to Higuchi's model confirming to be diffusion assisted mechanism. In vivo bioavailability studies were conducted for optimized formulation HF16 and reference standard. The optimized formulation of Atorvastatin trilayer matrix tablet was shown significant plasma concentration with controlled release and maintained for 24 hrs with patient compliance by reducing the dosage frequency, when compared with reference standard.

Conflict of Interest

The authors declare no conflict of interest.

References

[1]. Fahr A, Liu X. Drug delivery strategies for poorly water-soluble drugs. Expert Opin Drug Deliv.2007; 4:403–16.

[2]. Tapan Kumar Giri, Kulesh Kumar, Amit Alexander, Ajazuddin, Hemant Badwaik, Dulal Krishna Tripathi. A novel and alternative approach to controlled release drug delivery system based on solid dispersion technique, Bulletin of Faculty of Pharmacy, Cairo University, 2012: 50(2):147–159

[3]. Shajahan A, Pondar S. A flexible technology for modified release of drugs: multilayer tablets. J. Control. Release. 2004; 97: 393–405.

[4]. Conte U, Maggi L, Colombo P, La Manna A. Multi-layered hydrophilic matrices as constant release devices. J Control Rel. 1993; 26: 39-47.

[5]. Yihong Qui, Chidambaram N, Kolette F. Design and evaluation of layered diffusional matrices for zero order sustained-release tablets. J Control Rel. 1998; 51: 123-130.

[6]. Gohel MC, Parikh RK, Padshala MN, Sarvaiya KG, Jena DG. Formulation and optimization of directly compressible isoniazid modified release matrix tablet. IJPS. 2007; 69(5): 640-645.

[7]. Tobyn MJ, Stani forth JN, Baichwal AR, Mc Call TW. Prediction of physical properties of a novel polysaccharide controlled release system. Int J Pharm. 1996; 128: 113-22.

[8]. Talukdar MM, Mooter VD, Augustijns P, Maga TT, Verbeke N, Kinget R. In vitro evaluation of xanthan gum as potential excipients for oral controlled release matrix tablet formulation. Int J Pharm. 1998; 169: 105-13.

[9]. Talukdar MM, Vercammen JP. Evaluation of xanthan gum as a hydrophillic matrix for controlled release dosage forms. Drug Dev Ind Pharm. 1993; 19:1037-46.

[10]. Hong Wen, Kinam Park. Oral controlled release formulation design and drug delivery, Theory to practice. Wiley publication. New Jercy. 2010; 94-95.

[11]. Dinesh Kumar Mishra, Dinesh Kumar Jain, Formulation and evaluation of Atorvastatin sustained release matrix tablets. Bulletin of Pharmaceutical Research. 2014; 4(2): 81-5.

[12]. Abdelbary G, Prinderre P, Eouani C, Joachim J, Reynier JP, Piccerelle P. The preparation of orally disintegrating tablets using a hydrophilic waxy binder. Int J. Pharm. 2004; 278(2): 423-33.

[13]. Yihong Qui, Chidambaram N, Kolette F. Design and evaluation of layered diffusional matrices for zero order sustained-release tablets. J Control Rel. 1998; 51: 123-130.

[14]. Gohel MC, Parikh RK, Padshala MN, Sarvaiya KG, Jena DG. Formulation and optimization of directly compressible isoniazid modified release matrix tablet. IJPS. 2007; 69(5): 640-645.

[15]. Balakrishnaiah M, Rama Mohan Gupta V. Solubility Enhancement of Atorvastatin using Solid dispersion technique with novel carriers. Am. J. Pharm Tech Res. 2016; 6(3): 450-466.

[16]. Entidhar j A, akkam, abdul rasool , adnan a. Badwan , nawzat d. A- jbour, idal a. Qinna. Development and validation of a sensitive and accurate method for determination of atorvastatin and rosuvastatin in rat plasma by reversed- phase high performance liquid chromatography with uv detection. int j pharm pharm sci. 2011; 5: 211-219.