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Research Article

Formulation and *In Vivo* Evaluation of Trilayer Matrix Tablets of Rosuvastatin Solid Dispersions by Geomatrix Technology

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ABSTRACT

The current research aims to enhance the aqueous solubility and sustains the drug release of rosuvastatin BCS Class II drug. Fifteen (15) solid dispersion (SD) formulations of rosuvastatin were prepared by solvent evaporation technique and evaluated. *In vitro* drug dissolution study indicated a higher drug dissolution rate for SD13 of 99.74 ± 5.39 % within 60 min. Eight formulations of rosuvastatin trilayer matrix tablets (AF10-HF10) were prepared using optimized SD13 by direct compression method. These trilayer formulations are characterized for flow properties and physicochemical parameters. The maximum drug release was exhibited by trilayer matrix formulation (HF10) of 99.48 ± 5.40 % throughout 24 hours. The zero-order described the optimized formulation (HF10) release profile and best fitted to Higuchi and Korsmeyer-Peppa's model. The results demonstrated the sustainability of rosuvastatin trilayer tablets with enhanced release time and linearity up to 24 hours. From *in vivo* bioavailability studies, C_{max} of the rosuvastatin optimized ER tablets and the marketed product was found to be 28.46 ± 0.07 ng/mL and 30.94 ± 0.75 ng/mL, respectively. T_{max} of both rosuvastatin optimized ER tablets formulation and rosuvastatin marketed product was 5 ± 0.06 and 4 ± 0.03 h, respectively. $AUC_{0-\infty}$ infinity for the optimized formulation was higher (395.54 ± 1.37 ng.h/mL) than the rosuvastatin marketed product formulation 212.54 ± 0.42 ng.h/mL. Statistically, the AUC_{0-t} of the optimized ER tablets formulation was significantly higher ($p < 0.05$) than rosuvastatin marketed product formulation. *In vivo*, pharmacokinetic studies in rabbits confirmed the prolonged-release by showing an increase in bioavailability for rosuvastatin from optimized ER tablets than marketed formulation.

Introduction

The solid dosage forms of drugs administrated orally are considered an effective method of medication with the highest patient compliance. More than 40% of the drug molecules known till date suffer from lower aqueous solubility, leading to fewer drug dissolution rates that can be surmounted by converting the drugs to salt form, micronization, or surface-active agents.[1] Solid dispersion (SD) is a widely applied method for improved drug solubility and release rates, enhancing the bioavailability of sparingly soluble drugs. Numerous methods were adopted to modulate the drug dissolution rate from the specific drug delivery system.[2] Most of the orally administrated dosage forms exist as a polymer matrix, reservoir, or multi-layer systems. The multi-layer matrix systems are emerging as potential designs for sustained oral drug delivery. These systems comprise of hydrophilic core embedding the drug molecules sandwiched between semi-permeable polymeric layers (barrier-layer). These layers retard the interaction between solute and dissolution medium by minimizing the availability of the surface for the release of solute and simultaneously checking solvent penetration rate. Subsequently, the inflamed barriers erode, leading to an increase in the surface area accessible for drug release, simultaneously balancing the diffusion path length and area of drug release.[3]

Rosuvastatin is HMG CoA inhibitor that reduces the total cholesterol, low-density lipoprotein (LDL), plasma triglycerides, and Apo lipoprotein B levels. However, it belongs to BCS class II that suffers from lower water

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solubility and oral bioavailability. The main objectives of current research are to enhance these parameters of rosuvastatin solid dispersion technique and incorporate them into a trilayer polymer matrix.[4,5]

Materials and Methods

Materials

Rosuvastatin is a kind of gift sample from Aurobindo Pharma Ltd., Hyderabad. PEG 6000, kolliphor EL, kolliwax GMS II, kolliphor RH40 were obtained from BASF, Mumbai. SLS, methanol, HPMC K 100M, carbopol 934P, PVPK-30, xanthan gum, guar gum, magnesium stearate, and talc procured from SD fine Ltd, Mumbai. Crestor (Rosuvastatin marketed product) was procured from a local market.

Methods

Preliminary Solubility Studies of Rosuvastatin

Excess rosuvastatin stirred with 25 ml of carriers (crospovidone, croscarmellose, eudragit, labrafac PG, kolliwax RH 40, and GMS II, soluplus, kolliphor ELP, PEG 2000, and urea) for 24 hours. The suspension was clarified through filter paper and filtrate diluted with methanol for spectrophotoscopic analysis of the drug at 243 nm.[6,7]

Preparation of Rosuvastatin SD

Rosuvastatin weighed and mixed with various polymers and 0–2% SLS surfactant in different drug-polymer-surfactant ratios (1:1:1, 1:2:1.5, and 1:3:2) (Table 1). Fifteen SDs prepared by adopting solvent evaporation method in which the mixture is dissolved in minimal amount of CH_3OH followed by its evaporation at a temperature of 50°C. The SDs prepared were pulverized, passed through 45 µm sieve, and stored in a desiccator for further investigations.[7]

Evaluation of Rosuvastatin SD

All the SD formulations were evaluated for practical percentage yield,[8] %drug content,[9] *in vitro* drug dissolution study of rosuvastatin SD[10] as per the referred methods. The SDs are further characterized for FTIR,[11] X-Ray diffractometer,[12,13] and SEM Studies.[14]

In-vitro Drug Dissolution of Rosuvastatin SD

The dissolution of rosuvastatin SDs conducted by dissolving the formulation containing 80 mg of drug in 900 mL phosphate buffer (pH 6.8) using USP type II (paddle type) dissolution test apparatus as per the preferred method.[15]

Stability Studies

The prepared SDs were sealed in 40cc HDPE at controlled temperature in a stability chamber (Thermo Lab, India) with RH value 75% ± 5% RH and temperature maintained at 40°C ± 2°C. Samples collected after 1, 2, and 3 months were evaluated for various parameters.[16]

Formulation of Rosuvastatin Trilayer Tablets

Formulation of Controlled Release Rosuvastatin Trilayer Matrix Tablets

The trilayer matrix tablets of rosuvastatin were prepared by direct compression method.[17]

Preparation of active layer: Ten formulations (F1-F10) prepared by varying concentration of polymers HPMC K100M, carbopol 934P and guar gum, and rosuvastatin SD (80 mg), talc (1.5 mg), and magnesium stearate (1.5 mg). These materials passed through ≠60 and mixed using a motor, pestle. The final product was compressed by using 12mm diameter flat punches (Table 2).

Table 1: Composition of rosuvastatin SDs

Ingredient's formulation ratios	*Rosuvastatin (mg)*	*PVP K-30 (mg)*	*PEG 6000 (mg)*	*Kolliphor EL (mg)*	*Kolliphor RH 40 (mg)*	*Kolliwax GMS II(mg)*	*SLS (mg)*	*Methanol (mL)*
SD1 1:1:1	20	20	-	-	-	-	20	Qs
SD2 1:2:1.5	20	40	-	-	-	-	30	Qs
SD3 1:3:2	20	60	-	-	-	-	40	Qs
SD4 1:1:1	20	-	20	-	-	-	40	Qs
SD5 1:2:1.5	20	-	40	-	-	-	30	Qs
SD6 1:3:2	20	-	60	-	-	-	40	Qs
SD7 1:1:1	20	-	-	20	-	-	20	Qs
SD8 1:2:1.5	20	-	-	40	-	-	30	Qs
SD9 1:3:2	20	-	-	60	-	-	40	Qs
SD10 1:1:1	20	-	-	-	20	-	20	Qs
SD11 1:2:1.5	20	-	-	-	40	-	30	Qs
SD12 1:3:2	20	-	-	-	60	-	40	Qs
SD13 1:1:2	20	-	-	-	-	20	40	Qs
SD14 1:2:1.5	20	-	-	-	-	40	30	Qs
SD15 1:3:2	20	-	-	-	-	60	40	Qs

Preparation of barrier layer: The barrier layer was formulated using different polymers as shown in Table 3. *Formulation of rosuvastatin trilayer tablets*: The powder mixtures comprising active and barrier layers are thoroughly mixed for 20 minutes. Initially, 12 mm round volume of die cavity with weight equivalence to trilayer matrix tablets (500 mg) was prepared. A known quantity of powder mixture equivalent to the weight of the bottom barrier layer (100 mg) filled in the die cavity and compressed 300 mg of middle layer formulation spread uniformly on the lower layer of the die cavity and compressed gently. Then finally, the die cavity is then filled with 100 mg of top layer powder and compressed to obtain the final tri-layered tablets[18] (Table 4).

Evaluation of Rosuvastatin Trilayer Tablets

All the 10 tri-layered tablet matrices of rosuvastatin (AF10-HF10) were evaluated for angle of repose,[19] Carr's compressibility index, bulk density, and tapped density, and Hausner ratio as per the preferred methods.

Table 2: Formulation trails for active layer (F1-F10) of rosuvastatin

INGREDIENTS (mg)	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*	*F9*	*F10*
Rosuvastatin SD	80	80	80	80	80	80	80	80	80	80
HPMC K 100M	50	60	70	80	90	-	-	-	-	-
Carbopol 934P	-	-	-	-	-	50	60	70	80	90
Avicel pH 101	85	80	75	70	65	60	55	50	45	40
Guar gum	-	-	-	-	-	35	40	45	50	60
$CaHPO_4$	82	77	72	67	62	72	62	52	42	27
Magnesium stearate	1.5	1.5	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	1.5	1.5
Total weight (mg)	300	300	300	300	300	300	300	300	300	300

Table 3: Formulation trails for barrier layer(A–H) (total weight: 100 mg)

Ingredients (mg)	*A*	*B*	*C*	*D*	*E*	*F*	*G*	*H*
Polyox WSR 303	20	25	30	35	40	45	50	55
Xanthan gum	24	22	18	20	22	20	20	18
Ethyl cellulose	12	12	12	12	12	12	12	12
Dibasic calcium phosphate	41	38	37	30	23	20	15	12
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
Total weight (mg)	100	100	100	100	100	100	100	100

Table 4: Composition of trilayer matrix tablet

Ingredients (mg)	*AF10*	*BF10*	*CF10*	*DF10*	*EF10*	*FF10*	*GF10*	*HF10*
Middle layer (F10) (Total wt: 300 mg)								
Rosuvastatin SD	80	80	80	80	80	80	80	80
Carbopol 934 P	80	80	80	80	80	80	80	80
Avicel pH 101	45	45	45	45	45	45	45	45
Guar gum	50	50	50	50	50	50	50	50
Dibasic calcium phosphate	42	42	42	42	42	42	42	42
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 (Total wt: 100 mg)								
Polyox WSR 303	20	25	30	35	40	45	50	55
Xanthan gum	24	22	18	20	22	20	20	18
Ethyl cellulose	12	12	12	12	12	12	12	12
Dibasic calcium Phosphate	41	38	37	30	23	20	15	12
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

All the formulations were also evaluated for hardness, friability, weight variation, and % assay per the referred procedures.[20,21]

In-vitro Drug Release Studies of Rosuvastatin Trilayer Tablets (AF10-HF10)

The dissolution test apparatus, USP 2 (paddle method) were used for conducting in-vitro drug dissolution, and drug content was analyzed spectroscopically employing Shimadzu UV-visible spectrophotometer.[22]

Drug Release Kinetics Rosuvastatin Trilayer Tablets

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 based on the goodness-or-fit test.[23]

Stability Studies of Rosuvastatin Trilayer Tablet

Accelerated stability studies carried at 40°C/75 % RH for 180 days. The drug layered pellets were evaluated for drug concentration and cumulative %drug release.[24]

Pharmacokinetic Studies of Rosuvastatin in Rabbit Plasma

Animal Preparation

Twelve New Zealand white rabbits of either sex rabbits were (weighing 2–3 kg) selected for this study, all the animals were healthy during the experiment. Animals were maintained at room temperature 25°C, RH 45%, 12 hours alternate light and dark cycle with 100% fresh air exchange in animal rooms, uninterrupted power and water supply, and rabbits fed with standard diet and water ad libitum. An *in vivo* pharmacokinetic study was conducted following the ethical guidelines for investigations in laboratory animals and approved by the Institutional Animal Ethics Committee (IAEC NO :.....).

Study Design

Rabbits were randomly divided into 2 groups of six animals each. The rabbits selected for the study were housed in separate cages and had no medication for two weeks before the study. They were denied food and water during the study. The cages of rabbits have been placed in 18 hours light/6 hours dark conditions. The optimized ER tablet formulation (test patch) and marketed reference product tablet formulation containing rosuvastatin dose equivalent to rabbit dose (2.5 mg) of the drug were crushed and mixed with carboxymethylcellulose (CMC) 1% w/v solution, ensuring that rabbits consumed all the dose. The drug was prepared in a solution form and was administered through the feeding tube orally. The Group A rabbits were fed with rosuvastatin optimized formulation, and Group B fed with the marketed reference product (Crestor 20 mg) with an equivalent dose to animal body weight.[25]

Determination of Rosuvastatin in Rabbit Plasma by HPLC Method

The HPLC system consisted of a Shimadzu SCL-10A VP system controller (Koto, Japan), a Shimadzu LC-10AT VP pump (Kyoto, Japan), a Shimadzu SIL-10AD VP auto-injector with sample cooler (Kyoto, Japan), a Shimadzu DGU-14A VP degasser (Kyoto, Japan) and a Shimadzu SPD-10A VP ultraviolet detector (Kyoto, Japan). The data were acquired and processed using Shimadzu VP software (version 5.03). The analytical column was a Kromasil KR100-5C18-250 A, 4.6×250mm, 5 µm particle size (Hichrom, UK). The isocratic mobile phase consisted of 0.05 M formic acid, and acetonitrile mixture (55:45, v/v) was run at a flow rate of 1.0 mL/min. The eluate was monitored by an ultraviolet detector set at 240 nm, the maximal absorption for rosuvastatin (RST), and the same wavelength was found adequate for monitoring the internal standard.[26] Rosuvastatin and ketoprofen (IS) were well separated with retention time of 9.02 and 13.1 minutes, respectively.

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, the area under plasma concentration-time curve from zero to the last sampling time (AUC_{0-t}), area under the 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

Preparation of Rosuvastatin SD

Total 15 rosuvastatin SD formulations were prepared by a solvent evaporation method using different polymers summarized in Table 1. All the formulations are free-flowing powders.

Solubility studies of rosuvastatin SD: The solubility studies of formulated rosuvastatin SD'S indicate the highest solubility of 0.3432 ± 0.15 mg/mL for formulation containing rosuvastatin: kolliwax GMS II: SLS in equal ratios, which is 47-fold in comparison to the pure drug (0.008111 ± 0.09 mg/mL) (Fig. 1).

Percentage practical yield (PPY) and drug content: The PPY for all rosuvastatin SDs lie within 90.61 ± 0.21% – 98.96 ± 0.25%. A maximum yield of 98.96 ± 0.25% has been observed for formulation SD13. The drug content of all rosuvastatin SDs lie within 90.66 ± 0.20% – 99.45 ± 0.30%, with SD13 exhibiting maximum drug content.

*In-vitro D*rug Dissolution Studies of Rosuvastatin SDs

A significant increase in drug dissolution rate is observed in all the formulated SDs of rosuvastatin compared to the

pure drug, with formulation SD13 exhibiting the highest dissolution rate of 99.74 ± 5.39% (Figs. 2-4).

Drug Excipient Compatibility Studies of Rosuvastatin SDs

FTIR studies: Characteristics peaks of pure drug FTIR (Fig. 5) were seen at 2740.94 cm^{-1} for N-H stretching and C=O stretching of acid at 1741.38 cm^{-1}. The other principal peaks are at 1546.96 cm^{-1} for C=C stretching, 2694.65 cm^{-1} for =C-H stretching, 3387.11cm^{-1} strong and broadband for O-H stretching,1467.88 cm^{-1} and 1359.86 cm^{-1} for asymmetric and symmetric bending vibration of CH_3 group respectively, 1280.78 cm^{-1} bending vibration for C-H, 1149.61 cm^{-1} for C-F stretching vibrations. The same peaks were observed in the physical mixture (Fig. 6) and optimized formulation (Fig. 7) and concluded no incompatibility between drug and polymers used in the formulation.

X-ray diffraction patterns: The presence of abundant distinct peaks in the diffraction spectrum of pure rosuvastatin indicates crystalline form. The absence of diffraction peak in the spectrum of SD13 indicate that the

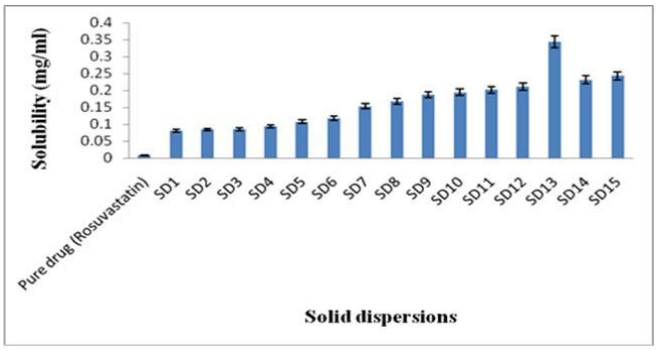

Fig. 1: Solubility studies of rosuvastatin SD

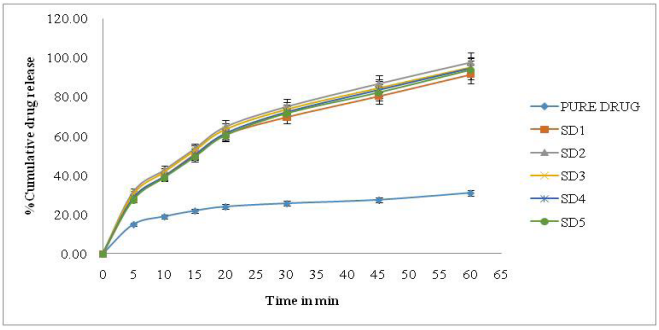

Fig. 2: *In vitro* drug dissolution of pure rosuvastatin and SD1-SD5

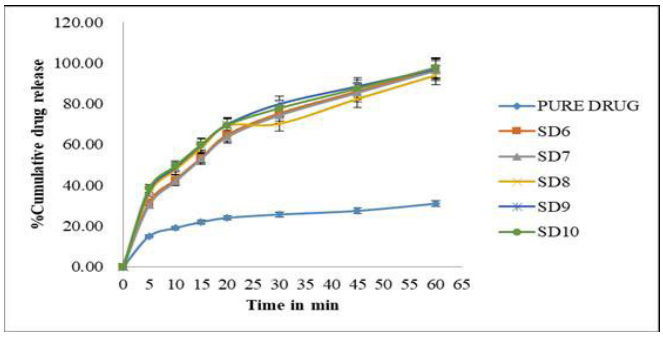

Fig. 3: *In vitro* dissolution of pure rosuvastatin and SD6-SD10

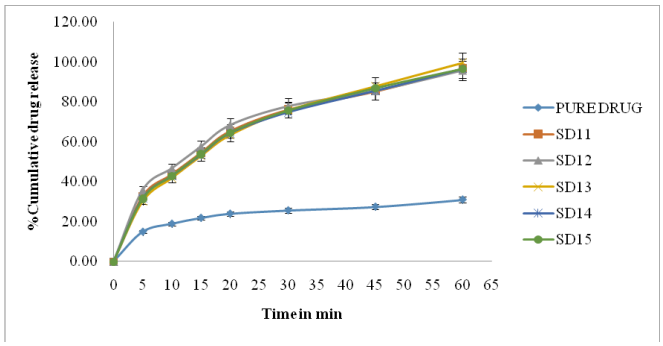

Fig. 4: *In vitro* dissolution profile of pure rosuvastatin and SD11-SD15

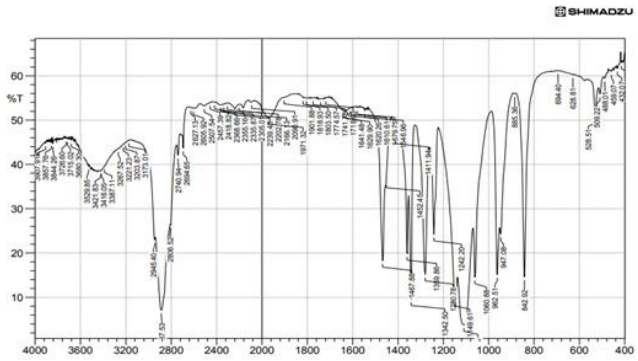

Fig. 5: FTIR of pure rosuvastatin drug

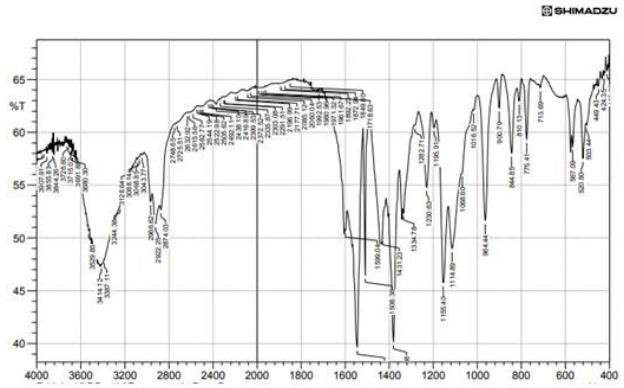

Fig. 6: FTIR of physical mixture

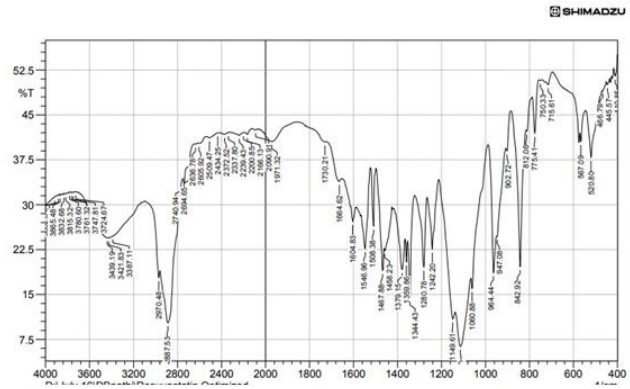

Fig. 7: FTIR spectrum of optimized rosuvastatin SD (SD13)

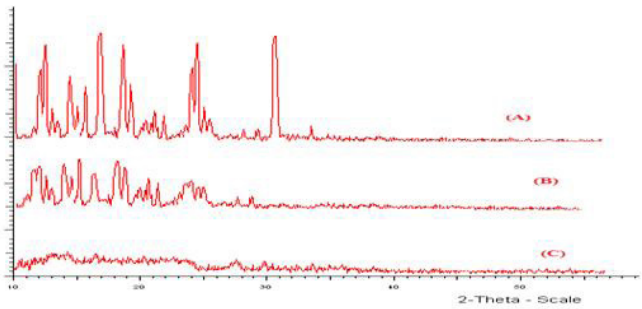

Fig. 8: PXRD (A) Rosuvastatin pure drug, (b) Physical mixture (c) Optimized formulation SD13

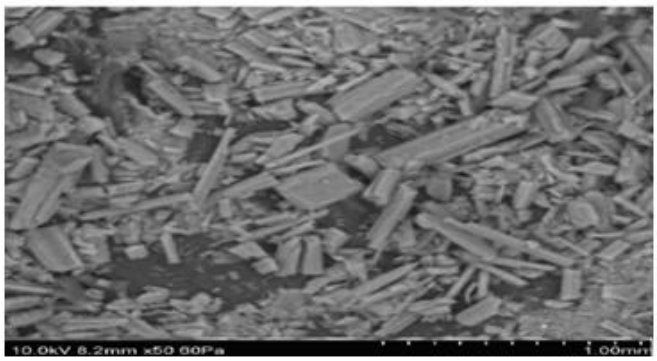

Fig. 9: Pure drug of rosuvastatin

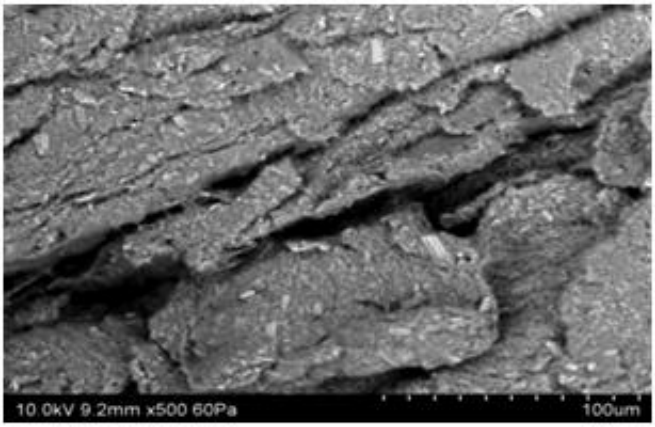

Fig. 10: Rosuvastatin optimized formulation SD13

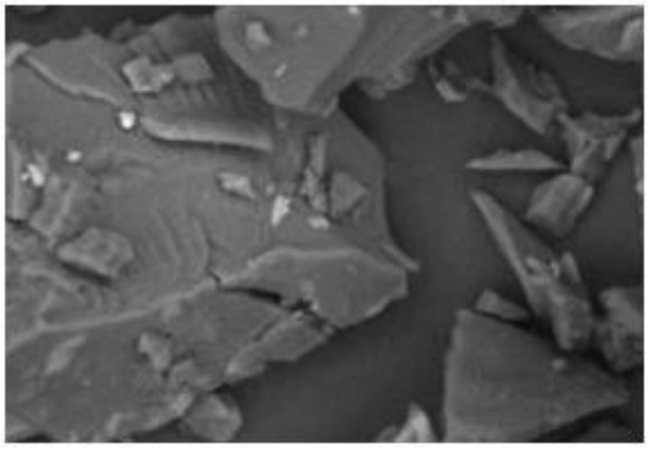

Fig. 11: Rosuvastatin optimized formulation SD13

formulation is amorphous (Fig. 8), which attributes to the higher dissolution of these formulations

SEM studies: The SEM data indicate smooth, irregular shape for the pure drug while SDs exhibited uniform and wrinkled surface with porous drug crystals (Figs. 9–11).

Stability Studies of Rosuvastatin SD (SD13)

Optimized formulation (SD13) was subjected to a stability study for 90 days at accelerated as per ICH guidelines. As a result, the optimized formulation was stable during 3 months period. Results indicate that optimized formulation (SD13) is stable with minor variations in its physical properties (Table 5).

Formulation of Rosuvastatin Tri Layer Tablets

Evaluation studies: The trilayer tablets were prepared and characterized for various pre-compression micrometric analyses to determine the flow properties. The bulk and tapped density of all tablet formulations vary between 0.59-0.66g/cc. The angle of response lies between 20.17 ± 0.49 to 27.32 ± 0.49 with minimum observed for HF10. Carr's index also ranges between 9.67 ± 0.96 to 15.39 ± 0.93. Thus, the formulation HF10 exhibited excellent flow properties.

The characteristic physicochemical evaluation of the trilayer tablets indicates that the hardness of all tablets varied between 3–5kg/cm^2 while the friability is between 0.18–0.45%. The weight variation varies between 496 ± 4.5 to 500 ± 0.5 mg. The % assay varies between 94.31 to 99.89%, with the maximum value exhibited by HF10.

Cumulative % Drug Release of Rosuvastatin Trilayer Matrix Tablets

All the trilayer tablets evaluated for drug release indicate drug release within 20–24 hours, with HF10 exhibiting a maximum release of 99.48 ± 5.40% over 24 hours (Fig. 12).

Release Order Kinetics of Rosuvastatin Trilayer Matrix Tablets

The drug release from HF10 fit zero-order with R^2=0.9965 and Higuchi and Korsmeyer-Peppa's model indicating diffusion and non-Fickian process of drug release while the marketed release formulation showed first-order release kinetics with R^2 = 0.9905 (Table 6) (Figs. 13-16).

Stability Studies of Rosuvastatin Trilayer Matrix Tablets (HF10)

Optimized formulation (HF10) was selected for stability studies based on high cumulative %drug release. The

Table 5: Stability studies of SD13 stored at 40 ± 2°C/75 ± 5% RH

Retest time	*Drug content*	*In vitro drug release (%)*
0 days	99.45	99.74
30 days	99.12	99.02
60 days	98.61	98.75
90 days	98.2	98.12

formulation is subjected to stability study for 180 days indicating no substantial change in drug content and dissolution data (Table 6).

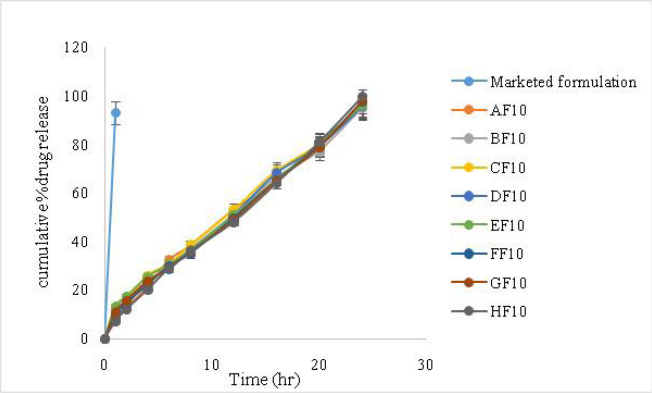

Fig. 12: Cumulative percentage drug release of rosuvastatin trilayer tablets

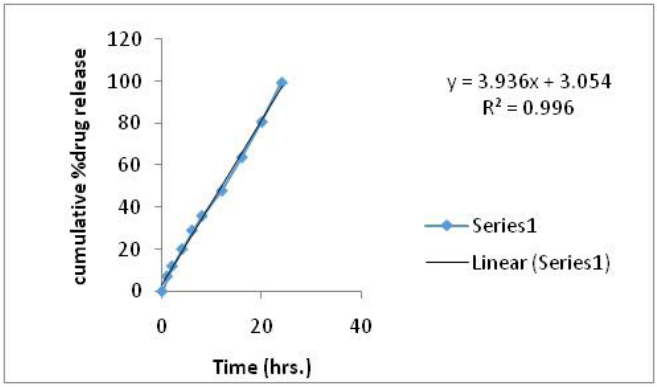

Fig. 13: Zero-order plot of optimized rosuvastatin trilayer tablet (HF10)

Table 6: Stability studies of rosuvastatin trilayer matrix tablet (HF10)

Retest Time for Optimized formulation HF10	*Drug content (%)*	*In-vitro drug release profile (%)*
0 days	99.89 ± 1.37	99.48 ± 5.40
30 days	98.8 ± 2.75	98.75 ± 2.73
60 days	98.12 ± 3.72	98.31 ± 3.72
120 days	97.36 ± 2.57	97.66 ± 2.74
180 days	97.01 ± 4.63	97.15 ± 1.46

n=SD ± 3

Table7: Pharmacokinetic parameters of rosuvastatin optimized ER tablets formulation and marketed product in rabbit plasma

Pharmacokinetic parameters	*Rosuvastatin marketed product*	*Rosuvastatin-optimized ER tablets formulation*
C_{max} (ng/mL)	30.94 ± 0.75	28.46 ± 0.07
AUC_{0-t} (ng. h/mL)	200.94 ± 1.84	358.64 ± 1.74
AUC_{0-inf} (ng. h/mL)	212.54 ± 0.42	395.54 ± 1.37
T_{max} (h)	4 ± 0.03	5 ± 0.06
$t_{1/2}$ (h)	7 ± 0.02	6.5 ± 0.04

Pharmacokinetic Parameters Comparison for Rosuvastatin Marketed Product and Optimized ER Tablets

Figures 17 to 19 show the plasma concentration-time curve in rabbits after a single oral dose of rosuvastatin optimized ER tablets formulation compared to rosuvastatin marketed product. At all the indicated time points, the Rosuvastatin plasma concentrations in rabbits treated with optimized ER tablets formulation were significantly higher than those treated with rosuvastatin marketed product. Pharmacokinetic parameters of rosuvastatin after oral administration of the two formulations in rabbits are shown in Table 7.

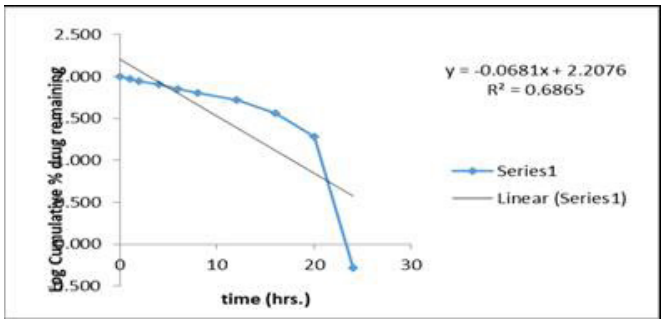

Fig. 14: First order plot of optimized rosuvastatin trilayer tablet HF10

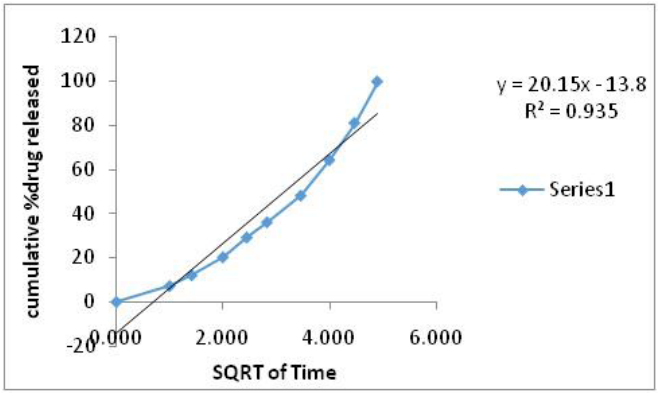

Fig. 15: Higuchi order plot of optimized rosuvastatin trilayer matrix formulation (HF10)

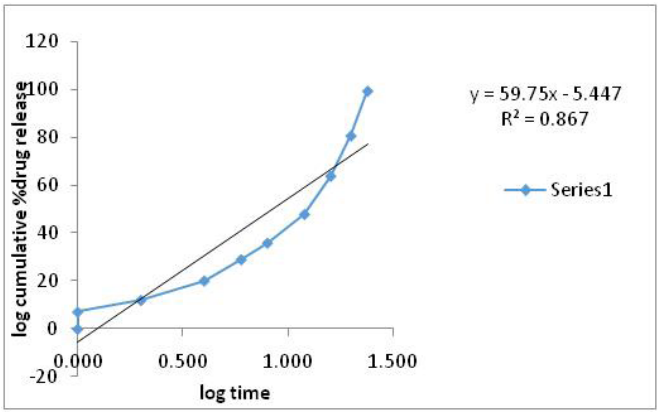

Fig. 16: Korsmeyer-Peppa's plot of optimized rosuvastatin trilayer tablet HF10

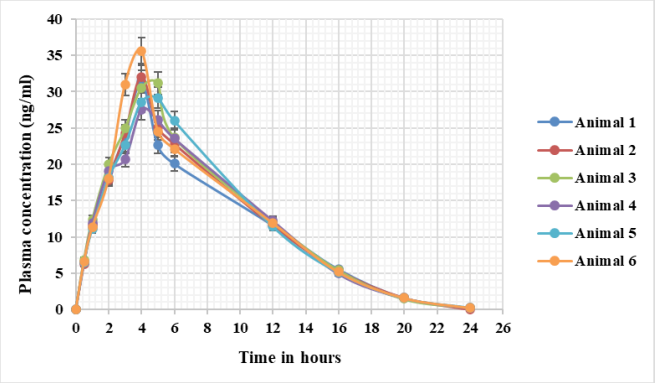

Fig. 17: Plasma concentration-time profile of rosuvastatin marketed product in rabbit plasma

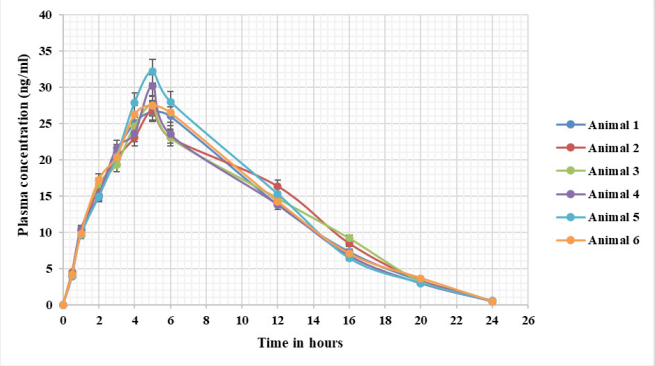

Fig. 18: Plasma concentration-time profile of rosuvastatin optimized ER tablets optimized in rabbit plasma

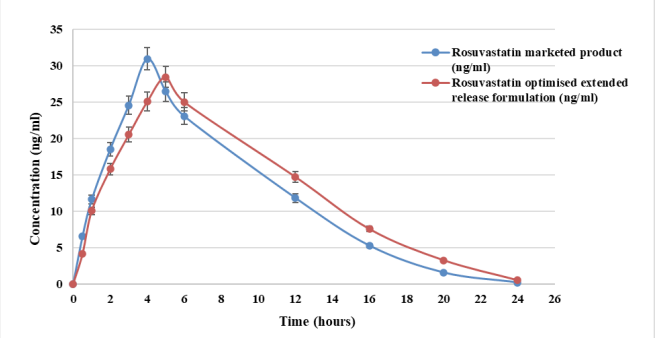

Fig. 19: Plasma concentration profiles of rosuvastatin optimized ER tablets and marketed product in rabbit plasma

C_{max} of the rosuvastatin optimized ER tablets formulation 28.46 ± 0.07 ng/mL was significant ($p < 0.05$) compared to the rosuvastatin marketed product formulation 30.94 ± 0.75 ng/mL. T_{max} of both rosuvastatin optimized ER tablets formulation and rosuvastatin marketed product was 5 ± 0.06 and 4 ± 0.03 h, respectively. AUC is an essential parameter in evaluating the bioavailability of drugs from the dosage form. 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. $AUC_{0-\infty}$ infinity for the optimized formulation was higher (395.54 ± 1.37 ng.h/mL) than the rosuvastatin marketed product formulation 212.54 ± 0.42 ng.h/mL. Statistically, the AUC_{0-t} of the optimized ER tablets formulation was significantly higher ($p < 0.05$) than the rosuvastatin marketed product formulation. Higher amounts of drug concentration in blood indicated better systemic absorption of rosuvastatin from optimized ER tablets formulation than rosuvastatin marketed product, and in-vivo pharmacokinetic studies in rabbits confirmed the prolonged-release by showing an increase in bioavailability for rosuvastatin from optimized ER tablets than marketed formulation.

Discussion

The rosuvastatin's solid dispersion was prepared, and the optimized rosuvastatin SD (SD13) was incorporated into trilayer matrix tablets. The rosuvastatin solid dispersion SD13 with the highest dissolution rate (99.74 ± 5.39%) than pure drug was further incorporated into trilayer matrix tablet and evaluated. Based on the evaluation parameters, drug dissolution profile and release drug kinetics HF10 were found to be an optimized formulation. The drug release of rosuvastatin trilayer matrix tablets (HF10) fit zero-order and best fitted to Higuchi and Korsmeyer-Peppa's model, confirming diffusion-assisted mechanism with non-Fickian drug release. Accelerated stability studies indicated stable physical properties. Hence the designed rosuvastatin SD incorporated trilayer matrix tablets approach led to drug release up to 24 hours and proved to be a successful tool for prolonged drug release. From *in vivo* bioavailability studies, C_{max} of the rosuvastatin optimized ER tablets and the marketed product was found to be 28.46 ± 0.07 ng/mL and 30.94 ± 0.75 ng/mL, respectively. T_{max} of both rosuvastatin optimized ER tablets formulation and rosuvastatin marketed product was 5 ± 0.06 and 4 ± 0.03 hour, respectively. $AUC_{0-\infty}$ infinity for the optimized formulation was higher (395.54 ± 1.37 ng.h/mL) than the rosuvastatin marketed product formulation 212.54 ± 0.42 ng.h/mL. Statistically, the AUC_{0-t} of the optimized ER tablets formulation was significantly higher ($p < 0.05$) than rosuvastatin marketed product formulation. In-vivo, pharmacokinetic studies in rabbits confirmed the prolonged-release by increasing bioavailability for rosuvastatin from optimized ER tablets than marketed formulation.

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