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Design And Evaluation Of Trilayer Matrix Tablets Of Rosuvastatin Solid Dispersions By Geomatrix Technology

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ABSTRACT

The research work aims to enhance the aqueous solubility and sustains the drug release of BCS Class II drug rosuvastatin. Solvent evaporation technique was used to prepare Fifteen(15) solid dispersion(SD) formulations of rosuvastatin and evaluated for Pre formulation and Post formulation studies. In-vitro drug dissolution study indicated a higher drug dissolution rate for SD13 of 99.74±5.39%within 60min. Eight formulations of rosuvastatin trilayer matrix tablets(AF10-HF10) were prepared using optimized SD13 by direct compression method. These trilayer formulations are characterize for flow properties and physic chemical parameters. The maximum drug release was exhibited by trilayer matrix formulation (HF10) of 99.48±5.40% throughout 24hours. The optimized formulation (HF10) had shown zero order 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 upto 24hours.

Keywords: Dyslipidemia, In-vitro bioavailability studies, Rosuvastatin, Solid dispersions, Trilayer matrix tablets.

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 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.]

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 [5.]

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 CH3OH followed by its evaporation at a temperature of 50°C. The SDs prepared were pulverized, passed through 45 µm sieve, and stored in a desiccators for further investigations [.6]

Table 1: Composition of Rosuvastatin SD

Ingredients & 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	-	-	-	60	Qs
SD6 1:3:2	20	-	60	-	-	-	80	Qs
SD7 1:1:1	20	-	-	20	-	-	40	Qs
SD8 1:2:1.5	20	-	-	40	-	-	60	Qs

SD9 1:3:2	20	-	-	60	-	-	80	Qs
SD10 1:1:1	20	-	-	-	20	-	40	Qs
SD11 1:2:1.5	20	-	-	-	40	-	60	Qs
SD12 1:3:2	20	-	-	-	60	-	80	Qs
SD13 1:1:1	20	-	-	-	-	20	40	Qs
SD14 1:2:1.5	20	-	-	-	-	40	60	Qs
SD15 1:3:2	20	-	-	-	-	60	80	Qs

Evaluation of Rosuvastatin SD

All the SD formulations were evaluated for practical percentage yield[7]. % drug content[8.] ,in-vitro drug dissolution study of rosuvastatin SD[9].as per the referred methods. The SDs are further characterized for FTIR [10],X-Ray diffractometer [11,12] and SEM Studies [13]

In-vitro Drug Dissolution of Rosuvastatin SD

The dissolution of rosuvastatin SDs conducted by dissolving the formulation containing 80mg of drug in 900mL phosphate buffer (pH 6.8) using USP type II (paddle type) dissolution test apparatus as per the preferred method [14]

Stability Studies

The prepared SDs were sealed in 40cc HDPE at controlled temperature in a stability chamber (Thermo Lab, India)withRHvalue75%±5%RHandtemperaturemaintainedat 40°C ± 2°C. Samples collected after 1, 2, and 3 months were evaluated for various parameters [15]

Pre-compression parameters: The angle of repose, Carr's compressibility index, bulk density, tapped density [16] and Hausner's ratio [17] evaluated, as per referred procedures

Formulation of Controlled Release Rosuvastatin Trilayer Matrix Tablets

The trilayer matrix tablets of rosuvastatin were prepared by direct compression method [18]

Preparation of active layer: Ten formulations(F1-F10) prepared by varying concentration of polymers HPMCK100M, carbopol934P and guargum, 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 (Table2).

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 20minutes. Initially, 12mm 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 300mg 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 100mg of to player powder and compressed to obtain the final tri-layered tablets(Table3).

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

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Rosuvastatin Solid dispersions	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**	**80**
HPMC K 100M	100	110	120	130	140	-	-	-	-	-
Carbopol 934P	-	-	-	-	-	100	110	120	130	140
Avicel pH 101	85	80	75	70	65	60	55	50	45	40
Guar gum	-	-	-	-	-	35	40	45	50	60
Dibasic calcium phosphate	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)	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**	**350**

Table 3: Formulation trails for barrier layer

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	91	88	87	80	73	70	65	62
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 Rosuvastatin Trilayer Tablets

All the formulations were also evaluated for hardness, friability, weight variation, and % assay per the referred procedures[19,20]

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 [21.]

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 them ost appropriate model was chosen based on the good ness-or-fit test [22.]

Stability Studies of Rosuvastatin Trilayer Tablet Accelerated stability studies carried at 40°C/75%RH for180days.Thedrug layered pellets were evaluated for drug Concentration and cumulative % drug release [23.]

RESULTS

Solubility studies of Rosuvastatin

The solubility of pure drug was found as low as 0.008111±0.09 mg/ml (Figure 1). The study results show that the mixture of drug and Kolliwax GMS II posses maximum drug solubility of 0.1216±0.02 mg/ml, which is 25-times increase than that of pure drug. For all carriers, PEG 6000, PEG 4000, Kolliphor EL, Kolliphor RH 40, PVP K-30, Urea, MCC, ethyl cellulose that displayed low solubility were not considered for SD formulation.

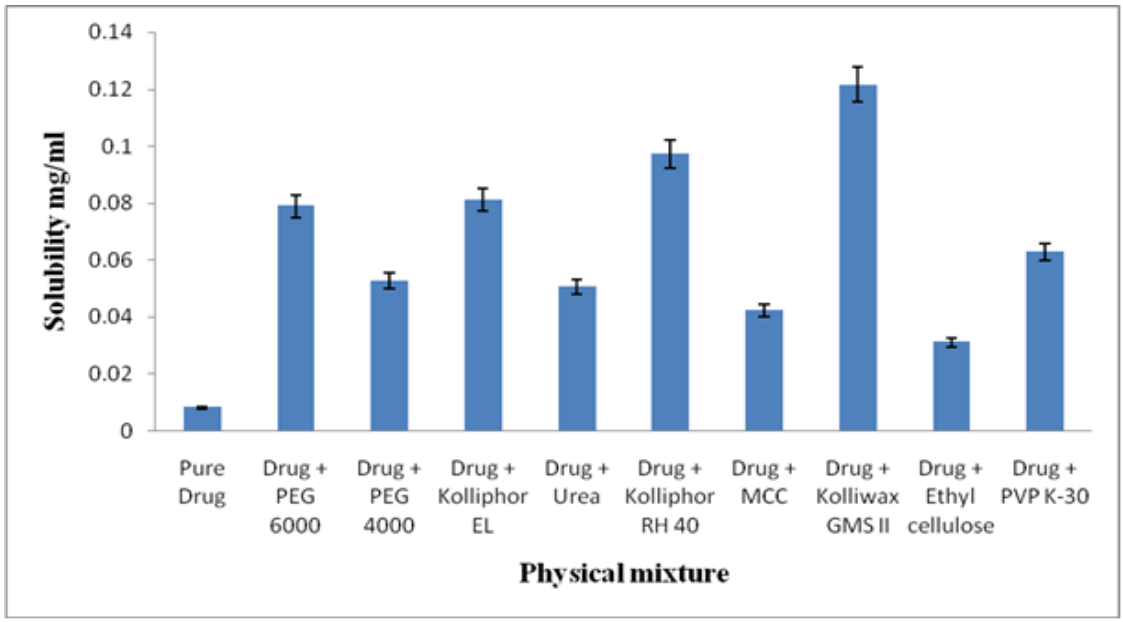

Figure 1: Solubility data of Rosuvastatin physical mixture

PREPARATION OF ROSUVASTATIN SD

Fifteen Rosuvastatin SD formulations were prepared using various polymers and SLS in 1:1:1, 1:2:1.5 and 1:3:2 ratios. All the formulations are free flowing powders Figure 2

Figure 2: Rosuvastatin SD formulation

Solubility data of Rosuvastatin SD

The formulation (SD 13) comprising of drug, Kolliwax GMS II and SLS in 1:1:1 ratio displayed maximum solubility of 0.3432±0.15 mg**/**ml, which 47-folds than that od that of pure drug (Pure drug solubility is 0.008111±0.09 mg**/**m**l**)(Figure 3).

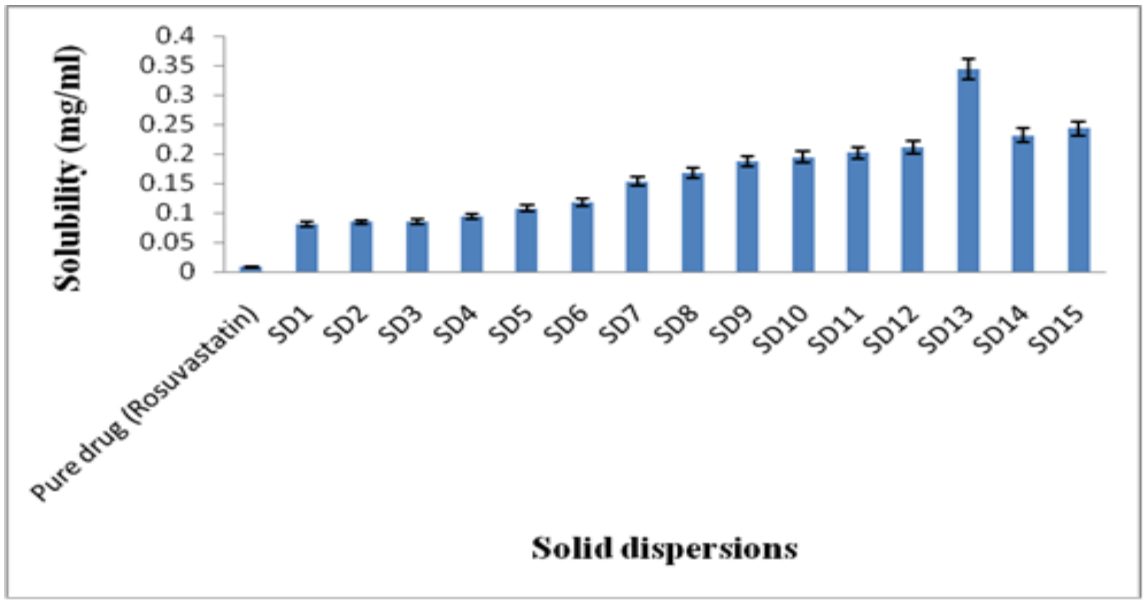

Figure 3: Solubility data of Rosuvastatin SD

Percentage Practical yield (PPY) and drug content (DC)

The results of **%PY** of all SD formulations ranged between 90.61±0.21percent - 98.96±0.25%. Maximum yield of 98% was displa**y**ed b**y** SD13. The actual DC of all 15 SD formulations ranged between 90.66±0.20 – 99.45±0.30 % with the maximum value of 99.45±0.30 % displayed b**y** SD 13.(Table 4)

Table 4: PPY and DC of Rosuvastatin SD

S. No	Formulation	% PY	% DC
1	SD1	92.98±0.21	95.63±0.26
2	SD2	90.61±0.21	94.33±0.26
3	SD3	93.44±0.23	92.18±0.25
4	SD4	91.12±0.21	93.37±0.25
5	SD5	96.32±0.24	95.19±0.26
6	SD6	95.46±0.224	90.66±0.20
7	SD7	92.19±0.21	93.94±0.25
8	SD8	94.38±0.23	95.49±0.26
9	SD9	93.69±0.23	92.63±0.25
10	SD10	91.51±0.21	94.68±0.26
11	SD11	90.66±0.20	96.34±0.27
12	SD12	94.45±0.23	91.34±0.25
13	SD13	98.96±0.25	99.45±0.30
14	SD14	92.61±0.21	96.32±0.27
15	SD15	93.66±0.23	95.48±0.26

*n=SD±3

In Vitro Dissolution data

The data showed an increase in dissolution of Rosuvastatin from all SD formulations when compared to pure drug itself. The formulation SD13 comprising of drug, Kolliwax GMSII and SLS (1:1:1 ratio) displayed maximum dissolution rate of 99.74±5.39%. This may be accredited to augment in drug wettability, adaptation to amorphous form and solubilization due to hydrophilic polymers. (Figure 4-6).

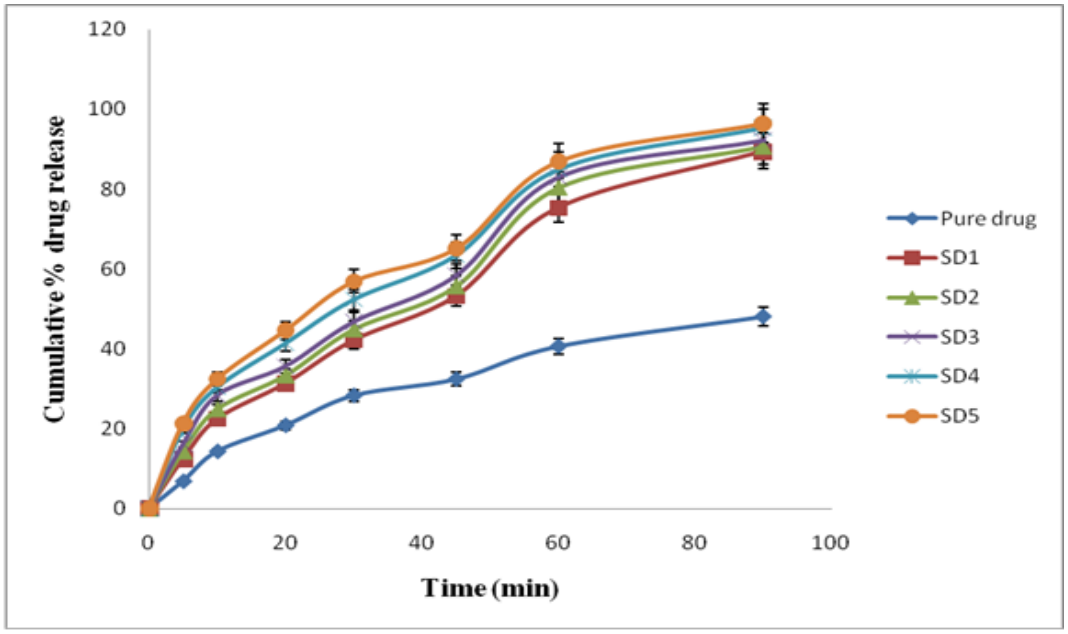

Figure 4: Dissolution profile of pure drug and Rosuvastatin SDs (SD1-SD5)

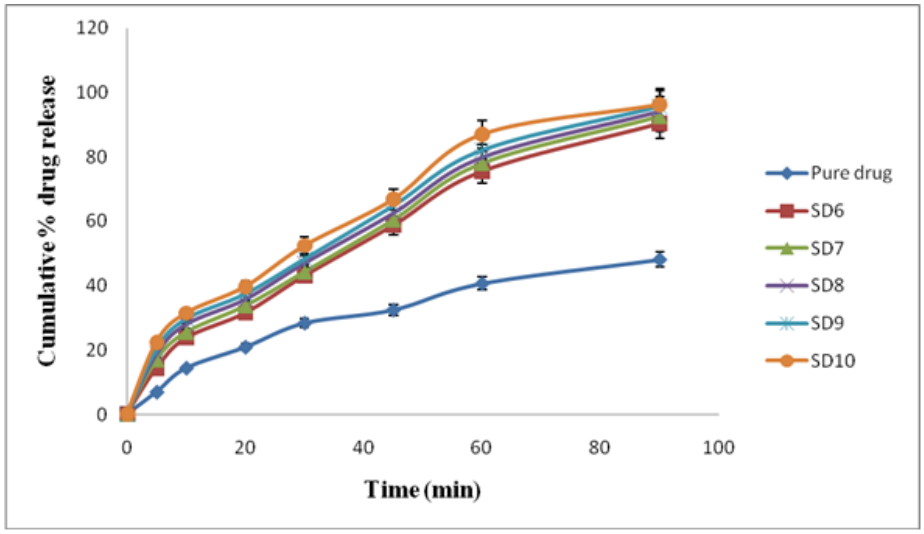

Figure 5: Dissolution profile of pure drug and Rosuvastatin SDs (SD6-SD10)

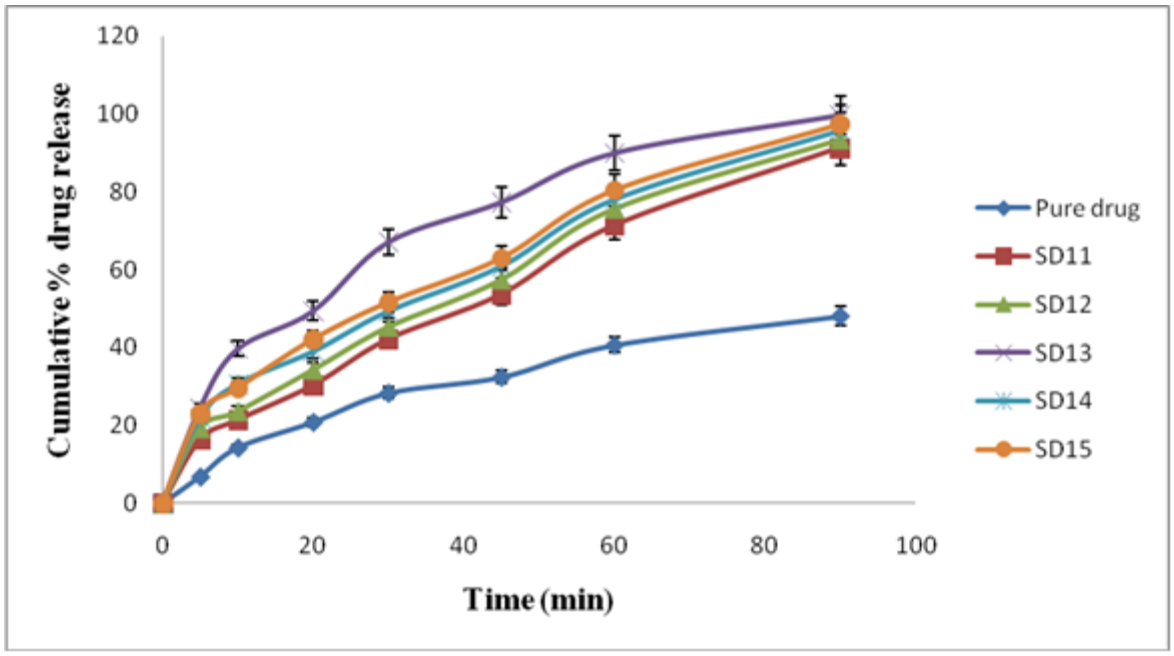

Figure 6: Dissolution profile of pure drug and Rosuvastatin SDs (SD11-SD15)

FTIR studies

The FTIR spectra of pure Rosuvastatin, physical mixture and SD13 are shown in Figure 7-9 respectively. The position of characteristic peaks of the drug remained same both in physical mixture and in SD formulation indicating compatibility between the excipients and the drug.

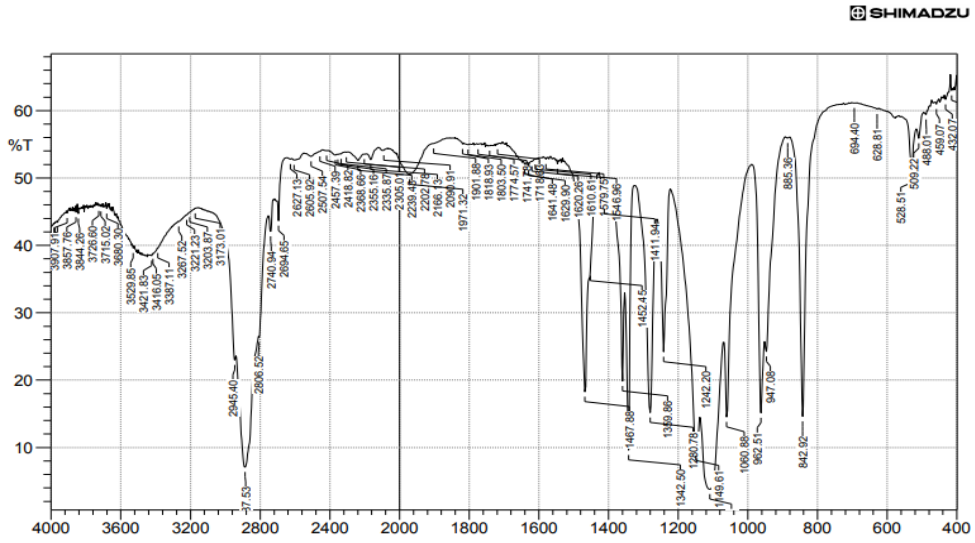

Figure 7: FTIR Spectrum of Rosuvastatin pure drug

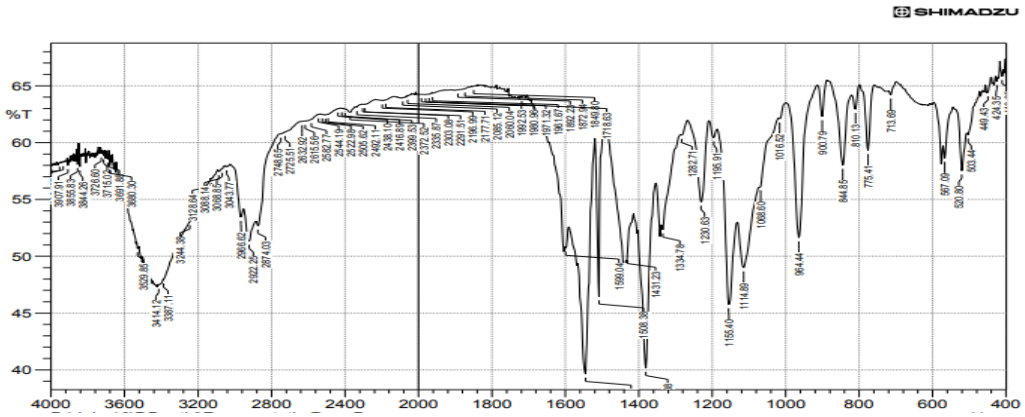

Figure 8: FTIR Spectrum of Physical mixture

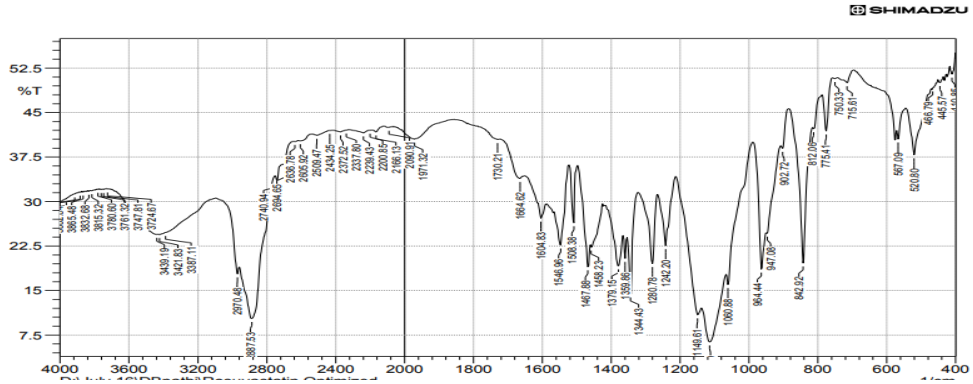

Figure 9: FTIR Spectrum of Rosuvastatin Optimized formulation SD13

X-RAY diffraction patterns:

The Rosuvastatin solid dispersions were carried out to find out whether the solid dispersions of various drug polymer ratios are crystalline or amorphous. The presence of numerous distinct peaks in the XRD spectrum of pure Rosuvastatin indicates that Rosuvastatin was present as a crystalline material. On the other hand, the spectrum of optimized formulation SD13 of solid dispersion was characterized by the complete absence of any diffraction peak, which is characteristic of an amorphous compound (Figure 10). The enhancement in the dissolution rate of the drug from the drug-Kolliwax GMS II and SLS solid dispersion is ascribed to the marked reduction in the crystallinity of the drug.

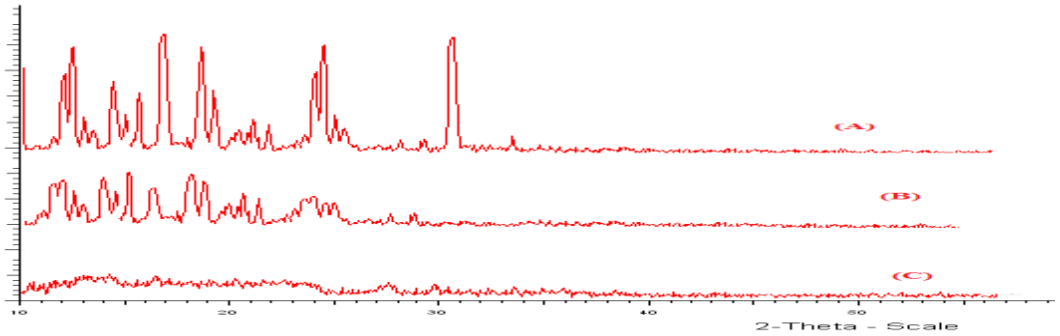

Figure 10: X-Ray diffractograms of (A) Rosuvastatin pure drug, (B) Physical mixture, (C) Optimized formulation SD13

SEM studies:

The surface of drug crystals appeared smooth and irregularly shaped and of different size. The presence of drug in particles of SD13 could not be distinguished with more porous surface. The dispersion seemed uniform and homogeneous with wrinkled surface. The drug crystals are completely incorporated into SD polymer attributing to complete dispersion of the drug .(Figure 11,12)

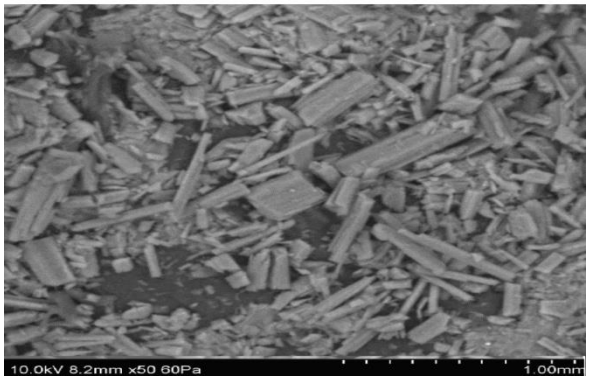

Figure11: Pure drug of Rosuvastatin

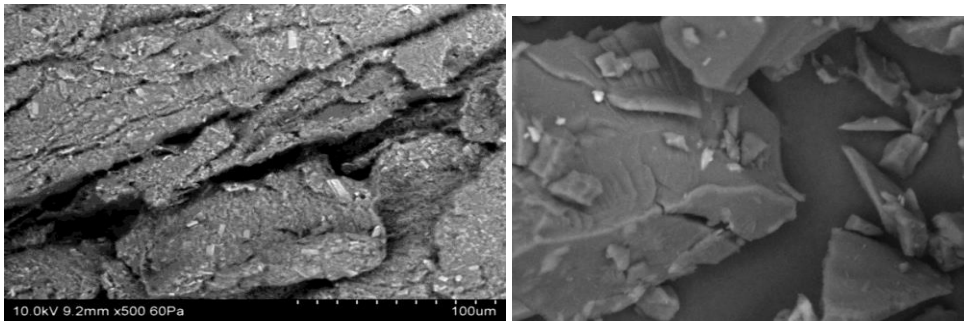

Figure 12: Rosuvastation optimized formulation SD13

STABILITY STUDIES

The optimized formulation (SD13) was subjected to stability studies for 3 months at accelerated stability conditions according to ICH guidelines.The results conclude that the formulation SD13 is stable and preserved their original properties with negligible variations .(Table 5)

Table 5: Evaluation parameters of optimized formulation (SD13) stored at 40 ±2^{0}c /75 ±5% RH

Retest time for optimized formulation	% 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	98.20	98.12

FORMULATION OF ROSUVASTATIN TRI LAYER TABLETS
ACTIVE LAYER FORMULATION

Preformulation Studies
The trilayer tablets prepared and characterized by various pre-compression micrometric analyses for the determination of flow properties. The bulk and tapped density of all tablet formulations vary between 0.57 to 0.63g/cc. The angle of repose lies between 20°.17±0.49 and26°.15±0.50,and Carr's index also range between 9.67±0.96 and 13.67±0.96. The formulation HF10 exhibited excellent flow properties (Table6).

Table 6: Powder flow properties of Trilayer tablets

Powder properties	Bulk density (g/cc)	Tapped density(g/cc)	Angle of repose (o)	Carr's index
AF10	0.60±0.05	0.62±0.02	25˚.20±0.51	14.98±0.93
BF10	0.59±0.06	0.65±0.02	23 ˚.32±0.50	13.46±0.94
CF10	0.61±0.06	0.64±0.02	26 ˚.15±0.50	11.39±0.96
DF10	0.62±0.06	0.62±0.03	25 ˚.41±0.46	12.68±0.93
EF10	0.63±0.06	0.66±0.02	27 ˚.32±0.49	15.39±0.93
FF10	0.60±0.05	0.63±0.02	23 ˚.29±0.46	13.67±0.94
GF10	0.59±0.05	0.61±0.01	21˚.32±0.42	11.24±0.89
HF10	0.57±0.06	0.61±0.04	20 ˚.17±0.49	9.67±0.96

In vitro Drug Dissolution of Rosuvastatin Active Layer
The matrix tablet of Rosuvastatin that were formulated without barrier layer were subjected to in vitro dissolution studies and results indicated that formulation F10 displayed maximum dissolution of i.e. 99.36±5.36% when compared to other formulations as active layer of the trilayer tablets. (Figure 13)

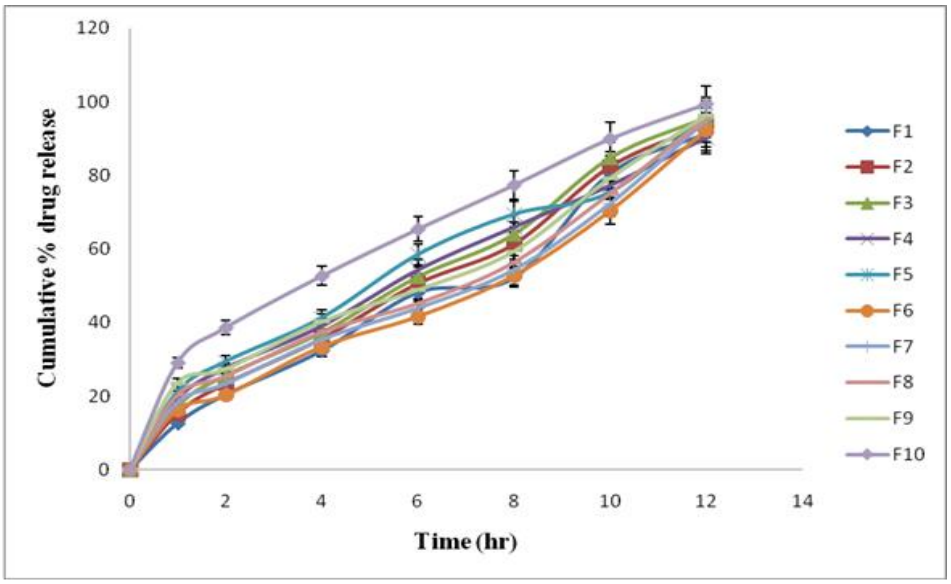

Figure 13: In vitro Dissolution profile of F1-F10 Rosuvastatin active layer formulation

Preparation of Trilayer Matrix Tablets of Rosuvastatin

The trilayer matrix tablet was prepared according to the composition and method described in the methods and shown in Figure 14.

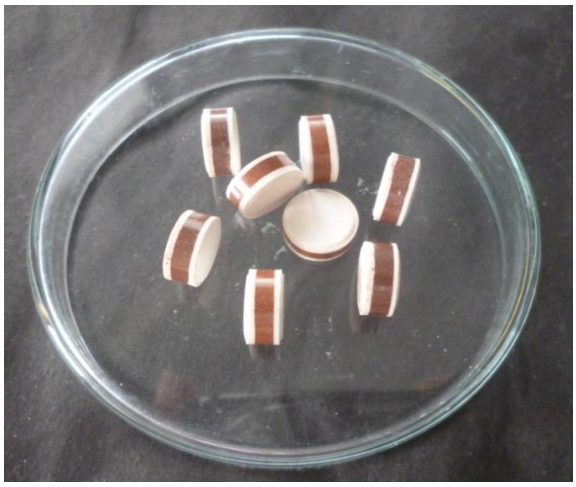

Figure 14: Rosuvastatin TLRT

Evaluation Parameters of Lovastatin Trilayer Matrix Tablets

The physicochemical characteristic evaluation of the trilayer tablets indicates that the hardness of all the tablets varied from 3 to 5 kg/cm^2, while the friability is between 0.18 and 0.39%. The percentage drug content of all formulations lies within 94.03 to 99.89% (Table 7).

Table 7: Physical evaluation of TLRT

Tests	Hardness (Kg/Cm^2)	Friability (%)	Weight variation (mg)	Assay (%)

AF10	3	0.40	346±4.5	94.61
BF10	4	0.45	345±4.5	96.31
CF10	3	0.39	348±4.8	95.10
DF10	5	0.35	342±4.2	94.03
EF10	3	0.29	348±4.8	96.58
FF10	4	0.26	349±4.9	94.31
GF10	4	0.18	347±4.8	96.98
HF10	5	0.24	350±5.5	99.89

In vitro Drug Dissolution of Lovastatin Trilayer Matrix Tablets

All eight trilayer matrix tablets (AF10–HF10) formulations were evaluated for drug release indicated release of drug within 20 to 24 hours, with HF10 exhibiting maximum release of 99.48±5.40% within 24hours (Figure15).

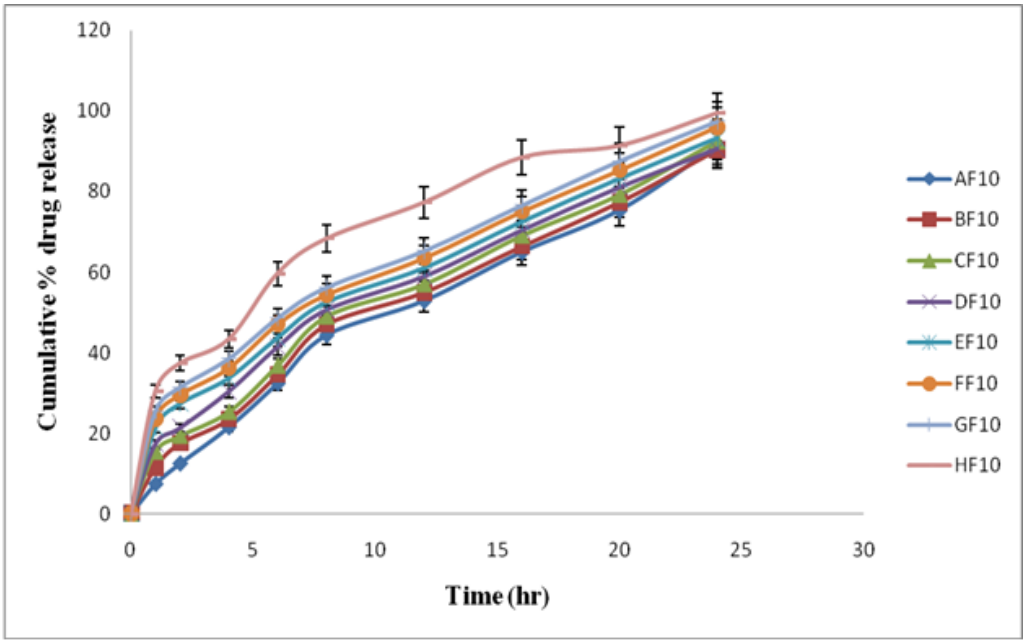

Figure 15: Comparison of % drug release of Rosuvastatin TLRT

Release Order Kinetics

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 8) (Figures 16-19)

Table 8: Release order kinetics of Rosuvastatin TLRT

Release kinetics	**R^2 values**

	Marketed formulation	AF10	BF10	CF10	DF10	EF10	FF10	GF10	HF10
Zero order	0.8035	0.9931	0.9915	0.9911	0.9947	0.9907	0.995	0.9933	0.9965
First order	0.9905	0.8737	0.86	0.8775	0.8638	0.8433	0.7864	0.7734	0.6865
Higuchi model	0.977	0.9588	0.9551	0.9626	0.9528	0.951	0.9436	0.9424	0.9352
Korsmeyer-Peppa's	0.9869	0.9047	0.8816	0.8997	0.8901	0.871	0.8717	0.8657	0.8675

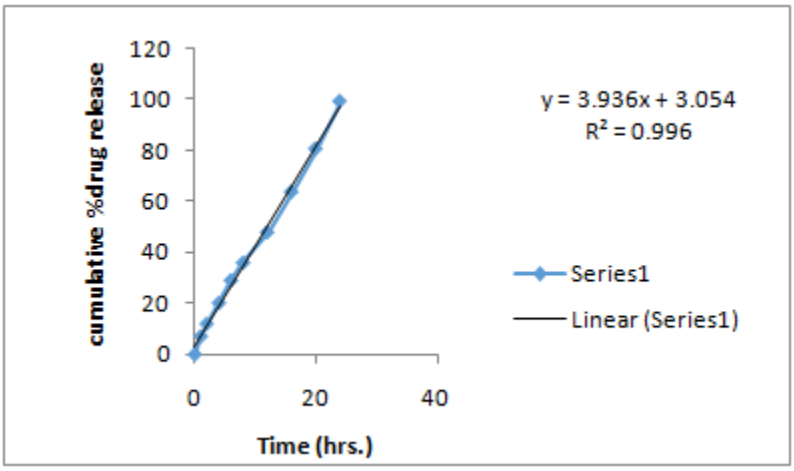

Figure 16: zero order plot of optimized Rosuvastatin HF10

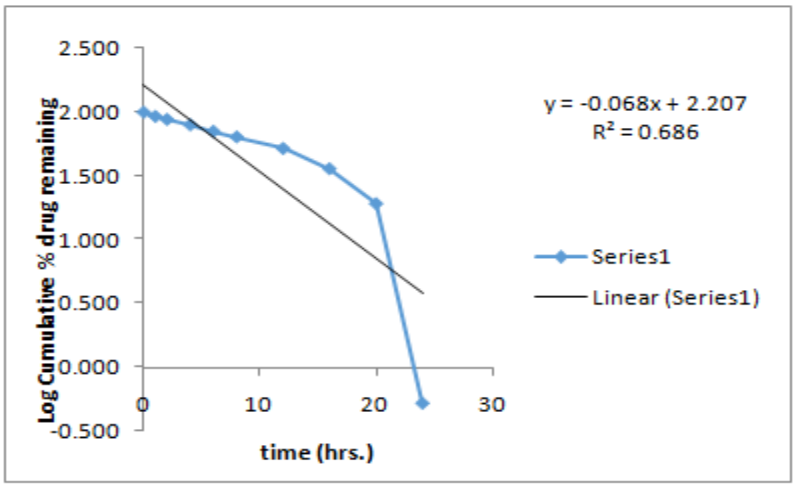

Figure 17: first order plot of optimized Rosuvastatin HF10

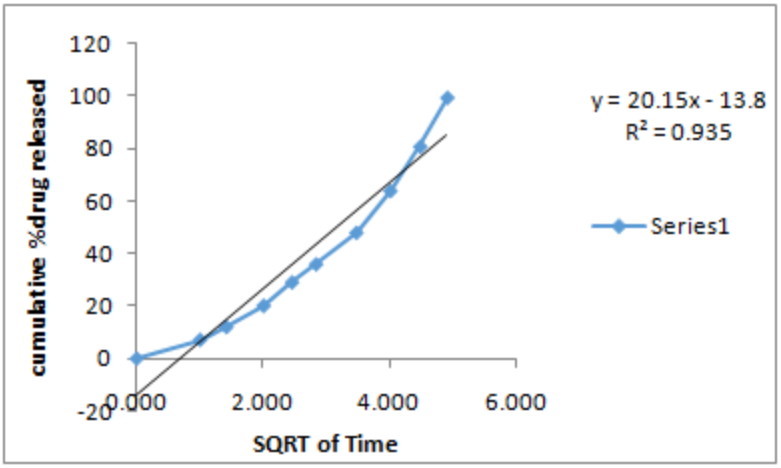

Figure 18: Higuchi order plot of optimized Rosuvastatin HF10

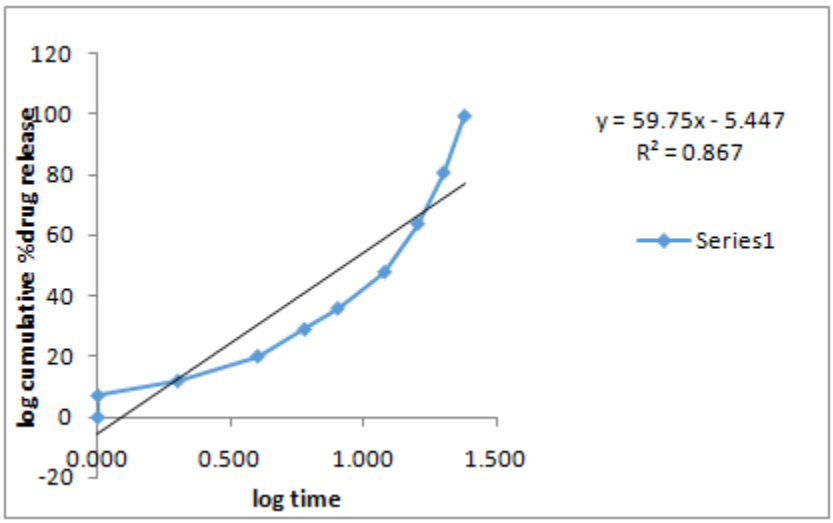

Figure 19: Korsmeyer-Peppa's plot of optimized Rosuvastatin HF10

Marketed Formulation Release Kinetics (Figure 20-23):

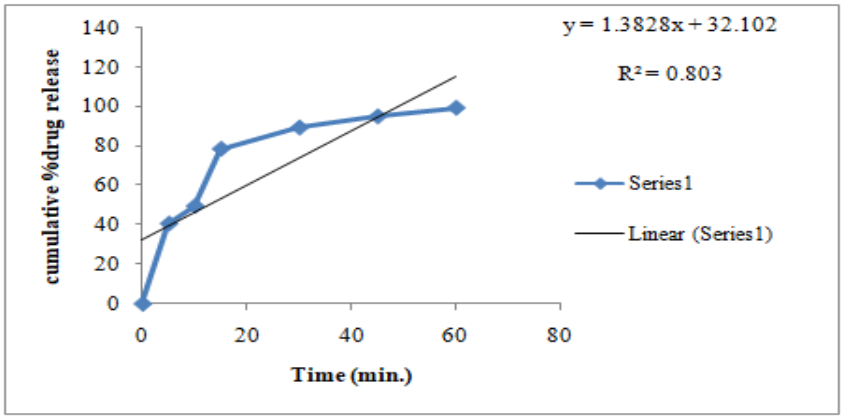

Figure 20: % Drug release vs. time plot of Marketed formulation showing zero order kinetics.

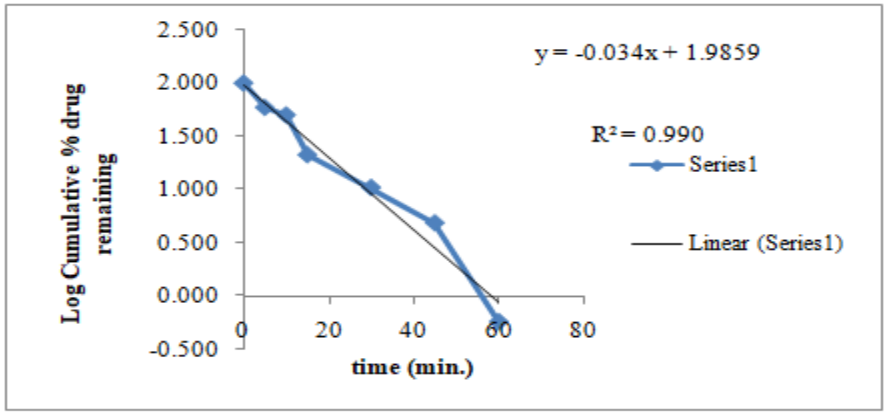

Figure 21: % Drug release vs. time plot of Marketed formulation showing first order kinetics.

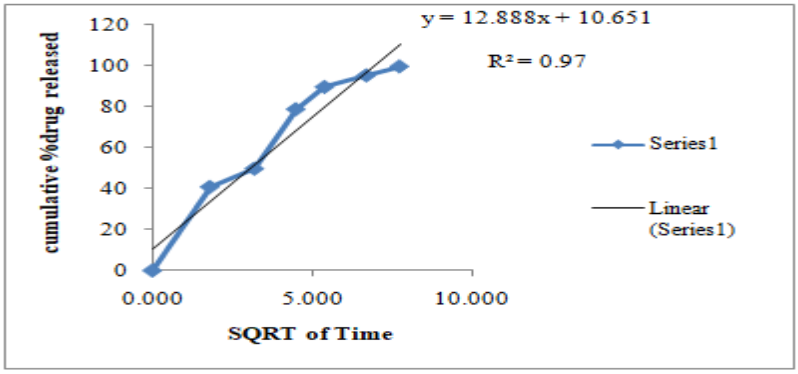

Figure 22: % Drug release vs. square root of time plot of Marketed formulation showing Higuchi's model

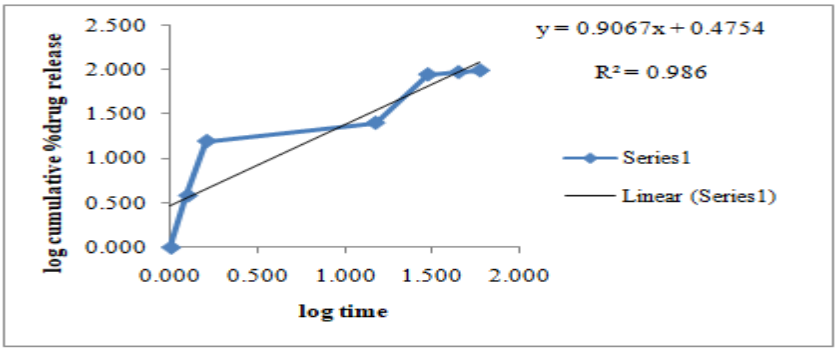

Figure 23: Log % drug release vs. time plot of Marketed formulation showing Korsmeyer-Peppa's model

STABILITY STUDIES

The formulation HF10 was subjected to stability study for 6 months and found stable with retention in original properties with no minor variations in physical parameters.(Table 9)

Table 9: Physico-chemical characteristics of optimized formulation HF10

Retest Time for Optimized formulation HF10	Friability (%)	Hardness (kg/cm^2)	Drug content uniformity (%) ± SD	In-vitro drug release profile (%)
0 days	0.24	5	99.89	99.48
30 days	0.25	5	98.80	98.75
60 days	0.28	4	98.12	98.31
120 days	0.31	4	97.36	97.66
180 days	0.33	4	97.01	97.15

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 The drug compatibility analysis by FTIR indicates no interaction between the rosuvastatin and excipients. The SEM results indicate amorphous structure for trilayer tablets indicative of more bioavailability and sustainable release of the drug. Thus, one may conclude that SD included trilayer matrix formulation of rosuvastatin have potential for consideration for drug delivery by enhancing solubility and dissolution rate and sustaining the drug release to 24 hours

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