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Formulation and Evaluation of Prolonged-Release Tablets Containing Solid Dispersions of Rosuvastatin Calcium

Bathala Anitha[1], Praveen Kumar C H[*2], Jampani Susmitha[1], Poolla Ramya Krishna[1]

[1]Ratnam Institute of Pharmacy, Pidathapolur, Pidathapolur (V & P), Muthukur (M), SPSR Nellore-524346, Andhra Pradesh, India

[2]Department of Pharmaceutics, Ratnam Institute of Pharmacy, Pidathapolur (V & P), Muthukur (M), SPSR Nellore-524346, Andhra Pradesh, India

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ABSTRACT

Pharmaceutical Industry is striving hard to improve the dissolution of drugs with limited water solubility. One of the approaches to improve the dissolution rate of poorly soluble drugs is solid dispersion. Hence in the present research, an attempt was made to improve the bioavailability of Rosuvastatin by formulating it as a solid dispersion. The release of Rosuvastatin calcium solid dispersion was prolonged using HPMC. Eudragit L-100 and PEG-6000 were used as carriers. Nine formulations of prolonged-release Rosuvastatin calcium (RS-SD 1 to RS-SD 9) were prepared and evaluated for pre and post formulation studies. Among all the formulations RS SD-3 showed an optimum release profile with 97.5±3.89 % indicating it to be the best formulation in the present research.

*Corresponding Author

Name: Praveen Kumar C H
Phone: +91 7382456321
Email: praveenchembeti@gmail.com

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INTRODUCTION

Rosuvastatin is an HMG-COA reductase inhibitor that lowers the levels of lipids and lipoproteins in the blood. HMG-COA reductase inhibitors competitively inhibit the conversion of 3-hydroxy-3-methyl glutamyl co-enzyme A(HMG CO-A) to mevalonate by the enzyme HMG COA reductase [1]. Rosuvastatin is a newer potent (BCS Class II drug) statin with plasma (half-life) of 18-24 hours. Bioavailability was found to be 20% which may lead to poor therapeutic effectiveness [2]. Several conventional methods such as micronization, mucoadhesive microspheres, nanosuspensions, liquisolid compacts [3, 4], solid dispersion, microemulsion, and self-emulsifying systems [5], nanocrystals [6], etc. are available to enhance the bioavailability of BCS Class II drugs. Solid dispersion tends to improve the solubility of poorly soluble drugs thereby improving their bioavailability. So, in the present research, an attempt was made to improve the bioavailability of Rosuvastatin calcium by formulating it as a solid dispersion. Drug release was extended with the help of various hydrophilic and hydrophobic polymers like PEG-6000, HPMC E 15, and Eudragit L-100. Hence in the present research prolonged-release solid dispersion of Rosuvastatin was formulated and evaluated.

MATERIALS AND METHODS

Materials

Rosuvastatin calcium was kindly gifted by Drugs India, Hyderabad. Polyethylene glycol -6000, Eudragit L-100, HPMC E-15, Potassium phosphate monobasic, Lactose, Magnesium stearate, Talc was obtained from New Himalaya Scientific Company, Nellore. All the chemicals used were of analytical

grade.

Methodology

Pre-formulation studies were performed for the drug and excipients and drug-excipient interactions were studied using FT-IR spectroscopy and the results were shown in Figure 1, Figure 2, Figure 3 and Figure 4.

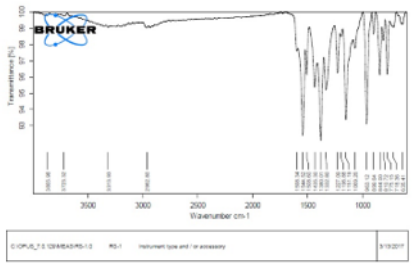

Figure 1: FTIR spectra of Rosuvastatin calcium

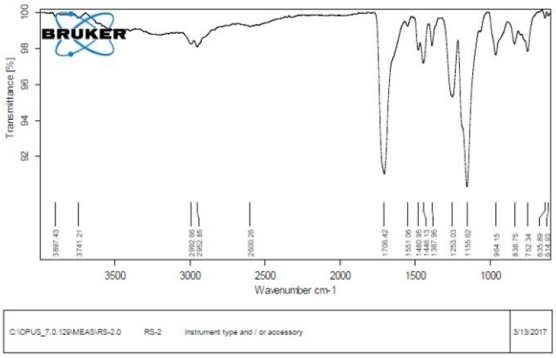

Figure 2: FTIR spectra of Eudragit

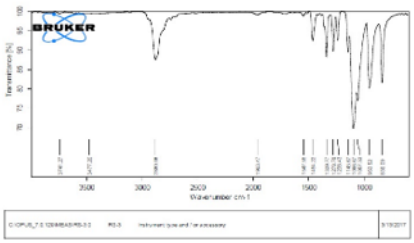

Figure 3: FTIR Spectra of PEG 6000

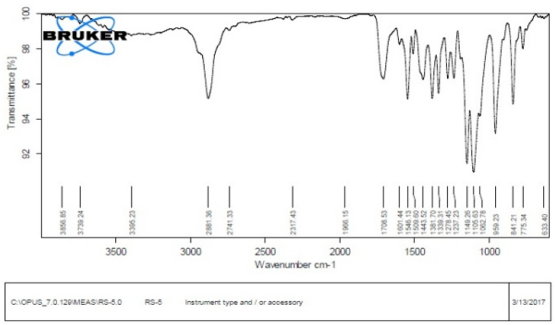

Figure 4: FTIR Spectra of Rosuvastatin + Polymer Mixture

Method of Preparation: Rosuvastatin SD

Rosuvastatin calcium and carrier are taken in different ratios as shown in Table 1 in a china dish and melted on a water bath. Then the mixture is set to cool on an ice bath and air-dried. The obtained solid dispersion is sieved through 60# [7, 8].

Estimation of Rosuvastatin in SD by UV Spectrophotometry

Accurately weighted amount of SD (dose equivalent to 40mg) was dissolved in 0.1M, pH 7.4 buffer solution in 100 ml of the volumetric flask which was previously cleaned and dry. This solution after suitable dilution was measured at 244 nm in UV/Vis spectrophotometer.

Method of Preparation: Rosuvastatin SD Prolonged Release Tablets

Prolonged-release tablets (Rosuvastatin SD dose equivalent to 40mg) of Rosuvastatin were prepared by direct compression method. The composition of prolonged-release tablets is given in Table 2. HPMC E15 was used as a polymer in all the formulations, magnesium stearate and talc were used as glidant and lubricant [9, 10].

The formulations were evaluated for various physicochemical parameters including the angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio [11]. Results were shown in Table 3.

After compression, the tablets were evaluated for hardness, thickness, friability, weight variation, and in-vitro dissolution studies.

Determination of Drug Content

From each formulation dose equivalent to 40mg was crushed to powder. The crushed powder was transferred into a 100 ml flask and diluted to 100 ml with methanol and stirred magnetically for 1 hr, centrifuged, and filtered. 1 ml of this solution was taken and it was diluted to 100 ml with chloroform and then absorbance was noted at 244 nm using a UV-visible spectrophotometer. Using calibration curve the drug content was determined from the absorbance of tablets. Results were shown in Table 4 [12].

In vitro drug release study

Rosuvastatin prolonged-release tablets were determined by using the dissolution test apparatus (Lab India DS8000). The in vitro studies were determined by using 900ml phosphate buffer pH 6.8 at 37 ± 2^{o}C temperature and 50 rpm. Every sample was taken at 1-hour intervals and calculated the absorbance at 244 nm by using the UV visible spectrophotometer [13]. Then calculated the cumulative

Table 1: Formulation of Rosuvastatin Calcium Solid Dispersion

F.Code	Drug	Carrier	Ratio (Drug: Carrier)
RS-SD 1	Rosuvastatin	Eudragit L 100	1:2
RS-SD 2	Rosuvastatin	Eudragit L 100	1:4
RS-SD 3	Rosuvastatin	Eudragit L 100	1:6
RS-SD 4	Rosuvastatin	PEG - 6000	1:2
RS-SD 5	Rosuvastatin	PEG - 6000	1:4
RS-SD 6	Rosuvastatin	PEG - 6000	1:6
RS-SD 7	Rosuvastatin	Eudragit: PEG	1:1:1
RS-SD 8	Rosuvastatin	Eudragit: PEG	1:2:2
RS-SD 9	Rosuvastatin	Eudragit: PEG	1:3:3

RS-SD: Rosuvastatin Solid Dispersion, PEG: Poly Ethylene Glycol

Table 2: Percentage Yield for Rosuvastatin Calcium Solid Dispersion

F-Code	Theoretical Yield (in gm)	Practical yield (in gm)	Percentage yield (in gm)
RS SD-1	3	2.50	83.3
RS SD-2	5	4.04	80.8
RS SD-3	7	4.714	67.3
RS SD-4	3	2.314	43.8
RS SD-5	5	2.74	54.8
RS SD-6	7	4.32	61.7
RS SD-7	3	2.705	90.1
RS SD-8	5	3.994	79.8
RS SD-9	7	1.11	15.8

Table 3: Formulation of Rosuvastatin SD Prolonged Release Tablets

S.No	Formulation ratios in (mg)	RS-SD 1	RS-SD 2	RS-SD 3	RS-SD 4	RS-SD 5	RS-SD 6	RS-SD 7	RS-SD 8	RS-SD 9
1	Rosuvastatin SD	120	200	280	120	200	280	120	200	280
2	Lactose	175	95	15	175	95	15	175	95	15
3	HPMC E 15	140	140	140	140	140	140	140	140	140
4	PVPK30	30	30	30	30	30	30	30	30	30
5	Magnesium stearate	20	20	20	20	20	20	20	20	20
6	Talc	15	15	15	15	15	15	15	15	15
7	Total	500	500	500	500	500	500	500	500	500

DRUG-Rosuvastatin (RS), HPMC-Hydroxy propyl methylcellulose (HPMC), Polyvinyl pyrrolidine K30 (PVP K30)

drug release.

RESULTS AND DISCUSSION

Rosuvastatin is an HMG-COA reductase inhibitor that lowers the levels of lipids and lipoproteins in the blood. From the FT-IR results, it is evident that when Rosuvastatin calcium Figure 1 was compared with Eudragit, PEG 6000, and mixture Figure 2, Figure 3, and Figure 4 there is no characteristic change in the peaks. These results confirm that there is no chemical interaction between Rosuvastatin calcium and excipients.

Percentage Yield of Rosuvastatin calcium SD was found to be satisfactory for RS SD-1 to RS SD-8 which ranges from 40 to 90%. The percentage yield of RS SD-9 was found to be very low i.e 15.8 %. Hence RS SD-9 was not used for the formulation of prolonged-

Table 4: Micromeritic Parameters of Rosuvastatin Prolonged-Release Tablets

F. Code	Derived Properties		Flow Properties		
	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Angle of repose (Degree)	Carr's index (%)	Hausner's ratio (%)
RS SD-1	0.47	0.59	35.7	20.3	1.25
RS SD-2	0.53	0.64	38.6	18.6	1.20
RS SD-3	0.58	0.61	16.17	4.91	1.044
RS SD-4	0.52	0.56	14.5	7.14	1.096
RS SD-5	0.66	0.70	21.3	5.71	1.06
RS SD-6	0.78	0.81	19.2	3.70	1.038
RS SD-7	0.58	0.61	16.17	4.91	1.044
RS SD-8	0.57	0.61	9.92	6.55	1.062

Table 5: Evaluation parameters of Rosuvastatin calcium prolonged-release tablets

F. Code	Thickness (mean ± SD) (mm)	Hardness (Kg/cm^2)	Weight variation (mean± SD) (mg)	Drug content (mean±SD)	Friability (%)
RS SD-1	5.25±0.2	6.2	495±0.5	97.34±0.6	0.215
RS SD-2	5.29±0.5	6.4	498±0.8	98.10±0.1	0.321
RS SD-3	5.31±0.3	5.9	497±0.5	97.87±0.1	0.220
RS SD-4	5.28±0.2	6.1	502±0.2	98.40±0.7	0.183
RS SD-5	5.35±0.3	5.9	495±0.3	98.50±0.2	0.179
RS SD-6	5.30±0.5	5.9	501±0.6	99.30±0.5	0.112
RS SD-7	5.28±0.6	6.4	496±0.1	98.43±0.5	0.134
RS SD-8	5.30±0.7	6.2	498±0.4	97.78±0.3	0.131

(*Data from each profile is presented in mean±SD (n=3))

Table 6: Cumulative drug release of Rosuvastatin prolonged-release tablets

Time (hrs)	% Cumulative drug release							
	RS SD-1	RS SD-2	RS SD-3	RS SD-4	RS SD-5	RS SD-6	RS SD-7	RS SD-8
1	18±1.32	16.2±2.11	10.8±2.01	12.6±1.11	16.2±1.32	15.3±1.10	10.2±1.23	9.30±1.21
2	30.6±2.34	28.8±2.34	18.0±1.34	21.6±2.32	36.0±3.21	28.9±1.33	16.1±2.12	16.4±2.11
3	46.8±3.23	39.6±3.21	28.8±2.34	28.8±2.61	41.4±2.45	36.2±2.34	23.2±1.32	14.2±3.12
4	55.8±3.12	52.2±3.24	37.8±3.21	41.4±3.23	54.0±3.21	51.3±3.12	31.4±3.24	29.6±2.13
5	76.0±4.21	55.8±4.23	48.6±3.33	54.0±2.34	63.0±2.12	60.1±3.28	39.6±2.33	36.4±2.34
6	92.5±4.81	68.4±2.32	57.6±3.18	63.0±4.32	70.2±3.56	68.1±3.12	48.4±2.11	49.2±4.32
7	-	70.2±3.34	64.8±2.19	70.2±4.23	81.0±5.21	79.6±4.23	58.8±3.45	56.3±2.32
8	-	93.3±4.54	76.7±4.32	84.6±2.43	86.0±2.35	85.4±2.34	66.4±4.12	64.3±3.45
9	-	-	89.2±4.15	96.2±4.53	94.6±5.62	90.1±2.34	78.2±4.87	71.4±2.13
10	-	-	97.5±3.89	-	-	95.2±2.11	85.3±4.32	79.6±4.23

(*Data from each profile is presented in mean±SD (n=3))

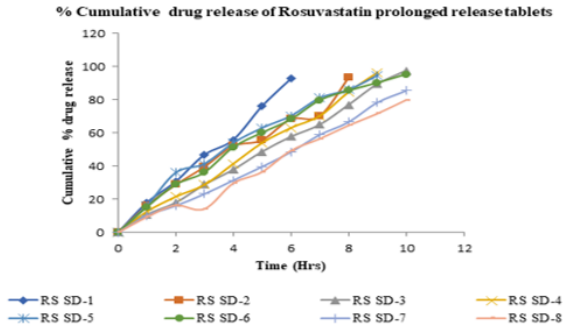

Figure 5: Cumulative % drug release of Rosuvastatin prolonged release tablets

release tablets. Results were shown in Table 3.

Micromeritic properties showed poor flow properties for Rosuvastatin API due to its amorphous nature when compared with the formulations RS SD-1 to RS SD-8 and the results are tabulated in Table 4.

Post-formulation parameters concluded that there should be a certain amount of strength and resistance to friability for the tablet, so that tablet should not break during handling which also shows an effect on dissolution. The hardness of Rosuvastatin calcium prolonged-release tablets ranges from 5.9 to 6.4 kg/cm^2. Friability ranges from 0.11 % to 0.32%. This indicates that acceptable resistance is shown by Rosuvastatin calcium prolonged-release tablets to withstand handling and the results are given in Table 5.

In-vitro dissolution studies showed that the percent drug release has been retarded using Eudragit L-100 and the results are shown in Table 6 and Figure 5. For all the formulations the dissolution was conducted for twelve hours and among all the formulations, RS SD-3 showed optimum release profile indicating it to be the best formulation in the present research.

CONCLUSION

From the present research, it was concluded that the formulation RS SD-3 (Rosuvastatin: Eudragit L100 at 1:6) of Rosuvastatin calcium has achieved 97.5 $\pm$ 3.89% drug release for 10 Hrs. Results indicated that drug release has been retarded with an increase in the viscosity of Eudragit L100. The above formulation may also decrease gastric irritation and may improve patient compliance with the reduction in dosage frequency.

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Conflict of Interest

The authors declare that no conflict of interest associated with this work.

Contribution of Authors

Authors declare that, the work done by the names mentioned in the article and all the liabilities and claims related to the content of the article will be borne by the authors.

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