Pharmacokinetic enhancement of poorly aqueous soluble rosuvastatin using natural gum as carriers: pharmaceutical modeling of release kinetics and bio-stastistical evaluation

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Abstract
The major focus of the present investigation is to enhance the solubility and dissolution rate of Rosuvastatin Calcium. Preaparation of Solid dispersions of Rosuvastatin Calcium by using Vitamin E TPGS, *A.Marmelos*, and Gum Karaya as carriers in different ratios through solvent evaporation method. As Solid dispersions have been traditionally used effective techniques to improve the dissolution properties and bioavailability of poorly-soluble drugs. The model drug selected Rosuvastatin Calcium, which is BCS class-II drug with anti-hyperlipidemic potential. The reported bioavailability from oral route of drug is only 20%. So aim of current study is to improve the solubility and dissolution rate of a poorly water-soluble drug Rosuvastatin Calcium, by solid dispersion technique. Physical mixtures and solid dispersions were prepared using Vitamin E TPGS, MGK & natural polymers *A.Marmelos* in different to drug to carrier ratios, dispersions were prepared by solvent evaporation technique. Prepared formulations were characterized in solid state by FTIR analysis, powder X-ray diffraction, Scanning electron microscopy and in-vitro dissolution study. The aqueous solubility of Rosuvastatin Calcium was favored by presence of both the polymers. Solid state characterizations indicated the Rosuvastatin Calcium was present in amorphous form and entrapped in polymer matrix. In contrast to the very slow dissolution rate of pure Rosuvastatin Calcium, the dispersion of the drug in the polymers considerably enhanced the dissolution rate. Solid dispersion prepared with TPGS showed maximum 91.19% Drug release. The best formulation of solid dispersion selected and subjected to fast dissolving tablets. The mixtures of solid dispersion and excipients were evaluated for pre-compression parameters. After then fast dissolving tablets were prepared by direct compression technique. The formulated tablets were evaluated by post compression parameters. *In-vitro* drug release performance of the developed formulations was investigated. Followed by that, the release mechanism of the formulations was also studied by applying various kinetic models. The overall results revealed that the formulated fast dissolving tablets complied with the standards and exhibited satisfactory performance in terms of drug release and other related parameters.

Keywords: Solid Dispersion. Natural gums, Anti-lipidemic activity.

Introduction
Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. Absorption of a drug through the oral route involves its dissolution from the formulation into gastric and/ or intestinal fluids followed by its permeation through gastrointestinal cell membranes and finally into the systemic circulation. Oral solid dosage forms are one of the most commonly used formulation types having multiple benefits over other formulations/routes. However, the challenge for a pharmaceutical scientist lies in the fact that dissolution of a drug from an oral solid formulation (a key factor in drug absorption) is dependent on the aqueous solubility of the drug. Therefore, a drug with poor aqueous solubility would exhibit dissolution rate limited absorption and similarly a drug possessing poor membrane permeability undergo permeation rate limited absorption. A drug is highly soluble when highest dose of drug is soluble in ≤250 ml of water over a pH range of 1 to 7.5 and a drug is highly permeable when extent of absorption in humans is to be ≥90% of an administered dose. It has been investigated that most of new chemical entities currently being discovered and intended to be used as a solid dosage form should produce an efficient and reproducible plasma concentration after oral administration.[1]

Process of Solubilization
Solubilization of poorly soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development. A number of methodologies can be adapted to improve solubilization of poor water soluble drug and further to improve its bioavailability. Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. Bioavailability depends on several factors, drug solubility in an aqueous environment and drug permeability through lipophillic membranes being the important ones. The techniques generally employed for solubilization of drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, solvency, micellar solubilization, hydrotropy etc.[2,3]

Drug and Excipient Profile
Rosuvastatin calcium is a statin having antilipidemic activity that synthetically inhibits the Hydroxymethylglutaryl-COA-reductase enzyme. Rosu cal is a noval active substance is a white yellowish powder which shows no polymorphism. It belongs to a new generation of

methane-sulphonamide pyrimidine and *N*-methane sulfonyl pyrrole-substituted 3,5-dihydroxy-heptenoates. Most of the statin drugs lack systemic bioavailability due to their absorption profile. So in order to reach effective therapeutic concentration, large doses of drugs in frequent intervals of time are needed to be administerted; this may lead to induce adverse effects and may lack patient compliance. Gum is obtained from fruits of *A. marmelos* belonging to family Rutaceae. In many investigations high aqueous solubility of *A.marmelos* gum has been evaluated. Gum karaya, or sterculia gum, is the dried exudates of sterculia urens. The applications of gum karaya due to its unique features such as high swelling and water retention capacity, high viscosity properties, inherent nature of antimicrobial activity and abundant availability. Rosuvastatin calcium was selected as model drug for the present work as it was categorized as BCS II class drug and its dissolution was rate limiting step for its absorption due to poor aqueous solubility.

Objectives

The objective of this research work was to increase the solubility of the Rosuvastatin calcium by increasing its release rate with the help of various carriers and also formulating fast dissolving tablets of the prepared solid dispersion of API. So, the present investigation deals with increasing the solubility by using solid dispersion technique. And then formulating these dispersions into fast dissolving tablets. The mathematical tools employed for the bio-statistical evaluation of the formulations.

Experimental

Preparation of *Aegle Marmelos* Gum

1kg fruit was obtained and gum extract from fruits manually. Dried at room temperature for 3 days. After then crush in mortar and powder pass through sieve no.#85.Gum was solublised in distilled water and wash with acetone upto 150 ml. precipitation occur then filter and filtrate gum dried at 30oc for 1day. Light brown color of *A.Marmelos* was obtained.[4]

Preparation of Formulation

Preparation of Physical Mixtures of Rosuvastatin Calcium with Three Different Carriers

Physical mixture were prepared by mixing accurate weight of Rosuvastatin Calcium with carriers in drug to polymers ratio 1:0.50,1:0.75,1:1 (A1,B1,C1,A2,B2,C2,A3,B3,C3) respectively. The physical mixture was pulverizes and then mixed thoroughly in mortar with a pestle until homogenous mixture was obtained. The mixture was passed through sieve no. #85 collected and stored in close container away from humidity until use.

Preparation of solid dispersion of Rosuvastatin Calcium with polymers

Solid dispersions of Rosuvastatin Calcium with polymers were prepared by the solvent evaporation method.

Table 1: Ingredients used in the preparation of solid dispersions

Drug:Polymer Ratio	Rosuvastatin Calcium (mg)	TPGS (mg)	*A.marmelos* (mg)	MGK (mg)	Solvent amount
1:0.5	500	200	250	250	100
1:0.75	500	375	375	375	100
1:1	500	500	500	500	100

In-vitro dissolution studies of rosuvastatin calcium, physical mixtures and solid dispersions

Rosuvastatin Calcium, physical mixtures and solid dispersion equivalent to 100 mg of Rosuvastatin Calcium were used for studying the rate and extent of drug dissolution. The study was performed using USP Type II (Paddle type).

Formulation of Fast Dissloving Tablets of Rosuvastatin Calcium

Direct compression method was used to prepare 10mg dose strength Rosuvastatin Calcium fast dissolving tablets. The materials were accurately weighed and mixed together to obtain homogeneous or uniform mass mixture which was sieved through mesh size #42. Sodium Starch Glycolate (SSG) was used as superdisintegrant. Micro-crystalline cellulose (MCC) was used as directly compressible material[5] and magnesium stearate was used as tablet lubricant. Talc as glident or anti-caking agent.

Mathematical Modeling of Release Kinetics

The in-vitro drug release data of the prepared tablet was fitted to various release kinetic models viz. zero-order, first-order, Higuchi and Korsemeyer-Peppas model employing the following set of equations.[6]

a) **Zero-order kinetic model**
$M_0-M_t = K_0t$

b) **First-order model**
$In (M_0/M_t) = K_1t$

c) **Higuchi model**
$M_t = K\sqrt{t}$

d) **Korsemeyer-Peppas model**
$M_t/M_\infty = Kt^n$

Where, M0, Mt and M∞ correspond to the drug amount taken at time equal to zero, dissolved at a particular time, t, and at infinite time, respectively. The terms W0 and Wt refer to the weight of the drug taken initially and at time t, respectively. Various other terms viz. k, k0,k1 and K refer to the release kinetic constants obtained from the linear curves of Korsemeyer-Peppas, zero-order, first-order and Higuchi model, respectively.[7-9]

Results

Pre-formulation studies

Physical Appearance

Rosuvastatin Calcium is a yellowish white powder with crystalline nature

Melting Point

Melting point of the drug was found to be 119ºC which is agreement with the reported value (122ºC)

Analytical Study

Determination of absorbance of Rosuvastatin Calcium

Rosuvastatin Calcium was estimated at UV-maxima of 243.2 nm in water+methanol, pH 6.8 & pH 7.4 phosphate buffers using UV-Visible double beam spectrophotometer**.** The scanning of the drug was done in the range of nm as shown in Fig.

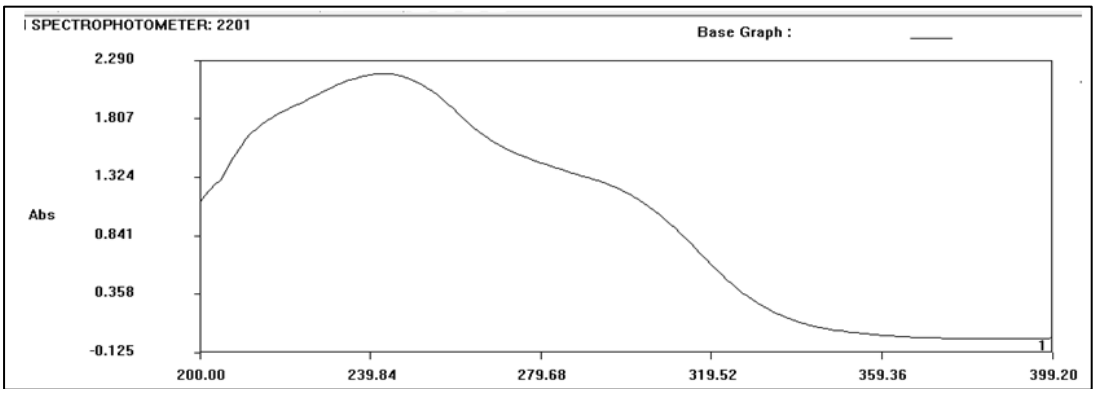

Fig. 1: Calibration curve of Rosuvastatin Calcium showing maximum absorbance at 243.2nm.

Table 2: Absorbance of Rosuvastatin calcium in three different solvents

Concentration (µg/ml)	PBS pH 6.8*±SD	PBS pH 7.4* ±SD	Distilled water +Methanol*±SD
2	0.014	0.059	0.010
4	0.138	0.17	0.155
6	0.285	0.3	0.285
8	0.434	0.461	0.433
10	0.557	0.589	0.554
12	0.720	0.721	0.684

Interday and Intraday precision

Interday precision was found to be in the range of 0.1-0.6 and Intraday precision was found to be 0.09 to 0.6

Table 3: Interday and Intraday precision data and statistical results

Solvent	Absorbance (intraday)(µg/ml)	Absorbance (interday)(µg/ml)	Interday (%age conc.) ±SD	Intraday (%age conc)±SD	Interday (%RSD)	Intraday (%RSD)
pH 6.8	0.720	0.721	98±0.005	97.4±0.003	0.195	0.654
pH 7.4	0.719	0.720	98.4±0.003	98±0.002	0.192	0.567
Distilled water+ Methanol	0.685	0.684	99.3±0.004	99.3±0.005	0.506	0.096

Repeatability

The repeatability mean concentration was found to be 0.693 µg/ml

Table 4: Results of repeatability studies in different solvents

Concentration (µg/ml)	Absorbance (pH 6.8)	Absorbance (pH 7.4)	Absorbance (Distilled water+ Methanol)
12	0.722	0.720	0.684
12	0.721	0.721	0.683
12	0.720	0.720	0.683
12	0.721	0.720	0.682
12	0.720	0.720	0.684
12	0.721	0.720	0.683
Mean	0.721±0.0012	0.720±0.0075	0.683±0.0018
SD	0.0010	0.00170	0.00271
%RSD	0.17	0.54	0.44

Characterization of *A.marmelos* fruit gum

Table 5: Characterization of *A.marmelos* fruit gum

Parameters	*A.marmelos*
Ash value	82.1%
Loss on drying	3%
Hydration capacity	0.887 0.0054

Thin layer chromatography of *A.marmelos*

Table 6: Thin layer chromatography of *A.marmelos*

Solvent system	Ratio	Distance travelled	Rf value
Methanol: glacial acetic acid: chloroform	16:10:4	8.6	0.89
n-butanol: acetic acid: water	15:10:5	6.5	0.543
Tolune:ethyl acetate: diethylamine	5:20:5	10.0	_

Rf values 0.89 shows the presence of marmelosin constituents in gum which are responsible for enhancing solubility and 0.543 shows the presence of umbelliferone.

Modified Gum Karaya
Characterization of MGK

Table 7: Characterization of MGK

Parameters	GK	MGK
pH Value	7.0	7.3
Viscosity(cps, min)	1870 ± 0.089	1694 ± 0.0076
Swelling index (%)	70.567 ± 1.016	60.143 ±0.786
Hydration capacity	0.697 ± 0.039	0.875 ± 0.008

Lower the viscosity and high the water retention capacity makes the carrier suitable for solubility and bioavailability enhancement of poorly soluble drug. The amount of water retained is maximum shows the hydrophilic nature of the carrier.[10]

Solubility Study
Phase solubility

Table 8: Phase solubility studies of Rosuvastatin Calcium

Concentration of Polymers (%w/v)	Solubility (mg/ml)		
	TPGS	MGK	*A.Marmelos*
0.005	0.198	0.154	0.019
0.5	0.601	0.328	0.291
0.75	0.645	0.387	0.336
50	0.731	0.432	0.398
100	0.798	0.479	0.376

Table 9: Percentage drug content of Rosuvastatin Calcium

Drug+Polymer ratio	TPGS	MGK	*A.Marmelos*
1:0.5	79.61	78.46	53.09
1:0.75	92.48	94.28	65.58
1:1	99.79	97.79	66.08

Drug Content
The uniformity in the drug content[11] for all the formulations was found to be within the limits of 90-100% and results are shown in table-9.

***In -Vitro* Dissolution Studies**
The in vitro release profile of Rosuvastatin Calcium in pH 6.8 phosphate buffer is shown in figure.

Table 10: Cumulative drug release of pure drug Rosuvastatin Calcium in pH 6.8 phosphate buffer

Time (min)	Pure Drug %C.D.R
0	12.54
5	25.84
10	34.08
15	35.11
20	36.07
30	36.14

***In Vitro* dissolution of solid dispersions of Rosuvastatin Calcium and different polymers**

Solid dispersion of Rosuvastatin Calcium in *A.Marmelos*, Gum karaya, TPGS containing three drug:polymer ratio (1:0.5,1:0.75,1:1) and using 6.8 phosphate buffer 900ml solvent were prepared[12-14.]

***In Vitro* dissolution of Solid Dispersion SD7, SD8, SD9**

In *solid* dispersion SD7, SD8, SD9, the drug to TPGS ratios vary from 1:0.5 to 1:1, and the solvent amount is used for the preparation remains same as used in other formulations i.e., 900 ml, which suggests that SD9 show maximum percentage drug release.

Table 11: Percentage Cumulative Drug Release of Solid Dispersion of Rosuvastatin and TPGS in Different Drug to Polymer Ratios

S. No.	Time (min)	Percentage Cumulative Drug Release ±SD		
		SD7	SD8	SD9
1	0	41.03	43.60	37.95
2	10	43.61	43.09	43.28
3	20	51.07	51.84	43.79
4	30	64.44	62.64	62.64
5	45	84.76	79.62	81.57
6	60	89.91	90.93	91.97

***In-Vitro* Dissolution of solid dispersion SD4, SD5, SD6**

In solid dispersion SD4, SD5, SD6, the drug to polymer ratio vary from 1:0.5 to 1:1. From table 12, it was observed that solid dispersion SD4 containing drug: gum karaya 1:0.5 showed maximum release of up to 76.98% in 1 hr. The cumulative release for SD5 and SD6 were 76.73%, 76.48% respectively.[15-18]

Table 12: Percentage Cumulative Drug Release of Solid Dispersion of Rosuvastatin Calcium and Modified Gum Karaya in Different Drug to Polymer Ratio

S. No.	Time (min)	Percentage Cumulative Drug Release ±SD		
		SD4	SD5	SD6
1	0	38.94	39.45	43.00
2	10	36.92	39.71	44.27
3	20	44.27	47.06	49.34
4	30	51.63	61.76	51.63
5	45	72.67	70.64	62.78
6	60	76.98	76.73	76.48

***In vitro* dissolution of solid dispersion SD1, SD2, SD3**

In solid dispersion SD1, SD2 and SD3, the drug to polymer ratio vary from 1:0.5 to 1:1, it was observed from the table 13. that solid dispersion SD2 shows maximum release upto 50.39% in 1 hr. SD2 and SD3 exhibit drug release of 46.08%, 42.25% respectively, in 1 hr.[19]

Table 13: Percentage Cumulative Drug Release of Solid Dispersion of Rosuvastatin Calcium and *A.Marmelos* in Different Drug to Polymer Ratios

S. No.	Time (min)	Percentage Cumulative Release±SD		
		SD1	SD2	SD3
1	0	40.49416901	33.64909859	31.34205634
2	10	37.96120742	38.98215511	34.63957221
3	20	40.24500639	41.51228849	37.1767078

4	30	38.98687981	51.14839732	38.44637861
5	45	41.26349206	48.8695484	39.7595806
6	60	46.0826854	50.39338963	42.25353953

Thus, it was concluded from the studies that the solid dispersion technique has improved the dissolution rate of Rosuvastatin Calcium to a great extent. The dissolution form solid dispersions were greater than that from the pure drug and marketed formulation.

Characterization of Optimized Solid Dispersions

Fourier Transform Infrared Spectroscopy

FT-IR spectra of TPGS, Drug, Physical mixtures and solid dispersions were recorded using
FT-IR spectrophotometer in below Figures respectively. Prominent peaks of spectral analysis shown in Table 14.

Table 14: Spectral analysis of Rosuvastatin Calcium, TPGS, MGK, *A.Marmelos*, Physical Mixture with different polymers and optimized solid dispersion

Pure Drug	**TPGS**	**MGK**	***Marmelos***	**Physical Mixture with TPGS**	**Physical Mixture with MGK**	**Physical Mixture with *A.Marmelos***	**Optimized Solid Dispersion with TPGS**
3253.73	2868.65	3436.43	1544.36	3387.37	3462.42	2969.23	3385.18
2931.64	1544.97	2967.03	1509.18	2869.91	2972.52	1543.37	2929.00
1546.73	1509.10	2082.41	1435.45	1738.23	2087.91	1509.15	1546.96
1509.27	1437.71	1634.66	1379.76	1544.30	1634.53	1435.65	1437.98
1380.26	1379.22	1509.22	1333.98	1509.17	1382.20	1379.59	1381.08
1227.50	1226.98	1382.00	1227.37	1436.20	1152.89	1151.13	1228.70
1151.44	1102.01	1230.25	1151.08	1379.21	964.31	961.56	1116.82
962.28	959.10	1154.29	961.88	1147.48	656.12	842.77	962.51
843.26	842.36	964.68	900.82	959.20		774.31	844.85
750.04	774.24	776.00	773.83	843.43			775.41

From the above observation it was evident that there was no major shifting in the frequencies of key functional groups. Hence the drug and polymers are compatible with each other. Hence IR showed absence of incompatibility between the Rosuvastatin Calcium and Polymers**.**

Scanning Electron Microscopy

The SEM images of Rosuvastatin Calcium, Physical Mixture and the solid dispersion are shown in Fig. 13,14,15 respectively.

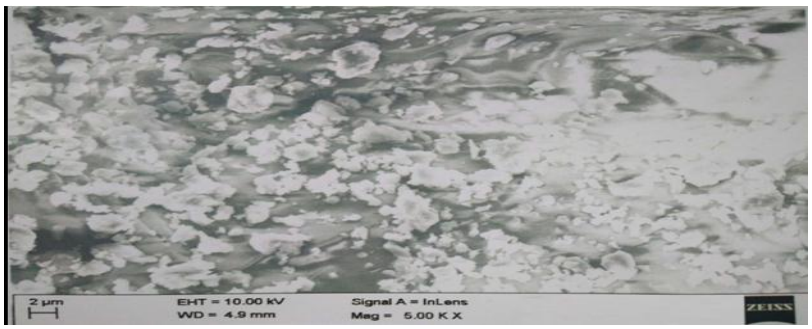

Fig. 2: Scanning electron micrograph of Rosuvastatin Calcium

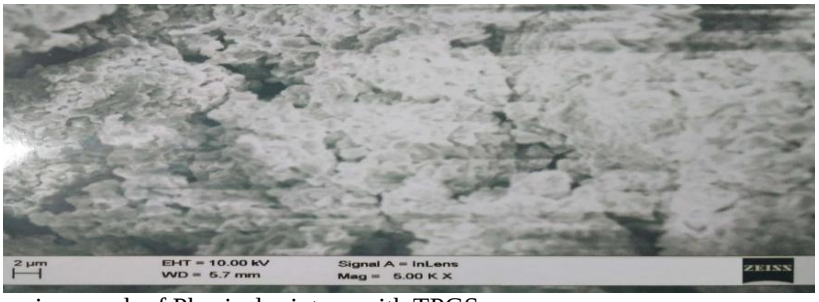

Fig. 3: Scanning electron micrograph of Physical mixture with TPGS

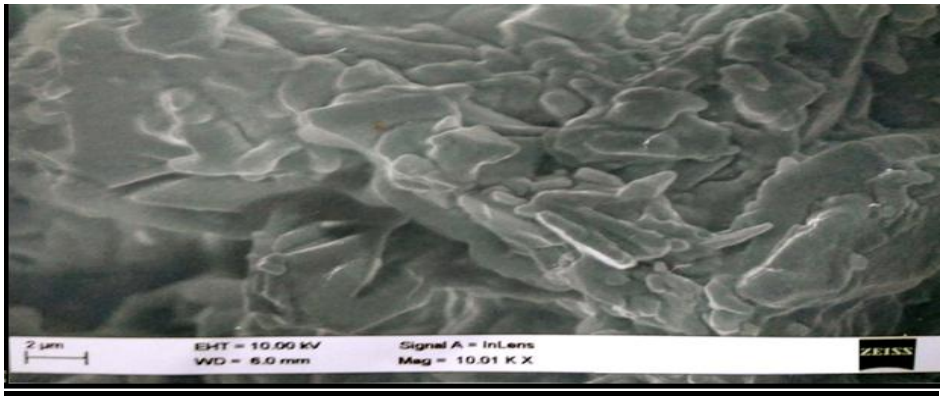

Fig. 4: Scanning electron micrograph of Solid dispersion

X-ray Diffraction Studies

X-ray studies were carried out of Rosuvastatin Calcium, optimized solid dispersion. X-ray diffraction of Rosuvastatin calcium shows characteristics peaks at 18.02, 22.54 which confirmed its crystalline nature. The X-ray diffraction of Solid dispersion exhibited the characteristic peaks of Drug, but with lower intensities. This indicates the formation of amorphous drug within crystalline polymer matrix.[20,21]

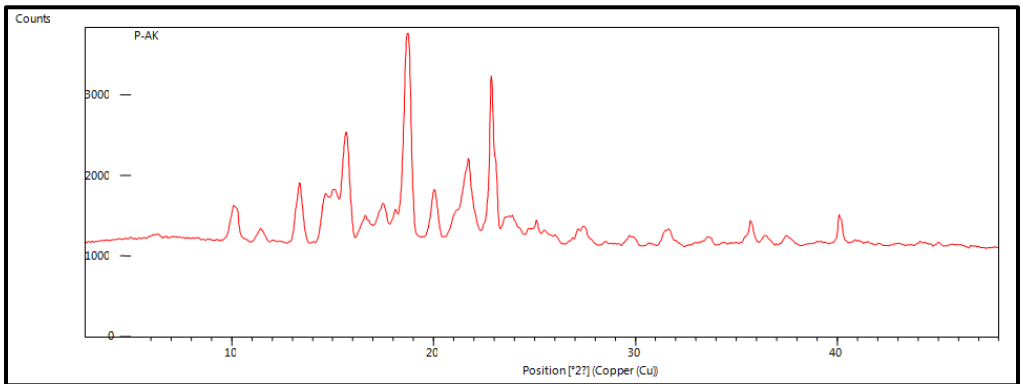

Fig. 5: X- ray diffraction of Rosuvastatin Calcium

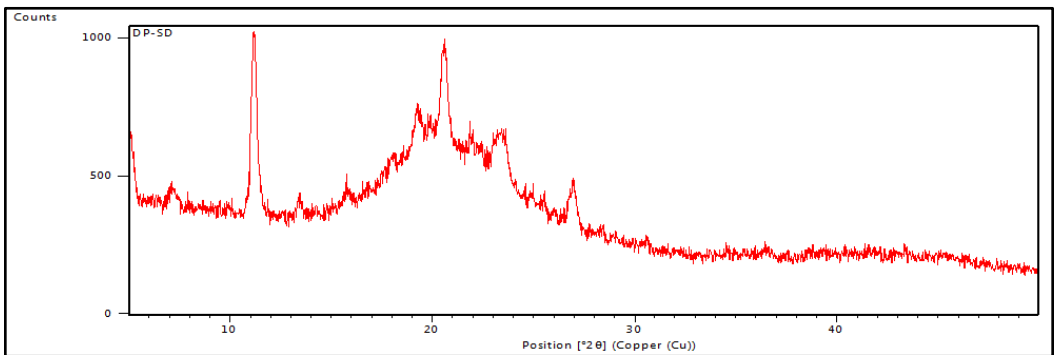

Fig. 6: X-ray Diffraction of Solid Dispersion

Fast Dissolving Tablets of Rosuvastatin Calcium

Fast dissolving tablets of Rosuvastatin Calcium was prepared using different excipients i.e., superdisintegrants, binders, lubricants and ten evaluated for various parameters to select the best combination to prepare Rosuvastatin Calcium tablets. Superdisintegrants play important role in case of fast dissolving tablets as they subject the tablet disintegrate in proper time to get its effect. The incorporation of superdisintegrant in the solid dispersion tablets can also strongly enhance the dissolution rate of the lipophillic drug. From the dissolution profile of solid dispersion it was concluded that the SD9 show maximum cumulative drug release in 1 hour. So the SD9 was selected for the preparation of fast dissolving tablets. Different trials were taken to formulate an optimized formulation with sufficient mechanical strength, disintegration time and dissolution profile. Table 7 shows the different trials, which were undertaken for formulating FDTs.[22-23]

Table 15: Composition of various ingredients used to prepare FDTs

S. No	Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Solid Dispersion	20	20	20	20	20	20	20	20	20
2	SSG	15	15	15	18	18	18	21	21	21
3	MCC	30	37.5	45	30	37.5	45	30	37.5	45
4	Mag.Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
5	Talc	3	3	3	3	3	3	3	3	3
6	Lactose	80.5	73	65.5	77.5	70	62.5	71.5	67	59.5
7	Total (mg)	150	150	150	150	150	150	150	150	150

For the preparation of Fast Dissolving Tablets of Rosuvastatin Calcium, various excipients were screen for the best formulation and their concentrations were optimized thereafter. In earlier studies it was suggested that the sodium starch glycolate has positive impact on the disintegration time of solid dispersion of various poorly soluble drugs increasing their dissolution rate. So the SSG selected as superdisintegrant in the present study.

The batches F1 to F9 were prepared and the uniform mass was sieve through mesh #85. The powder mass was also evaluated for angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index. After the evaluation of the powder, tablets were prepared using direct compression method. Microcrystalline cellulose was used as directly compressible material which also has disintegrant property. The prepared tablets were evaluated for hardness, uniformity of weight, thickness, wetting time, wetting ratio, disintegration time, friability, dissolution test.

Evaluation of Fast Dissolving Tablets

Pre-compression evaluations for the powder blend

Pre-compression evaluation studies were carried out to ensure the flow properties of the powder blend. Good flow properties of the powder blend will yield the tablets of desired quality and ease the tableting process. So, it was mandatory to assess the flowbility of the blend before compression. The results of pre-compression evaluation were shown in Table8

Table 16: Pre-compression parameters of Powder Blends

S. No.	Batch code	Angle of Repose	Bulk density(g/cm^3)	Tapped density(g/cm^3)	Hausner's ratio	Compressibility index %
1	F1	30.19	0.2987	0.3671	1.179	16.57
2	F2	27.94	0.3091	0.3599	1.178	16.40
3	F3	29.11	0.3001	0.3665	1.179	16.39
4	F4	31.04	0.3087	0.3569	1.177	16.39
5	F5	32.87	0.3127	0.3601	1.179	16.51
6	F6	32.32	0.3030	0.3665	1.177	16.49
7	F7	25.67	0.3026	0.3811	1.181	16.54
8	F8	30.01	0.3101	0.3891	1.180	16.54
9	F9	31.76	0.3212	0.3671	1.182	16.57

Post compression Evaluations

The tablets obtained after compression were evaluated on various parameters to determine their quality and to ensure that the resultant product meets all necessary criteria's required for the fast dissolving tablets.

Table 17: Post Compression Parameters of Prepared Formulation

S. No.	Batch code	Disintegration time (seconds)	Hardness (kg/cm^3)	Friability (%w/w)	Wetting time (seconds)	Water absorption ratio (%w/v)	Drug content (%)
1	F1	90±5	3.2±1.0	0.78	37	40.49	101.51
2	F2	87±5	3.3±1.0	0.76	33	41.44	89.81
3	F3	90±5	3.3±1.2	0.83	39	43.45	104.43
4	F4	62±5	3.0±1.1	0.82	40	41.98	103.08
5	F5	60±5	3.4±1.2	0.76	35	43.01	98.79
6	F6	60±5	3.0±1.3	0.79	33	45.21	109.65
7	F7	40±5	3.5±1.5	0.69	39	41.90	105.22
8	F8	40±5	3.1±1.2	0.81	36	42.99	108.94
9	F9	40±5	3.2±1.0	0.82	40	43.56	99.51

The probable reason for the better results with F7 batch might be due to the amount of superdisintegrant used in the formulations.

Table 18: Post compression parameters of formulation (F7**)**

Evaluation parameters	Results
Hardness	3.5±1.5 kg/cm
Diameter	12±1mm
Thickness	6±2mm
Weight variation test	Complies (±5%)
Drug content	Complies (105.22)
Friability	0.69%
Wetting time	39 sec
Water absorption ratio	41.90%
Disintegration	40±5

Dissolution Studies

The dissolution studies were performed to evaluate the release profile of the drug, which relates the percentage of drug release from its dosage form with the function of time. The percentage cumulative release of fast dissolving tablet and marketed tablets of Rosuvastatin Calcium is shown in figure.21.

Table 19: Percentage cumulative release of fast dissolving tablets of Rosuvastatin Calcium and Marketed tablets of Rosuvastatin Calcium

S. No.	Time (min)	% Cumulative drug release of FDT of Rosuvastatin Calcium	% Cumulative drug release of Marketed tablet of Rosuvastatin Calcium
1	0	13.5759	10.7473
2	5	77.6799	44.762
3	10	83.2538	49.5103
4	15	86.7993	52.0978
5	20	91.519	55.3411
6	30	97.6765	57.4437

From the dissolution studies, it can be concluded that the dissolution rate of the drug of the marketed tablets was low as compared to the fast dissolving tablets of the Rosuvastatin Calcium prepared by direct compression method after the formulation of solid dispersions. Table shows that of fast dissolving tablets of solid dispersion of Rosuvastatin Calcium with sodium starch glycolate as super-disintegrant releases 77.67% drug in just 5 minutes and 97.67% in 30 minutes which is quite higher than the marketed tablets of Rosuvastatin Calcium.[24]

Mathematical Models Employed

Table 20: Fitting of drug release from prepared fast dissolving tablets to various release kinetic models

Mechanism	Zero-order		First-order		Higuchi		Hixson-Crowell		Korsemeyer-Peppas	
F7	Slope	R^2	Slope	R^2	Slope	R^2	Slope	R^2	Slope	R^2
	0.6777	0.943	0.003	0.978	0.133	0.989	0.013	0.982	25.20	0.965

Table 21: Various Parameters used to calculate the drug release from FDTs.

Time	Log time	Square of time	%CDR	Log %CDR
5	0.698	2.23	77.67	1.89
10	1.0	3.16	83.25	1.92
15	1.176	3.87	86.79	1.938
20	1.3	4.47	91.51	1.961
30	1.477	5.64	97.67	1.989

The R^2 value was found to be highest for Higuchi model i.e., 0.989 which indicates that the polymer formed a hydrophilic matrix in which drug gets entrapped in an amorphous form. As the matrix depletes, the drug in the amorphous form is available for dissolution.[25]

Conclusion

Aim of the present investigation was to enhance the solubility and dissolution rate of Rosuvastatin Calcium. Solid dispersions of Rosuvastatin Calcium were prepared by using Vitamin E TPGS, *A.Marmelos*, and Gum Karaya as carriers in different ratios through solvent evaporation method. On the basis of maximum percentage drug release the optimized formulation of solid dispersion of Rosuvastatin Calcium was characterized by Fourier Transfer-Infrared Spectroscopy, X-ray diffraction analysis, and Scanning electron microscopy. The fast dissolving tablets of the optimized solid dispersion were prepared and evaluated for various parameters. Solubility studies of Rosuvastatin Calcium in different pH solutions. Phase solubility studies indicate that the carriers increase the solubility of Rosuvastatin Calcium in the water and the

CMC of the carriers was found to be 0.02% w/v. The solid dispersion of drug with polymer TPGS ratio 1:1 in 50ml solvent shows maximum percentage drug release of 91.97% and maximum dissolution rate in 1hr. Direct compression technology was employed for the formulation of fast dissolving tablets of optimized solid dispersion. Among various excipients investigated sodium starch glycolate (14%) as superdisintegrant, microcrystalline cellulose (20%) as directly compressible vehicle, magnesium stearate (1%) as lubricant and talc (2%) as glidant or anti-caking material were used to develop fast dissolving tablets. The tablets were evaluated for various pharmacopeial tests. A released kinetic data through mathematical tools indicated the drug release follow Higuchi model, which indicates that the carrier formed a hydrophilic matrix in which drug gets entrapped in an amorphous form. As the matrix depletes, the drug in the amorphous form is available for dissolution. Thus, it can be concluded that the solid dispersion technology can be used as that alternative to produced fast tablets especially for drugs having poor water solubility.

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