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Original Article

Application of SeDeM ODT Expert System in Formulation Development of Orodispersible Tablets of Antihyperlipidemic Agent

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ABSTRACT

Background: Rosuvastatin calcium exhibits poor oral bioavailability due to extensive pre-systemic metabolism. Orodispersible tablets (ODTs) were prepared that disintegrate rapidly in oral mucosa thus preventing pre-systemic metabolism and enhancing the bioavailability of the drug. **Objective:** The objective of this study was to employ SeDeM ODT Expert system for characterization of excipients and formulation development of orodispersible tablets of rosuvastatin calcium. **Materials and methods:** ODTs were prepared by direct compression method using starlac as diluent and lycatab C and crospovidone as superdisintegrants in different concentrations. SeDeM ODT expert system was used on the excipients to predict their suitability for direct compression method. **Results:** SeDeM ODT expert system employed revealed that starlac, lycatab C and crospovidone were suitable and xylitol and sodium starch glycolate were unsuitable for direct compression method. FTIR studies revealed that there was no physico-chemical interaction between drug and other excipients. Preformulation studies were carried out to study the powder flow characteristics in order to achieve tablets of uniform weight. The values were well within the permissible limits. The tablets were subjected to post formulation evaluation parameters like thickness, weight variation, hardness, friability, wetting time, water absorption ratio, drug content uniformity, *in vitro* disintegration and *in vitro* dissolution studies. **Conclusion:** Suitability of the material for direct compression was successfully predicted using the SeDeM expert system. Formulations were developed based on the results of the SeDeM ODT expert system. Formulation F3 containing 15%w/w lycatab C as superdisintegrant exhibited minimum disintegration time and wetting time of 14.02±0.151s and 12.31±0.139s respectively and a maximum cumulative drug release of 93.06% at 15min. Hence, F3 formulation was the optimized formulation subjected to stability studies. Stability studies revealed that the formulation F3 was stable when stored at 40±2°C/75±5%RH for one month.

Key words: Direct compression, Lycatab C, Orodispersible tablets, SeDeM ODT Expert system, Starlac, Crospovidone.

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INTRODUCTION

Orodipsersible tablets (ODTs) are solid dosage forms that rapidly disintegrate when kept on the tongue or buccal mucosa.[1] ODTs are also known as "orally disintegrating tablets", "rapimelts", "porous tablets" and "quick dissolving tablets".[2] European Pharmacopoeia has used the term orodispersible tablet for the tablets that disperses readily and within 3 min in mouth before swallowing.[3]

Antihyperlipidemic agents are the drugs that lower the levels of lipids and lipoproteins in blood. They have attracted considerable attention because of their potential to prevent cardiovascular disease by retarding the accelerated atherosclerosis in hyperlipidemic individuals. Rosuvastatin calcium is used for treating dyslipidemia.[4,5] It is a competitive inhibitor of 3-hydroxy-3methylglutaryl coenzyme A (HMG CoA) reductase which catalyzes an early rate limiting step in cholesterol biosynthesis. It is absorbed incompletely from the gastrointestinal tract.[5] It has a low oral bioavailabilty of 10-20%. It undergoes extensive first-pass metabolism in liver, which is the main reason for the lower bioavailability.[6] Thus, the present study aims at design and formulation of ODTs of rosuvastatin calcium, to increase the bioavailability of the drug by absorption through the oral mucosa and prevention of pre-systemic metabolism.

SeDeM is known as "Sediment delivery model".[7] SeDeM expert system is a new galenic system to be applied in tablet preformulation and formulation studies of medicines, specifically in solid dosage forms. It is a new innovative tool based on the concept of Quality by Design described in ICH Q8. It evaluates critical quality attributes that have an impact on final product's quality. It helps to predict the aptitude of excipients to obtain orodispersible tablets and their suitability for direct compression.[8-10]

MATERIALS AND METHODS

Materials

The following materials were used in the experiment:

Rosuvastatin calcium, lycatab C, crospovidone, starlac, xylitol, sodium starch glycolate, neusilin, magnesium stearate, aerosil and saccharin sodium were gifted by VerGo Pharma Research Pvt. Ltd. Verna, Goa.

Method

Standard calibration curve

The standard calibration curve preparation of API was carried out in pH 6.8 phosphate buffer solution. 100 mg of the drug was weighed and

dissolved in 100 ml of the buffer solution. Further dilutions were made in order to achieve solutions within the Lambert- Beer's range of 2-22 µg/ml. The absorbance of each concentration was measured at 242 nm against the reagent blank. This procedure was performed in triplicate in order to validate calibration curve.

Compatibility study of drug with excipients

The IR Spectra of Rosuvastatin calcium and the physical mixtures of API and excipients were recorded using FTIR Spectrophotometer. 2-3 mg of samples were mixed with about 400 mg of dry potassium bromide and compressed into transparent disks under a pressure of 10.000-15.000 psi. The IR Spectra were recorded in the scanning range of 500-4000cm^{-1} and resolution of 4cm^{-1}.[11]

Optimization of diluents and disintegrants: SeDeM ODT Expert System

The new expert system SeDeM-ODT helps to calculate the index of good compressibility and bucodispersibility (IGCB) for powdered substances. A value of ≥ 5 indicates that a powder could be compressed by direct compression and that the resulting tablet would have good bucodispersible properties. It is based on the experimental study and quantitative determination of the characterization parameters of substances in powder form. Thus it gives a high probability of the formulations to provide rapid disintegration and release of the drug.

The SeDeM-ODT methodology is composed of 6 factors derived from 15 main parameters. The experimental values of the parameters evaluated are to be converted into the radius acquiring values between 0-10 (Table 1). The IGCB Diagram is made up of 15 parameters which are circumscribed into a 15 sided irregular polygon.[7,9]

The following 3 indices must be calculated; Index parameter (IP_1), Index Profile Parameter (IPP) and Index of Good Compressibility and Bucodispersibility (IGCB).

Index Parameter (IP_1):

$$\text{Index Parameter } (IP_1) = \frac{N°P \geq 5}{N°Pt}$$

Where, N°P≥ 5 is the number of parameters with a value equal or higher than 5

N°Pt is the total number of parameters studied.

Acceptance limit of Index parameter (IP_1) is ≥ 0.5

Index Profile Parameter (IPP):

Mean radius(r) of all the parameters studied.

Acceptance limit of Index Profile Parameter (IPP) is ≥ 5

Index of Good Compressibility and Bucodispersibility (IGCB):

$$IGCB = IPP \times f$$

Where, f is the reliability factor and is calculated as:

f = polygon area/ circle area

Acceptance limit of Index of Good Compressibility and Bucodispersibility (IGCB) is ≥ 5.[9]

Formulation Design

Eight formulations were prepared using direct compression method. The specified quantity of the drug and the other excipients were weighed accurately. The ingredients were passed through sieve no # 80. The drug, diluents and superdisintegrants were added in a geometrical ratio in a mortar and mixed thoroughly for 15 min. To the above powder blend required quantity of aerosil and neusilin were added prior to compression. The resulting powder blend was compressed into tablets using 6.5 mm punch. The formulated tablets were subjected to evaluation.[12] (Table 2).

Preformulation Studies

Bulk density: It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and initial weight was noted. This initial volume is called bulk volume. The bulk density was calculated as per the formula mentioned below:[13]

$$\text{Bulk density} = \frac{\text{Weight of the powder}}{\text{Bulk volume of powder}}$$

Tapped density: It is the ratio of total mass of the powder to the tapped volume of the powder. Tapped densitometer USP I apparatus was used. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If the difference is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2%. The tapped density was calculated as per the formula mentioned below:[13]

$$\text{Tapped density} = \frac{\text{Weight of the powder}}{\text{Tapped volume of the powder}}$$

Carr's index

Compressibility index of granules was determined by Carr's compressibility index.[1] It indicates powder flow properties. Carr's index is calculated by the following formula:[14]

$$\text{Carr's Index (\%)} = \frac{\text{Tapped density-untapped density}}{\text{Tapped density}} \times 100$$

Hausner's ratio

Hausner's ratio is the ratio of tapped density to bulk density. It is calculated by the following formula:[1]

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{untapped density}}$$

Angle of repose

The angle of repose of powder blends was determined using fixed funnel method. Accurately weighed powder blends were taken in funnel. The blend was allowed to flow through the funnel freely on to the surface. The diameter and the height of the pile were measured. The angle of repose was measured using the following formula:[12,14]

$$\tan \theta = h/r$$

Where, α is the angle of repose, h is the height of pile, r is radius of pile.

Post formulation evaluations

Thickness: The thickness of the tablets was determined using vernier callipers. Three measurements were taken.[1]

Weight variation: Twenty tablets were selected randomly from each formulation and weighed individually using digital balance. The individual weights were noted and compared with the average weight to account for the weight variation.[13,14]

Hardness: The hardness of tablet was measured with the monsonto hardness tester.[1,11]

Friability: Twenty tablets were weighed and then placed in a USP type Roche friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were reweighed and the percentage weight loss was calculated using the formula:[12]

$$\text{Friability} = \frac{\text{Initial weight-Final weight}}{\text{Initial weight}} \times 100$$

Wetting time and water absorption ratio: A threefold tissue paper was taken and placed in a petridish containing 10 ml water. A tablet was

placed on the top of the tissue paper in the petridish. Wetting time was noted as the time required for water to reach the upper surface of the tablet and to completely wet it.[12]

Water absorption ratio is calculated using the following equation:[1]

$$\text{Water absorption ratio} = \frac{W_a - W_b}{W_b}$$

Where, W_b is the initial weight of tablet

W_a is the weight of tablet after water absorption.

Content Uniformity: Ten tablets were weighed and crushed to a fine powder, and a quantity of powder equivalent to 10mg of the drug was transferred into a volumetric flask of 100 ml and extracted using pH6.8 phosphate buffer and filtered. The drug content was determined by measuring the absorbance at 242 nm using UV spectrophotometer. The drug content uniformity was determined using the standard linear equation y=0.044×+0.005 with R^2 value of 0.998.[11]

***In vitro* Disintegration:** The tablet disintegration test apparatus was used to determine the disintegration time of all the formulations. 6 tablets were placed individually in each tube of disintegration test apparatus. The medium was maintained at a temperature of 37±2°C, and the time was noted for the entire tablet to disintegrate completely.[1]

In vitro Dissolution Study

The USP dissolution test apparatus type II (paddle) was used for the study. 900 ml of the phosphate buffer pH 6.8 was taken in a vessel and the temperature was maintained at 37 ± 0.5°C. The speed of the paddle was fixed at 50 rpm. Dissolution samples were withdrawn at every 5 min intervals and the absorbance was noted at 242 nm using UV Spectropho-

Table 1: Parameters and equations used for SeDeM ODT Expert System

Factor/ Incidence	Parameter	Symbol	Unit	Equation	Limit	Radius	Factor Applied
Dimension	Bulk density	Da	g/ml	P/Va	0-1 g/ml	0-10	10v
	Tapped density	Dc	g/ml	P/Vc	0-1 g/ml	0-10	10v
Compressibility	Inter particle porosity	Ie	-	Ie= Dc - Da / Dc x Da	0-1.2	0-10	10v/1.2
	Carr's index	IC	%	IC= Dc – Da x 100 / Dc	0-50 (%)	0-10	v/5
	Cohesion Index	Icd	N	Experimental	0-200 (N)	0-10	v/20
	Hausner's ratio	IH	-	IH= Dc/Da	3-1	0-10	(30-10v)/2
Flowability/ Powder flow	Angle of repose	(θ)	°	tan α = h/r	50-0 (°)	0-10	10-(v/5)
	Powder flow	t"	s	Experimental	20-0 (s)	0-10	10-(v/2)
Lubricity/ Stability	Loss on drying	%HR	%	Experimental	10-0 (%)	0-10	10-v
	Hygroscopicity	%H	%	Experimental	20-0 (%)	0-10	10-(v/2)
Lubricity/ Dosage	Particles < 50	%Pf	%	Experimental	50-0 (%)	0-10	10-(v/5)
	Homogeneity index	(Iθ)	-	Iθ = Fm + Δ Fmn/100	0.2 x 10^{-2}	0-10	500v
Disgregability	Effervescence	DE	min	Experimental	0-5 min	0-10	(5-v)2
	Disintegration time with disk	DCD	min	Experimental	0-3 min	0-10	(3-v)3.333
	Disintegration time without disk	DSD	min	Experimental	0-3 min	0-10	(3-v)3.333

Table 2: Detailed composition of orodispersible tablets

Sl.No	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
1	Rosuvastatin calcium	10	10	10	10	10	10	10	10
2	Lycatab C	5	10	15	20	-	-	-	-
3	Crospovidone	-	-	-	-	5	10	15	20
4	Neusilin	10	10	10	10	10	10	10	10
5	Magnesium stearate	2	2	2	2	2	2	2	2
6	Aerosil	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
7	Starlac	70.7	65.7	60.7	55.7	70.7	65.7	60.7	55.7
8	Saccharin Sodium	2	2	2	2	2	2	2	2
9	Flavor	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
10	Total weight	100	100	100	100	100	100	100	100

tometer. The concentration of the drug was calculated from the standard calibration curve and expressed as cumulative percent drug release.[1]

Stability Studies: The optimized formulation was subjected for accelerated stability study as per ICH guidelines. The tablets were packed in a 60cc HDPE container and sealed. The stability study was carried out at 40 ± 2°C/75 ± 5% RH for 1 month.[15]

RESULTS

Standard calibration curve

The linear regression analysis was done on absorbance data points. The results are as follows:

For standard curve in pH 6.8 phosphate buffer

The slope = 0.044

The intercept = 0.005

The correlation coefficient = 0.998

A straight line equation (y = mx + c) was generated to facilitate the calculation of amount of drug. The evaluation is as follows: Absorbance = 0.044 x concentration + 0.005.

Compatibility study of drug with excipients

Physical mixture of drug and polymers were subjected to FTIR spectral analysis for any physical or chemical interactions between drug and the excipients (Figure 1).

Optimization of diluents and disintegrants: SeDeM ODT Expert System

The SeDeM-ODT methodology is composed of 6 factors derived from 15 main parameters. The 6 factors include; dimensions, compressibility, flowability/ powder flow, lubricity/ stability, lubricity/dosage and disgregability. The parameters include; Bulk Density (Da), Tapped Density (Dc), Inter-particle porosity (Ie), Carr's index (IC), Cohesion Index (Icd), Hausner's ratio (IH), Angle of repose (α), Powder flow (t"), Loss on Drying (%HR), Hygroscopicity (%H), Particle size (%Pf), Homogeneity index (Iθ), Effervescence (DE), Disintegration time with disk (DCD) and Disintegration time without disk (DSD). The parameters were calculated and corresponding radii were evaluated and plotted in a SeDeM ODT diagram. (Figure 2)

Preformulation Studies

Preformulation Studies including bulk density, tapped density, % Carr's index, Hausner's ratio and angle of repose were evaluated and tabulated (Table 3).

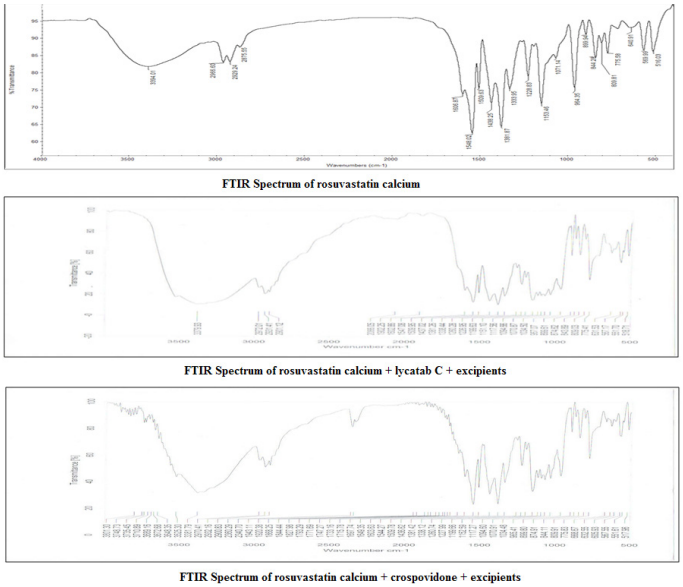

Figure 1: FTIR Spectra of drug and excipients.

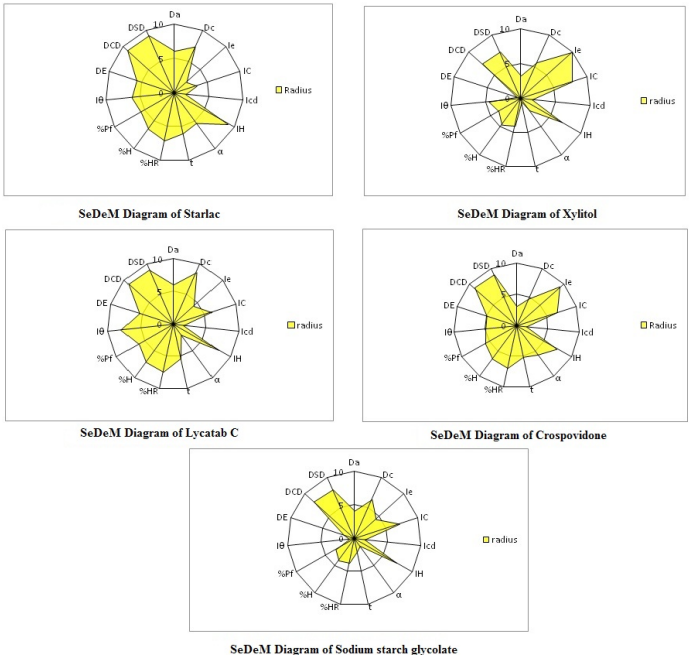

Figure 2: SeDeM Diagram of excipients.

Table 3: Preformulation Studies for physical mixtures of all the formulations

Formulation code	Bulk Density (g/ml) (n=3)	Tapped Density (g/ml) (n=3)	% Carr's Index (n=3)	Hausner's Ratio (n=3)	Angle of repose (n=3)
F1	0.624±0.001	0.713±0.0005	12.56±0.087	1.143±0.001	24°26'±0.104
F2	0.608±0.0005	0.693±0.0005	12.24±0.011	1.139±0.000	23°59'±0.358
F3	0.624±0.0005	0.734±0.001	14.89±0.058	1.175±0.001	22°34'±0.025
F4	0.608±0.001	0.713±0.001	14.76±0.196	1.172±0.003	28°33'±0.088
F5	0.511±0.001	0.605±0.001	15.53±0.263	1.183±0.003	30°34'±0.020
F6	0.526±0.0005	0.625±0.001	15.89±0.165	1.188±0.002	29°28'±0.135
F7	0.510±0.0005	0.608±0.001	16.21±0.298	1.193±0.004	26°79'±0.005
F8	0.519±0.001	0.623±0.0005	16.73±0.176	1.201±0.003	28°45'±0.015

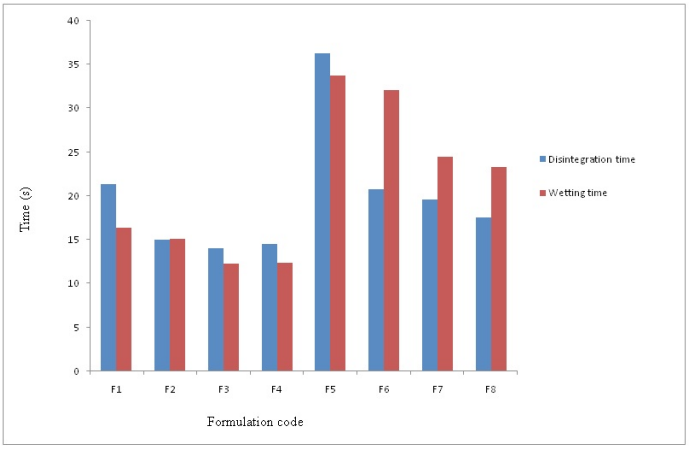

Figure 3: Comparison of disintegration time and wetting time of formulations F1- F8.

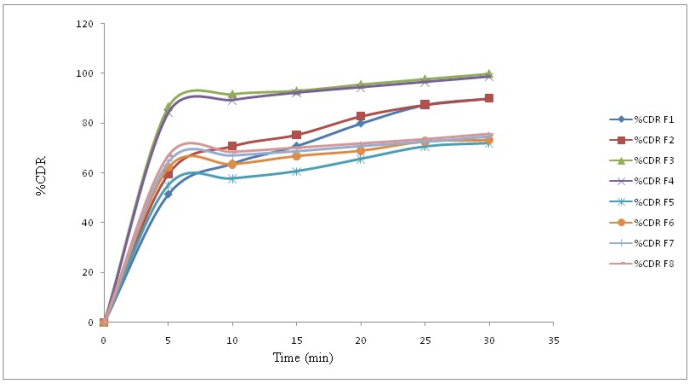

Figure 4: *In vitro* % drug release of formulations F1-F8.

Post formulation evaluations

Post formulation evaluation parameters including thickness, weight variation, hardness, friability, wetting time, water absorption ratio, disintegration time, drug content and *in vitro* % drug release were evaluated and represented (Figure 3 and Figure 4).

The optimized formulation F3 was subjected for stability studies and exposed to accelerated stability conditions of 40±2°C/75±5%RH for one month.

DISCUSSION

Eight formulations were prepared by direct compression technique and subjected to evaluation. The IR spectra of the physical mixtures have shown all the peaks of API indicating there was no interaction between the drug and the excipients. From the IR studies, it was evident that the drug was found to be compatible with the excipients used in the formulation of orodispersible tablets. The three main indices of SeDeM ODT expert system IP_1, IPP and IGCB were calculated for all the excipients. The excipients are suitable for direct compression only if IP_1 value is ≥ 0.5 and IPP and IGCB values are ≥ 5. From the values it was evident that starlac, lycatab C and crospovidone showed acceptable indices values hence, they were selected for direct compression method. Since, xylitol and sodium starch glycolate indices value were not within the permissible range, they were not suitable for direct compression technique. The physical mixtures containing drug and various excipients ready for compression were subjected to preformulation parameters to study the flow properties of the physical mixture in order to achieve uniform tablet weight. The loose bulk density of all the formulations varied from 0.510±0.0005 g/ml to 0.624±0.0005 g/ml and the tapped bulk density for all the formulations varied from 0.605±0.001 g/ml to 0.734±0.001 g/ml. Carr's consolidation index or compressibility index for the entire formulation blend ranged from 12.24±0.011% to 16.73±0.176% showing good to excellent flow properties. Hausner's ratio for all the formulations was found to be in the range of 1.139±0.000 to 1.201±0.003. The angle of repose of all the formulations was found to be in the range of 22°34'±0.025 to 30°34'±0.020. All the formulations showed angle of repose less than or equal to 30° which reveals excellent flow property. Thickness of tablets from all the formulations showed uniform thickness ranging from 2.73±0.01 mm to 2.78±0.005 mm. The weight variation of all the formulations ranged between 99.45±1.394 mg to 100.95±1.986 mg. The weights of all the tablets were uniform with low standard deviation. The hardness value for the various formulations ranged from 3.53±0.251 kg/cm^3 to 4.23±0.251 kg/cm^3. The % friability of the formulations was found to be in the range of 0.234±0.028 to 0.368±0.029 which were well within the approved range of < 1%. The wetting time for the formulations was found to be in the range from 12.31±0.139 s to 33.78±0.485 s. Water absorption ratio values for the formulations were found to be in the range of 88.33±2.081 to 97.34±2.051. The disintegration time range of the formulations ranged from 14.02±0.151s to 36.28±0.370s. The formulation F3 containing 15%w/w lycatab C showed rapid disintegration within 14.02±0.151s when compared to other formulations. The % drug content of all the formulations was found to be in the range of 96.36±0.230 to 99.45±0.395. All the formulations showed %CDR in a range of 60.66% to 93.06% in 15 min. Formulations F1, F2, F3, F4, F5, F6, F7 and F8 showed drug release of 70.90%, 75.40%, 93.06%, 92.23%, 60.66%, 66.81%, 68.86% and 70.09% respectively at the end of 15 min. Amongst them of the various formulations F3 showed a maximum drug release of 93.06% at 15 min.

Hence, formulation F3 was optimized based on the least wetting time and disintegration time and maximum % cumulative drug release. The optimized formulation F3 was subjected to stability studies as per ICH guidelines by storing the formulated tablets at 40°±2°C/75±5%RH for a period of one month. Every seven days sampling was done and the tablets were subjected to hardness test, disintegration test, drug content uniformity and *in vitro* dissolution study. From the results it was evident that there was no significant change in the values. Thus, indicating F3 as a stable and optimized formulation.

CONCLUSION

Orodispersible tablets of rosuvastatin calcium were successfully formulated by direct compression method. The analytical studies of the drug and the physical mixture revealed that the drug and the excipients employed were compatible which was confirmed by FTIR spectral analysis. SeDeM ODT Expert system was applied on the excipients and it was found that the starlac, lycatab C and crospovidone were suitable to be used for direct compression method and showed a good IGCB value (≥5) while sodium starch glycolate and xylitol were not suitable for direct compression method since they had IGCB value <5. This technique helped in the selection of excipients suitable for direct compression thus saving time employed in enhancing the flow properties and yielding formulations of good texture, disintegration time and *in vitro* drug release. The preformulation studies revealed that the physical mixtures of all the formulations showed good to excellent powder flow property. By the overall study F3 was found to be the best formulation based on its disintegration time, wetting time and *in vitro* drug release. The stability studies carried out at 40±2°C/75±5%RH for one month showed no change in the drug content and drug release profiles revealed good stability of the formulation.

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CONFLICT OF INTEREST

No conflict of interest are declared.

ABBREVIATION USED

API: Active pharmaceutical ingredient; **Da:** Bulk density; **Dc:** tapped density; **DCD:** Disintegration time with disk; **DE:** effervescence; **DSD:** Disintegration time without disk; **FTIR:** Fourier transform infra red; **HDPE:** High density polyethylene; **HMG CoA:** 3-hydroxy-3methylglutaryl coenzyme A; **IC:** Carr's index; **Icd:** Cohesion index; **ICH:** International Conference on Harmonization; **IGCB:** index of good compressibility and bucodispersibility; **Ie:** Inter-particle porosity; **IH:** Hausner's ratio; **IP1:** Index parameter; **IPP:** Index profile parameter; **ODTs:** Orodispersible tablets; **SeDeM:** Sediment delivery model; **USP:** United States Pharmacopoeia; **UV:** Ultra violet; **Mg:** Milligram, t" powder flow; **%HR:** loss on drying; **%H:** Hygroscopicity; **%Pf:** Particle size; **Iθ:** homogeneity index; **µg:** microgram, **mm:** millimeter; **ml:** millilitre; **nm:** nanometer; **cm:** centimeter.

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