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Rosuvastatin Calcium Immediate Release Tablets

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A B S T R A C T

In the present research Rosuvastatin calcium immediate release tablets were formulated and evaluated. Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of cholesterol. Rosuvastatin calcium is highly susceptible to light, moisture and low pH environment. In acidic environment, it undergoes conversion into lactone through intramolecular esterification, which takes place between carboxylic acid and hydroxyl groups that are present on β and δ carbons in this compound. This phenomenon reduces the stability of the compound and lowers the shelf life. To prevent this basic agents are added to the formulation, which reverse the reaction and improve the stability. In the present work, different basic agents such as sodium bicarbonate, sodium alginate, tri-sodium citrate, disodium hydrogen phosphate, tri-calcium phosphate were used in the formulations whose aqueous solutions produce pH of nearly 8 to overcome the above problem. Initially rosuvastatin IR tablets were prepared by direct compression technique using different alkalizers. From dissolution profile in pH-6.6 citrate buffer, di-sodium hydrogen phosphate was found to be optimum alkalizer, which stabilizes the drug in the acidic environment of stomach to produce desired effect. But the above formulated batches showed higher release rate than marketed which may result in drug decomposition in stomach. In order to prevent it further batches are prepared by wet granulation. Out of 12 formulations, F_{12} is the most promising one as indicated by its F2 values both in the official medium and in the discriminating medium. The dissolution profile of the formulation F_{12} was found to have equivalent percentage drug release with that of the Innovator in the official medium. The stability studies on F_{12} and marketed product in HDPE container at 40^0C / 75 % RH for 2 months were conducted as per ICH protocol shown better dissolution profile in F_{12} than marketed product.

Keywords: Rosuvastatin, Immediate release tablets, Sodium bicarbonate, Sodium alginate, Tri-sodium citrate, Disodium hydrogen phosphate, Tri-calcium phosphate etc.

A R T I C L E I N F O

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1. Introduction

Pharmaceutical oral solid dosage forms have been used widely for decades mainly due to their convenience of administration and their suitability for delivery of drugs for systemic effects. Drug products are designed to deliver drug for local or systemic effects [1,2]. The development in the field of API, excipients, and tableting machinery during the past decade has made tablet manufacturing a science and tablets the most commonly used dosage form [3]. The most commonly used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules [4]. Rosuvastatin reduces total cholesterol (total-C), LDL-C, ApoB, and non HDL-C (total cholesterol minus HDL-C) in patients with homozygous and heterozygous familial hypercholesterolemia (FH), non-familial forms of hypercholesterolemia, and mixed dyslipidemia. Rosuvastatin also reduces TG and produces increases in HDL-C. 12 formulations were prepared using sodium bicarbonate, sodium alginate, tri-sodium citrate, disodium hydrogen phosphate, tri-calcium phosphate to produce pH of nearly 8 to overcome conversion into lactone through intramolecular esterification, which takes place between carboxylic acid and hydroxyl groups that are present on β and δ carbons in this compound in acidic environment. After formulating, the finished dosage forms are evaluated for pre-formulation and post formulation studies.

2. Experimental

Materials and Methods

Rosuvastatin calcium, Pre-gelatinized starch was procured from Hetero drugs, Hyderabad. Lactose DCL 11 from DMD International, Hyderabad. MCC (Avicel pH 112) from FMC Biopolymer, Hyderabad. Tri-sodium citrate, Sodium bicarbonate, Sodium alginate, Di sodium hydrogen phosphate were obtained from Merck, Hyderabad. Tribasic calcium phosphate was obtained from Innophos, Hyderabad. PVP K-30 and cross-linked povidone from BASF chemicals, Hyderabad. Magnesium stearate from Ferro Industries and all the other chemicals used are of analytical grade.

Method

Compilation of rosuvastatin calcium tablet formulations using direct compression: Direct compression is used to optimize the best alkalizer by using different alkalizers. Sift rosuvastatin calcium, lactose DCL 11, microcrystalline cellulose, pre-gelatinized starch, cross povidone (kollidon CL) through # 40 mesh. Blend all the sifted material for 15 minutes. Sift magnesium stearate through mesh #80. Add the sifted magnesium stearate to the above blend and blend again for 5 minutes. The blend was collected and compressed into tablets using round punches with a tablet weight of 400 mg. Formulations were shown in table no.1.

Compilation of rosuvastatin calcium tablet formulations using wet granulation technique: To optimize the percentage of alkalizer in the formulation and mapping the dissolution profile in the discriminating dissolution medium (0.1 N HCl), wet granulation is used. Sift rosuvastatin calcium, lactose monohydrate, micro-crystalline cellulose, di-sodum hydrogen phosphate, PVP K30, crospovidone through #40 mesh. Mix all the sifted intragranular material for 10 minutes. Take the sifted blend in a stain less steel container and add sufficient quantity of iso-propyl alcohol and mix well to get granules. Granules are then dried by using a rapid drier. The dried granules are then passed through #20 mesh. Sift crospovidone through #40 mesh and add the sifted material to the intra-granular material. Blend it for 15 minutes. Sift magnesium stearate through #80 mesh and add the sifted magnesium stearate to the blended material. Blend it for 5 minutes. Collect the blend and compress into tablets using 8.5 mm round punches. Formulations were shown in table no.2.

Evaluation: Pre-formulation studies on active pharmaceutical ingredients (API), inactive ingredients (Excipients), and their combinations were carried out to serve following purposes:

- To Finalize specifications of active pharmaceutical ingredients (API)
- To Study the compatibility between active and inactive ingredient

The use of pre-formulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product.

Organoleptic evaluation:

These are preliminary characteristics of any substance, which is useful in identification of specific material. Following physical properties of API were studied.

a) Color b) Odor

Table 3: Organoleptic evaluation and solubility analysis of rosuvastatin calcium

Parameter	Rosuvastatin Calcium
Organoleptic Evaluation	White to off white colored powder
Solubility Analysis	Shows pH dependent solubility and is relatively soluble at pH above 4.

Loss on drying:

1.5 g of sample of rosuvastatin calcium was accurately weighed and the powder was kept in a moisture balance apparatus for 5 min at 105ºC and the moisture content was calculated [6].

Density

Bulk density: Bulk density was determined by pouring gently 25 gm of sample (rosuvastatin calcium) into 100 ml graduated cylinder. The volume occupied by the sample was recorded. Bulk density was calculated as [7]:

Bulk density = weight of sample in grams / volume occupied by the sample

Tapped density:

Tapped density was determined by using electro lab density tester, which consists of a graduated cylinder mounted on a mechanical tapping device. An accurately weighed sample of powder was carefully added to the cylinder. Typically, the initial volume was noted, and the sample is then tapped (500, 750 or 1250 tapping) until no further reduction in volume is noted or the percentage of difference is not more than 2% [7]. A sufficient number of taps should be employed to assure reproducibility for the material in question. Volume was noted and tapped density is calculated using following formula.

Tapped density = Wt. of sample in grams / Tapped volume

Compressibility Index and Hausner ratio:

In recent years the compressibility index and the closely related Hausner ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. Both the compressibility index and the Hausner ratio were determined by using bulk density and the tapped density of a powder [7,8].

C.I=tapped-untapped*100/tapped.

Angle of repose:

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane [7,8].

$$\theta = \mathbf{Tan}^{-1}\ \mathbf{h / r}$$

Whereθ = angle of repose, h = height, r = radius.

Particle Size Distribution

API particle size by sieve analysis:

The main aim of sieve analysis is to determine the different size of drug particles present. A series of standard sieves were stacked one above the other so that sieves with larger pore size (less sieve number) occupy top position followed by sieves of decreasing pore size (larger sieve number) towards the bottom.

Sieve analysis of rosuvastatin calcium:

Clean and dry # 20, # 30, # 40, # 60, # 80 and collector were collected and individual weight of each sieve was noted. These sieves were arranged in ascending order. Weighed quantity of rosuvastatin calcium (50 gm) was placed in #20 mesh. Sieve shaker was set for 5 min at amplitude of 40 (Intermittent shaking). The set up was removed from the sieve shaker after 5 min and each mesh was weighed individually and the % drug retained in each size of mesh was calculated with the following formula.

$$\% \text{ Retained} = \frac{\text{Final weight} - \text{initial weight}}{\text{Total weight taken}} \times 100$$

Drug Excipient Compatibility Studies

The compatibility of drug and formulation components is important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of product or any other unwanted effects on the formulation. As a part of the product development, the compatibility of various excipients with active was evaluated. According to the functional category, these excipients were mixed in different ratios with drug. The mixtures were exposed to room temperature, 40°C / 75 %RH, and 60°C, in a 5-ml amber colored glass vial in exposed condition for 1 month. Observations for physical appearance are made at initial, 2 week, and 4 week, the samples were withdrawn for analysis of following parameter:

- Description
- Related substances

Results of the above excipients were used to fabricate robust formulation of rosuvastatin calcium tablets. The prepared drug and excipient mixtures were evaluated at various intervals for related substances as per the following conditions and time interval.

Table 4: Sampling schedule

S. No.	Storage condition	Sampling intervals
1	Initial	Initial
2	40 ± 2 °C / 75 ± 5% RH	2 weeks
3	60 °C	2 weeks
4	Room temperature	Control sample

Solubility Studies

Rosuvastatin calcium is classified under class II according to BCS i.e., highly permeable and low soluble. Solubility studies of rosuvastatin calcium were conducted at all pH ranges from 1 to 12. The solubility of API was determined by dissolving the highest unit dose of the drug in 250 ml of buffer adjusted between pH 1.0 and 12.0

Solubility study:

Solubility study was performed at room temperature or ambient temperature. 250 ml of solvent or medium was taken into 250 ml volumetric flask in which the solubility of the rosuvastatin calcium was to be established. Rosuvastatin calcium equivalent to 40 mg of rosuvastatin was added. Ultrasonicated for 15 minutes with handshaking until the material was completely dissolved. Solution was filtered through 0.45 µm filter to get clear solution. Filtered solution was diluted to get a concentration approximately equal to that of standard preparation. Content of rosuvastatin calcium was estimated by HPLC method. Amount of the rosuvastatin calcium dissolved was calculated by using the following formula.

The quantity of the rosuvastatin calcium dissolved in percentage (wt/v):

$$Q = \frac{A}{B} \times \frac{\text{Std.wt.}}{\text{Std. dil}} \times \frac{\text{Test dil.}}{\text{test wt.}} \times \frac{\text{Std. purity}}{100} \times \frac{100}{\text{Test purity}} \times 100$$

A= Response of the test solution, B= Response of the standard solution. The actual amount of rosuvastatin calcium dissolved in mg:

$$m = \frac{Q \times Wt}{100}$$

The solubility of the drug substance in mg/ml in the solvent/medium tested.

$$S = m/250$$

Weight variation

20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The tablets meet the USP specifications if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits [9].

Table 5: Weight variation limits

Average weight of tablet (mg)	% Difference
130 or less	10 %
From 130 to 324	7.5%
> 324	5%

Thickness

Thickness was determined for 20 pre-weighed tablets of each batch using a digital vernier calipers and the average thickness was determined in mm. The tablet thickness should be controlled within a ± 5% variation of a standard.

Hardness test

The crushing load which is the force required to break the tablet in the radial direction was measured using a Dr. Schluenzier hardness tester. The hardness of 10 tablets was noted and the average hardness was calculated. It is given in kp or kg/cm^2. [10]

Friability

In friability testing, the tablets are subjected to abrasion and shock. It gives an indication of the tablets ability to resist chipping and abrasion during transportation and shipping [11]. The percentage friability is expressed as the loss of weight and is calculated by the formula**:**

$$\% \text{ Friability} = [(W_0 — W_f) / W_0] \times 100$$

W_0 = Initial weight of tablets, W_f = Final weight of tablet

Disintegration Time

Disintegration time is the time taken by the tablet to breakup into smaller particles. The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15 mm in diameter, the bottom of which consists of a #10 mesh sieve. The basket is raised and lowered 28-32 times per minute in a medium maintained at 37 ± 2^0C. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the mesh (# 10) was considered as the disintegration time of the tablet [12].

Dissolution

Dissolution is a process by which the disintegrated solid solute enters the solution. The test determines the time required for a definite percentage of the drug in a tablet to dissolve under specified condition [13].

Chromatographic Conditions:

1. Column : Phenomenex Luna C18, 250 4.6 mm, 5µ or equivalent
2. Flow rate : 1 ml/min
3. Wavelength : 242 nm
4. Injection volume : 20 µl
5. Column temperature : 30ºC
6. Run time : 10 min

3. Results and Discussion

The present study was undertaken to formulate rosuvastatin calcium immediate release tablets. The study involves pre-formulation studies of drug and excipients, formulation and processing development along with evaluation of tablets made with the optimized formulation. Finally these tablets were evaluated by *in-vitro* methods.

Pre-formulation studies for API

Pre-formulation studies of pure drug were conducted for angle of repose, bulk density, tapped density, carr's index, hausner's ratio. The results indicate that angle of repose of pure drug is 46° indicating poor flow properties. The carr's index was found to be 30.95% indicating poor flow properties. The hausner's ratio wasn't within the limits indicating poor flow properties. These results indicated the drug possessed poor flow properties and compressible characteristics. The results were shown in table no 7-11.

Table 7: Pre-formulation studies

S. No.	Characteristics	Results
1.	Organoleptic evaluation	Off white to white colored powder
2.	Bulk density	0.542 gm/ml
3.	Tap density	0.786 gm/ml
4.	Compressibility index	30.95%
5.	Hausner's ratio	1.450
6.	Angle of repose	46°
7.	Melting point	122.0^0C

Table 8: Particle Size analysis of Rosuvastatin Calcium

Distribution of particle size	Particle size in microns
D10	3µm
D50	23µm
D90	98µm

Particle size distribution of drug

This was done by malvern master sizer 2000 analyzer. The results indicated that the distribution of particles in 3m range was 10%, distribution of particles in 23 m range was 50%, and distribution of particles in 98m range was 90%. The results were shown in table no.8.

Solubility studies: Equilibrium solubility measured at a range of pH values shows pH dependance. The compound rosuvastatin calcium is relatively soluble at pH values above 4 and highly soluble at pH 6.6 citrate buffer. The results were shown in table no. 9.

Drug excipients compatibility study: Drug excipient compatibility studies showed that there was no interaction or physical change between the drug and excipients. So the selected excipients were found to be compatible with the drug. Lubricated blend parameters of various formulations

prepared i.e. bulk density lied in between 0.375 and 0.436. The tapped densities lied in between 0.422 and 0.535. The Hausner's ratio lied between 1.12, 1.27 and compressibility index lied in between 11.13 and 21.4. The results were shown in table no – 10.

Post compression parameters

Weight variation was found to be within the limits (below 5%). Thickness of all the formulation batches lied in between 5.15 mm and 5.45 mm. Hardness of all batches lied between 10.0 kp and 15.0 kp. Friability of all batches lied in between 0.1 to 0.9%. Disintegration time of all batches tablets ranged from 30 sec to 2 min 40 sec. The results were shown in table no – 12, 13.

Dissolution: Different alkalizers were taken from trials F_1 to F_7 and the dissolution profiles of all the trials in the official medium (pH 6.6 sodium citrate buffer) were found to be nearer to innovator but the dissolution profile of trial F_5 was found to be matching and was found to be the best alkalizer but as a whole the dissolution profiles of the trials F_1 to F_6 in discriminating medium (0.1 N HCl) were found to be higher when compared to the innovator. So, Trial F_7 was taken with similar formulation of F_5 but with inclusion of the binder which was also not a hopeful event as there is a chance of increased higher C_{max} values biologically. Thus using wet granulation the dissolution was planned to be controlled and in-vitro dissolution was performed on formulations F_7 to F_{12}. The dissolution studies showed that the drug release from all the formulation (F_1 to F_{12}) was complete and uniform in pH 6.6 sodium citrate buffer (official medium) and showed difference in 0.1 N Hcl (Discriminating medium). The results were shown in table no – 14-16 and fig no.1-6.

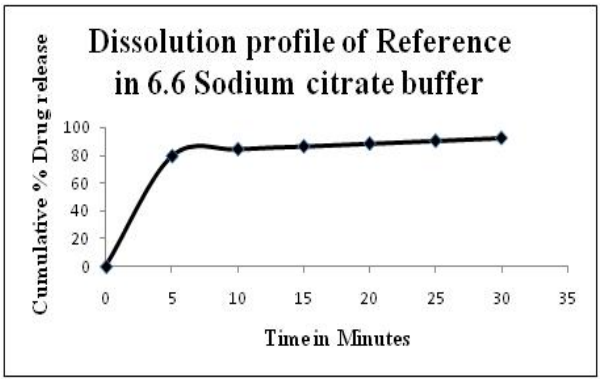

Figure 1: Dissolution profile of reference in 6.6 Sodium citrate buffer.

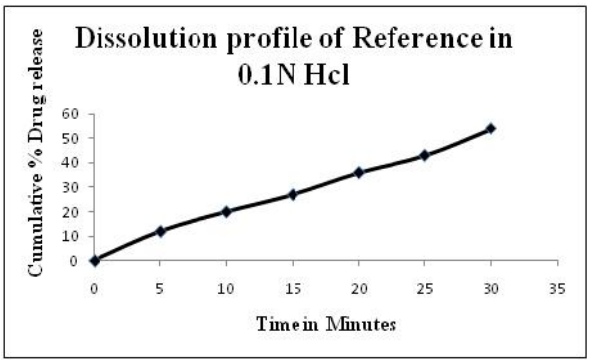

Figure 2: Dissolution profile of reference in 0.1N HCl

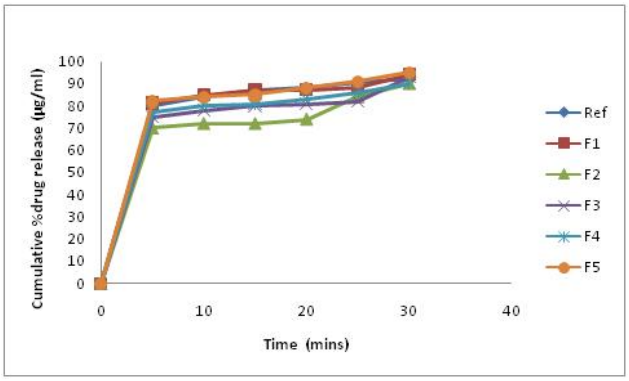

Figure 3: Comparative dissolution profiles of formulations F_1- F_5 in pH 6.6 Sodium citrate buffer with reference

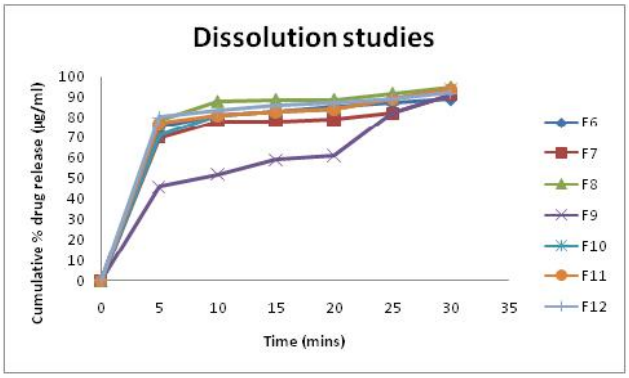

Figure 4: Comparative dissolution profiles of formulations F_6- F_{12} in pH 6.6 sodium citrate buffer with reference

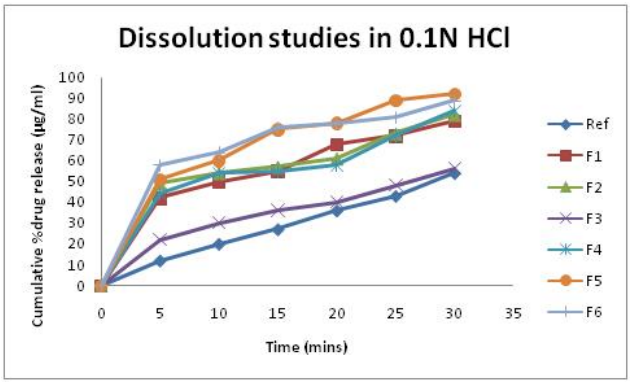

Figure 5: Comparative dissolution profiles of formulations F_1- F_6 in 0.1N HCl with reference.

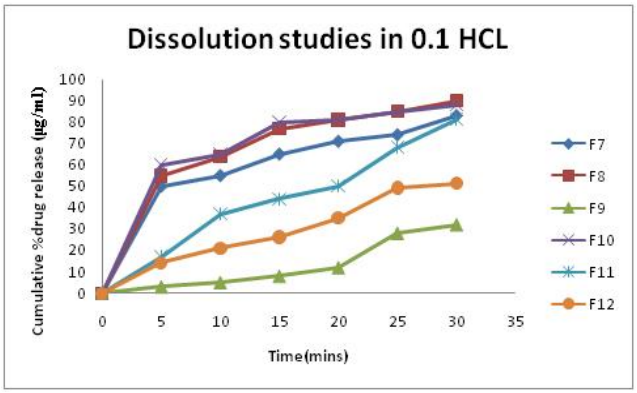

Figure 6: Comparative dissolution profiles of formulations F_7- F_{12} in 0.1N HCl with reference.

Related substance studies for formulated tablets F_1 to F_{12}: Relative substances study was performed as rosuvastatin calcium degrades at acidic pH to lactone ring formation and other unknown impurities, these impurity levels are checked in all formulations at a period of 1 month and 3 month which clearly states that F_{12} formulation is the best by showing the lower limit of relative substances 0.704 % out of 1% limit. The results were shown in table no – 17,18.

Similarity Factor f2:

Finally, the dissolution profiles of formulation F_{12} and Innovator product was compared by calculating f 2. The formulation F_{12} was found to be similar with the innovator product based on the obtained f2 value 77.45. The results were shown in table no–19,20.

Accelerated stability studies

From the stability data it was evident that there was optimized formula (F_{12}) showed less degradation after 3 months when it compared with the marketed product during the stability studies conducted at 40°C & 75%RH for1 month period and 2 months at 40°C & 75% RH. The results were shown in table no – 21 and fig no – 7,8.

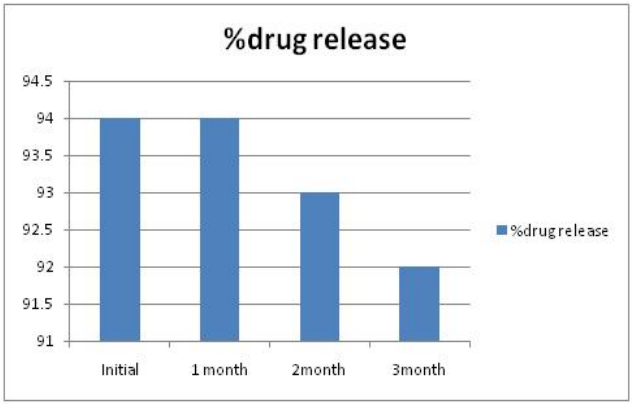

Figure 7: Accelerated stability studies – Dissolution profile of marketed product

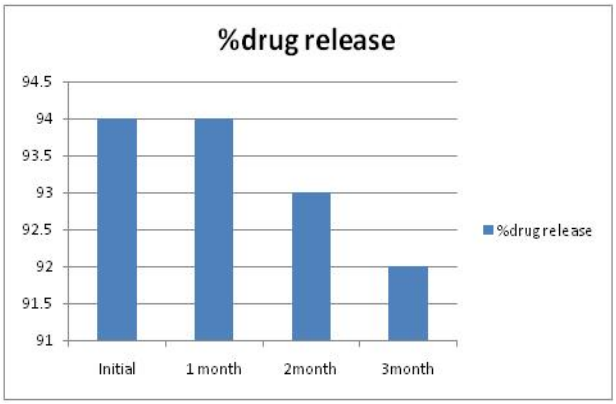

Figure 8: Accelerated stability studies – dissolution profile of optimized formula

Assay: No significant change was observed in the assay value of rosuvastatin calcium tablets 40 mg, after a storage period of 1 month at 40^0C / 75 % RH and 2 months at 40^0C / 75 % RH.

4. Conclusion

The dissolution profile of the formulation F_{12} was found to have equivalent percentage drug release with that of the Innovator in the official medium. So, the formulation F_{12} and its process can be easily scaled up for large scale production as it is simple, cheap, and precise and also yields reproducible tablets. Rosuvastatin calcium immediate release tablets are better than other formulations as rosuvastatin calcium release immediately and is not allowed to stay for longer time in solution or suspension form as it lowers the shelf life, also the effervescent tablets shows insufficient dissolution and failure to form a clear solution, so there is no need to formulate an extended release tablets as rosuvastatin has a half-life of 19 hours. So rosuvastatin calcium immediate release tablets are more stable and cost effective than other formulations.

Table 1: Compilation of rosuvastatin calcium tablet formulations using direct compression

S. No	Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7
1	Rosuvastatin calcium	43.4	43.4	43.4	43.4	43.4	43.4	43.4
2	Lactose DCL 11	197.2	219.1	219.1	219.1	233.1	233.1	225.1
3	MCC(Avicel pH 112)	71.4	85	85	85	85	85	85
4	Tri-sodium citrate	-	-	-	28	-	-	-
5	Sodium bicarbonate	-	28	-	-	-	-	-
6	Sodium alginate	-	-	-	-	-	28	-
7	Di-sodium hydrogen phosphate	-	-	-	-	28	-	28
8	Pre-gelatinized starch	60	-	-	-	-	-	
9	Tri calcium phosphate	-	-	28	-	-	-	-
10	PVP K-30	-	-	-	-	-	-	8

11	Crosspovidone (kollidon CL)	24	20	20	20	6	6	6
12	Magnesium stearate	4	4.5	4.5	4.5	4.5	4.5	4.5
13	Total tablet weight	400	400	400	400	400	400	400

Table 2: Compilation of rosuvastatin calcium tablet formulations using wet granulation technique

S. No	**Ingredients (mg)**	F_8	F_9	F_{10}	F_{11}	F_{12}
DRY MIX						
1	Rosuvastatin calcium	43.4	43.4	43.4	43.4	43.4
2	Lactose (Impalpable)	221.1	221.1	221.1	221.1	221.1
3	MCC (Vivapur 101)	99	91	103	85	95
4	Disodium hydrogen phosphate	28	28	20	20	20
5	PVP K-30	-	12	4	12	8
6	Crosspovidone (Kollidon CL)	4	-	-	8	8
Granulation						
IPA		qs	qs	qs	qs	Qs
Extra-granular						
7	Crospovidone(kollidon CL)	-	-	4	6	-
8	Magnesium stearate	4.5	4.5	4.5	4.5	4.5
	Core tablet weight	400	400	400	400	400

Table 6: Dissolution parameters

Official medium for rosuvastatin calcium is 0.05M sodium citrate buffer pH 6.6±0.05						
Drug name	Dosage form	USP apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended sampling times (minutes)
Rosuvastatin calcium	Tablet	II (Paddle)	50 at 37°C ±0.5	0.05 M sodium citrate buffer pH 6.6 ± 0.05	900	10, 20, 30 and 45 min
Since, rosuvastatin calcium is acid labile, its dissolution profile should also be checked in 0.1N HCL.						
Drug name	Dosage form	USP apparatus	Speed (RPMs)	Multi medium	Volume (mL)	Recommended sampling times (minutes)
Rosuvastatin calcium	Tablet	II (Paddle)	50 at 37°C ±0.5	0.1N HCl buffer	900	10, 20, 30, 45, 60, 90, 120, and INF min

Table 9: Solubility Studies

Buffer	**Solvent solubility (mg/ml)**	**Final pH**
pH 1.2 Hydrocloric acid (0.1N)	0.5±0.0	1.2
pH 1.2 Hydrocloric acid buffer (USP)	0.5±0.0	1.2
pH 3.6 Acid Pthalate buffer (USP)	1.6±0.1	4.1
pH 4.0 Acid Pthalate buffer (USP)	2.2±0.2	4.5
pH 4.6 Neutralized Pthalate buffer (USP)	3.7±0.2	5.0
pH 5.6 Neutralized Pthalate buffer (USP)	9.2±0.5	5.3
pH 6.0 Phosphate buffer (USP)	10.7±0.3	5.6

pH 6.6 Citrate buffer (0.005M)	48.8±0.6	6.7
pH 7.0 Phosphate buffer (USP)	17.1±0.0	6.8
pH 7.4 Phosphate buffer (USP)	21.0±0.7	7.1
Deionized water (USP)	7.8±0.1	7.0

Table 10: Results of compatibility study

S. No.	Drug + Excipient	Ratio	Initial	40 °C/ 75 % RH	
				15 Days	1 Month
1	Rosuvastatin calcium(API)	-	White	Off White	Off White
2	API + DCL11	1 :5	White	White	White
3	API + MCC-101	1 : 1	White	White	White
4	API + MCC-112	1 : 1	White	Off White	Off White
5	API + Pregelatinized starch	1 :1	White	Off White	Off White
6	API + Sodium bicarbonate	1:1	White	Off White	Off White
7	API + Sodium alginate	1:1	White	Off White	Off White
8	API + DHP	1:1	White	Off White	Off White
9	API + Tri sodium citrate	1:1	White	Off White	Off White
10	API + PVP K_{30}	1: 0.05	White	Off White	Off White
11	API +HPC	1: 0.05	White	Off White	Off White
12	API + Mg Stearate	1: 0.05	White	Off White	Off White

Table 11: Lubricated blend parameters

Trial	Wt taken	Volume Initial	Volume after tapping	Bulk density	Tapped density	Carr's index	Hausner's ratio	Report
F_1	32	80	63	0.4	0.503	21.4	1.25	passable
F_2	34.3	80	64	0.42	0.535	21.4	1.27	Passable
F_3	35.8	82	68	0.436	0.526	17.11	1.206	Fair
F_4	34.6	80	66	0.432	0.5242	17.6	1.123	Fair
F_5	34.3	80	65	0.428	0.527	18.7	1.23	Fair
F_6	34.1	80	67	0.426	0.508	16.32	1.192	Fair
F_7	30.1	80	68	0.3765	0.442	14.9	1.173	Good
F_8	30.6	80	69	0.3825	0.445	13.8	1.163	Good
F_9	31.1	80	69	0.388	0.450	13.9	1.15	Good
F_{10}	31.7	80	70	0.396	0.452	12.5	1.14	Good
F_{11}	30.8	80	71	0.375	0.422	11.13	1.125	Good
F_{12}	30.2	80	69.5	0.3775	0.434	13.1	1.149	Good

Table 12: Results of physical evaluation (Tablets)

S. No	Physical parameter	Innovator	F_1	F_2	F_3	F_4	F_5	F_6
1.	Avg. weight variation	1.18 ±0.12	1.5 ±1.2	1.2 ±0.74	4 ±2.38	2.3 ±0.46	3.36 ±1.5	1.32 ±0.36
2.	Hardness (Kp)	15.1 ±0.52	13.3 ±0.51	12.2 ±0.29	10.64 ±0.54	13.26 ±0.4	13.28 ±0.3	13.12 ±0.7
3.	Thickness (mm)	4.61	5.45	5.36	5.40	5.42	5.02	5.42

4.	Friability	0.38	0.45	0.52	0.21	0.18	0.38	0.57
5.	Disintegration Time	1 min 40sec	30 sec	35 sec	39 sec	1 min 26 sec	50 sec	1 min 45 sec

Table 13: Results of physical evaluation (Tablets)

S. No	Physical parameter	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
1	Avg. Weight variation	4.2± 0.37	1.4± 0.3	1.2± 0.54	0.37± 0.67	0.7± 0.41	0.2 ±0.63
2	Hardness (Kp)	13.66 ±0.4	14.06 ±1.1	13.66 ±0.37	14.34 ±0.37	14.04 ±0.24	14.9 ±0.63
3.	Thickness (mm)	5.15	5.27	5.38	5.28	5.30	5.18
4.	Friability	0.46	0.48	0.55	0.49	0.42	0.48
5.	Disintegration time	2 min 46 sec	1 min 37 sec	4 min 41 sec	1 min 22 sec	2 min 3 sec	2 min 30 sec

Table 14: Dissolution profile of Reference rosuvastatin calcium tablets

Time (min)	Cumulative % Drug Release in 0.1N Hcl	Cumulative % Drug Release in pH6.6 Citrate buffer
0	0	0
5	12	79
10	20	84
15	27	86
20	36	88
25	43	90
30	54	92

Table 15: Comparative dissolution profiles of formulations in 0.1N HCl

Time in Minutes	Cumulative % Drug release												
	Ref	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	80	81	70	75	77	82	75	70	79	46	71	77	80
10	84	85	72	78	80	84	81	78	88	52	74	81	83
15	87	87	72	80	81	85	83	78	89	59	75	83	86
20	88	87	74	81	83	88	85	79	89	61	79	84	87
25	90	88	84	82	86	91	87	82	92	82	87	89	89
30	92	94	90	93	90	95	89	91	95	91	94	94	92

Table 16: Comparative dissolution profiles of formulations in 0.1N HCl

Time in Minutes	Cumulative % Drug release												
	Ref	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}
0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	12	42	49	22	44	51	58	50	55	3	60	17	14
10	20	50	54	30	54	60	64	55	64	5	65	37	21
15	27	55	57	36	55	75	76	65	77	8	80	44	26
20	36	68	61	40	58	78	78	71	81	12	81	50	35
25	43	72	73	48	72	89	81	74	85	28	85	68	49
30	54	79	82	56	84	92	89	83	90	32	88	81	51

Table 17: Related substance studies for formulated tablets F_1 to F_6

1 Month Study							
Related substances	F_1	F_2	F_3	F_4	F_5	F_6	**Limit**
RRT1.45(lactone impurity)%	0.312	0.411	0.114	0.311	0.124	0.29	0.5 %
Total Unknown Impurities %	0.402	0.401	0.189	0.359	0.188	0.45	0.5 %
Total Related Substances %	0.714	0.812	0.303	0.67	0.312	0.74	
3 Months Study							
Related substances	F_1	F_2	F_3	F_4	F_5	F_6	**Limit**

RRT1.45(lactone impurity)%	0.621	0.645	0.302	0.584	0.312	0.5	0.5 %
Total Unknown Impurities %	0.721	0.912	0.402	0.711	0.411	0.41	0.5 %
Total Related Substances %	1.342	1.557	0.704	1.295	0.723	0.91	

Table 18: Related substance studies for formulated tablets F_7 - F_{12}

1 Month Study							
Related substances	**F_7**	**F_8**	**F_9**	**F_{10}**	**F_{11}**	**F_{12}**	**Limit**
RRT1.45(lactone impurity)%	0.414	0.351	0.404	0.211	0.191	0.164	0.5 %
Total Unknown Impurities %	0.432	0.371	0.429	0.239	0.203	0.198	0.5 %
Total Related Substances %	0.846	0.722	0.833	0.450	0.394	0.362	
3 Months Study							
Related substances	**F_7**	**F_8**	**F_9**	**F_{10}**	**F_{11}**	**F_{12}**	**Limit**
RRT1.45(lactone impurity)%	0.652	0.563	0.621	0.384	0.362	0.302	0.5 %
Total Unknown Impurities %	0.762	0.692	0.721	0.461	0.442	0.402	0.5 %
Total Related Substances %	1.414	1.255	1.342	0.845	0.804	0.704	

Table 19: In official medium (pH 6.6 sodium citrate buffer)

Trial	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**	**F_{10}**	**F_{11}**	**F_{12}**
f2	88.7	48.2	60.4	68.2	84.9	71.5	55.3	79.1	30.1	53.7	74.8	77.45

Table 20: In discriminating medium (0.1N Hcl)

Trial	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**	**F_8**	**F_9**	**F_{10}**	**F_{11}**	**F_{12}**
f2	26.8	25.5	56.4	26.6	18.7	18.5	23.1	18.1	37.2	17.4	36.1	75.4

Table 21: Accelerated stability studies of optimized formulation F_{12}

S.No	**Test**	**Specifications**	**Initial**	**After 1 month**	**After 2 months**
1	Description	Pink coloured tablets	Complies	Complies	Complies
2	Identification	The retention time of major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation as obtained in the assay.	Complies	Complies	Complies
3	Dissolution (In pH 6.6 Sodium Citrate Buffer)	NLT 90% release with in 45 min	92.10%	91.7%	91.1%
4	Related Substances (%)	NMT 1.0%	Complies	Complies	Complies
5	Assay (ByHPLC)	NLT 98 %w/w, NMT102%w/w	99%w/w	98.77%	98.69%

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