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Formulation and Evaluation of Rosuvastatin Calcium Immediate Release Tablets Using Beta Cyclodextrin

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Abstract

In order to treat Hyperlipidaemia, Rosuvastatin, a Dyslipidaemia drug, inhibits the HMG-CoA reductase enzyme. However, the calcium form of Rosuvastatin (RST) has low bioavailability, undesirable dissolving characteristics, and issues with absorption. Thus objective of the study is to increase the solubility and dissolution rate of Rosuvastatin calcium a poorly water-soluble 3-hydroxy 3-methyl glutaryl CoA (HMG-CoA) Reductase inhibitor through inclusion Complexation with β-cyclodextrin (β-CD). Therefore, the goal of the current study was to create a Rosuvastatin tablet formulation for oral dissolution. Rosuvastatin immediate tablets were developed using the direct compression showed good results, the prepared inclusion complex with β-CD by kneading method exhibited greatest enhancement in solubility and fastest dissolution (97.363) % RST release in 15 min. The inclusion complex contains RST: β-CD (1:1) and (1:2) was formulated into tablets using super disintegrants like Sodium starch glycolate, Cross povidone and Croscarmellose. All the mentioned batches were prepared and granules were evaluated for pre-compression parameters such as bulk density, tapped density and compressibility index. Tablets were evaluated for weight variation, thickness, hardness, friability; disintegration time and were found to be within the limits. In vitro dissolutions were carried out in 0.05M phosphate buffer with a pH of 6.8. The prepared tablet was evaluated for various post compression parameters like hardness, friability, weight variation, thickness, and in-vitro dissolution.

Keywords: Hyperlipidaemia, Rosuvastatin calcium, Beta Cyclodextrin, Bioavailability, Complexation, Pre-compression parameters.

I. INTRODUCTION

Due to the low level of patient acceptability for invasive procedures, the requirement to investigate potential new drug markets, and the high cost of illness management, there is an ongoing demand for innovative oral drug delivery systems [1]. Pharma businesses must create innovative medication delivery methods and use them in product development if they want to thrive in the twenty-first century. Immediate release dose forms are ones that dissolve quickly and disintegrate to release the medication [2]. A suitable pharmaceutically acceptable diluent or carrier that doesn't significantly slow down the rate of drug release and/or absorption can be used to deliver immediate release [3]. Immediate release dose forms are ones that dissolve quickly to release the medication. This phrase does not include medication formulations that have been adjusted to provide for "controlled," "sustained," "prolonged," "extended," or "delayed" drug release [4]. Rapid or slow dissolving rates are used to categorise immediate release solid oral dose forms. An immediate release dose form is one in which less than 85% of the prescribed quantity dissolves in 30 minutes [5]. For tablets with a quick release, the sole hurdle to drug release is the straightforward breakdown or erosion step, which often happens in less than an hour. Disintegration is a crucial process that can improve a drug's bioavailability and, consequently, its capacity to dissolve from quick release tablets [6]. Only a few super-disintegrants, such as croscarmellose sodium, Cross povidone, and SSG, are commercially marketed. For the production of immediate release tablets, several methods are available [7]. Moulding, lyophilisation or freeze drying, direct compression, spray drying, and sublimation are the most used preparation techniques. One approach that necessitates adding super disintegrants to the formulation is direct compression [8, 9].

When used to produce tablets of the appropriate hardness without compromising the rapid disintegration characteristics, direct compression is very sensitive to changes in the type and proportion of excipients as well as compression forces [10]. During the formulation process, direct compression does not require the use of heat or water. Cyclodextrin is an oligosaccharide formed by the enzymatic breakdown of starch that has six, seven, or eight glucopyranose units respectively. With a hydrophilic exterior surface and a hydrophobic interior chamber, these torus- shaped molecules may hold a range of lipophilic medications [11]. The objective of present study is to develop immediate release tablets of Rosuvastatin using different types of super disintegrants and beta cyclodextrin to enhance the disintegration and dissolution of Rosuvastatin to improve bioavailability of the drug. A HMG CoA reductase inhibitor with a 20% absolute bioavailability, Rosuvastatin calcium is used to treat Dyslipidaemia [12-15].

II. MATERIALS AND METHOD

2. MATERIALS

Rosuvastatin calcium wasobtained as gift sample from MSN laboratories, Hyderabad. Beta cyclodextrin, Micro crystalline cellulose (MCC), Lactose spray dried. Cross povidone, Sodium starch glycolate (SSG), Colloidal silicon dioxide, Magnesium stearate. There were just analytical-grade chemicals and solvents utilised.

Table 1: Materials used in formulation of immediate release tablets of Rosuvastatin calcium

S.no	CHEMICAL NAME	CATEGORY
1	Rosuvastatin calcium	Anti-hyperlipidemic agent
2	Beta cyclodextrin	Dissolution enhancer
3	Micro crystalline cellulose	Diluent
4	Lactose spray dried	Binder
5	Cross povidone	Disintegrant
6	Sodium Starch glycolate	Disintegrant
7	Colloidal silicon dioxide	Glidant
8	Magnesium stearate	Lubricant

2.1 METHODOLOGY

2.1.2 Drug- Excipient Compatibility Study (FTIR) [16, 17]

By establishing compatibility blends with various ratios of different excipients to drug based on a rough average weight, compatibility tests were carried out to explore and anticipate the physicochemical interaction between drug substance and excipients. The dosage of the medicine to the excipient. The most effective method to pinpoint the drug's functional groups, FTIR spectrometry, is used to assess chemical compatibility. In the current investigation, the potassium bromide disc (pellet) technique was used.

2.1.3 Formulation of Rosuvastatin Immediate release tablets [18]

Weigh all the ingredients accurately according to Formulas (F1- F8) were prepared by direct Compression method in which all constituents were mixed and compressed directly by tablet machine. Except for the colloidal silicon dioxide and magnesium stearate, combine all the components geometrically.

- Then lubricate the blend with colloidal silicon dioxide and magnesium stearate. Using a rotating tablet Machine- 12 station with an 8mm flat punch, the mixture was compressed. Each tablet contains 20 mg rosuvastatin calcium.

2.1.4 PREPARATION OF INCLUSION COMPLEXES [19, 20]

- Different methods were used to formulate the cyclodextrin complex of Rosuvastatin

KNEADING METHOD

- Rosuvastatin and Beta cyclodextrin (ß CD) in the proportion of 1:1 & 1:2 molar ratios.
- Concentrations and distilled water were combined in a mortar for an hour along with minor amounts of methanol. Occasionally to get slurry-like consistency. The paste was dried in the oven for 24 hours at a temperature of 45 °C.
- Dried complex were pulverized into fine powder and sifted with sieve # 8.

Table 2: Formulation table of Rosuvastatin tablets

	1:1				1:2			
Ingredients(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Rosuvastatin calcium (mg)	20	20	20	20	20	20	20	20
Beta cyclodextrin(mg)	20	20	20	20	40	40	40	40
Micro crystalline cellulose(mg)	80	90	70	60	70	80	50	60
Lactose spray dried(mg)	70	60	80	90	60	50	80	70
Cross povidone(mg)	-	6	-	3	-	6	-	3
Sodium starch glycolate(mg)	-	-	6	3	-	-	6	3
Colloidal silicon dioxide(mg)	2	2	2	2	2	2	2	2
Magnesium stearate(mg)	2	2	2	2	2	2	2	2
Total(mg)	200	200	200	200	200	200	200	200

3. Evaluation of Flow Properties of Prepared Granules

Determination of Powder Flow Properties [21-23]

a) Angle of Repose

The funnel technique was used to calculate the API powder's angle of repose. The greatest angle that may be formed between the surface of a pile of powder and the horizontal plane is known as the Angle of Repose. The funnel was filled with the carefully weighed powder combination. The funnel's height was changed such that it now stands 2.5 cm above the ground. The powder mixture is allowed to freely flow through the funnel and onto the surface.

The diameter of the powder cone is measured, and after repeating the process three times, the average value is determined.

Equation is used to determine the angle of repose:

$$\boldsymbol{Angle\ of\ Repose\ =\ Tan\,\theta = h/r}$$

Where
h = height of pile
r = radius of the base of the pile
θ = angle of repose

b) Bulk Density

Weighed quantity of the powder (W) is taken in a graduated measuring cylinder and volume (V0) is measured and bulk density is calculated using the formula.

$$\boldsymbol{Bulk\ density\ (BD)\ =\ W/Vo}$$

W=Weight of the powder
VO=Volume of powder

c) Tapped Density

The powder sample under examination was screened via sieve No. 18, and a 100 mL graduated cylinder was filled with a weight of the sample equal to 25 gm. At first, the mechanical tapping of the cylinder was done at a nominal rate for 500 times using the tapped density tester, and the tapped volume Vo was recorded. The difference between two tapping volume was less than 2%, Vf is considered as a tapped volume. Calculations of the tapped density, Hausner's ratio, and Carr's Index were made using the blend volume.

$$\boldsymbol{Tapped\ density\ (TD)\ =\ W/V\,f\ g/ml}$$

W=Weight of the powder 000
V f =Volume of powder

d) Carr's Index

Carr's index is also known as compressibility. It is inextricably linked to particle size, cohesiveness, and relative flow rate.

$$\boldsymbol{Carr's\ index = \frac{Tapped\ Density}{Bulk\ Density} \times 100}$$

Tapped Density was used to get Carr's index.

f) Hausner's Ratio

By comparing the ratio of tapped density to bulk density, Hausner's ratio provides information on the powder's flow characteristics.

$$\boldsymbol{Hausner's\ Ratio\ =\ Tapped\ density\ /\ Bulk\ density}$$

4. Evaluation of Post Compression Parameters of Prepared Tablets [24, 25]

a) Thickness

The thickness of tablets was determined by using digital vernier callipers. The average of the data was calculated using ten individual pills from each batch. It should be in a range of ±5% variation of a standard value. The results were expressed in mm.

$$\boldsymbol{MSR\ +VSR\ *\ LC}$$

MSR = main scale reading, VSR = Vernier scale reading, LC= Least count

b) Weight Variation

Twenty tablets were chosen at random from each batch and weighed one by one. Only two of the individual tablet weights may differ from the average weight by more than the permitted percentage deviation, and no weight may deviate by more than twice the percentage indicated, for the test to be considered successful.

c) Hardness

To determine the average tablet hardness or crushing strength, ten tablets from each batch were chosen, and hardness was assessed using a digital hardness tester. Hardness should be in between 3-6 kg/cm2

d) Friability

Using a Roche friabilator, the friability values of the tablets were calculated. It is stated in percent. 20 pills were placed to the friabilator after being originally weighed (starting weight). Friabilator was run for 4 minutes at a speed of 25 rpm. The following equation was used to get the percentage of friability. Tablets with less than 1% friability were deemed acceptable.

$$\boldsymbol{\%\ Friability = \frac{Initial\ weight - Final\ weight}{Intial\ weight} \times 100}$$

f) Disintegration Time

Six tablets, chosen at random from each batch, were put into USP disintegration equipment baskets, which are periodically submerged 30 times per minute into a fluid that is thermostatically regulated to be 37°C and examined for the duration specified in the specific monograph. The tablets must totally dissolve into a soft substance with no audibly stiff core in order to pass the test. The medicine should be released from an immediate release tablet within 3 minutes.

g) In Vitro Dissolution Test

Using the Electro lab equipment II, the produced tablets' dissolving investigations were conducted. Dissolution was performed in 900 ml phosphate buffer of pH 6.8 at 37 ± 0.5°C at 100 rpm. An auto sampler, coupled to the dissolution apparatus was programmed to withdraw and replace 10 ml of the dissolution media at 0, 5, 10, 15, and 30 min. Within 15 minutes, around 80% of the medication should be discharged.

Dissolution Parameters

Medium	**:** Phosphate buffer pH 6.8
Volume	**:** 900 ml Apparatus
Apparatus	**:** Type II of USP (paddle)
Rotation speed	**:** 75 rpm
Temperature	: 37 ±0.5°C

III. RESULTS AND DISCUSSION

5. UV Spectroscopic Analysis

- UV-visible spectroscopic method for Rosuvastatin
- A double beam UV spectrometer Schimadzu (1800) with UV probe software (2.31) and 10mm matched quartz cells were used for determination.
- Preparation of standard stock solution using methanol
- Standard stock solution of Rosuvastatin sample was prepared by transferring 100 mg of drug in 100 ml of volumetric flask and adds 100 ml of water. The solution was sonicated for 2-3 minutes to dissolve the drug and the solution was then diluted and make up with water

5.1 Determination of Absorption Maxima by UV Spectrometer in Water

From the working standard solution, a range of concentration were prepared and scanned in double beam spectrophotometer against respective blank by using spectrophotometric method:

- The absorption maxima of Rosuvastatin in water was deliberated in range of 700 to 200 nm
- The spectrum of rosuvastatin showed maximum absorption at wavelength of 240 nm
- The correlation coefficient R^2 was found to be 0.9991 which is near to 1

5.2 Calibration Curve of Rosuvastatin Calcium

- The calibration curve of Rosuvastatin was plotted by using water as a solvent.
- 100mg of drug was taken in volumetric flask and dissolved in few ml of water; make up the volume with 100 ml of water (1000ppm).
- From the above solution take 1ml and makeup with 10 ml of water (100ppm).
- From the above solution take 1ml and make up the volume up to 10 ml with water (10ppm).
- From the stop solution dilutions were made to produce concentration of 0.5, 1, 1.5, 2, 2.5 ppm.
- The absorbance was measured at 243 nm using photometric method from the data obtained, calibration curve (standard plot) was done regression coefficient, slope, y axis intercept was calculated.

Table 3: Linearity of Rosuvastatin calcium

Concentration(ppm)	Absorbance
1	0.002
2	0.132
3	0.252
4	0.4
5	0.521

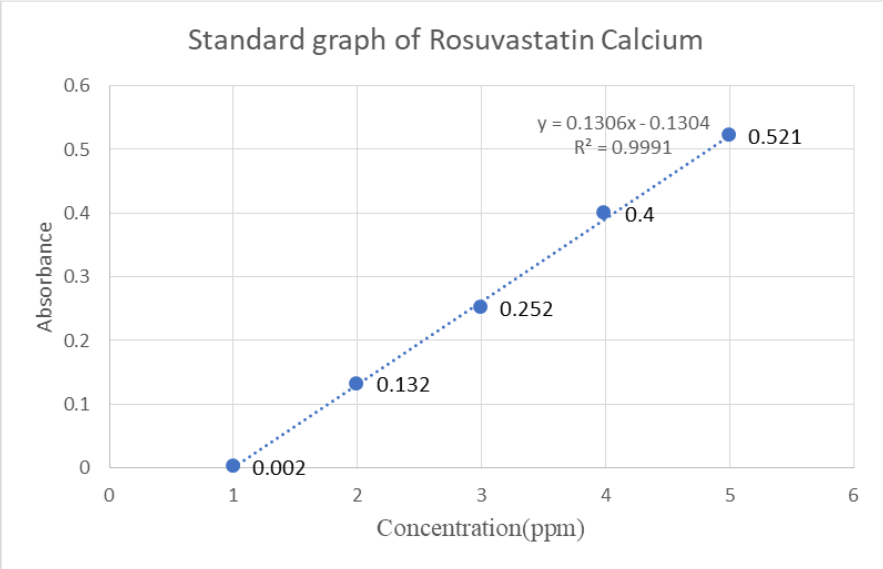

Fig. 1: Standard graph of Rosuvastatin calcium

5.3 DRUG EXCIPIENT COMPATABILITY STUDIES FTIR

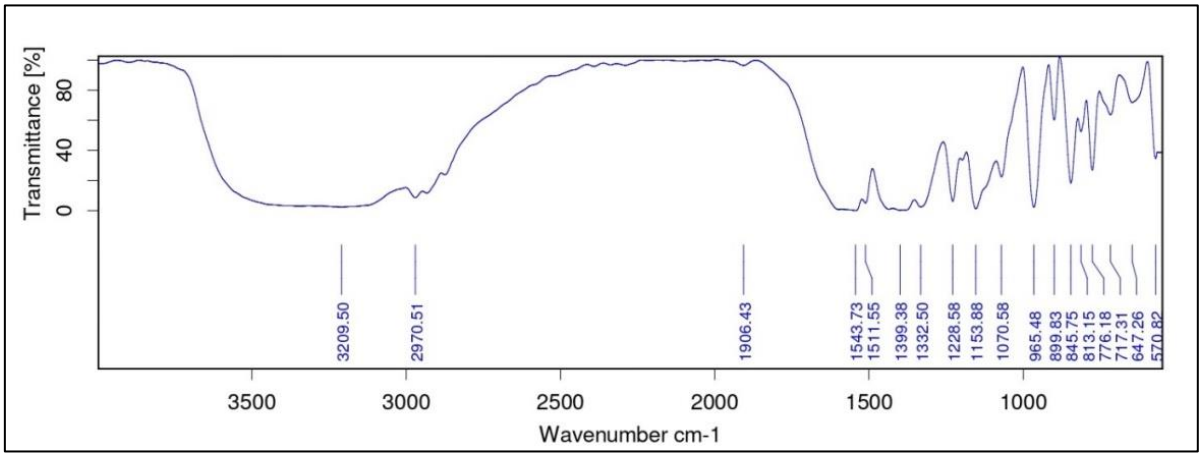

Fig. 2 : FTIR Spectra of Rosuvastatin

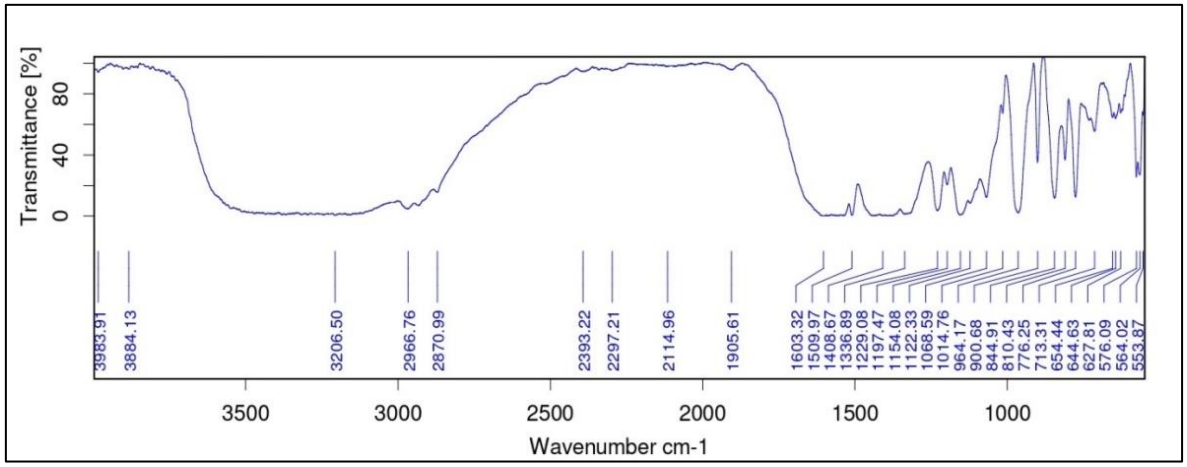

Fig. 3: ROSUVASTATIN E5

INFERENCE: Characteristics peaks were obtained for pure drug as well as excipients.

6. EVALUATION OF GRANULES

Table 4: Pre formulation studies

S. No	Test	Specification	Result
A	Description	White to off white colored crystalline powder	White powder
B	Solubility	Freely Soluble in methanol, slightly soluble in ethanol, very slightly soluble in water	Complies
C	Drug Identification	Performed by FTIR	Functional groups identified
D	Identification of λ max	Based on highest peak	At 248 nm

Table 5: Evaluation of pre-compression parameters

Batch no	Angle of repose	Bulk density (g/ml)	Tapped density (g/ml)	Carrs index (%)	Hausners ratio
(1:1) F1	30.10±0.03	0.444	0.543	18.239	1.223
F2	32.72±0.01	0.439	0.549	20.039	1.249
F3	30.74±0.04	0.464	0.529	12.287	1.140
F4	31.60±0.02	0.468	0.533	16.880	1.201
(1:2) F5	29.48±0.01	0.453	0.540	11.259	1.152
F6	33.25±0.03	0.459	0.571	14.884	1.154
F7	30.98±0.05	0.448	0.519	13.331	1.153
F8	29.92±0.02	0.481	0.555	13.135	1.152

Table 6: Evaluation of post compression parameters

Batch No	%Weight variation(mg)	Thickness (mm)	Hardness (kg/cm^2)	% Friability	Disintegration time(sec)
(1:1) F1	198.3± 1.262	1.4±0.011	4.1±0.073	0.36±0.2	120 sec
F2	199.1±0.787	1.8±0.008	5.2±0.077	0.31±0.3	78 sec
F3	200± 1.401	1.5±0.011	4.2±0.156	0.20±0.4	98 sec
F4	199.3±0.831	1.3±0.011	6.1±0.123	0.19±0.5	69 sec
(1:2) F5	200±1.731	1.3±0.008	4.3±0.069	0.31±0.3	90 sec
F6	200±0.909	1.5±0.011	6.1±0.124	0.28±0.6	60 sec
F7	199.9±0.912	1.4±0.008	4.5±0.159	0.18±0.3	120 sec
F8	198.6±01.341	1.5±0.011	4.4±0.194	0.20±0.9	78 sec

All formulations tested for physical parameters like hardness, thickness, weight variation, friability, disintegration and found to be within the pharmacopeial limits. The results of the tests were tabulated.

Table 7: In vitro Dissolution profile of different formulation (F1 to F8)

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
5	60.6±1.89	63.25±2.32	61.69±3.21	70.42±2.54	67.6±4.31	83.6±2.12	75.6±3.87	80.6±2.35
10	64.01±3.23	69.81±4.21	65.36±2.89	75.36±1.98	73.31±3.21	94.11±4.83	80.21±1.29	84.01±1.76
15	70.45±2.12	75.45±1.87	72.25±1.76	81.25±4.21	77.15±2.56	97.45±1.23	87.45±5.43	91.65±4.87
30	79.45±5.43	84.45±3.56	81.05±4.18	92.95±5.98	89.45±1.37	99.35±5.34	94.45±2.65	97.35±3.65

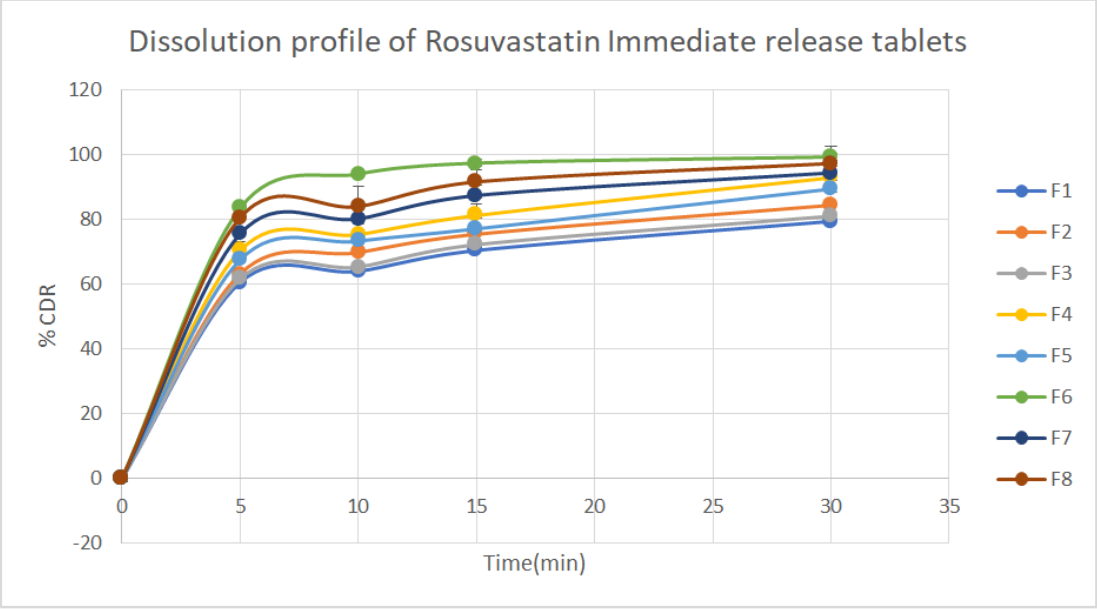

Fig. 4: Dissolution profile of Rosuvastatin calcium

Among all formulations F6 shows better drug release when compared with all other formulations.

IV. CONCLUSION

From the above experimental results, it can be concluded that immediate release tablet of Rosuvastatin calcium can be prepared by using beta cyclodextrin and different proportion and combination of superdisintegrants and binder and selected F6 as best formulation based on dissolution profile and physical characteristics. Formulation F6 showed 97% drug release in 15 min when compared to other formulations and showed fair flow properties.

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