To Develop Fast Disintegrating Tablets of *Rosuvastatin* by Using New generation *Super Disintegrates* by Direct Compression Method

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Abstract: **In the present work, an attempt has been made to develop fast disintegrating tablets of Rosuvastatin. New generation super disintegrates *Explotab,* Ion exchange resin *Tulsion 334 and Eudragit E100* were selected as super disintegrates. All the formulations were prepared by *direct compression method* using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations, F3 formulation showed maximum % drug release i.e., 99.4 % in 2 min. Hence it is considered as Optimized formulation. The F3 formulation contains Eudragit E100 as super disintegrate in the concentration of 30 mg. The formulations prepared with Tulsion 334 showed maximum percentage drug release in 6 min i.e., 98.7% (F6 formulation and the concentration of super disintegrate is 30 mg). The formulations prepared with Explotab showed maximum percentage drug release in 6 min i.e., 99.5%. F3 formulation was considered as optimized formulation.**

Index Terms: **Rosuvastatin, Eudrgait E100, Tulsion 334 and Explotab**

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Introduction

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS make a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly. Drug delivery systems are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance.

Despite of tremendous advancements in drug delivery, the oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, ease of administration lead to high levels of patient compliance.It is always the aim of a scientist or a dosage form designer to enhance the safety of a drug molecule while maintaining its therapeutic efficacy. Recent advances in NDDS aim for the same by formulating a dosage form, convenient to be administered so as to achieve better patient compliance. Mouth Dissolving Tablet (MDT) is one among such approaches. Improved patient compliance has achieved enormous demand. Consequently, demand for their technologies is also increasing many folds. To develop a chemical entity, a lot of money, hard work and time are required. So, focus is rather being laid on the development of new drug delivery systems for already existing drugs, with enhanced efficacy and bioavailability, thus reducing the dose and dosing frequency to minimize the side effects.

The oral route of administration is the most preferred route due to its many advantages like ease of administration, accurate dosage, self-medication, pain avoidance, versatility and patient compliance. Tablets and capsules are the most popular dosage forms. One important drawback of such dosage forms is Dysphasia or difficulty in swallowing. This is seen to afflict nearly 35% of the general population. This disorder is also associated with a number of pathological conditions including stroke, Parkinson's disease, neurological disorders, AIDS etc.

Materials and methods: Materials: Rosuvastatin was a gift sample from Natco Pharma Pvt ltd, Hyderabad. India. Reagents used Eudragit E100, Tulsion 334, Explotab, Magnesium stearate, Talc MCC, pH 102(Asian Scientifics, Hyderabad).The materials used were of pharmaceutical grade.

Method: Analytical method: Determination of UV Absorption maxima: Rosuvastatin solution was prepared in 0.1 N HCL and diluted suitably. The UV spectrum of the solution was taken on Lab India 3200 UV/Visible double beam Spectrophotometer. The Solution exhibited UV maxima at 243 nm.

Preparation of Standard Calibration Curve of Rosuvastatin:
100 mg of Rosuvastatin was accurately weighed and dissolved in little amount of Methanol and make up the final volume up to 100 ml with 0.1 N HCl (pH 1.2) to prepare stock solution. The 10 ml of stock solution was further diluted with 0.1 N HCl (pH 1.2) in 100ml to get 100µg/ml (working standard).

Then 0.2,0.4,0.6,0.8 and 1 ml of working standard was taken in 10 ml standard volumetric flask and made up the volume with 0.1N HCl to prepare 2µg,4µg,6µg,8µg, and 10µg drug per ml solution. Then the absorbance was measured in a UV spectrophotometer at 243 nm against 0.1 N HCl (pH 1.2) as blank. The absorbance so obtained were tabulated as in **Table 1.** Calibration curve was constructed and shown in **table1**.

FORMULATION DEVELOPMENT

Formulation of Rosuvastatin Dispersible Tablet by Direct- Compression: Composition of preliminary trials for Rosuvastatin Dispersible Tablet by direct compression. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-8 station with 6mm flat punch, B tooling. Each tablet contains 10 mg Rosuvastatin and other pharmaceutical ingredients.

Formulation of Rosuvastatin Oro- dispersible tablets

INGREDIENT	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Rosuvastatin	10	10	10	10	10	10	10	10	10
Eudragit E100	10	20	30	-	-	-	-	-	-
Tulsion 334	-	-	-	10	20	30	-	-	-
Explotab	-	-	-	-	-	-	10	20	30
Talc	2	2	2	2	2	2	2	2	2
Mg. Stearate	2	2	2	2	2	2	2	2	2
MCC pH102	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
TOTAL	100	100	100	100	100	100	100	100	100

EVALUATION PARAMETERS
Evaluation parameters:
I. Precompression parameters:
1. Bulk Density (D_b): It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by,

$$D_b = M/V_b$$
Where, M is the mass of powder
V_b is the bulk volume of the powder.

2. Tapped Density (D_t): It is the ratio of total mass of the powder to the tapped volume of the powder. 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 it 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 % (in a bulk density apparatus). It is expressed in g/ml and is given by,

$$D_t = M/V_t$$
Where,
M is the mass of powder
V_t is the tapped volume of the powder.

3.Angle of Repose (Θ): The friction forces in a loose powder can be measured by the angle of repose (q). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane

$$\tan(Θ) = h/r$$
$$Θ = \tan^{-1}(h/r)$$
Where,
Θ is the angle of repose.
h is the height in cm
r is the radius in cm

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property.

Table 2: Angle of Repose as an Indication of Powder Flow Properties

Sr. No.	Angle of Repose (^{0})	Type of Flow
1	<20	Excellent
2	20-30	Good
3	30-34	Passable
4	>34	Very Poor

4. Carr's index (or) % compressibility: It indicates powder flow properties. It is expressed in percentage and is give by,

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where, Dt is the tapped density of the powder and
Db is the bulk density of the powder.

Table 3: Relationship between % compressibility and flow ability

Sr no.	% Compressibility	Flow ability
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair Passable
4	23-35	Poor
5	33-38	Very Poor
6	<40	Very Very Poor

5. Hausner ratio: Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$\text{Hausner ratio} = \frac{D_t}{D_b}$$

Where, D_t is the tapped density, D_b is the bulk density.
Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

II. Post compression parameters:

1. Weight variation: 20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in table No. 4

Table 4: Weight Variation Specification as per IP

Average Weight of Tablets	%Deviation
80 mg or less	±10
More than 80 mg but less than 250 mg	±7.5

 2. Hardness: Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm^2.

3. Thickness: Three tablets were selected randomly from each batch and thickness was measured by using Vernier Caliper.

4. Friability (F): Friability of the tablet determined using Roche Friabilator. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at the height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the Friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

5. In-Vitro drug release: Release of the drug *in vitro*, was determined by estimating the dissolution profile.
 Dissolution test: USP II Paddle apparatus was used and paddle was allowed to rotate at 50 rpm, acid buffer 0.1N HCL (pH 1.2, 500 ml) was used as a dissolution medium.**(Refer table no:6 &fig-6.1,6.2,6.3)**

6. Assay: 10 tablets were weighed and triturated. The tablet triturate equivalent to 10 mg of the drug was weighed accurately, dissolved in pH 1.2 buffer and diluted to 100 ml with the same. Further dilution were done suitably to get a concentration of 10 µg/ ml with simulated gastric fluid pH 1.2. Absorbance was read at 210 nm against the reagent blank, and the concentrations of rosuvastatin in µg/ ml was determined by using the regression equation.

$$Y = 0.007x + 0.001$$

Drug content in mg / tablet = conc. µg/ml * dilution factor

% Drug content = drug content in mg * 100 / label claim.

7. Drug- excipient compatibility studies by FT-IR:
 The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany (Alpha T). The potassium bromide pellets were prepared on KBr press by grounding the solid powder sample with 100 times the quantity of KBr in a mortar. The finely grounded powder was then introduced into a stainless-steel die and was compressed between polished steel anvils at a pressure of about 8t/in^2. The spectra were recorded over the wave number of 8000 to 400cm^{-1}.**(See figure 6.4,6.5).**

RESULTS & DISCUSSION
 Standard Calibration curve of Rosuvastatin:
Table 1: Concentration and absorbance obtained for calibration curve of Rosuvastatin in 0.1 N hydrochloric acid buffer. It was found that the estimation of Rosuvastatin by UV spectrophotometric method at λ_{max} 243.0 nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2- 10µg/ml. The regression equation generated was y = 0.056x –0.003.

S. No.	Concentration (µg/ml)	Absorbance* (at 243nm)
1	2	0.113
2	4	0.220
3	6	0.337
4	8	0.445
5	10	0.566
Correlation Coefficient = 0.999 **Absorbance y = 0.056x -0.003**		

Standard graph of Rosuvastatin in 0.1 N HCl
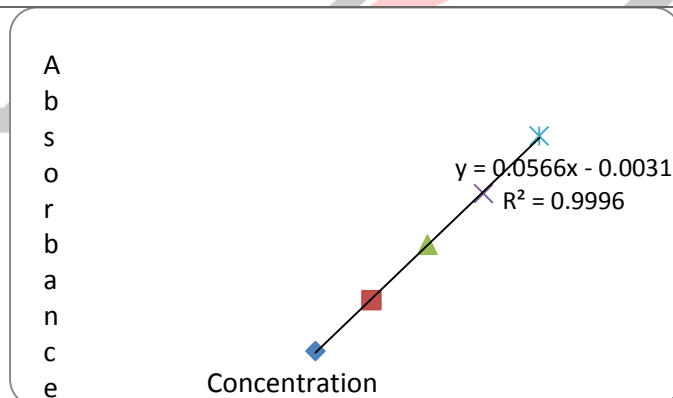
Evaluation Parameters for Fast Dissolving Tablets of Glimipride:
Pre-compression parameters:
        The data were shown in **Table (5.1,5.2)**. The values for angle of repose were found in the range of 25°-30°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.41 to 0.50 (gm/cc) and 0.50 to 0.58 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 13.06% to 18.18%. The Hausner ration fall in range of 1.14 to 1.22. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Table 5.1 : Pre-compression parameters

Formulations	Bulk Density (gm/cm²)	Tap Density (gm/cm²)	Carr's Index (%)	Hausner ratio	Angle of Repose (Θ)
F₁	0.40	0.54	17.18	1.20	26.91
F₂	0.50	0.56	15.54	1.18	28.23
F₃	0.50	0.58	13.79	1.19	29.34
F₄	0.46	0.56	16.36	1.19	26.71
F₅	0.44	0.58	13.79	1.16	29.34
F₆	0.48	0.56	14.54	1.17	28.23
F₇	0.50	0.58	13.79	1.16	29.34
F₈	0.42	0.50	18	1.20	26.78
F₉	0.49	0.50	18	1.20	26.78

Table 5.2: Post-Compression parameters

FD	Weight variation (mg)	Hardness (kg/cm²)	Thickness (mm)	Disintegration Time (sec)	Friability (%)	Assay (%)
F₁	100	2.5	3.49	19.33	0.44	96.20
F₂	100	2.6	3.44	22.66	0.30	97.15
F₃	102	2.5	3.49	20.33	0.43	96.11
F₄	109	2.6	3.48	20.00	0.41	99.24
F₅	104	2.3	3.49	20.33	0.41	96.26
F₆	101	2.7	3.44	21.66	0.44	96.25
F₇	101	2.5	3.49	20.33	0.45	98.26
F₈	104	2.6	3.46	27.00	0.39	97.23
F₉	102	2.5	3.46	19.00	0.40	97.25

Table 6: Dissolution data for all the formulations

Time(Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	28.4	39.5	98.9	24.3	31.7	48.3	18.4	35.2	62.4
4	35.2	76.3	99.4	31.6	34.5	82.9	25.2	48.9	89.1
6	48.9	96.2	99.2	49.3	41.9	98.7	48.7	66.8	99.5
8	66.8	99.7	-	58.3	62.4	-	58.3	79.3	-
10	78.1	-	-	74.3	89.1	-	74.3	88.9	-
15	86.4	-	-	88.1	99.5	-	87.4	93.5	-
20	100.3	-	-	94.6	-	-	98.77	-	-
25	-	-	-	98.1	-	-	-	-	-
30	-	-	-	-	--	-	-	-	-

Weight variation test: Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the **Table 5.2**. The average weight of the tablet is approximately in range of 107 to 98.5, so the permissible limit is ±10% (110-90mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test: Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in **Table 5.2**. The results showed that the hardness of the tablets is in range of 2.5 to 3.00 kg/cm², which was within IP limits.

Thickness: Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in **Table-5.2**.The result showed that thickness of the tablet is raging from 3.56 to 3.64.

Friability: Tablets of each batch were evaluated for percentage friability and the data's were shown in the **Table 5.2**.The average friability of all the formulations lies in the range of 0.30 to 0.51% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

In vitro disintegration time Tablets of each batch were evaluated for in vitro disintegration time And the time was found to be in the range of 19.33 to 27 seconds. The data was shown in the **Table 5.2.**

Assay: Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 97.23 -99.25 %.The data was shown in the **Table 5.2.**

Invitro Dissolution studies: Invitro dissolution studies were carried out by using 500ml of 0.1 N HCl in USP dissolution apparatus by using paddle method. The dissolution studies were carried out for about 30 min. The dissolution data for all the formulations were given in the **Table 6.**

Fig 6.1: Dissolution profile of formulations prepared with Eudragit E100 as Super Disintegrate
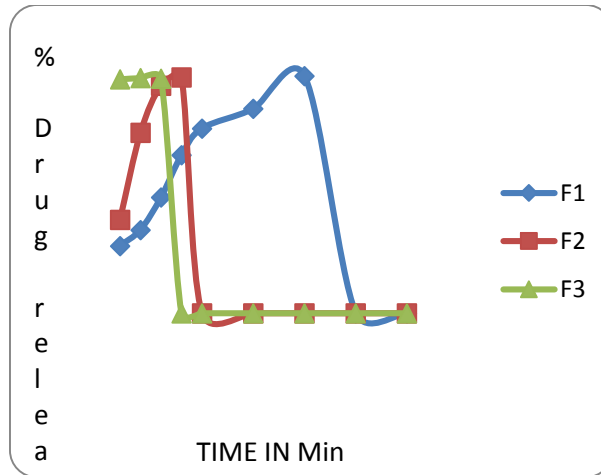
Fig 6.2: Dissolution profile of formulations prepared with Tulsion 334 as Super Disintegrate
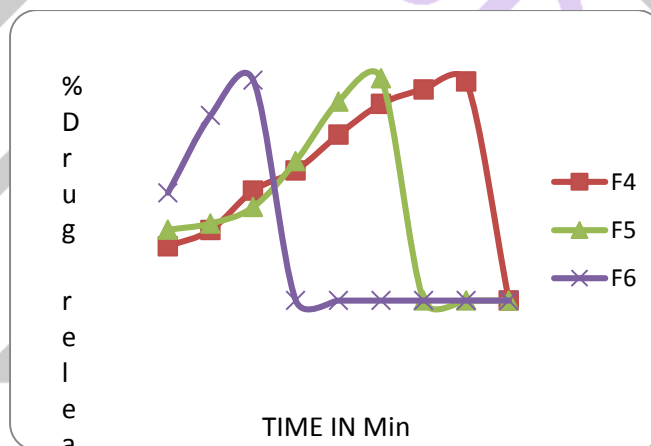
Fig 6.3: Dissolution profile of formulations prepared with Explotab as Super Disintegrate
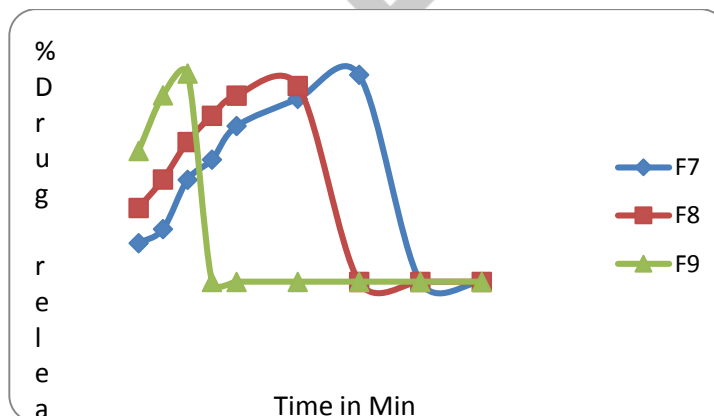
From the tabular column 5. it was evident that the formulations prepared with super disintegrate Eudragit E 100 showed maximum % drug release in 2 min i.e.99.4% (F3 formulation and the concentration of super disintegrate is 30 mg).The formulations prepared with Tulsion 334 showed maximum percentage drug release in 6 min i.e., 98.7% (F6 formulation and the concentration of super disintegrate is 30 mg).The formulation's prepared with Explotab showed maximum percentage drug release in 6 min i.e.,99.5%.

Irrespective of super disintegrate type the disintegration time decreases and Dissolution time also decreases as the concentration of super disintegrate increases. The dissolution profile was represented in above graphs.

Fourier Transform-Infrared Spectroscopy:

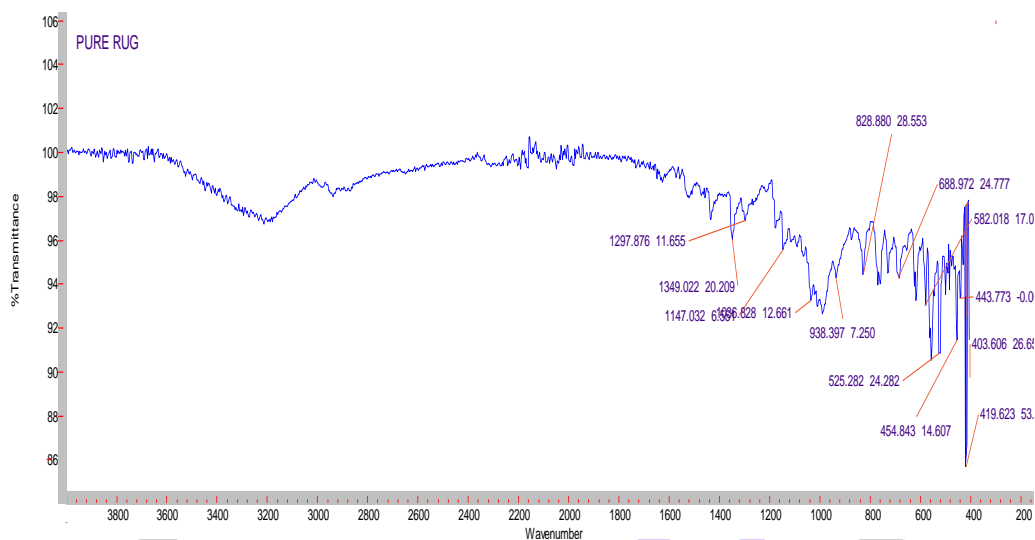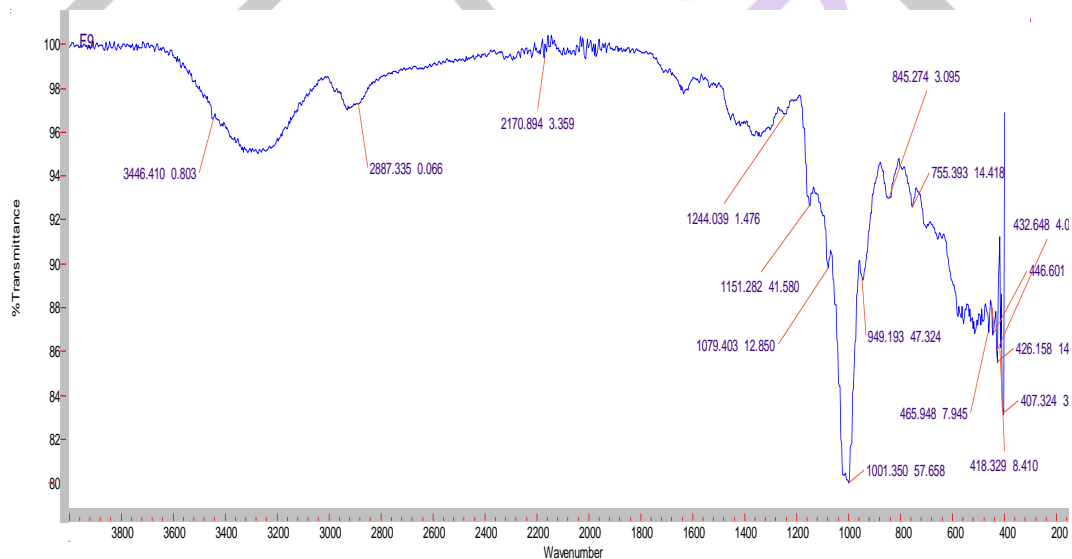**Figure 6.4: FT-TR Spectrum of Rosuvastatin pure drug.**

Figure 6.5 FT-IR Spectrum of Optimized Formulation

From the FTIR data it was evident that the drug and super disintegrates, other excipients doses not have any interactions**.** Hence, they were compatible.

CONCLUSION: In the present work, an attempt has been made to develop fast disintegrating tablets of Rosuvastatin. New generation super disintegrates Explotab, Ion exchange resin Tulsion 334 and Eudragit E100 were selected as super disintegrates. All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F3formulation showed maximum % drug release i.e., 99.4 % in 2 min hence it is considered as optimized formulation. The F3 formulation contains Eudragit E100 as super disintegrate in the concentration of 30 mg. The formulations prepared with Tulsion 334 showed maximum percentage drug release in 6 min i.e., 98.7% (F6 formulation and the

concentration of super disintegrate is 30 mg).The formulation's prepared with Explotab showed maximum percentage drug release in 6 min i.e.,99.5%. F3 formulation was considered as optimized formulation.

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