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Formulation, Development and Evaluation of Rosuvastatin Calcium Immediate Release Tablets

Satyabrata Bhanja*[1], P.Rushikesh[1] , K. Lakshmi Deepthi [1], V.Neelima [1]
1.Department of Pharmaceutics, Malla Reddy College of Pharmacy, Maisammaguda Secunderabad. Andhra Pradesh.

ABSTRACT

The objective of the study was to increase the stability, and dissolution rate of Rosuvastatin Calcium, an acid labile antihyperlipedemic drug which acts as 3-hydroxy3-methyl glut aryl CoA (HMG-CoA) Reductase inhibitor through incorporation of different alkalizers. The different alkalizers used in the study are trisodium citrate, sodium bicarbonate, sodium alginate, di sodium hydrogen phosphate and meglumine. The tablets are prepared by direct compression and wet granulation method. The prepared tablets were evaluated for various post compression parameters like hardness, friability, weight variation, thickness, drug content and in-vitro dissolution. The results of the study revealed that the organic monovalent alkaliser meglumine shows the best results when compared with the innovator formulation. The dissolution studies showed that the drug release from all the formulation was complete and uniform in pH 6.6 sodium citrate buffer and T12 hardness (8.2 ±0.6) kp ,thickness(4.18 ±0.12)mm, friability (0.44)%, drug content uniformity (102±0.9)% and dissolution profile(99.5%) shows near to that of innovator and found to be the best formulation showing the drug release matched with that of innovator. The stability of tablets was studied at 40°C & 75%RH for period of 3 months at 40°C & 75% RH and no significant changes were detected in the hardness, friability, assay and dissolution profile of tablets after 3 month. The release kinetics studies performed and it follows the first order release kinetics and Peppas model indicates the mechanism of drug release i.e. Fickian diffusion. From the study it can be concluded that the formulation T12 can be considered as the optimized formulation.

Key words*:* Anti hyper lipidemic, alkaliser, dissolution, stability.

*Corresponding Author Email: satyabrata_bhanja@rediffmail.com
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INTRODUCTION

Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing; however in many cases immediate onset of action is required than conventional therapy. Immediate release pharmaceutical dosage form has emerged as alternative oral dosage forms. There are novel types of dosage forms that act very quickly after administration. The basic approach used in development tablets is use of superdisintegrants like Cross linked carboxymelhylcellulose (Croscaramellose), Sodium starch glycolate (Primogel, Explotab), Polyvinylpyrrolidone (Polyplasdone) etc. which provide instantaneous disintegration of tablet after administration. Immediate release liquid dosage forms & parenteral dosage form have also been introduced for treating patients. Dosage form can be suspensions with typical dispersion agents like hydroxypropyl methylcellulose, (dioctylsulfosuccinate) etc. The development of immediate release therapy also provides an opportunity for line extension in the marketplace. A wide range of drugs (e.g., neuroleptics, cardiovascular , analgesics, antihistamines) can be considered candidates for this dosage form[1-3].

The term "immediate release" pharmaceutical formulation includes any formulation in which the rate of release of drug from the formulation and/or the absorption of drug, is neither appreciably, nor intentionally, retarded by galenic manipulations. In the present case, immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluents or carrier, which diluents or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. Thus, the term excludes formulations which are adapted to provide for "modified", "controlled", "sustained", "prolonged", "extended" or "delayed" release of drug [4-6]

Rosuvastatin calcium is a HMG Co-A reductase inhibitor used for the treatment of the Primary hyperlipidemia and mixed dyslipidemia and hypertriglyceridemia.[7-8] It is a selective and competitive inhibitor of HMG-CoA reductase, the rate limiting enzyme that converts 3-hydroxy-3-methyl glutaryl coenzyme A to mevalonate, a precursor of cholesterol. It increases the catabolism of LDL& inhibits the hepatic synthesis of VLDL and increases the synthesis of HDL.

The purpose of this work is to develop a stable, pharmaceutically equivalent and robust formulation of Rosuvastatin calcium having anti-lipidemic activity. The tablet produced should be a stable, bioequivalent to the Innovator sample (CRESTOR).

MATERIALS AND METHOD:

Rosuvastatin calcium was obtained as gift sample from MSN laboratories, Hyderabad. Crospovidone and Pregelatinized Starch were obtained from Amit Cellulose Products. Pune.

Microcrystalline cellulose pH 101 grade was obtained from JRS Pharma. Sodium bicarbonate, Sodium alginate, Tri sodium citrate Meglumine, OpaDry Orange and Magnesium stearate were obtained from S.D. Fine Chemicals. Pvt Ltd, Mumbai, India. All chemicals and solvents used were of analytical grade

Drug excipient Compatability studies [9]

Identification of pure drug:

The IR spectrum of pure drug was found to be similar to that of the standard spectrum of Rosuvastatin Calcium. The spectrum of the Rosuvastatin shows the following functional groups at their frequencies.

Method: The potassium bromide disc method was employed. The powdered sample was intimately mixed with dry powdered potassium bromide. This mixture was then compressed into transparent disc under high pressure using special dies. This disc was placed in IR spectrometer and spectrums were recorded.

Preformulation studies.

Preformulation testing is an investigation of physical and chemical properties of drug substance and when combined with other excipients. It is the first step in the rationale development of dosage forms. Preformulation studies on active pharmaceuticals, inactive excipients and their Combinations were done for following purposes:

To finalize the specifications of active pharmaceutical ingredient. To study the compatibility between active and inactive pharmaceutical ingredients used in the formulation development.

Physical characterization [10]**:**

a)Organoleptic evaluation:

These are preliminary characteristics of any substance which is useful in identification of specific substance. Following physical properties of the API such as colour, odour was studied.

b) Loss on drying:

1 gm of Rosuvastatin calcium was accurately weighed and the powder was placed in the moisture balance and the moisture content was calculated. This is employed in BP, EP and USP. Loss in weight of the sample is due to water and small amount of some volatile substances evaporation. This apparatus combines both drying process and weight recording.

c) Solubility studies:

The solubility studies of drug were carried out using Rotary shaking method, which includes 24 hrs rotary shaking at 200 rpm by the addition of excess amount of drug till saturation was observed. The samples were filtered and required dilutions were prepared and analyzed.

A semi quantitative determination of the solubility was made by adding solvent in small incremental amount to a test tube containing fixed quantity of solute or vice versa. After each addition, the system is vigorously shaken and examined visually for any undissolved solute particles. The solubility is expressed in terms of ratio of solute and solvent.

d) Flow Properties determination [11]:

Bulk density:

Bulk density of the Rosuvastatin calcium was determined by pouring 20-30 gm of powder into 100ml measuring cylinder via glass funnel and the weight and volume were measured. It was calculated by using following formula. Bulk density was expressed in gm/cc.

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

Tapped density:

It was determined by using Electro lab tap density tester. It consists of a graduated cylinder mounted on a mechanical tapping device. An accurately weighed API powder sample was carefully added to the cylinder with the help of funnel and the initial volume was noted. Then sample was tapped(500,750 and 1250 tapping) until no further reduction in volume is noted or the percentage difference is not more than 2%.Final volume was noted and tap density was calculated by using the following formula.

Tapped density = weight of the sample in gm/Tapped volume

Compressibility Index (CI):

Carr's index is determined by using bulk density and tap density values.

It is calculated using following formula

$$CI = TD-BD / BD \times 100$$

Where TD= tap density, BD = bulk density.

Hausner's ratio:

It is the ratio of tap density to bulk density.

$$\text{Hausner's ratio} = TD/BD$$

Both CI and Hausner's ratio are useful for predicting powder flow characteristics.

Angle of repose:

It is used to characterize the flow property of solid powders. It is related to inter particulate friction or resistance to movement between particles. For this, a funnel was fixed at a height of 5-6 cm over a platform and powder is passed slowly along the wall of the funnel till cone shape of powder is formed. Then calculate angle of repose by using following formula after measuring height and radius of the powder cone.

$$\text{Tan } \Theta = h/r$$

Where h = height, r = radius, Θ= angle of repose.

Formulation of Rosuvastatin Calcium immediate release tablets:

The following formulations (T-1 to T-7) are prepared by direct compression process using different alkalizer.

Procedure:

1. Rosuvastatin calcium and other ingredients were weighed accurately and dispensed.
2. Weighed quantities of diluents, alkalizer and disintegrant are sifted through mesh # 40.
3. Accurately weighed quantity of the drug was sifted separately through mesh no # 40.
4. The sifted drug and the above sifted excipients were mixed geometrically and thoroughly for 10 minutes.
5. Weighed quantity of magnesium stearate was sifted through mesh # 60.
6. The powder mixture was lubricated with sifted magnesium stearate for 5 minutes and the immediate release tablets were compressed by using 12.7×7.5 mm round shaped punches.
7. The compressed tablets are coated with opadry orange after preparing coating solution up to a weight gain of 2.5% w/w of the core tablet weight.

Direct compression process is considered as simplest and most cost effective method for manufacturing of tablets and hence this method was selected for the development of Rosuvastatin calcium 20 mg tablets..

The following formulations (T-8 to T-12) were prepared by wet granulation process using Meglumine as alkalizer.

Procedure:

1. Rosuvastatin calcium and other ingredients were weighed accurately and dispensed.
2. Weighed quantity of alkalizer and other diluents were sifted through mesh # 40.
3. Weighed quantity of drug was sifted using mesh # 40 and the above sifted materials are mixed geometrically with the drug.
4. The powder mixture was kept under dry mixing in rapid mixer granulator for 15 min at an impeller speed of 150 rpm.
5. Granulating fluid was prepared by dissolving weighed quantity of poly vinyl Pyrrolidone k-30 in iso propyl alcohol slowly to form a clear lump solution.
6. To the powder mixture in granulator, the granulating fluid was added slowly in a time of 105 sec

7. The chopper was run for 30 sec and the wet mass was allowed to dry for 25 min until LOD of less than 2 is obtained.
8. The dried granules were sifted through mesh #25 and blend the granules for 10 min.
9. Weighed quantity of magnesium stearate was sifted through mesh # 60 and added to the above granules and lubricated for 5 min.
10. Compression was performed using12.7×7.5 mm round shaped punches .
11. The compressed tablets were coated with Opadry orange solution until a weight gain of 2.5 % w/w of the core tablet was obtained.

Tablet coating solution preparation:

Weighed quantity of purified water was taken in a beaker and weighed quantity of opadry orange was added to water while stirring and continue stirring for 45 min. Core tablets were transferred to coating pan and warmed while jogging the pan until the tablet bed temperature reaches approximately 50±0.5°c.Coating suspension was sprayed and recorded the weight gain of the tablets. Coating was continued until the average weight gain is 2.5% w/w of the core tablet weight.

EVALUATION OF TABLETS:

Hardness [12]:

Tablet hardness is defined as the force required to break a tablet in a diametric compression test. It was determined by using Monsanto hardness tester, which consists of barrel with a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet, and a zero reading is taken. The upper plunger is then forced against a spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force.

Thickness[12]:

Thickness of a tablet is measured by Vernier callipers scale. It is related to tablet hardness and is an initial control parameter. It should be controlled within ±5%.Inaddition it must be controlled to facilitate packaging.

Friability[13]:

Initially 20 tablets were weighed and placed in friabilator and rotated at 25 rpm for 4 min. The difference in weight was noted and it was expressed as percentage. Friability is calculated using the following formula,

$$\% \text{ Friability} = W_1 - W_2 / W_1 \times 100$$

Where W_1 =weight of the tablets before test ,W_2 =weight of the tablets after test.

Weight variation[12]:

All tablets of a batch should be uniform in weight. If any weight variation occurs, it should fall within the prescribed limits.20 tablets were randomly selected and weighed collectively and individually. Then from collective weight, average weight was calculated and each tablet weight was compared with average weight to determine whether it was within the limits or not. Not more than two of the individual weights deviated from the average weight by more than ±5% for 300 mg tablets and none by more than double the percentage.

Disintegration time[13]:

To test disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1- L beaker of water maintained at 37°c±2°c and operated at a frequency of 28-32 cycles per minute and the disintegration time of tablet should be recorded. If one or more tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met until 16 out of 18 tablets tested were disintegrated.

***In vitro* Dissolution test [9]:**

Dissolution was performed by using HPLC.

Dissolution Parameters:

Apparatus**:** USP Type Π (Paddle)

Speed: 50 rpm

Volume: 900 ml

Medium: 0.05M Sodium Citrate buffer, pH 6.6±0.05

Temperature: 37°c ± 0.5°c

Sampling points: 10, 20, 30 and 45 minutes.

Chromatographic conditions:

Column: Phenomenex Luna C18 250×4.6 mm, 5µ or equivalent.

Flow rate: 1.0 ml/min.

Wavelength: 244 nm

Injection volume: 20µL

Column temperature: 30°c

Run time: 10 min.

Note: After analysis, wash the column with water for at least 60 minutes followed by water and acetonitrile (30:70% v/v).The percentage of drug released was calculated.

Drug content uniformity[13]:

Drug content was performed by using HPLC.

Chromatographic Conditions:-

Column - Phenomenex Luna C18, 250 x 4.6mm, 5µ or equivalent

Flow rate - 1ml/min

Wavelength - 242 nm

Injection volume - 20 µl

Column temperature - 30°C

Run time - 10 min

Note:- After analysis, wash the column with water for at least 60min followed by water and Acetonitrile (30:70%v/v).

For Tablets Assay

Weigh and powder NLT 10 tablets. Accurately weigh and transfer Rosuvastatin Calcium 80mg equivalent powder into a 200ml volumetric flask, to this add 120ml of diluents and sonicate for NLT 30min with occasional shaking (maintain the sonicator bath temperature b/w 20 -25°C). Dilute to volume with diluents and mix, filter through 0.45µ membrane filter and discard first few ml of the filtrate. Transfer 3ml of above solution into 25ml volumetric flask, dilute to volume with diluents and mix. The percentage of drug content was calculated.

Drug release kinetic studies.

To examine the release mechanism of Rosuvastatin calcium from the prepared immediate release tablets, the results were analyzed according to the following equation

$$M_t / M = k.t^n$$

$$Mt/M=k.t^n$$

Where M_t / M is the fractional drug released at time t, k is a kinetic constant incorporating structural and geometrical characteristics of the drug/polymer system and n is the diffusional exponent that characterizes the mechanism of drug release. It is known that for non-swelling tablets, the drug release can generally be expressed by the Fickian diffusion mechanism, for which n = 0.5, whereas for most erodible matrices, a zero-order release rate kinetics is followed, for which n = 1. For non-Fickian release, the n value falls between 0.5 and 1.0 [0.5 <n< 1.0]; whereas in the case super case II transport n> 1.

To analyze the mechanism for the release and release kinetic of the dosage form, the data obtained was fitted in to Zero order, First order, Higuchi matrix and Peppas model.

Zero order kinetics:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can

be represented by the following equation-

$$Q_t = Q_0 + K_0 t$$

Where Q_t = amount of drug dissolved in time t,

Q_0 =initial amount of drug in the solution and

K_0 zero order release constant

First order kinetics:

To study the first order release rate kinetics the data were fitted to following equation.

$$\log Q_t = \log Q_0 + K_1 t/ 2.303$$

Where Q_t = is the amount of drug release in time t,

Q_0 = is the initial amount of drug in the solution and

K_1 is the first order release constant.

Higuchi model:

Higuchi developed several theoretical models to study the release of water soluble and low soluble drugs incorporated in semisolids or solid matrices. Mathematical expressions were obtained for drug particle dispersed in uniform matrix behaving as the diffusion media, and the equation is

$$Q_t = K_H. T 1/2$$

Where Q_t = amount of drug release in time t,

K_H = Higuchi dissolution constant.

Krosmeyer and Peppas release model:

To study this model the release rate data are data fitted to the following equation

$$M_t/ M_\infty = K.t_n$$

Where M t/ M∞ is the fraction of drug release,

K is the release constant,

t is the release time and

n is Diffusional exponent for the drug release that is dependent on the shape of matrix dosage form.

Stability studies of the optimized formulation [14]:

This includes storage at both normal and accelerated temperature conditions, with the necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated. Stability studies was conducted according to ICH guidelines. Optimized formulation was charged for 3 months at accelerated and intermediate stability conditions i.e., at 40^0C/75% RH and 30°c/65%RH. The samples were

compared with control samples for this month and assay, physical parameters were compared.

RESULTS AND DISSCUSION:

API Characteristics:

The results were found to be as per specifications and within the limit. shown in Table 3.

Table 3. Preformulation Studies of API

S.no.	Characteristics	Results
1	Organoleptic evaluation	Off white to white powder
2	Melting point	122°c
3	Loss on drying	<5.0%

Solubility data

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 are shown in Table 4.

Table 4. Solubility Data of Rosuvastatin Calcium in Various Solvents.

Buffer	Solvent solubility (mg/ml)	Final pH
pH 1.2 Hydrochloric acid (0.1N)	0.5±0.0	1.2
pH 1.2 Hydrochloric acid Buffer (USP)	0.5±0.0	1.2
pH 3.6 Acid Phthalate Buffer (USP)	1.6±0.1	4.1
pH 4.0 Acid Phthalate Buffer (USP)	2.2±0.2	4.5
pH 4.6 Neutralized Phthalate Buffer (USP)	3.7±0.2	5.0
pH 5.6 Neutralized Phthalate 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
Deionised Water (USP)	7.8±0.1	7.0

From the above results, it was concluded that API Rosuvastatin calcium has poor flow property. The results are shown in Table 5.

Table 5. Flow Properties of API.

Flow property	Result
Bulk density(gm/ml)	0.542 gm/ml
Tap density(gm/ml)	0.786 gm/ml
Compressibility index (%)	30.95%
Hausner's ratio	1.448

Flow properties:

Particle Size Distribution of drug:

The results indicated that the distribution of particles in 3µ range was 10%, distribution of particles in 23 µ range was 50% & distribution of particles in 98µ range was 90%. Lubricated blend parameters of various formulations prepared i.e. bulk density lied in between 0.78 & 0.70.

The tapped densities lied in between 0.68 & 0.75. Hausner's ratio lied between 1.30 & 1.42. The compressibility index lied in between 12.40 & 14.54. The results are shown in Table 6.

Table 6. Particle Size Distribution of Rosuvastatin Calcium

Parameter	Angle of repose(^{0})	Bulk density(mg/ml)	Tapped density(mg/ml)	Hausner ratio	Compressibility Index(%)
T1	29.43	0.76	0.72	1.42	14.54
T2	27.46	0.74	0.75	1.41	14.05
T3	28.31	0.71	0.82	1.39	13.82
T4	27.29	0.72	0.83	1.41	13.63
T5	29.14	0.70	0.75	1.38	13.74
T6	28.54	0.78	0.69	1.38	13.89
T7	27.49	0.73	0.68	1.37	13.88
T8	24.56	0.75	0.71	1.38	13.68
T9	25.45	0.73	0.70	1.35	13.45
T10	24.23	0.77	0.70	1.32	13.24
T11	23.12	0.71	0.69	1.31	12.85
T12	23.45	0.70	0.68	1.30	12.40

Drug –excipient Compatability studies:

The drug excipient Compatability was studied by comparing the IR spectra of Rosuvastatin calcium & the blend of optimized formulation. The results are shown in Table 7 & Figure 1-2.

Table 7. Compatibility studies

Cm^{-1}	Group
3364	O-H Stretching
3320	RCO-OH Stretching
1338	S=O Asymmetric
1863	C=N/C=O Stretching
1380	C-N Stretching
2935	AR-CH

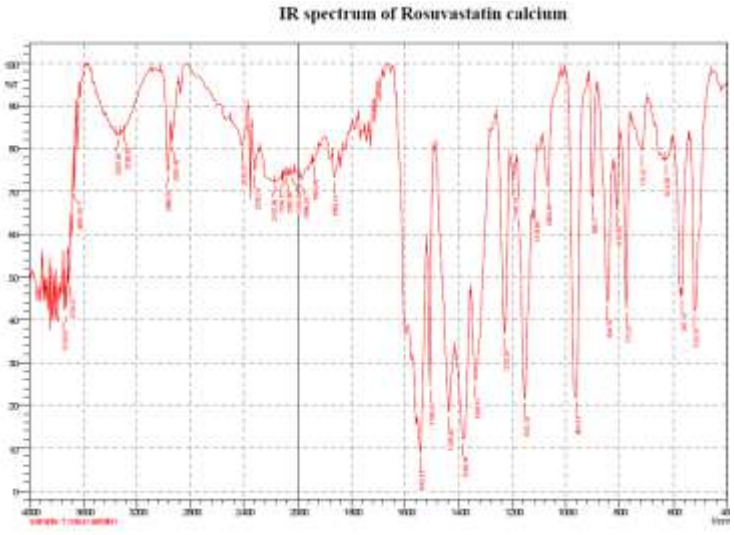

Figure 1. I.R Spectra of Rosuvastatin Calcium.

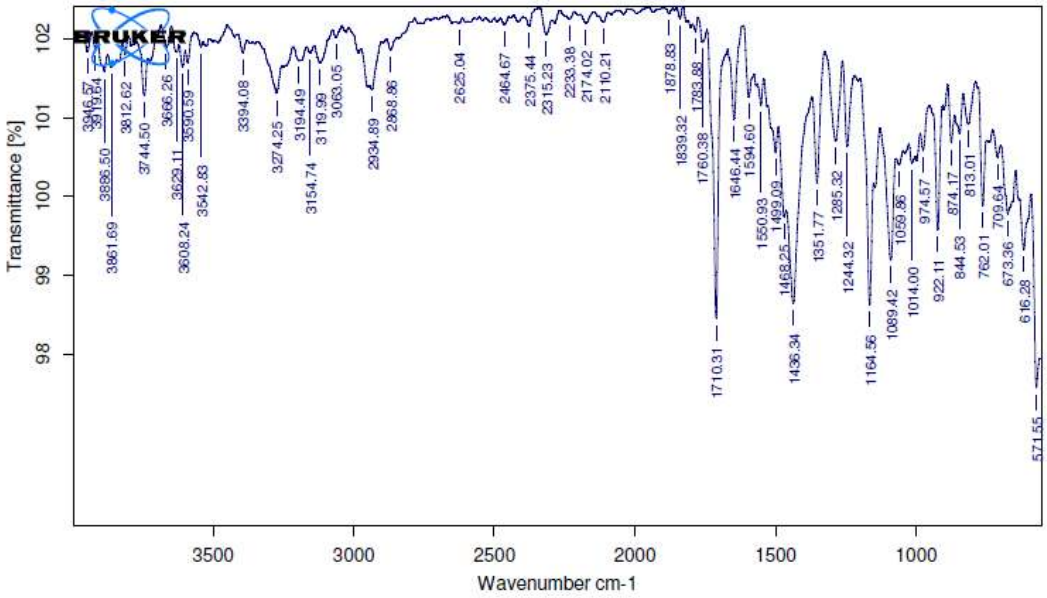

Figure 2. I.R Spectra of Blend Optimized Formulation.

From the spectra of pure drug Rosuvastatin calcium and the combination of drug with polymers, it was observed that all the characteristic peaks of Rosuvastatin calcium were present in the combination spectrum, thus indicating Compatability of the drug and polymer.IR spectra of the pure drug and in combination with the polymer are shown.

From the above Compatability results, it was clear that Rosuvastatin calcium is compatible with all excipients tested above.

Evaluation parameters:

From the formulations T1-T7, The average thickness of the tablet was found to be in the range of 4.3±0.15 (mm), the tablet hardness was found to be 8.3±0.5(kp), the average weight variation of the prepared tablets was found to be 300±5mg, the friability and disintegration was found to be within the specifications. From the above data, it was observed that formulated tablets are lying within the weight variation limits and are possessing sufficient hardness and thickness and exhibiting little variation in disintegration time results with that of innovator.

From the formulations T8-T12, the average thickness of the tablet was found to be in the range of 4.28±0.12(mm), the tablet hardness was found to be 8.4±0.7(kp), the average weight variation of the prepared tablets was found to be 298±5mg, the friability and disintegration was found to be within the specifications

From the above results, it was derived that, the formulated tablets were possessing sufficient hardness and thickness are within the weight variation limits. The results are shown in Table 8 & 9.

Table 8. Evaluation Parameters of Formulations by Direct Compression (T-1 to T-7)

Formulation	Thickness (mm) (±SD)	Hardness (kp)(± SD)	Friability (%)(± SD)	Weight variation(mg)	Disintegration time(min)
Pharmacopeia limits	-	-	Not more than 1%	±5 %	Within10 minutes
T-1	4.45±0.15	8±0.5	0.38	301±3	1±1
T-2	4.35±0.10	8.4±0.4	0.30	302±3	0-1
T-3	4.40±0.10	8±0.6	0.34	300±4	0-1
T-4	4.42±0.08	8.3±0.5	0.45	298±5	1±2
T-5	4.02±0.18	8.2±0.6	0.39	296±6	0-1
T-6	4.42±0.18	8.3±0.7	0.32	301±4	1±2
T-7	4.15±0.15	8.4±0.6	0.46	299±5	2±1

n=3±S.D.

Table 9. Evaluation Parameters for the Formulations (T-8 to T-12)

Formulation	Thickness (mm)(±SD)	Hardness (kp)(± SD)	Friability (%)(± SD)	Weight variation (mg)	Disintegration time(min)
Pharmacopeia limits	-	-	Not more than 1%	±5 %	Within10 minutes
T-8	4.26 ±0.14	8.6 ±0.6	0.32	298 ±5	3 ±1
T-9	4.38 ±0.12	8.4 ±0.6	0.34	301 ±4	2 ±1
T-10	4.28 ±0.12	8.6 ±0.6	0.36	300 ±5	3 ±2
T-11	4.30 ±0.10	8.6 ±0.8	0.45	297 ±4	2 ±2
T-12	4.18 ±0.12	8.2 ±0.6	0.44	298 ±5	1±2

n=3±S.D.

Drug content uniformity.

The drug content results of table indicated the drug Rosuvastatin calcium formulations T1-T12 complies with the specification. The results are shown in Table 10.

Table 10. Drug content uniformity of formulations (T1-T12)

Formulation	%Drug content
T1	91±0.8
T2	96±0.2
T3	96±0.9
T4	99.3±0.8
T5	99.4±0.5
T6	100.2±1
T7	100±0.6
T8	101.3±1.1
T9	99.6±0.7
T10	99.4±0.5
T11	102.6±1
T12	102±0.9
Innovator	99±1

Dissolution Studies:

From the dissolution profile of the T1-T7 formulations, the cumulative percentage drug release were found to be slower in comparison to the innovator formulation. The drug release were found to be on the lower side in the initial time points. At the initial time point the drug release of the innovator was found to be 84.2 where as the T1-T7 formulations showed 75.4%,72.3%, 78.4%, 79.1%, 81.5%, 78.4% and 82.2%, respectively. At the final time point the drug release of the innovator was found to be 92.1 where as the T1-T7 formulations showed 89.4%,90.1%, 88.3%, 90.2%, 93.4%, 90.3% and 94.1%, respectively**.**

From the above data, it was derived that both Innovator and T-5 showed similar dissolution profile and in T-5, Meglumine was used as alkalizer. So, further batches from T-7 are formulated with Meglumine and this batch T-7 also similar dissolution profile in pH-6.6 sodium citrate buffer. Since, Rosuvastatin calcium is acid labile, its dissolution profile should be checked in 0.1 N HCL.

Dissolution profile in 0.1 N HCL

As Rosuvastatin calcium is acid labile drug there is a need for an alkalizer in the formulation. The presence of meglumine in the T-5 and T-7 formulations make them stable in the acidic environment i.e., in 0.1 N HCL, where as the remaining formulation showed very poor release. From the above data, it was concluded that T-5&T-7**(**prepared by direct compression) showed higher release rates than Innovator. So, in order to match the dissolution profiles to Innovator, further batches are prepared by wet granulation where release rate can be reduced somewhat.

As, Rosuvastatin calcium is acid labile, the dissolution profiles of further batches i.e., from T-8 to T-12 were checked in 0.1 N HCL and also simultaneously checked in pH-6.6 sodium citrate buffer.

The dissolution profile of the formulations T-8 to T-12 in 0.1N HCL show that all the formulations are stable in the acidic medium due to the presence of an alkalizer meglumine and the dissolution profile was comparable with that of the innovator formulation. When the dissolution compared to innovator data the formulation T12 is near to innovator and it is a best formulation over all.

The dissolution profile of T8-T12 compared to innovator the release rate of T12 near to innovator as compared to other formulations this shows the T12 is best optimized formulation. The results are shown in Figure 03-08.

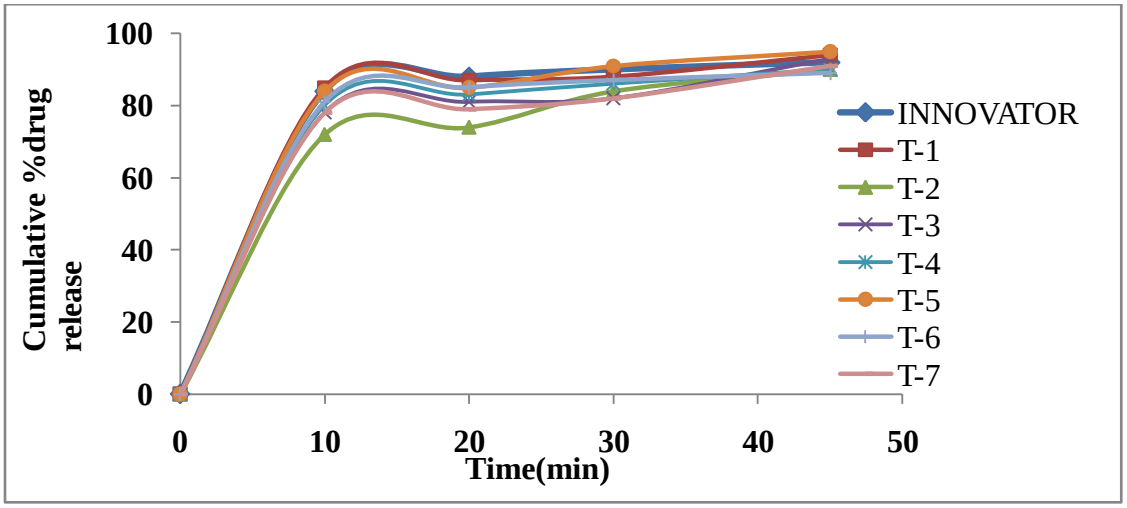

Figure 3. Comparative Dissolution Profiles of Formulations by Direct Compression (T-1 to T-7 with INNOVATOR) in pH-6.6 Sodium Citrate Buffer.

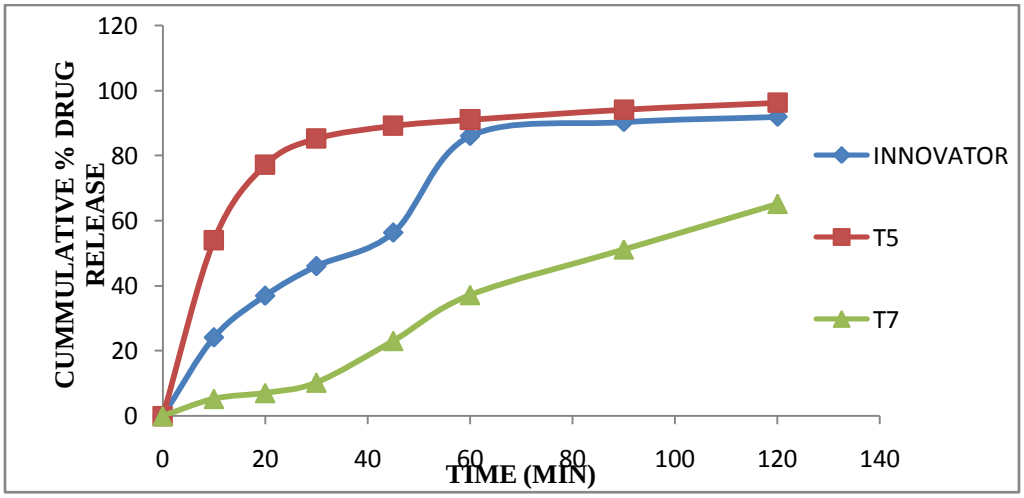

Figure 4. Comparative Dissolution Profiles of Formulations by Direct Compression (T-5,T-7 with INNOVATOR) in 0.1 N HCL.

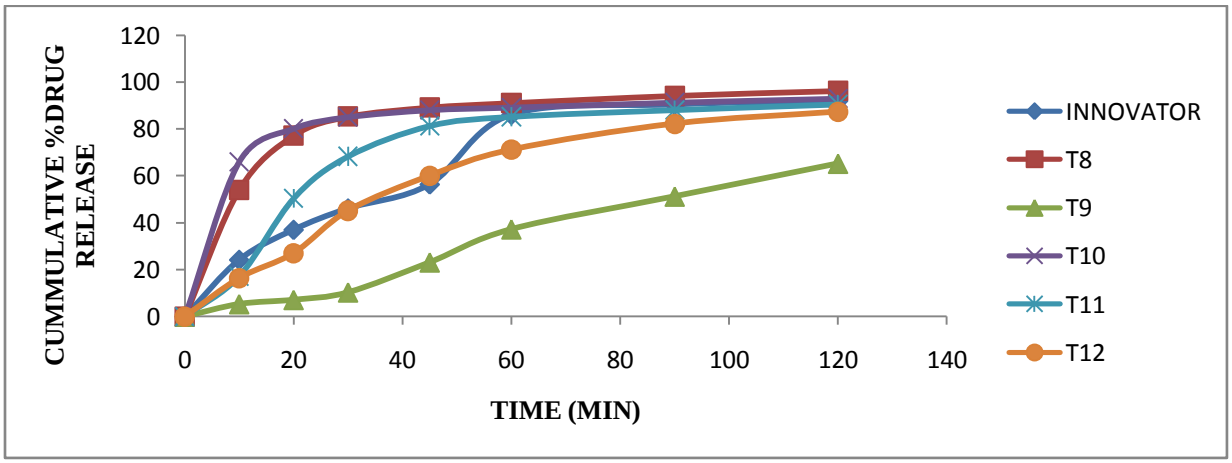

Figure 5. Comparative Dissolution Profiles of Formulations by Wet Granulation (T-8 to T-12 with INNOVATOR) in 0.1 N HCL.

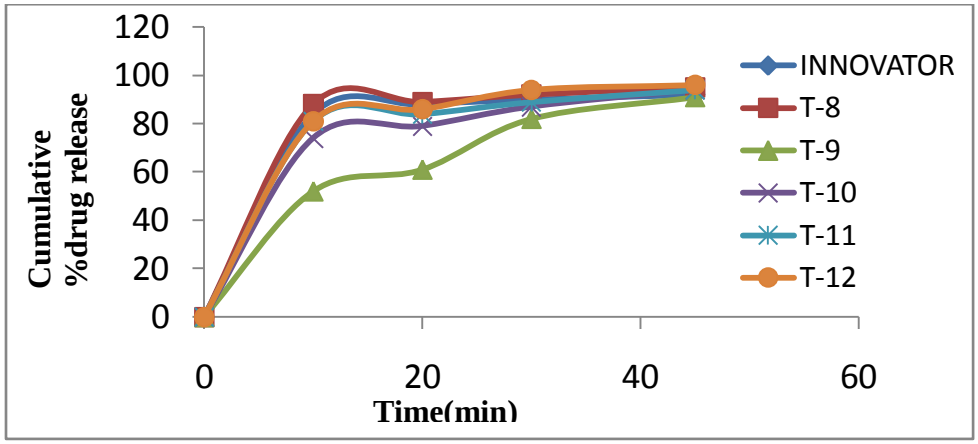

Figure 6. Comparative Dissolution Profiles of Formulations by Wet Granulation Method (T-8 to T-12 with INNOVATOR) in pH-6.6 Sodium Citrate Buffer.

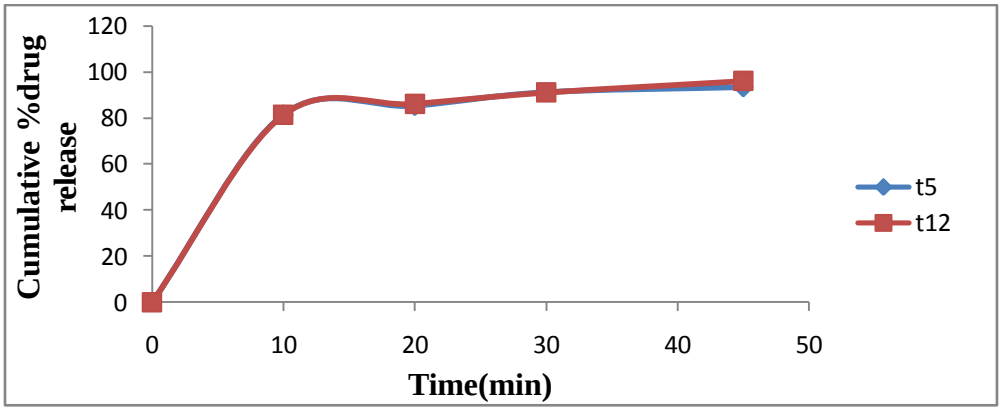

Figure 7. Comparative Dissolution Profiles of T5 and T12 in pH 6.6 Sodium Citrate Buffer.

From above graph the dissolution profile between T5 and T12 shows T12 have more drug release rate compare to T5. This shows T12 is best optimized formulation.

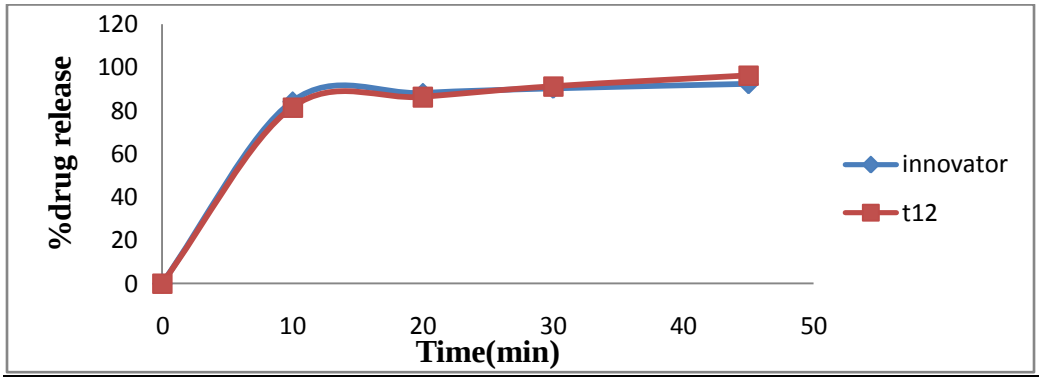

Figure 8. Comparative Dissolution Profiles of Innovator and T12 in pH 6.6 sodium Citrate Buffer.

From above graph the dissolution profile between innovator and T12 shows nearby similar drug release rate.

Stability study:

The stability studies on Rosuvastatin Calcium Tablets 20mg in HDPE container at 40^0C / 75 % RH for 3 months were conducted as per ICH protocol. After the specified time period, the samples were unloaded from the stability chambers and were tested for any physical or chemical changes. Also the tests for dissolution and assay were conducted to assess the stability of product. The results are shown in Table 11.

Table 11. Stability Studies of best formulation F12.

Conditions	Parameter	Initial data	Data after 3 month
Room temperature	Hardness(kp)	4.3	4.3
Room temperature	Friability	0.3	0.27
Room temperature	Assay(%)	99.8	98.7
Room temperature	Invitro drug release(%)	96.1	95.9
Intermediate	Hardness(kp)	4.3	4.3
Intermediate	Friability(%)	0.3	0.27
Intermediate	Assay(%)	99.8	98.5
Intermediate	Invitro drug release(%)	96.1	95.5
Accelerated	Hardness(kp)	4.3	4.1
Accelerated	Friability(%)	0.3	0.27
Accelerated	Assay(%)	99.8	98.1
Accelerated	Invitro drug release(%)	96.1	95.2

Table 12. Release kinetics of Formulations T1 to T12

S. NO.	Formulation Code	Zero – Order (R^2)	First-Order (R^2)	Higuchi (R^2)	Korsemeyer-Peppas R^2	'n' Value
1	T1	0.506	0.735	0.784	.947	0.09
2	T2	0.560	0.825	0.827	0.932	0.12
3	T3	0.457	0.628	0.744	0.926	0.06
4	T4	0.474	0.683	0.755	0.810	0.06
5	T5	0.878	0.841	0.865	0.992	0.07
6	T6	0.559	0.841	0.817	0.748	0.11
7	T7	0.862	0.818	0.833	0.984	0.09
8	T8	0.890	0.605	0.775	0.912	0.03
9	T9	0.848	0.983	0.984	0.950	0.39
10	T10	0.851	0.930	0.894	0.958	0.16
11	T11	0.875	0.843	0.842	0.940	0.09
12	T12	0.892	0.969	0.913	0.988	0.20

Drug release kinetic studies.

The I*n-vitro* drug release data of all Rosuvastatin calcium immediate release tablets were subjected to goodness of fit test by linear regression analysis according to Zero order equation, 1st order equation, Higuchi's equation and Krosmeyer-Peppas equation to ascertain the mechanism of drug release. The results of linear regression analysis including regression coefficient are presented in Table 12.Among the regression correlation co-efficient (R^2) values

of first order equation was found to be higher, similarly among the Higuchi's equation and Krosmeyer-Peppas equation, the (R^2) values of Krosmeyer-Peppas equation was found to be higher. Hence the drug release followed the first order release kinetics and Peppas model indicates the mechanism of drug release i.e. Fickian diffusion.

CONCLUSION :

An optimized formulation of Rosuvastatin calcium immediate release tablets was found and was prepared by wet granulation process using Meglumine as alkalizer. The best *in-vitro* drug release observed in formulation T12 was found to be 99.5% which contain the drug Rosuvastatin calcium and Crospovidone as superdisintegrant agent with other excipients. Hence, the drug release followed the first order release kinetics and Peppas model indicates the mechanism of drug release i.e. Fickian diffusion.

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