Singapore Journal of Pharmaceutical Research

Journal homepage: www.mcmed.us/journal/sjpr

FORMULATION AND EVALUATION OF ROSUVASTATIN IMMEDIATE RELEASE TABLETS 20MG

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Article Info

Received 25/10/2013
Revised 18/11/2013
Accepted 25/11/2013

Key words:
Hyperlipidemia, Rosuvastatin Calcium, Immediate release Formulation, Film coated.

ABSTRACT

The objective of the present study was to develop the immediate release film coated formulation of Rosuvastatin Calcium to improve the distribution of Rosuvastatin calcium, improve the product stability. In the present study immediate release formulation of Rosuvastatin Calcium was prepared by wet granulation method and by using fluidized bed coating method. Different formulations were made by using various concentrations of superdisintegrant Polyplasdone XL-10 and granulating fluids like water, iso propyl alcohol (IPA) and Butyl hydoxy tuolene (BHT). Opadry pink 03k540019 was used as film coating mateial .The Prepared formulations were evaluated for the physical characteristics, *in vitro*dissolution and stability at 40°C/ 75% RH for three months. The formuation (F8) of film coated rosuvastatin calcium tablets showed best release profile.

INTRODUCTION

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They are the most widely preferred form of medication both by pharmaceutical manufacturer as well as physicians and patients. They offer safe and convenient ways of active pharmaceutical ingredients (API) administration with excellent physicochemical stability in comparison to some other dosage forms, and also provide means of accurate dosing. They can be mass produced with robust quality controls and offer different branding possibilities by means of colored film coating, different shapes, sizes or logos [1, 2]

Hyperlipidemia is a common chronic lipoidal disorder that is characterized by unbalanced lipoprotein levels. Hyperlipidemia is an excess of fatty substances called lipids, largely cholesterol and triglycerides, in the blood. It is also called hyperlipoproteinemia because these fatty substances travel in the blood attached to proteins. This is the only way that these fatty substances can remain dissolved while in circulation. Hyperlipidemia, in general, can be divided into two subcategories: hypercholesterolemia, in which there is a high level of cholesterol hypertriglyceridemia, in which there is a high level of triglycerides, the most common form of fat. Hydroxymethyl Hydroxy methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) currently form the mainstay of lipid-regulating therapy, and are the most effective agents for reducing serum cholesterol concentrations and cardiovascular mortality **[**3-5].

Rosuvastatin calcium is a new and highly effective inhibitor of HMG-CoA reductase that has completed Phase-III clinical development for the treatment of patients with dyslipidaemia. In clinical trials, Rosuvastatin (1–80mg) produced reductions in LDL-C, total cholesterol (TC), and triglycerides (TG), and increases in high density lipoprotein cholesterol (HDL-C) [6-10]

Usually superdisintegrants are added to a drug formulation to facilitate the break-up or disintegration of tablet into smaller particles that can dissolve more rapidly

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than in absence of disintegrants [11]. Immediate release tablets are designed to disintegrate and release their medicaments with no special rate-controlling features, such as special coatings and other techniques [12]. Immediate release tablets are expected to achieve fast tablet disintegration which would dissolve for absorption into the bloodstream [13] Conventional immediate release drug delivery is desirable for drugs having long biological half life, high bioavailability, lower clearance and lower elimination half life. But main criterion for immediate release dosage form is poor solubility of the drug and need the immediate action of drug to treat any unwanted defect or disease. Coated Rosuvastatin calcium expected to reduce the frequent exposure of dose to upper GIT and thus facilitate in proper distribution to liver rather than skeletal muscles leading to improved patient compliance, maintain therapeutic action [14]

EXPERIMENTAL SECTION

Materials

Rosuvastatin (Derived from MSN Laboratories Ltd) Microcrystalline cellulose-pH-101 & pH-102 (FMC Biopolymer), Maize starch, Tri calcium phosphate, Meglumine, mannitol 60c, Iso propyl alcohol, Butylated Hydroxy Toulene, Starch 1500M and Mannitol SD-200 were derived from MSN Laboratories Ltd. Lactose monohydrate obtained from Domo Friesland campina. Calcium carbonate obtained from Speciality Minerals, ziffardi. Polyplasdone XL-10 obtained from FMC Biopolymer. Magnesium stearate obtained from Synpro, sunshine organics pvt ltd, Opadry pink 03k540019 and Insta coat universal white were obtained from Colorcon Asia pvt.Ltd.All the other ingredients were of analytical grade.

Preparation of Rosuvastatin Calcium by Wet Granulation

The critical parameters to formulate an immediate release tablet are choice and optimization. All the ingredients were accurately weighed as per formula (Table 1&2) and dispensed in clean polythene covers. Rosuvastatin Calcium, MCC, Polyplasdone XL-10 were sifted through sieve no-40.Meglumine, magnesium stearate passed through sieve no-60. After sifting all the above ingredients were transferred into a big polythene cover and mixed for 5 min. Binder solution was prepared by mixing purified water and IPA in given ratio. The above blend was taken in a stainless steel container to which the earlier prepared binder solution was added slowly until a wet mass like substance was formed. The wet mass was passed through sieve no- 20 to get wet granules which were later dried in a tray drier at 38^0c -39^0c for 1 hour. The dried granules were again passed through sieve no- 20 and thoroughly mixed with polyplasdone xl-10 for 5 min in a poly bag and magnesium stearate for 5 min in a polybag.

Evaluation of prepared granules [15]

Angle of repose

The angle of repose of tablet blends was determined by the funnel method. The blends were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\mathbf{Tan\ \theta = h/r}$$

Where ‘h’ and ‘r’ are the height and radius of the powder cone, respectively.

Bulk density

Apparent bulk density was determined by pouring a weighed quantity of tablet blends into graduated cylinder and measuring the volume and weight.

Bulk Density = Mass of powder / Bulk Volume of the powder

Tapped bulk density

It was determined by placing a graduated cylinder, containing a known mass of drug-excipient blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals. The tapping was continued until no further change in volume was noted.

Tapped density = Weight of powder / Tapped volume of the powder

Carr’s index

Carr’s compressibility index CI (Carr, 1965) is defined as follows:

$$\mathbf{CI = \rho t - \rho a / \rho t = Va - Vt / Vt}$$

Where ρt and ρa – tapped and poured bulk density; And Vt and Va – tapped and poured bulk volume respectively.

Hausner’s ratio

A similar index has been defined by Hausner [16].

Hausner’s ratio = Tapped density / Poured Density

Procedure for Scale up of Rosuvastatin Tablets

Mixing and granulation was carried out in a Rapid Mixing Granulator. This blend is then subjected to compression on a Compression Machine (8 station) at 10 rpm to yield rosuvastatin calcium tablets.

Tablet Compression

F1 and F8 formulation blends were compressed using 9 mm concave punches as per company requirement.

Film coating of immediate release Rosuvastatin tablets

Preparation of Coating Solution

All the ingredients were accurately weighed as per formula (Table.No.3)and dispensed. Insta coat universal

white (or) Opadry pink is dissolved in water. The obtained solution is stirred for 45 min to get a homogenous solution. The initial checks on the tablets after film coating were carried out. The appearance, average weight, thickness of tablets, disintegration and drug release etc were also checked.

Evaluation of Tablets [17]

Thickness

The thicknesses of the tablets were determined using a Vernier caliper, 20 tablets from each batch were used and average values were calculated.

Uniformity of weight

Every individual tablet in a batch should be in uniform weight and weight variation in within permissible limits. The weights were determined to within ±1mg by using digital balance. Weight control is based on a sample of 20 tablets.

Percent drug content

For this at least 30 tablets were randomly selected. Out of 30 tablets 10 tablets were crushed into fine powder assayed individually after proper dilution at 242 nm using a UV spectrophotometer.

Hardness and friability

For each formulation, the hardness and friability of 20 tablets each were determined using the Pfizer hardness tester and Electro lab friabilator test apparatus, respectively.

Disintegration

The disintegration test is carried out using the disintegration tester which consists of a basket rack holding 6 plastic tubes, open at the top and bottom, the bottom of the tube is covered by a 10-mesh screen. The basket is immersed in a bath of suitable liquid held at 37oC, preferably in a 1L beaker.

***In-vitro* dissolution study**

The dissolution test was performed using USP dissolution testing apparatus 2 (paddle method);
Medium - Phosphate buffer (pH 6.8)
Volume- 900 ml
Temperature- 37ºC
RPM – 50
Time intervals- 0, 5, 10, 15 and 30 mins.
Volume of sample replaced- 5ml
Absorbance of these solutions was measured at the wavelength of 242nm by using UV-Visible spectro photometer.

Accelerated Stability Studies [18]

Rosuvastatin immediate release tablets were evaluated for accelerated stability studies and parameters like hardness, disintegration time, drug content and in vitro drug release were analyzed after storing them at 40 ± 2^0c / 75±5% RH for 3months.

RESULTS AND DISCUSSION

Preformulation studies

Drug excipient compatibility studies were performed by force degradation and Fourier transform infrared spectroscopy. Results obtained from (Figure 1&2) showed that drug and excipients were compatible with each other.

Evaluation of pre-compression parameters

Tablet blends were evaluated for micromeritic parameters. Table.No.5 showed that for all trial batches bulk density and tapped density for the tablet blend were in the range of 0.479 - 0.545 gm/ml. The angle of repose for the formulations was found to be in the range of 28.9-39.6°. Compressibility index was found within the range of 19.99-22.64% which is within the specified limit of fair to passable flow properties.

Physicochemical evaluation of tablets

Formulations trials from F1 to F10 (Table.No.6) had thickness with ±5% variation of standard value and hardness was found within the range 4-6 kg/cm^2. Friability was less than 1% which was acceptable. Average weight of all the tablets was around 300±7.5%. Disintegration time was within the range of 2 -3.5 min.All the formulations satisfied the official compendial requirements.

***In vitro* drug release studies**

In –vitro drug release studies (Table.No.7& Figure.No.3) revealed that 100% drug release was found in 30 min. it was found that formulation F8 have shown best results and comparable with the innovator. So, formulation (F8) was taken as optimized formulation.

Accelerated stability studies

Accelerated stability studies (Table 8&9, Fig 4) were carried out for a period of 3 months at 45°C/75% RH for F8 formulation. Stability studies for physical appearance, friability, hardness, disintegration time, assay and *in vitro* drug release were done at different time periods. It was found that there were no changes even after three months of stability study.

Table 1. Formulae for Preparation of Immediate Release Rosuvastatin Calcium Tablets

S.No	Ingredients	F1	F2	F3	F4	F5
1	Rosuvastatin Calcium	20.80	20.80	20.80	20.80	20.80
2	MCC p^H102	241.20	234.20	19.60	-	188.20
3	MCC p^H 101	-	-	-	91.80	-
4	Maize starch	-	-	-	-	60.00
5	Tricalcium phosphate	-	-	-	80.00	-
6	Meglumine	20.00	25.00	-	-	20.00
7	Lactose monohydrate	-	-	182.60	182.60	-
8	Calcium carbonate	-	-	60.00	-	-
9	Mannitol 60c	-	-	-	-	-
10	Polyplasdone xl-10	6.00	9.00	6.00	10.00	6.00
11	Purified water+IPA	70:30 Q.S	50:50 Q.S	50:50 Q.S	Q.S	70:30 Q.S
12	Purified water+BHT	-	-	-	Q.S+ 0.20	-
13	Starch 1500	-	-		-	-
14	Mannitol sd-200	-	-	-	-	50.00
15	Polyplasdone xl-10	9.00	9.00	9.00	10.00	3.00
16	Magnesium stearate	3.00	2.00	2.00	4.80	2.00
17	Total amount(mg)	300.00	300.00	300.00	300.00	300.00

Table 2. Formulae for Preparation of Immediate Release Rosuvastatin Calcium Tablets.

S.No	INGREDIENTS	F6	F7	F8	F9	F10
1	Rosuvastatin Calcium	20.80	20.80	20.80	20.80	20.80
2	MCCp^H102	198.20	-	80.00	-	80
3	MCC p^H 101		80.00		179.20	-
4	Maize starch	-	-	-	-	40
5	Tricalcium phosphate	-	-	-	-	10
6	Meglumine	20.00			5.00	-
7	Lactose monohydrate	-	108.20	88.20	-	20
8	Calcium carbonate	-	60.00	60.00	-	-
9	Mannitol 60c	-	-	-	60.00	60
10	Polyplasdone xl-10	6.00	6.00	6.00		10
11	Purified water+IPA	70:30 Q.S	Q.S	Q.S	Q.S	-
12	Purified water+BHT	-	-	-	-	-
13	Starch 1500		20.00	40.00	30.00	50
14	Mannitol sd-200	-	-	-	-	-
15	Polyplasdone xl-10	3.00	3.00	3.00	3.00	5.00
16	Magnesium stearate	2.00	2.00	2.00	2.00	5.00
17	Total amount(mg)	300.00	300.00	300.00	300.00	300.00

Table 3. Formulae for Preparation of Film Coating Solution for final formulae

S.No	INGREDIENTS	QUANTITY
1	Opadry pink (03k540019)	9.00
2	Purified water	Q.S

Table 4. Coating conditions

S.No	Parameters	Limits
1	Pan size	8 inch
2	Pan speed	35 to 40 rpm
3	Inlet air temperature	55 to 60°C
4	Exhaust air temperature	<40°C

5	Bed temperature	<40°C
6	Atomizing air pressure	3.0 to 4.0 kg/cm²
7	Spray gun nozzle diameter	1.0 mm
8	Peristalitic pump speed	001 rpm
9	Spray rate	6.0 ml to 8.0 ml/min

Table 5. Evaluation of Pre-Compression Parameters

Formulation code	Evaluation of precompression parameters					
	Bulk density (g/ml)	Tapped density (g/ml)	Porosity (%)	Carr's index (%)	Hausner's ratio	Angle of repose(⁰)
F1	0.489	0.604	0.200	20.11	1.229	35.55
F2	0.488	0.600	0.201	19.19	1.222	33.43
F3	0.479	0.610	0.199	19.99	1.221	33.33
F4	0.482	0.607	0.207	20.12	1.122	39.61
F5	0.488	0.603	0.190	19.07	1.23	37.13
F6	0.481	0.604	0.204	20.36	1.25	32.16
F7	0.488	0.606	0.222	19.99	1.299	33.66
F8	0.545	0.704	0.225	16.25	1.194	29.14
F9	0.504	0.601	0.199	22.64	1.29	30.15
F10	0.500	0.606	0.190	21.20	1.999	28.99

Table 6. Evaluation of Post-Compression Parameter

Formulation	Evaluation of Post-Compression Parameters				
	Hardness of tablets* (kg/cm²)	Friability of tablets* (%)	Weight variation of tablets* (mg)	Thickness of tablets* (mm)	Disintegration n time (min)*
F1	5.51±*0.01*	0.23±0.05	300±2%	*5.12±0.02*	2.4±0.31
F2	4.54±*0.06*	0.21±0.06	300±2%	4.52±*0.05*	2.5±0.27
F3	4.12±*0.03*	0.20±0.05	300±2%	*4.23±0.01*	3.45±0.14
F4	4.35±*0.09*	0.17±0.04	300±2%	*6.13±0.03*	3.5±0.21
F5	5.42±*0.02*	0.19±0.03	300±2%	*4.0±0.06*	2.1±0.34
F6	4.58±*0.08*	0.20±0.08	300±2%	*4.4±0.08*	2.26±0.2
F7	4.31±*0.19*	0.23±0.05	300±2%	*4.2±0.01*	2.2±0.25
F8	4.47±*0.11*	0.21±0.06	300±2%	*5.5±0.02*	2.14±0.17
F9	4.49±*0.14*	0.20±0.05	300±2%	*5.3±0.04*	2.15±0.10
F10	5.4±*0.12*	0.20±0.05	300±2%	5.2±*0.03*	2.56±0.13

*** Average (n=3)**

Table 7. In-Vitro Drug Release Study of Various Formulations

	% DRUG RELEASED										
Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	Innovator
0	0	0	0	0	0	0	0	0	0	0	0
5	88.9	88.9	88.8	89.9	90.9	90.4	92.4	95.8	97.6	90.7	96.9
10	92.6	92.8	95.4	93.5	94.3	94.2	94.9	96.0	99.7	93.5	98
15	93.0	94.5	96.4	95.4	96.0	96.2	98.3	98.2	101.2	95.2	100.5
30	95.6	95.9	97.4	96.4	96.9	96.0	98.9	99.9	102.9	96.3	101.2

Table 8. Accelerated stability studies of optimized formulation (F8) 40±2 °C & 75±5%RH

S. No	Time period	Description (color)	Friability (%)	Hardness(kg/cm^2)	D.T(min)	Assay (%)
1	Initial	White to off-white	0.20±*0.05*	5.3±*0.02*	2.15±0.01	99.2
2	1st month	White to off-white	0.21±*0.04*	5.22±*0.05*	2.16±0.04	99.5
3	2th month	White to off-white	0.21±*0.05*	5.20±*0.03*	2.19±0.02	99.6
4	3rd month	White to off-white	0.23±*0.03*	5.17±*0.04*	2.20±0.01	99.8

***Average (n=3)**

Table 9. Dissolution profile of optimized batch (F8) and innovator after accelerated stability studies at 40±*2*°C & 75±*5*% RH

S. No	Time period	% drug release			
		Time (min)			
		5	10	15	30
1	Initial	95.2±*0.2*	96.1±*0.3*	98.8±*0.1*	99.4±*0.1*
2	1st month	97.1±*0.3*	98.9±*0.2*	*100.8±0.2*	*102.2±0.1*
3	2th month	96.8±*0.1*	98.2±*0.2*	*100.5±0.3*	*101.6±0.1*
4	3rdmonth	96.3±*0.1*	97.6±*0.3*	*99.7±0.1*	*100.8±0.3*

***Average (n=3)**

Fig 1. FTIR spectrum of Rosuvastatin pure drug

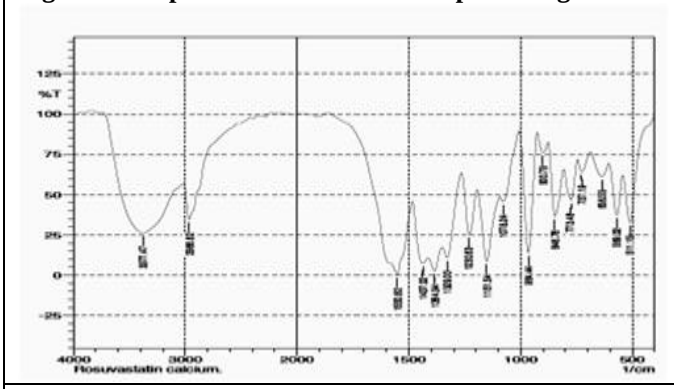


Fig 2. FTIR spectrum of optimised formula

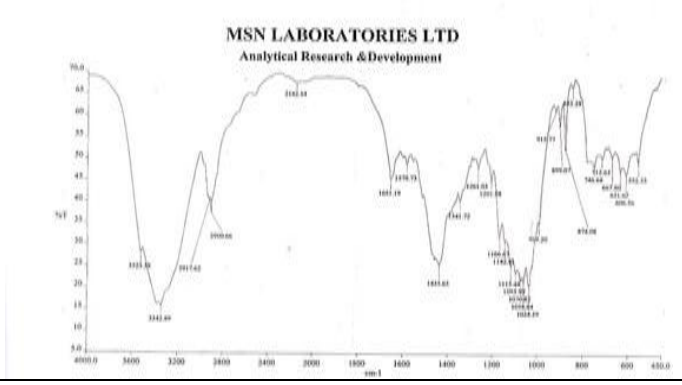


Fig 3. Dissolution profile graphs

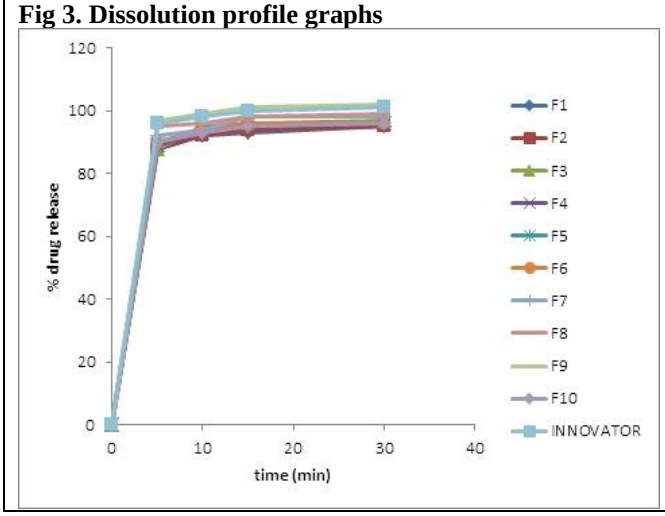
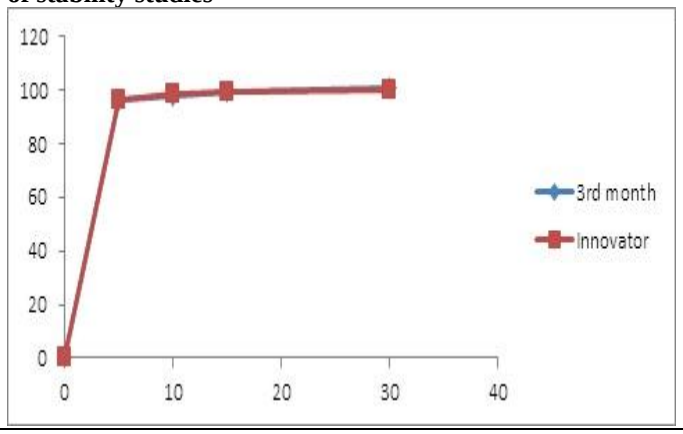


Fig 4. Graphical representation of dissolution profile of innovator versus optimized batch (F8) after three months of stability studies



CONCLUSION

From the above experimental results it can be concluded that film coated Rosuvastatin *calcium immediate release tablets (F8 formulation) can be prepared by wet granulation method using* different superdisintegrants in varying percentages.

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