Research Article

Formulation and Evaluation of Orally Disintegrating Tablets of Rosuvastatin

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ABSTRACT

Rosuvastatin is a dyslipidaemic agent, which acts by inhibition of HMG-CoA reductase enzyme used in the treatment of hyperlipidemia. The purpose of this investigation was to develop "orally disintegrating tablets of Rosuvastatin" by direct compression technique. Fourteen batches were prepared using various super disintegrants like sodium starch glycolate, croscaramellose sodium, LycoatRs720 and crospovidone in different concentrations. This Superdisintegrant addition method exhibits lowest disintegration time, hence it is ranked as the best among the methods. All the formulations were evaluated for weight variation, hardness, friability, *in-vitro* disintegration time, drug content, wetting time, *in-vitro* dissolution study. Among all the formulations F13 (containing 8% of super disintegrants i.e., crospovidone and sodium starch glycolate {1:1}) was considered to be the best formulation, which releases up to 97% drug in 5 minutes. A comparative study of *in-vitro* drug release was made with marketed product of Rosuvastatin which shows 93% drug release in one hour. From this study we can conclude that, formulated tablets of Rosuvastatin containing crospovidone and sodium starch glycolate are better and effective than conventional tablets to meet patient compliance.

Keywords: Croscaramellose sodium, Crospovidone, Disintegration time, LycoatRs720, Oral disintegrating tablet, Rosuvastatin, Superdisintegrant addition method, Sodium starch glycolate, Wetting time.

INTRODUCTION

Drug delivery systems (DDS) are a strategic tool for expanding markets/indications, extending product life cycles and generating opportunities. DDS makes a significant contribution to global pharmaceutical sales through market segmentation, and are moving rapidly.[1] 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.[2] But one important drawback of such dosage forms is dysphasia or difficulty in swallowing. This is seen to afflict nearly 35% of the general population.[3] To solve the above-mentioned problems, pharmaceutical technologists have put in their best efforts to develop a fast dissolving drug delivery, i.e. mouth dissolving tablet that disintegrates and dissolves rapidly in the saliva, within few seconds without need of drinking water or chewing.[4] Rosuvastatin is a dyslipidaemic agent, incompletely absorbed in the GI tract. Bioavailability of Rosuvastatin is about 20%. Oral disintegrating tablet avoids first pass effect and increases its bioavailability.[5]

MATERIALS AND METHODS

Materials

Rosuvastatin was a gift sample from Spectrum pharmaceuticals, Hyderabad, India. The super disintegrants were Crospovidone (SD Fine Chem Ltd. Mumbai), Sodium starch glycolate (SD Fine Chem Ltd, Mumbai), Croscarmellose sodium (Spectrum pharmaceuticals, Hyderabad), LycoatRs720 (Roquette pharma, France). Aspartame (Spectrum pharmaceuticals, Hyderabad), Microcrystalline cellulose gifted from Otto Chemicals, Mumbai, Magnesium stearate from Central Drug House (p) Limited, New Delhi, Aerosil from Sisco Research Laboratories, Mumbai, Citric acid from RFCL Limited, New Delhi.

Methods

Preparation of Orally Disintegrating Tablets[6-8]

Weigh all the ingredients accurately according to Table 1. Mix all the ingredients geometrically except Aerosil, Talc and Magnesium Stearate. Then lubricate the blend with Aerosil, Talc, Magnesium Stearate. The blend was compressed using rotary tablet machine-12 station with 8mm flat punch, B tooling. Each tablet contains 10mg Rosuvastatin and other pharmaceutical ingredients as in Table 1.

Scanning of drug buffer solution (P^H 6.8)[9]

Accurately weighed 10mg of Rosuvastatin was dissolved in 10 ml of Phosphate buffer solution (P^H 6.8) (Conc. 1000 µg/ml). From this solution 1ml was pipetted out into 10 ml volumetric flask and volume was made up to 10 ml with Phosphate buffer solution (P^H 6.8) (Conc. 100 µg/ml). From this solution 1ml was pipetted out into 10 ml volumetric flask and volume was made up to 10 ml with phosphate buffer solution (P^H 6.8) (Conc. 10 µg/ml). The solution containing 10 µg/ml of Rosuvastatin in Phosphate buffer solution (P^H 6.8) was scanned over the range of 200 to 400 nm against buffer solution (P^H 6.8) as blank using double beam UV spectrophotometer. The maximum absorbance obtained in the graph was

considered as λ_{max} for the pure drug. The solution exhibited UV maxima at 242 nm.

Fourier Transform Infra-Red (FT-IR) studies

Fourier transform infrared (FT-IR) spectroscopy was employed to characterize the possible interactions between the drug and the carriers in the solid state on Perkin Elmer Spectrum GX by the conventional KBr pellet method. The spectra were scanned over a frequency range 4000–400 cm^{-1}.

Evaluation of Pre-Compression Parameters of the Powder

Bulk Density (D_b)[10]

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the powder (passed through standard sieve # 20) into a measuring cylinder and initial volume 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.

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. 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.

Table 1: Formulation of oral disintegrating tablets of Rosuvastatin using direct compression technique

Ingredients (mg)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}	F_{13}	F_{14}
Rosuvastatin	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Croscarmellose sodium	7.5	0	0	0	12	0	0	0	6	6	6	0	0	0
Crospovidone	0	7.5	0	0	0	12	0	0	6	0	0	6	6	0
Lycoat Rs.720	0	0	7.5	0	0	0	12	0	0	6	0	6	0	6
Sodium starch glycolate	0	0	0	7.5	0	0	0	12	0	0	6	0	6	6
Aspartame (3%)	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Microcrystalline cellulose	123.5	123.5	123.5	123.5	119	119	119	119	119	119	119	119	119	119
Aerosil (0.5%)	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Citric acid (0.5%)	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Mg. Stearate (2%)	3	3	3	3	3	3	3	3	3	3	3	3	3	3
TOTAL	150	150	150	150	150	150	150	150	150	150	150	150	150	150

Angle of Repose (Θ)

The friction forces in a loose powder can be measured by the angle of repose. 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.

$\tan(\Theta) = h / r$

$\Theta = \tan^{-1} (h / r)$

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.

Compressibility index

It is calculated by the following formulae

$I = V_o – V_t / V_o X 100$

Where,

V_o is the tapped density of the powder

V_t is the bulk density of the powder.

Hausner's ratio[11]

It is used for flow property of the blend. It is calculated by the following formulae.

$H = \tilde{n}_t / \tilde{n}_b$

Where,

$\tilde{n}_t$ = tapped density

$\tilde{n}_b$ = bulk density.

If the hausner ratio is less than 1.25, indicates better flow property of the powder.

Evaluation of post-compression parameters of the powder

Weight variation[12]

Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

Friability

Friability of the tablet determined using Roche friabilator. This device subjects the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping the tablet at the height of 6 inches in each revolution. Pre weighed sample of tablets was placed in friabilator and were subjected to 100 revolutions. Tablets were dusted. After 100 revolutions the tablets were reweighed. Then calculate friability by the given equation.

$F= (1-W_o/W)\ 100$

W_o = weight of the tablet before the test

W = weight of the tablet after the test.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while packaging, handling and transportation. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and analyzed for hardness.

Uniformity of Thickness

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using Vernier caliper.

Disintegration time[13]

The *in-vitro* disintegration time was determined using disintegrating apparatus. A tablet was placed into each of the six tubes of the apparatus and one disk was added to each tube. The time was recorded after completion of the disintegration of the tablets.

Water absorption ratio[14]

A small petri plate containing 6 ml of water was taken and a piece of tissue paper folded twice was placed. A tablet was placed gently on it and the time for complete wetting was measured. The wetted tablet was reweighed.

Water absorption ratio R was determined according to the following equation:

$R = (W_a-W_b) / W_b * 100$

Where W_a is the weight of tablet after water absorption

W_b is the weight of tablet before absorption.

Dissolution[15]

Dissolution of Rosuvastatin (10mg) was assessed at 37°C ± 0.5°C using USP II (USP XXII) dissolution test apparatus (Paddle), in 900ml of phosphate buffer (P^H 6.8) as the dissolution medium and at a rotation speed of 75 rpm. Aliquots, each of 5 ml, from the dissolution medium were withdrawn at time intervals of 5, 10, 15, ..., up to 60 mins and replenished by an equal volume of fresh dissolution medium to maintain sink condition. The samples withdrawn were filtered (0.45µ) and analyzed for drug release by measuring its absorbance at 242 nm using phosphate buffer (P^H 6.8) as blank.

RESULTS AND DISCUSSION

Standard Calibration Curve of Rosuvastatin

It was found that the estimation of Rosuvastatin by UV spectrophotometric method at λ_{max} 242 nm in phosphate buffer (P^H 6.8) 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 1- 5 µg/ml.

Fourier Transform Infrared spectroscopy

The IR spectrum shown in Figure 1, reveals characteristic shoulders in the IR spectrum that occur at 1658 cm^{-1} for C=C Stretching (alkene), 1520 cm^{-1} for C=C Stretching (aromatic), 1756 cm^{-1} for C=O Stretching (acid), 1224 cm^{-1} for S=O Asymmetric,1658 cm^{-1} for C=N/ C=O Stretching and 3736 cm^{-1} for O–H Stretching. Peaks that occur at 1224 cm^{-1} represents asymmetric. These bands were also observed for the physical mixture of superdisintegrants and Rosuvastatin with the same absorbance. From these results, it can be confirmed that there is no interaction between Rosuvastatin and superdisintegrants (SSG, CPVP) in the physical mixture as shown in Figure 2.

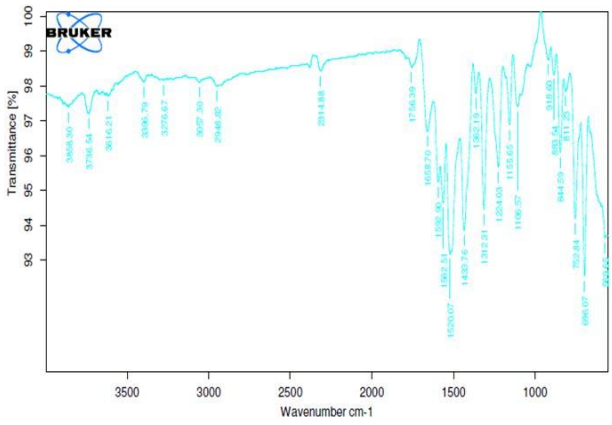

Figure 1: FTIR spectra of pure Rosuvastatin

Evaluation Parameters for Orally Disintegrating Tablets of Rosuvastatin

Pre-compression parameters

The data as shown in Table 2, the values for angle of repose were found in the range of $27^0.32'$ to $30^0.17'$. Bulk densities and tapped densities of various formulations

were found to be in the range of 0.55 to 0.64 (gm/cc) and 0.67 to 0.75 (gm/cc) respectively. Carr's index of the formulated blend falls in the range of 12.5% to 17.910%.The Hausner's ratio falls in range of 1.15 to 1.218. From the results it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

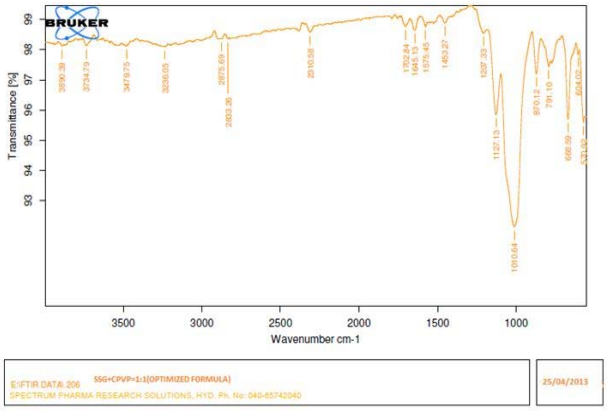

Figure 2: FT-IR spectra of pure optimized formula

Post-compression Parameters

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 Table 3. The average weight of the tablet is approximately in range of 148.4 to 151.92, so the permissible limit is ±7.5%. The results of the test showed that, the tablet weights were within the Pharmacopoeial limits.

Hardness test

Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data shown in Table 3. The results indicate that the hardness of the tablets were in the range of 4.00 to 4.65 kg/cm^2, which was within IP limits.

Thickness

Thickness of three tablets of each batch was checked using Vernier calipers and data shown in Table 3. The results reveal that thickness of the tablets were within the range of 4.01 to 4.54 mm.

Friability

Tablets of each batch were evaluated for percentage friability and the data shown in the Table 3. The average friability of all the formulations lies in the range of 0.227 to 0.449% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Wetting time

The average wetting time of all the formulations was obtained in the range of 15.2-39.8 seconds as shown in the Table 3. The formulation **F7** showed maximum wetting time of 39.8 seconds and the formulation **F13** showed minimum wetting time of 15.2 seconds. Comparing superdisintegrants, the formulation containing lycoat Rs720 takes more wetting time than SSG, Croscarmellose and Crospovidone. Wetting is related to the inner structure of the tablets and hydrophobicity of the components. This may be due to the fact that CCS is disintegrated by swelling mechanism leading to longer wetting time.

***In-vitro* disintegration time**

Tablets of each batch were evaluated for *in-vitro* disintegration time and the data shown in the Table 3. The results showed that the disintegration time of prepared tablets were in the range of 13.15 to 50.15 seconds. The tablets of batch **F13** prepared using 8% of cpvp: ssg (1:1) showed the faster disintegration time of 13.15 seconds. These trials indicated that amongst the disintegrants used cpvp and ssg were better disintegrants to formulate fast dissolving tablets of Rosuvastatin.

Table 2: Pre-compression parameters of Rosuvastatin dispersible tablet

Formulation	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index (%)	Hausner's ratio	Angle of repose (Θ)
F1	0.64	0.75	14.66	1.171	29.13
F2	0.60	0.69	13.04	1.15	29.53
F3	0.59	0.68	13.235	1.152	28.13
F4	0.60	0.71	15.492	1.183	29.13
F5	0.59	0.69	14.492	1.169	30.17
F6	0.55	0.67	17.910	1.218	29.21
F7	0.61	0.72	15.28	1.180	28.13
F8	0.60	0.73	17.80	1.216	29.53
F9	0.61	0.72	15.28	1.180	28.13
F10	0.59	0.69	14.492	1.169	30.01
F11	0.62	0.75	17.33	1.209	30.17
F12	0.60	0.71	15.492	1.183	29.13
F13	0.63	0.72	12.5	1.142	27.32
F14	0.56	0.67	16.417	1.196	28.63

Table 3: Post-compression parameters of Rosuvastatin dispersible tablet

Formulation	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration time (sec)	Wetting time (sec)	Assay (%)
F1	149.19	4.55	4.12	0.234	24.5	19.33	98.65
F2	148.89	4.21	4.02	0.296	29.7	24.5	97.31
F3	151.92	4.53	4.38	0.348	34.34	38.5	98.44
F4	149.06	4.18	4.02	0.376	22.15	25.4	98.38
F5	149.86	4.22	4.48	0.336	19.52	30.2	97.13
F6	150.63	4.32	4.12	0.376	24.52	24.7	99.21
F7	148.60	4.65	4.32	0.336	50.15	39.8	99.43
F8	151.15	4.41	4.17	0.227	20.54	15.33	99.25
F9	149.4	4.00	4.28	0.309	22.32	24.66	96.25
F10	150.25	4.5	4.19	0.339	22.66	30.1	98.42
F11	150.35	4.17	4.01	0.321	35.4	15.33	99.65
F12	148.4	4.11	4.10	0.268	18	19.33	98.16
F13	149.86	4.24	4.18	0.329	13.15	15.2	99.9
F14	149.4	4.01	4.54	0.449	21.52	18	99.29

Table 4: Dissolution profile and percentage of drug release of all formulations

Formulations	Percentage of drug release								
	5mins	10mins	15mins	20mins	25mins	30mins	40mins	50mins	60mins
F_1	19.1	26.02	30.8	37.1	48.3	66.9	77.5	83.9	94.5
F_2	20.1	22.3	48.3	79.6	99.84	-	-	-	-
F_3	11.1	12.2	16.9	17.5	18.05	23.3	26.5	31.8	35.05
F_4	27.08	29.2	72.2	79.6	97.1	-	-	-	-
F_5	6.37	21.2	69.04	95.5	-	-	-	-	-
F_6	44.08	98.2	-	-	-	-	-	-	-
F_7	8.49	18.5	19.1	26.5	30.2	38.7	42.4	48.3	55.7
F_8	11.15	39.3	70.6	97.1	-	-	-	-	-
F_9	90.8	98.7	-	-	-	-	-	-	-
F_{10}	5.31	16.9	20.1	20.7	22.8	25.4	29.7	36.1	43.01
F_{11}	24.4	49.3	72.2	99.3	-	-	-	-	-
F_{12}	11.6	38.7	61.07	77.5	86.03	90.2	99.8	-	-
F_{13}	97.19	-	-	-	-	-	-	-	-
F_{14}	20.7	25.4	31.8	45.1	57.8	92.4	97.7	-	-

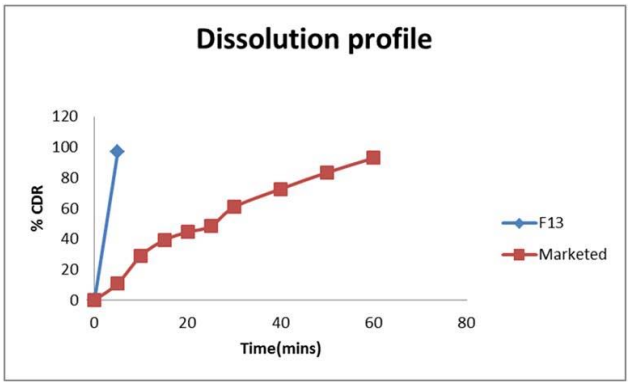

Figure 3: *In-vitro* release profile for Optimized formulation F13 and Marketed product

In-vitro dissolution studies

Finally, the tablets were evaluated for *in-vitro* dissolution studies in phosphate buffer P^H 6.8 and the results were shown in the Table 4. Formulations F2, F4, F5, F6, F8, F9, F11 and F13 showed, more than 90% of drug release within 25 mins. This result exhibit a direct relationship between concentration of superdisintegrants and drug release. Amongst various formulations, tablets of batch **F13** prepared with 8% superdisintegrants i.e, crospovidone and sodium starch glycolate (1:1) showed better (97.19%) release of Rosuvastatin within 5 mins as shown in Table 4.

Assay

The percentage drug content of the tablets found to be between 96.25% and 99.9% of Rosuvastatin, which was within the acceptable limits. This result indicates that there was uniform distribution of the drug throughout the batch.

Comparison with conventional marketed product

The promising formulation was compared with marketed product (Crestor 10 mg Tablet) formulation by checking

various physicochemical parameters. A comparative study of *in-vitro* drug release was made with marketed product of Rosuvastatin which shows 93% drug release in one hour as shown in Figure 3. From this study we can conclude that, formulated tablets of Rosuvastatin containing crospovidone and sodium starch glycolate are better and effective than conventional tablets to meet patient compliance.

CONCLUSION

In the present work, an attempt has been made to develop orally disintegrating tablets of Rosuvastatin. The IR spectra revealed that, there was no interaction between Super disintegrants and drug. All Super disintegrants used were compatible with drug.

The result of physical parameter of preliminary trials by direct compression showed good flow property. Amongst the various combinations of diluents and super disintegrants used in the study, tablets that were formulated (direct compression) using Crospovidone and Sodium starch glycolate 1:1 (8%) exhibited quicker disintegration.

Formulation **F13** was the optimized formulation having least disintegration time as well as other parameters within acceptable range. *In-vitro* release of optimized formulation of Rosuvastatin fast dissolving tablets of **F13** was found to be 97.19% drug release within 5 mins with *in vitro* dispersion time being 13.15sec.

The final optimized formulation **(F13)** was compared with marketed product of Rosuvastatin tablets (crestor) which shows 93% drug release in 1 hr. From this observation it was concluded that the formulated tablets of Rosuvastatin **(F13)** were superior and effective in achieving patient compliance.

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