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Formulation and Evaluation of Orally Disintegrating Tablets of Rosuvastatin

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Abstract: Rosuvastatin is a Dyslipidaemic Agents, which acts by inhibition of HMG-CoA reductase enzyme. Used in the treatment of hyperlipidemia. Therefore the present investigation was to design a formulation of orally disintegrating tablets of Rosuvastatin. Orally disintegrating tablets of Rosuvastatin were formulated by Superdisintegrant addition method by direct compression technique. All the fourteen formulations were evaluated for disintegration time, hardness and friability, this Superdisintegrant addition method exhibits the lowest disintegration time, hence it is ranked as the best among the methods. Further fourteen batches were prepared by using sodium starch glycolate, croscaramellose sodium, Lycoat Rs720 and cross povidone in different concentrations. All the formulations were evaluated for weight variation, hardness, friability, drug content, *invitro* disintegration time, wetting time, *in-vitro* dissolution study. Among all the formulations F13 (containing crosspovidone and sodium starch glycolate (1:1) (8%)) was considered to be the best formulation, which release up to 97% of the drug in 5 mins. A comparison of *In vitro* drug release was made with marketed product of Rosuvastatin which shows 93% drug release in 1 hour. From this study we can made the conclusion that formulated tablets of Rosuvastatin containing crosspovidone and sodium starch glycolate are better and effective than conventional tablets to meet patient compliance.

Key words: Rosuvastatin · Superdisintegrant Addition Method · Sodium Starch Glycolate · CrosCaramellose Sodium · Cross Povidone · Fast Dissolving Tablet · Disintegration Time · Wetting Time

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 [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 a few sec without the need of drinking water or chewing [4]. Rosuvastatin is a dyslipidaemic Agent.Rosuvastatin is incompletely absorbed in the GI tract. Bioavailability of Rosuvastatin is about 20%.Oral disintegrating tablet avoid first pass effect and increase its bioavailability [5].

MATERIAL AND METHODS

Rosuvastatin was gifted from Spectrum pharmaceuticals (Hyderabad, India). The superd is integrants were Crosspovidone (SD Fine Chem Ltd. Mumbai), Sodium starch glycolate (SD Fine Chem Ltd. Mumbai), Croscarmellose sodium (Spectrum pharmaceuticals, Hyderabad), Lycoat Rs720 (Roquettepharma, France). Aspartame gifted from Spectrum pharmaceuticals, Hyderabad, Microcrystalline cellulose gifted from Otto Chemicals, Mumbai,

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Magnesium stearate from Central Drug House (p) Limited, New delhi, Aerosil from Sisco Research Laboratories, Mumbai, Citric acidfrom RFCL Limited, New Delhi.

Evaluation of Pre Compression Parameters of the Powder

Bulk Density[6]: 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 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: 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.

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 and
V_t is the bulk density of the powder.

Angle of Repose (ɵ): 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

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

Where,

- ɵ 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.

Hausnerratio[7]: It is used for flow property of the blend. It is calculated by the following formulae.

H = ñ t / ñ b
ñt = Tapped density
ñb = Bulk density

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

Evaluation of Post Compression Parameters of the Powder

Weight Variation [8]: Ten 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 the friabilator and were subjected to the 100 revolutions. Tablets were dusted. After 100 revolutions the tablets were reweighed. Then calculate friability by the given equation.

F = (1-Wo/W) 100
Wo = 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.

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 [9]: The *in-vitro* disintegration time was determined by 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 [10]: A small culture Petri dish can be taken containing 6ml of water 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:

$$R = (Wa-Wb) / Wb * 100$$

Where

Wa is the weight of tablet after water absorption
Wb is the weight of tablet before absorption.

Dissolution [11]: 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.

Formulationof Orally Disintegratingtablets [12-14]: Weigh all the ingredients accurately according to Table 1. ix all the ingredients geometrically except Aerosil, Talc, 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): 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 ëmax for the pure drug.The Solution exhibited UV maxima at 242 nm as in Figure 1.

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
Microcrystallinecellulose	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

Table 2: Concentration and absorbance obtained for calibration curve of Rosuvastatin in 1 N Phosphate buffer (pH 6.8)

S.No.	Concentration (µg/ml)	Absorbance* (at 242 nm)	Average absorbance
0	0	0	0
1	5	0.097	0.097
2	10	0.174	0.174
3	15	0.266	0.266
4	20	0.354	0.354
5	25	0.436	0.436
6	30	0.513	0.513

Correlation Coefficient = 0.9998 Slope = 0.01704

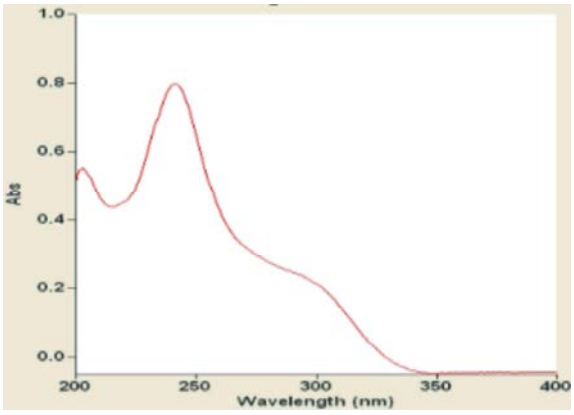

Fig. 1: Determination of Lambda max of Rosuvastatin

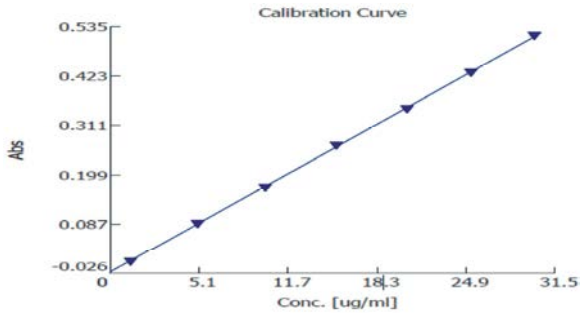

Fig 2: Standard Calibration Curve of Rosuvastatin

Preparation of Standard Calibration Curve of Rosuvastatin [15]: 10 mg of Rosuvastatin was accurately weighed and make up the final volume upto 10 ml with 1 N Phosphate buffer (P^H 6.8) to prepare stock solution. The 1 ml of stock solution was further diluted with 1 N Phosphate buffer (P^H 6.8) in 10ml to get 100µg/ml (working standard). Then 5,10,20,25 and 30 ml of working standard was taken in 10 ml standard volumetric flask and made up the volume with 1 N Phosphate buffer (P^H 6.8) to prepare 5µg, 10µg, 20µg, 25µg and 30µg drug per ml solution. Then the absorbance was measured in a UV spectrophotometer at 242 nm against 1 N Phosphate buffer (P^H 6.8) as blank as shown in Table 2 & Figure 2.

Fourier Transform Infrared (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}.

RESULTS AND DISCUSSION

Standard Calibration Curve Ofrosuvastatin: It was found that the estimation of Rosuvastatin by UV spectrophotometric method at ëmax242 nm in Phospahate 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- 5µg/ml.

Fourier Transform Infrared Spectroscopy: The IR spectrum shown in Figure 3, 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),1224cm^{-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 1224cm^{-1} represents asymmetric. These bands were also observed for the physical mixture of superdisintegrants and Rosuvastatin with the same absorbance as shown in Figure 4-9. From these results, it can be confirmed that there is no interaction betweenRosuvastatin and superdisintegrants (SSG, CPVP) in the physical mixture.

Evaluation Parameters for Fast Dissolving Tablets of Rosuvastatin:

Pre-Compression Parameters: The data's were shown in Table 3.The values for angle of repose were found in the range of 270.32' to 300.17'. 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 prepared blends fall in the range of 12.5% to 17.910%.The Hausner's ratio fall in range of 1.15 to 1.218. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

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 the Table 3. The average weight of the

Table 3: Pre-compression parameters of Rosuvastatin dispersible tablet

Formulation	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Compressibility index (%)	Hausner's ratio	Angle of repose (?)
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

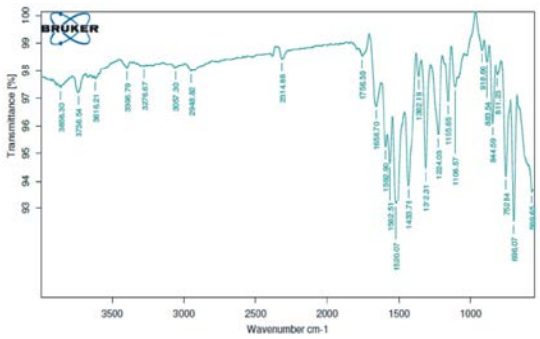

Fig. 3: FT-IR spectra of pure ROSUVASTATIN

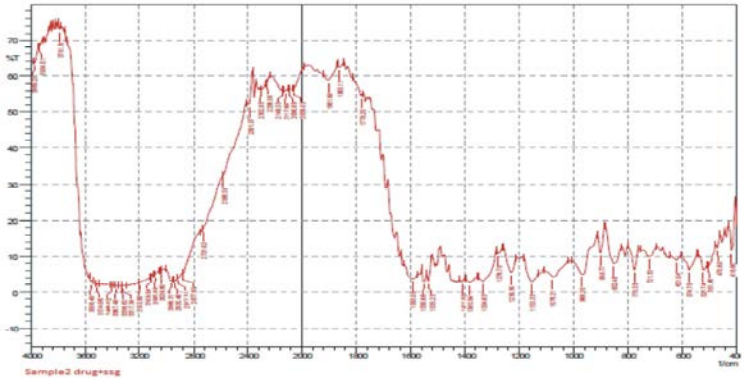

Fig. 4: FT-IR spectra of Rosuvastatin + SSG

tablet is approximately in range of to 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 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 3. The results showed that the hardness of the tablets is in 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 by using Vernier Caliper and data shown in Table 3. The result showed that thickness of the tablet is in range of 4.01 to 4.54.

Friability: Tablets of each batch were evaluated for percentage friability and the data's were 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.

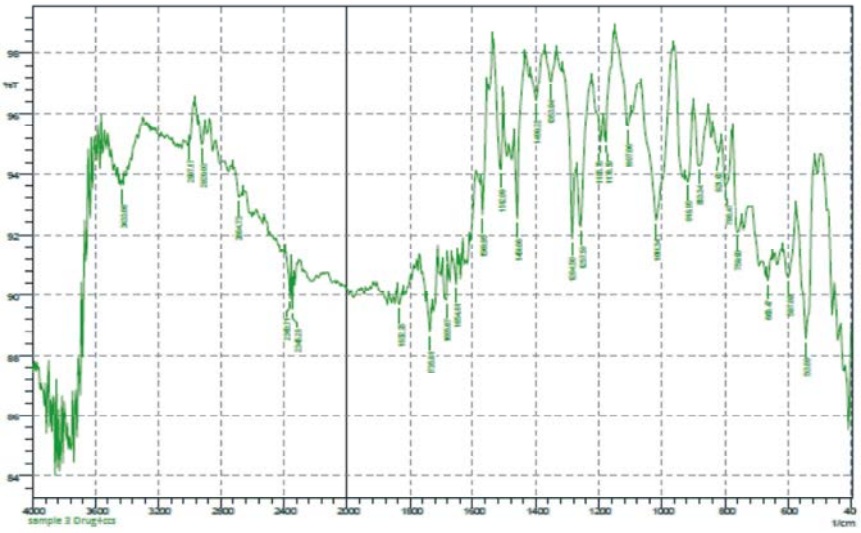

Fig 5: FT-IR spectra of Rosuvastatin + CCS

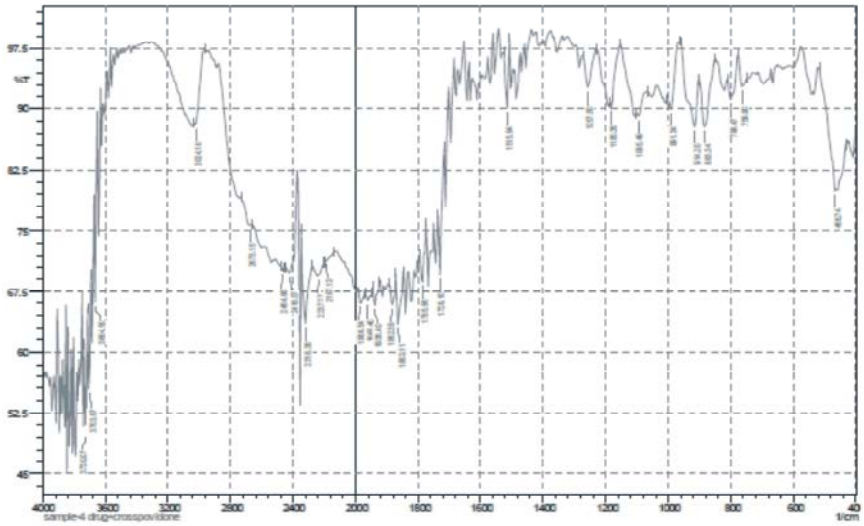

Fig 6: FT-IR spectra of Rosuvastatin + CPVP

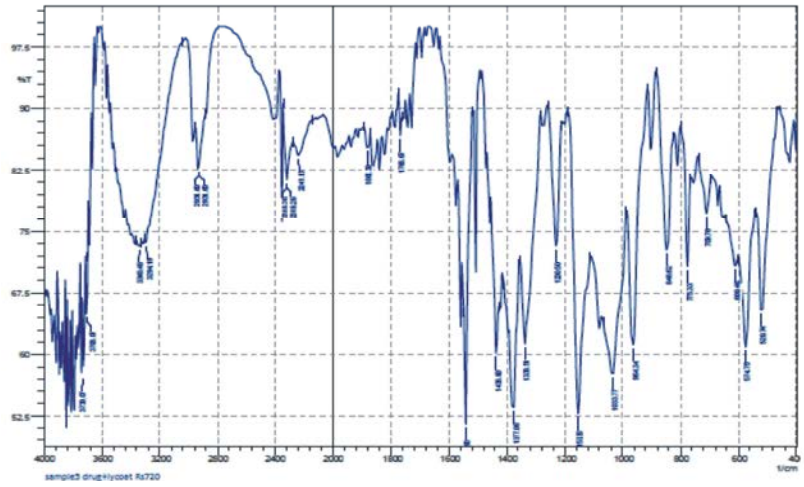

Fig 7: FT-IR spectra of Rosuvastatin +LycoatRs720

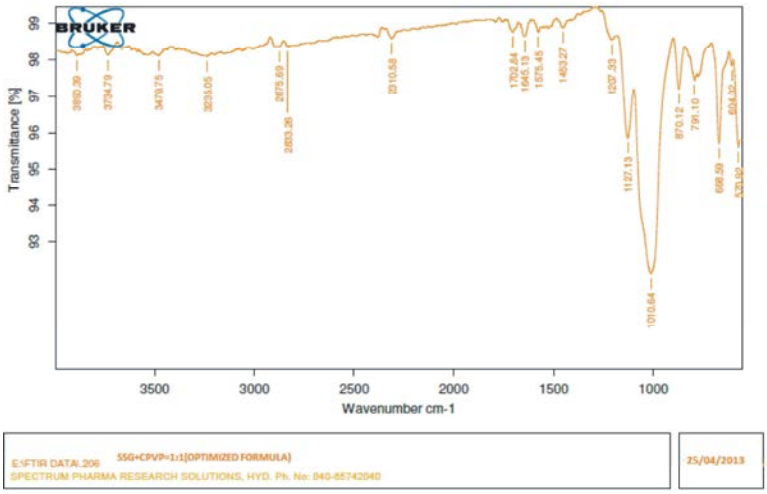

Fig. 8: FT-IR spectra of pure optimized formula

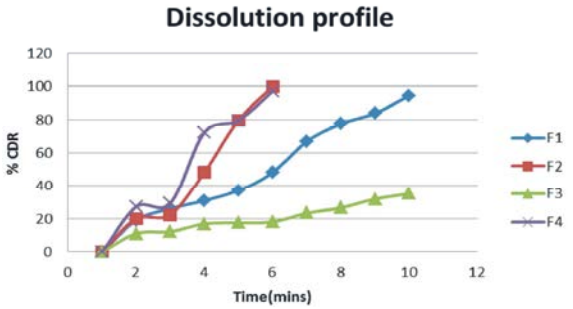

Fig. 9: Effect of super-disintegrants on dissolution profile

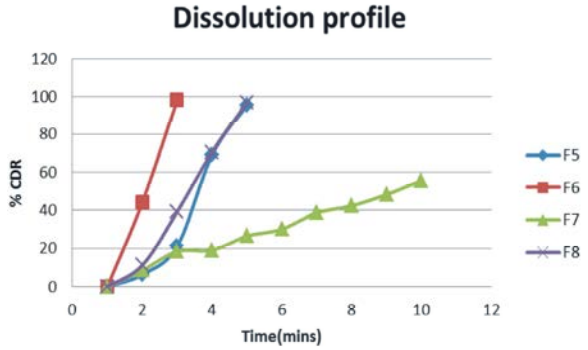

Fig. 10: Effect of super-disintegrants on dissolution profile

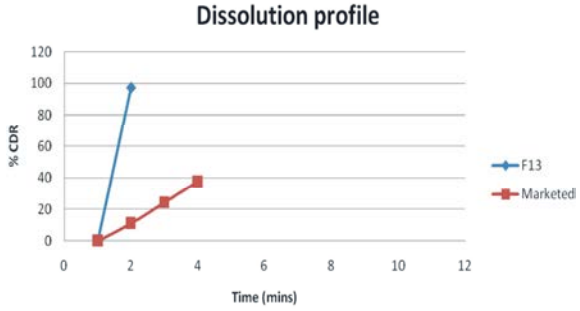

Fig. 11: Effect of super-disintegrants on dissolution profile

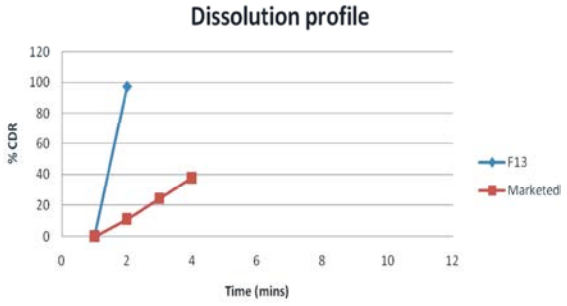

Fig 12: *In vitro* release profile for Optimized formulation F13 and Marketed product

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 F7showed maximum wetting time of 39.8 seconds and the formulation F13 had showed minimum wetting time of 15.2seconds. On comparing superdisintegrants, the formulation containing lycoat Rs720 take more wetting time than SSG, crosscarmellose 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 timeand the data's were shown in the Table 3.The results showed that the

Table 4: Post-compression parameters of Rosuvastatin dispersible tablet

Formulation	Weight variation(mg)	Hardness (kg/cm2)	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 5: Dissolution profile and percentage of drug release of all formulations:

Formulations	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		

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 ssgwere better disintegrants to formulate fast dissolving tablets of Rosuvastatin.

***In vitro* Dissolution Studies:** Finally, the tablets were evaluated for *In vitro* dissolution studies in Phosphate buffer P^H6.8 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 exhibits a direct relationship between concentration of superdisintegrants and drug release. Among the various formulations tablets of batch F13 prepared with crospovidone and sodium starch glycolate and (1:1) 8% showed 97.19% release of drug within 5 mins.

Assay: The percentage drug content of all the tablets was 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 10mg. Tablet) formulation by checking various physicochemical parameters.

The conventional marketed product gave 37.83 of d rug release in 15 minutes ofdissolution study. *In vitro* dissolution profile of marketed product in comparison tothe Optimized formulation were shown in Figure 10 and showed that the formulation F13 with 97.19 % of drug release has better control over release of drug in comparison to the conventional marketed product.

CONCLUSION

In the present work, an attempt has been made to develop fast 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 disintegrants used in the study, tablets that were formulated (direct compression) using Crosspovidone and Sodium starch glycolate 1:1 (8%) exhibited quicker disintegration of tablets than compared to those other combination of disintegrants in different concentration.

Formulation F13 was the optimized formulation having least disintegration time as well as other parameters was in acceptable range. *In vitro* release of optimized formulation of Rosuvastatin fast dissolving tablets of F-13 was found to be 97.19% drug release within 5 min with *In vitro* dispersion time being 13.15 sec.

The final optimized formulation (F13) was compared with marketed product ofRosuvastatin 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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