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Research Article

FORMULATION AND EVALUATION OF ROSUVASTATIN ORODISPERSIBLE TABLETS

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ABSTRACT

Rosuvastatin is a member of the drug class statins, used to treat high cholesterol and to prevent cardiovascular disease.

The objective of present study is to develop orodispersible tablets of Rosuvastatin using different types of superdisintegrants to enhance the disintegration and dissolution of Rosuvastatin to improve bioavailability of the drug.

Many trials were made to prepare a satisfactory rosuvastatin orodispersible tablet using direct compression and wet granulation method. Prepared tablets were evaluated for various parameters like weight variation, hardness, friability, wetting time, in vitro disintegration time, drug content, water absorption ratio and in vitro drug release.

Formulas prepared by direct compression showed good flowability, while formulas prepared by wet granulation showed very poor flow properties. Various superdisintegrants were used including croscarmellose (CCS), sodium starch glycolate (SSG) and crospovidone (CP), the latter found to be the best in term of showing the fastest disintegration time.

Among the two diluents utilized, it was found that mannitol was the best one in preparing rosuvastatin tablet with fastest disintegration time in mouth. The optimized selected formula (F11) was prepared using 15% w/w crospovidone, by direct compression showed the shortest disintegration time in mouth (11 seconds), superior drug release profile [the time required for 80% of the drug to be released ($t_{80\%}$) and percent drug dissolved in 2 min (D_{2min}) were 6 min. and 56 %respectively]. In addition to that the selected formula had an acceptable hardness and friability, so it was selected as the best formula.

The overall results showed that crospovidone was the best superdisintegrant of showing the shortest disintegration time while mannitol was the best diluent in preparing Rosuvastatin orodispersible tablet and this suggested the possibility of utilizing the selected best formula (F11) in the preparation of Rosuvastatin orodispersible tablet as a new dosage form for oral administration.

Keywords: Orodispersible, Rousovastatin, Superdisintegrant.

INTRODUCTION

Many patients groups; such as the elderly, children, and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid-intake/diets, have difficulties of swallowing ordinary tablets. To improve the quality of life and treatment compliances of such patients fast disintegrating or orally disintegrating tablets dosage form is a better alternative for oral medication [1, 2]. A Fast disintegrating tablet dissolves or disintegrates in the oral cavity without the need of water or chewing [3].

Rosuvastatin, as rosuvastatin calcium is a HMG-CoA reductase inhibitor used for the treatment of dyslipidaemia with absolute bioavailability 20% [4].

The objective of present study is to develop orodispersible tablets of rosuvastatin using different types of super disintegrants to enhance the disintegration and dissolution of rosuvastatin to improve bioavailability of the drug.

MATERIALS AND METHODS

Determination of λ max of Rosuvastatin

Rosuvastatin solution; 200 µg/ml in 2% Brij 35 in phosphate buffer solutions (pH 6.8) were prepared then scanned by a UV spectrophotometer at wavelengths ranging from 400nm to 200nm, and the λ_{max} for solution was determined. Calibration curve of rosuvastatin in 2% Brij 35 in phosphate buffer (pH 6.8) was constructed by preparing a series of solutions with different concentrations of rosuvastatin (4, 8, 16, 24, 28µg/ml) from stock solution containing 200 µg /ml Rosuvastatin, Then the absorbance measured at λ_{max} 241. Measured absorbencies were plotted against concentrations.

Formulation of Rosuvastatin orodispersible tablets

Different formulas were prepared as shown in table (1). Formulas (F_1- F_{12}) were prepared by direct compression method in which all constituents were mixed and compressed directly by tablet machine.

Table 1: Composition of different formulas

Formula No.	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F*13
Material (mg)													
Rosuvastatin	10	10	10	10	10	10	10	10	10	10	10	10	10
Croscarmillose	10 %	10 %			10 %								
Sodium Starch Glycolate			10 %			10 %		10 %				5 %	
Crospovidone				10 %			10 %		5 %	10 %	15 %	5 %	15 %
Aspartam	6	6	6	6	6	6	6	6	6	6	6	6	6
Talc	2							2	2	2	2	2	2
Mg-stearate	2	2	2	2	2	2	2	2	2	2	2	2	2
PVP		2	2	2									
Spray.dry lactose					68	68	68						
Mannitol Q.S	160	160	160	160	100	100	100	160	170	160	150	160	150
Total weight	200	200	200	200	200	200	200	200	200	200	200	200	200

* Prepared by wet granulation method

F_{13} was prepared by wet granulation method and as following:

The drug, super disintegrant, sweetening agent (aspartam) and mannitol were mixed, Then conveyed to a mill and milled for 2 min. Sufficient quantity of alcoholic solution of poly vinyl pyrrolidone (1% w/v) was added to form a coherent mass. The wet mass was granulated using sieve no. 10 and regranulated after drying (at 65°C for 10 min) through sieve no. 12 then weighted Talc and the lubricant (Mg. stearate) were incorporated and mixed for 2 minute, Granules were then compressed using a double punches, korech, tablet machine of 7mm flat punch.

Evaluation of the prepared formulas

Wetting time and water absorption ratio

The wetting time of the tablet was measured by placing five circular tissue papers (10 cm in diameter) in a Petri dish of 10 cm diameter. Artificial saliva (10 ml) containing methylene blue (0.1% w/v) was added to the Petri dish. A tablet was carefully placed on the surface of tissue paper, and the time required for the dye to reach the upper surface of the tablet was recorded as wetting time. Measurements were carried out in triplicate. Water absorption ratio was calculated using the following [5-6].

$$\text{Water absorption ratio} = (Wa - Wb)/ Wb$$

Where Wb = weight of tablet before absorption of water, and Wa = weight of tablet after absorption of water.

Table 2: Composition of artificial saliva

Materials	Amount (gm/L)
Sodium chloride (NaCl)	0.4
Potassium chloride (KCl)	0.4
Calcium chloride($CaCl_2.2H_2O$)	0.8
Sodium di hydrogen phosphate ($NaH_2PO_4.2H_2O$)	0.78
Sodium sulfide ($NaS.9H_2O$)	0.005
Urea	1

Content uniformity

The content uniformity of the prepared formulas orodispersible tablets was performed by taking ten tablets and assayed individually. The requirement for this test is met if the amount of ingredient in each of the ten tablets lies within the range of 95%-102%.

Hardness

Tablets require a certain amount of strength or hardness and resistance to Friability to with stand mechanical shocks. The hardness of tablet was measured by Monsanto hardness tester and results were expressed in Kg/cm^2 [7-8].

Friability

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Ten tables were initially weighed (W initial) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W final). The percentage friability was then calculated using the following equation.

$$F = \frac{I_{nitial} - F_{inal} \times 100}{I_{nitial}}$$

% Friability of tablets less than 1% are considered acceptable [9].

In vivo disintegration test

Three human volunteers were involved in the determination of the disintegration time for each tablet formula; the time required for complete disintegration of the tablet when placed on the tongue was determined by tactile feedback using a stop watch [10].

In-vitro disintegration test

The in-vitro disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds [11].

The disintegration tests were done for the prepared orodispersible tablets using the USP disintegration apparatus, the basket rack assembly containing six open ended tubes and 10- mesh screen on the bottom was used, and the six tubes are filled with artificial saliva instead of water, in order to stimulate the in vivo environment as much as possible.

In vitro dissolution studies

In vitro dissolution studies were performed only for formulas (F10 ,F11 F12) and Crestor® as a reference tablet (10mg) using type II (paddle) dissolution apparatus (Copley, UK) at 50 rpm, and 900 ml of phosphate buffer (pH 6.8) was used as a dissolution medium. Temperature of dissolution medium was maintained at 37 ± 0.5°C. Five milliliters aliquot of the dissolution medium was withdrawn at specific time intervals (0.5, 1,2,3,4,6,8,10,15,20,25,30,35,40,45,and 50 minute). Absorption of filtered solution was measured by UV–visible spectrophotometer at $\lambda = 241$ nm, and the percent of drug released was determined using standard curve. Dissolution rate was studied for the prepared formulations and conventional tablet. The time required for 80% of drug to be released ($t_{80\%}$) and percent drug dissolved in 2 min ($D_{2\,min}$ %) were considered for comparing the dissolution results. The $t_{80\%}$ and $D_{2\,min}$ were determined by fitting the dissolution data to a four parametric logistic model using the Marquardt–Levenberg algorithm (Sigma plot 11 SPSS) [12].

Effect of type and concentration of the superdisintegrants

Formulas (1-12) (table 1) were utilized to study the effect of super disintegrant type (croscarmillose, sodium starch glycolate and crospovidone) and their concentration, (5, 10 and 15% / 200mg tablet) on the flowability of the prepared formula and the physical properties of the prepared tablet.

Effect of diluents type

Table1 were utilized to check the effect of diluents types (mannitol and spray dry lactose) on the physical properties of Rosuvastatin.

Effect of hardness of the prepared formulas on disintegration time

The selected formula F11was compressed with different compression force to get tablet with Hardness (3, 4, 5 and 6 Kg / Cm^2) to study the effect of hardness on disintegration time of prepared Rosuvastatin orodispersible tablet.

Effect of preparation method

F13 (table 1) was prepared by wet granulation method compared to F11 which was prepared by direct compression method to study the effect of preparation method on the flowability of prepared granules and physical properties of the prepared Rosuvastatin orodispersible tablet.

Comparison of selected formula with conventional Rosuvastatin tablet

A final comparison was done for the selected formula (F11) with Rosuvastatin tablet available in the market (Crestor®) for disintegration and dissolution.

Statistical analysis

The results of the experiments are given at least as a mean of triplicate samples ± standard deviation and were analyzed according to the one way analysis of variance (ANOVA) at the level of ($P < 0.05$).

RESULTS AND DISCUSSION

Determination of λ max of Rosuvastatin

The UV scans of Rosuvastatin in phosphate buffer (pH 6.8) showed peak, fig. 1 with λ_{max} at 241 [13].

Determination of calibration curve of Rosuvastatin

The calibration curve of Rosuvastatin, in 2% Brij 35 in phosphate buffer pH 6.8 shows straight line with high regression coefficient (R^2) as shown in fig. 2 which was obtained as a result of plotting the absorbance versus concentration, which indicates that this curve obeys Beer's-Lambert law within the concentrations used.

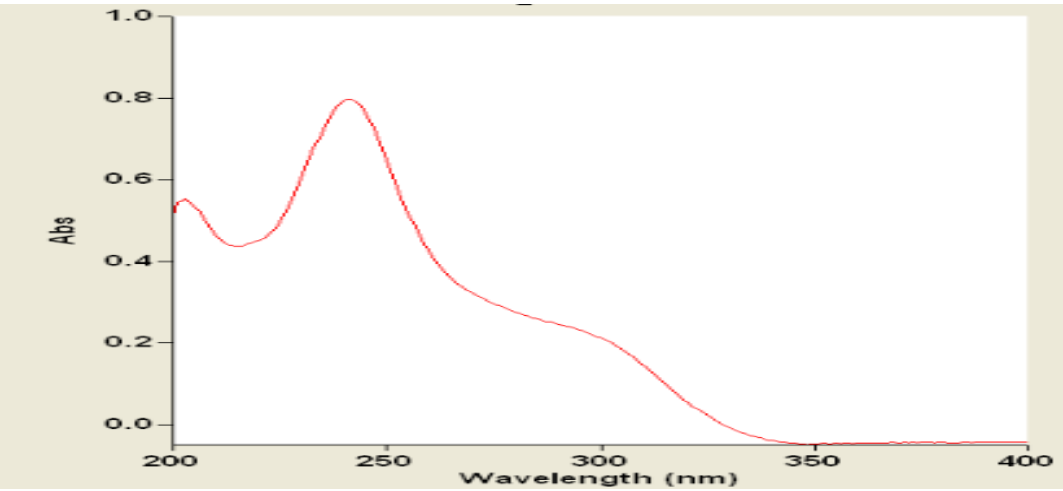

Fig. 1: UV scans Rosuvastatin in phosphate buffer

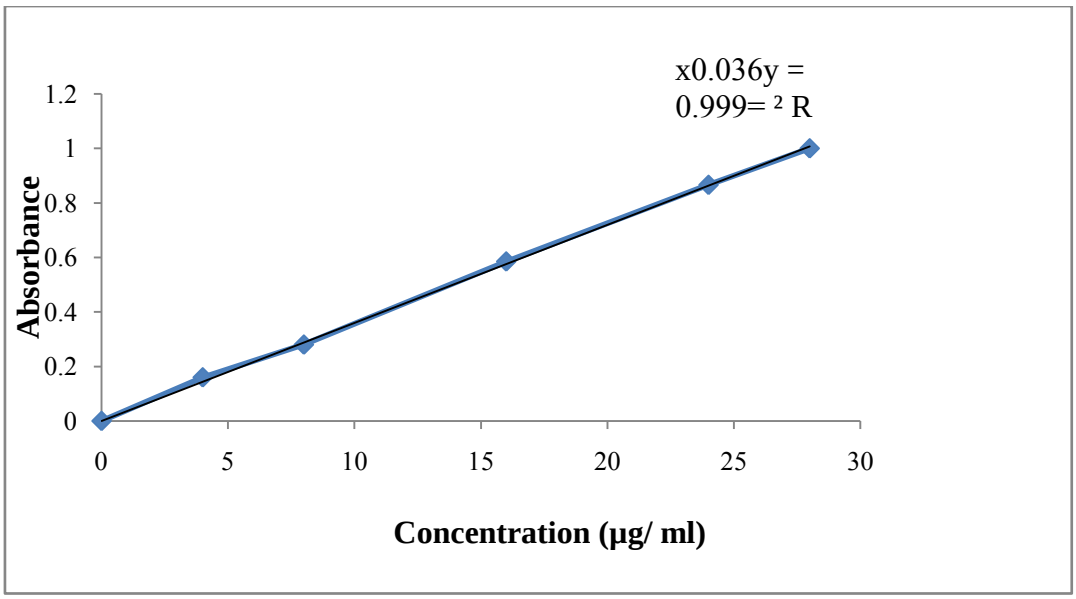

Fig. 2: Standard calibration curve of Rosuvastatin

Formulation of orodispersible tablets

The size of Rosuvastatin orodispersible tablets was selected carefully with 7 mm diameter, this size can be handled easily and at same time can be swallowed easily since the orodispersible tablet disintegrates as soon as it contact with saliva and converts subsequently to a suspension that can be swallowed easily.

Effect of Type and concentrations of the superdisintegrant

Study the effect of different superdisintegrant type (croscarmellose, sodium, sodium starch glycolate and crospovidone) and concentrations (5, 10 and 15 w/w %) on the flowability and physical properties of the prepared Rosuvastatin tablets are shown in table 3.

Table 3: Angle of repose, compressibility index and flow characters

Formula code	Angle of repose(º)	Carr's index	Flow character*
F1	60	16	Very poor & good
F2	61	16.6	Very poor & good
F3	54	12.5	Very poor & Excellent
F4	61	20	Very poor & Fair to passable
F5	43	25	Very poor & poor
F6	34	20	Passable & Fair to Passable
F7	61	22.22	Very poor & Fair to passable
F8	87	9.52	Very poor & Excellent
F9	64	22.45	Very poor & Fair to passable
F10	65	20	Very poor & Fair to passable
F11	34	21.57	Passable & Fair to Passable
F12	47	23.91	Very poor & poor
F* 13	41	8.33	Very poor & Excellent

* According to USP

The results also showed that best super disintegrant type was crospovidone with a concentration of 15% which represent in formula 11 as it gave shortest in vitro disintegration time (11 s) followed by F10 , F12 (15 s) , F9 (16) and F13 (20 s) fig. 3, the results are in agreement with those reported in literature [14].

Formula containing crospovidone showed quick disintegration followed by croscarmellose, sodium and sodium starch glycolate. Fig. 4.The probable reason for delayed disintegration of the tablets with croscarmellose, sodium and sodium starch glycolate might be due to their tendency to gel more than crospovidone. So, worthwhile to mention that crospovidone has a little tendency to form a gel so it exhibits the shortest in vitro disintegration time (11s) [15].

Generally, the wetting time for tablets containing croscarmellose, sodium and sodium starch glycolate is longer than tablets containing crospovidone was shown in fig. 5. The shortest wetting time for crospovidone (F11) (6 s) is due to the fact that crospovidone quickly wicks saliva into the tablet to generate the volume expansion necessary to provide rapid disintegration in mouth, the major mechanism of disintegration for crospovidone is wicking , while for croscarmellose, sodium and sodium starch glycolate is the swelling mechanism [16].

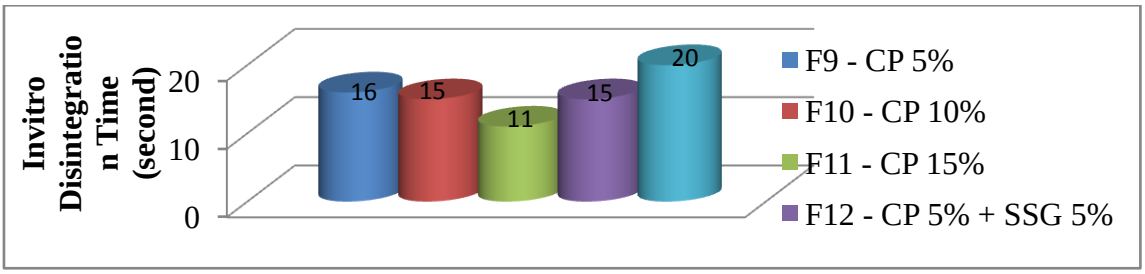

Fig. 3: In-vitro disintegration time F (9, 10, 11, 12, and 13)

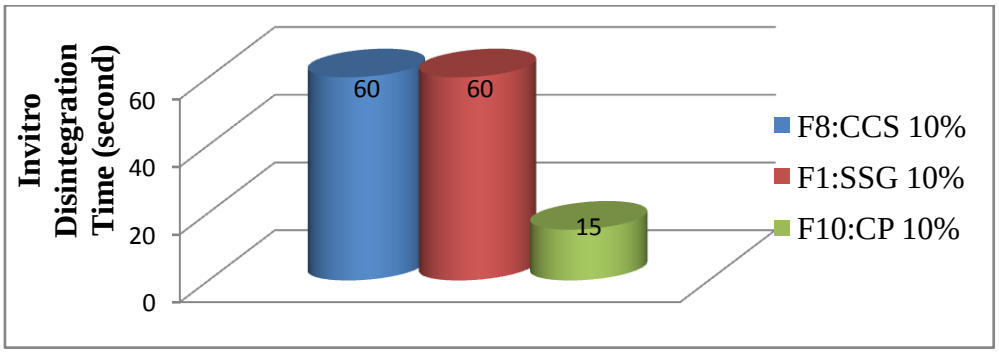

Fig. 4: In-vitro disintegration time for F1, F8, and F10

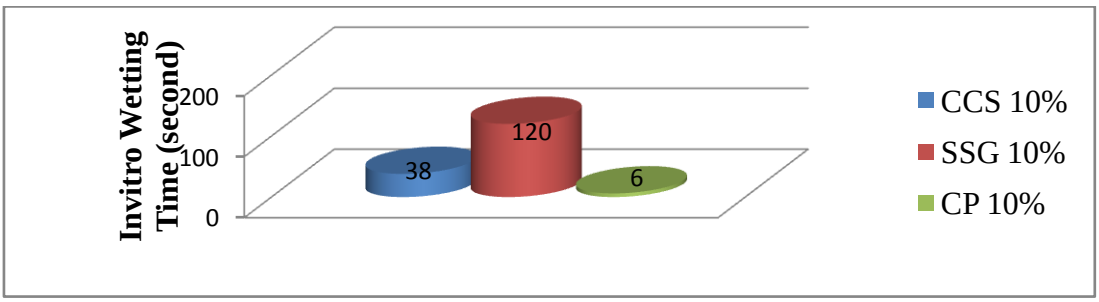

Fig. 5: In-vitro wetting time in second for F1, F8 and F10 (CCS, SSG, CP)

Crospovidone quickly wicks saliva into the tablet to generate the volume expansion and hydrostatic pressures necessary to provide rapid disintegration in the mouth. Unlike other superdisintegrants, which rely principally on swelling for disintegration Crospovidone superdisintegrants use a combination of swelling and wicking. When examined under a scanning electron microscope, crospovidone particles appear granular and highly porous. This unique, porous particle morphology facilitates wicking of liquid into the tablet and particles to generate rapid disintegration. Due to its high crosslink density, crospovidone swells rapidly in water without gelling. Other superdisintegrants have a lower crosslink density and, as a result, form gels when fully hydrated, particularly at the higher use levels in tablet formulations. Swells very little and returns to original size after compression but act by capillary action .Unlike other super disintegrants, which rely principally on swelling for disintegration, crospovidone disintegrants use a combination of mechanisms to provide rapid disintegration. Although crospovidone polymers swell by 95% to 120% upon contact with water, swelling is not the only mechanism for tablet disintegration. Swelling or swell volume is mainly a measure of the change in volume of the disintegrant after it is introduced to an aqueous solution and the system has reached equilibrium. However, swell volume does not measure the rate at which a disintegrant absorbs water and swells or the pressure generated by swelling. Crospovidone polymers, with their porous particle morphology rapidly absorb water (wicking) via capillary action. As the deformed crospovidone particles come in contact with water that is wicked into the tablet, the crospovidone particles recover their normal structure and then swell, resulting in rapid volume expansion and high hydrostatic pressures that cause tablet disintegration [17].

In addition, an acidic medium significantly reduce the liquid uptake rate and capacity of sodium starch glycolate and croscarmellose sodium but not crospovidone, where a significant

reduction in swelling capacity is also observed for croscarmellose, sodium in 0.1 N HCL ,which swells to half that in water. The strong decrease in swelling capacity of chemically modified starches and celluloses may attribute to the converting of the carboxyl methyl sodium moieties. Since the acid form has less hydration capacity than its salt form, the liquid holding capacity of the disintegrant particle reduces after deionization in the acidic medium [18].

Table 4: Physical properties of the prepared formulas

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F 13
Wetting time (second)	38	120	40	6	180	90	27	120	6	6	6	12	30
Water absorption ratio	24	23.85	23.33	23	12.5	16	22.22	20	19.5	21	21.75	19	20.6
Invivo disintegration time (second)	50					90		48	13	12	10	13	30
In Vitro DT. (second)	60	300	180	170	240	170	120	60	16	15	11	15	20
Hardness (Kg/Cm²)	4.3	4	4.2	4.1	4.1	4.3	4.3	4.2	4.3	4.3	4.3	4	4.3
Friability (%)										0.65		0.88	
Drug content (%)	99	97	98.5	97	97.4	100.5	98.2	98.3	98	97.2	100	101	100.8

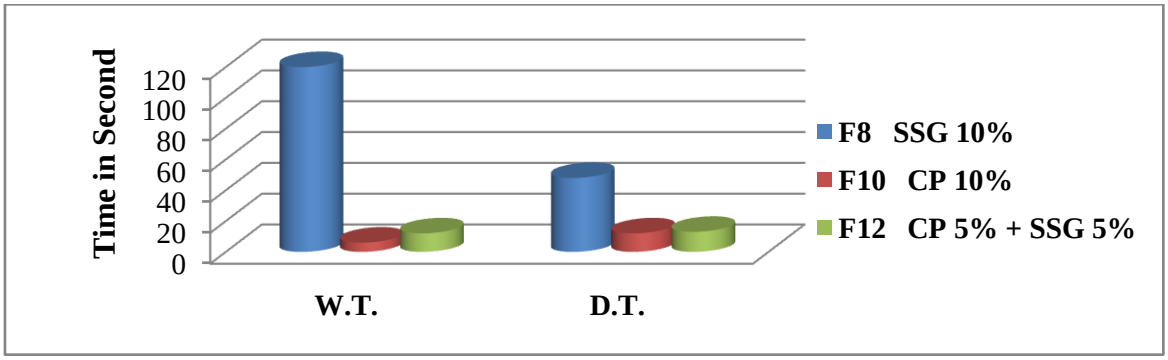

Fig. 6: Wetting and in vivo disintegration time for F8, F10, and F12

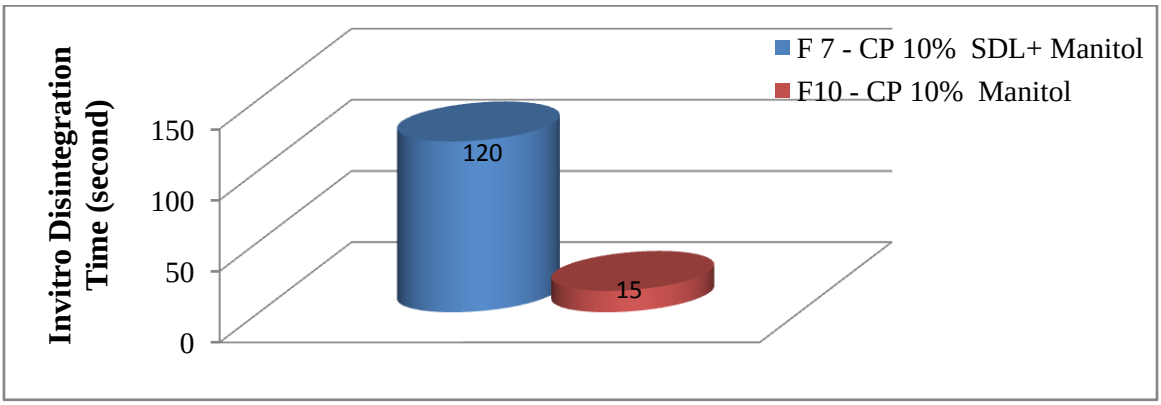

Fig. 7: In-vitro disintegration time for formulas F7, and F10

Content uniformity

All the formulas prepared are within the required limits [7].

Effect of diluents type

Fig. 7 shows The disintegration time of tablets of F7 (120 s) containing spray-dried lactose was also more than F10 (15 s), probably because of the formation of a sticky layer due to the dissolution of lactose and subsequent hindrance in the further ingress of water into the tablet [19].

Effect of the hardness of the prepared tablet on disintegration time

The selected formula F11 was compressed with different compression force to get tablet with hardness (3, 4, 5 and 6 Kg / Cm²) and in-vitro disintegration time of (15, 11, 12 and 14 second).

Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down [20].

Effect of preparation method

F11 in table 4 was prepared by direct compression method, it contain the same ingredients and concentrations corresponding to F13, which is prepared by wet granulation method to investigate the effect of preparation method on the flowability (angle of repose and Carr's index) of the tablet blend granules and the physical properties of the compressed tablets.

The results for the flowability of the tablets prepared by direct compression (F11) and wet granulation (F13), where the angle of repose (34) compared to (41) and Carr's index 21.57 compared to 8.33, respectively fig. 8.

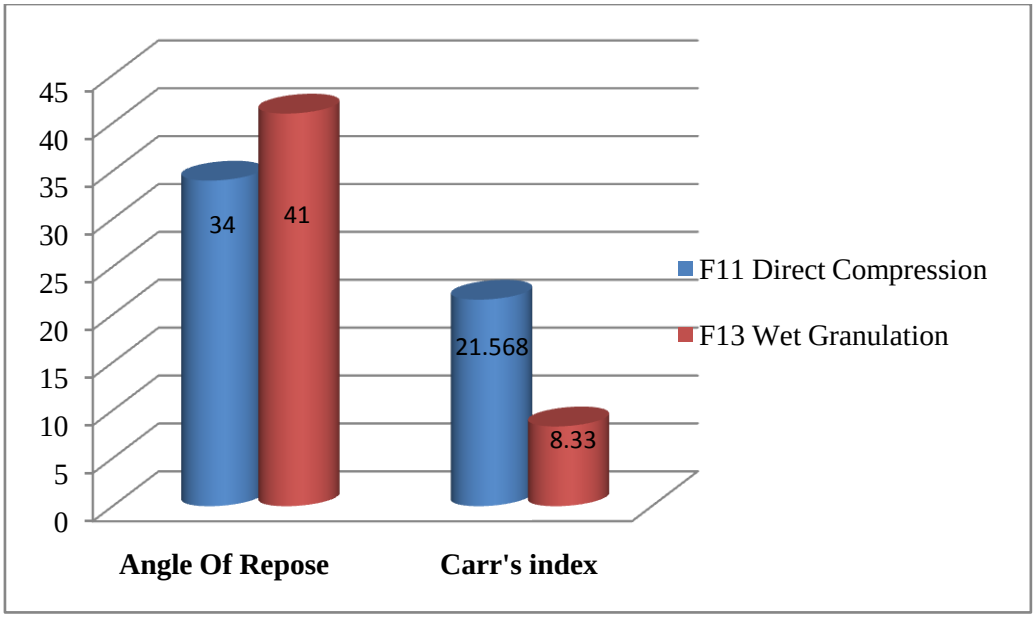

Fig. 8: Effect of preparation method on flowability of the prepared granules

The poor flowability may lead to drawback of feeding the blend into the dies of the rotary tablet press, tablet weight variation and content uniformity problem may arise [21].

The effect of wet granulation method on the disintegration time and wetting time is shown in fig10, and 11, in which it results long disintegration time and wetting time for formula 13 (20s) and (30s) respectively, than those prepared by direct compression F11 (11s) and (6s) respectively, statistically a highly significant difference ($p < 0.05$) these results in agreement with that in direct compression. Tablet disintegration to primary drug particles rather than granules associated with wet granulation and this provide faster disintegration time [22].

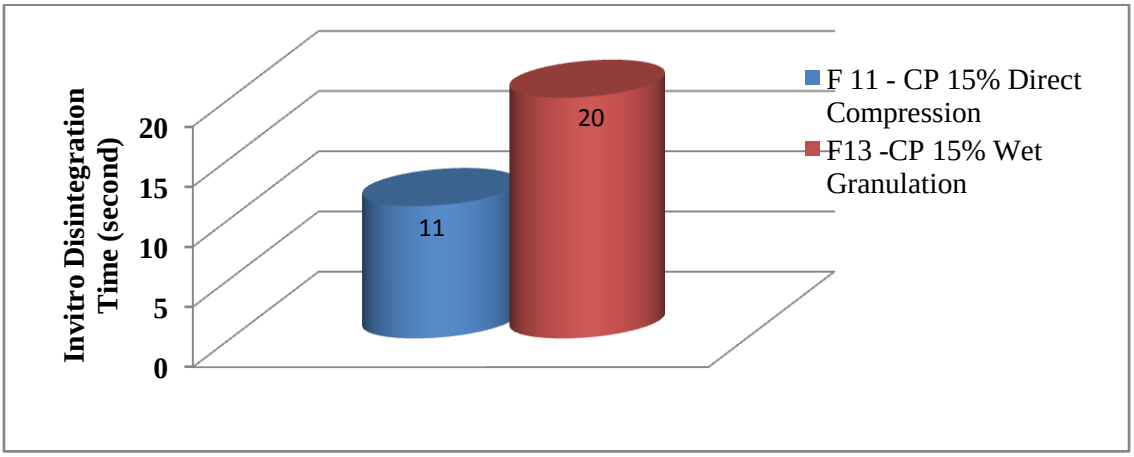

Fig. 9: In-vitro disintegration time in formulas F11, and F13

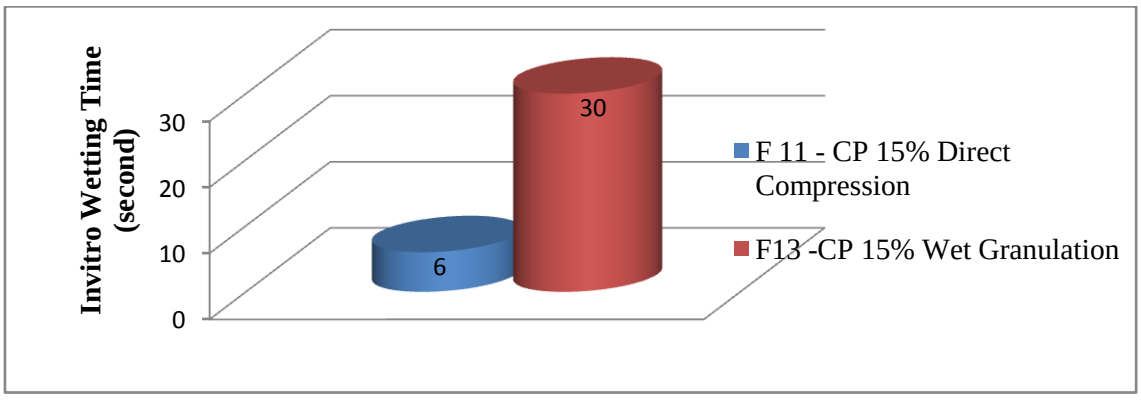

Fig. 10: In-vitro wetting time in formulas F11, and F13

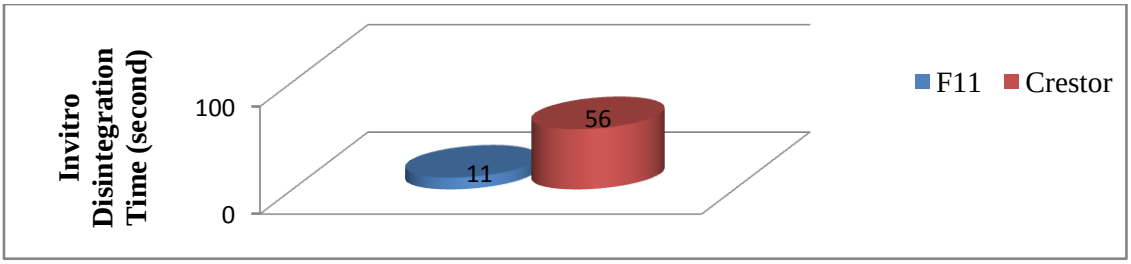

Fig. 11: In-vitro disintegration time for F11 and Crestor® tablet

On other hand the disintegration time of formula 11 was compared to conventional plain tablets (Crestor®) as reference fig. 11, the results showed highly significant difference ($p<0.05$) in vitro disintegration time between F11 (11 seconds) and plain tablets (Crestor®) (56 seconds).

It was seen that the in-vivo disintegration time for all formulas is shorter than the in-vitro disintegration time.

In Vitro Dissolution Studies

In vitro dissolution studies, as they are important for conventional tablets, are also important for ODTs [23]. In vitro drug release studies of the optimized formulations were carried out at pH 6.8. The pH 6.8 was selected to assess any pregastric absorption that may take place when some of the particles from the orodispersible formulation get lodged into the denture and gradually may get absorbed through buccal mucosa.

There is statistically significant difference ($p<0.05$) in the release profile between F11 (pH 6.8 , Brij 2%) and plain tablet Crestor® (pH 1.2) in which the $t_{80\%}$ for F11 (6 minute) compared with (15 minute) for Crestor® , also D_{2min} for F11 (56%) compared with (18%) for Crestor® These results are represented in fig. 12.

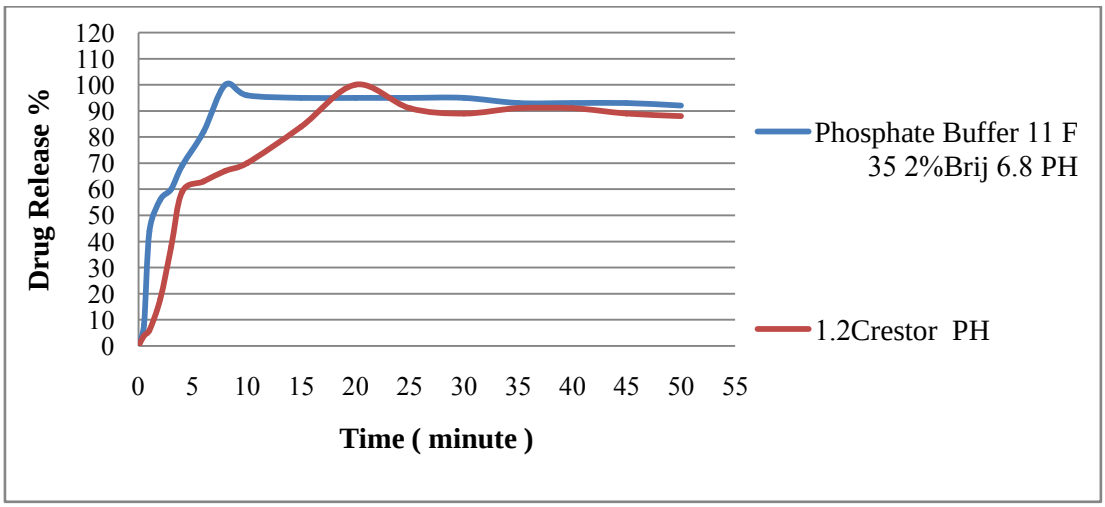

Fig. 12: Dissolution profile for selected formula F11 and Crestor

CONCLUSSION

Crospovidone was the best super disintegrant of showing the shortest disintegration time while mannitol was the best diluent in preparing Rosuvastatin orodispersible tablet. This study indicates the possibility of utilizing the selected best formula (F11) in the preparation of Rosuvastatin orodispersible tablet as a new dosage form for oral administration because of desired properties of the prepared tablets concerning sufficient hardness, low friability, fast disintegration and dissolution.

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