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Original Article

Formulation and stability study of lipid-based formulations for oral administration of poorly water-soluble drug

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ABSTRACT

Rousuvastatin calcium (ROS) is a model of poorly water-soluble drug. The objective of the study was to increase the dissolution rate and stability of ROS through formulation of basic tablets, contain nanoemulsion of the drug. Full factorial design (2^3) was applied for a screening study in which three factors were used at two levels (low and high). The factors were the type of disintegrants (Ac-di-sol, Explotab), the concentration of disintegrant (3%w/w, 5%w/w) and the binder type (Avicel PH101, PEG6000). The tablets are prepared by direct compression. The weight variation, content uniformity, friability, hardness, disintegration time, and in-vitro dissolution of the prepared formulae were evaluated. The stability of tablets was also studied at 40°C & 75% RH for period of 3 months at 40°C. The tablets were prepared by direct compression technique. The formula F6 containing Ac-di-sol (5%w/w) with AvicelPH101 (30%w/w) has the least disintegration time (45.55 ± 4 seconds) and the highest dissolution rate (95±3.6%). The stability of tablets was studied at 40°C & 75 % RH for period of 3 months. The results indicate that ROS tablets may serve as a successful strategy for enhancing the dissolution and stability.

Key words*:* Poor soluble drug, dissolution, stability, Karl fisher test

INTRODUCTION

ROS (Figure I) is a hydroxyl-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitor used in the treatment of patients with dyslipidemia ROS (CAS: 287714-41-4) is a synthetic lipid lowering drug acts by competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase, which is a rate limiting enzyme involves in the conversion of HMG-CoA to mevalonate, a precursor of cholesterol. It is used in conjunction with the diet and regular exercises to treat patients with hypertriglyceridemia and other cardiovascular diseases [1-5]. Following oral administration of ROS under fasting conditions the peak plasma levels of ROS occur at 3 to 5 hours and the elimination half life is around 16-19 hours [6, 7].

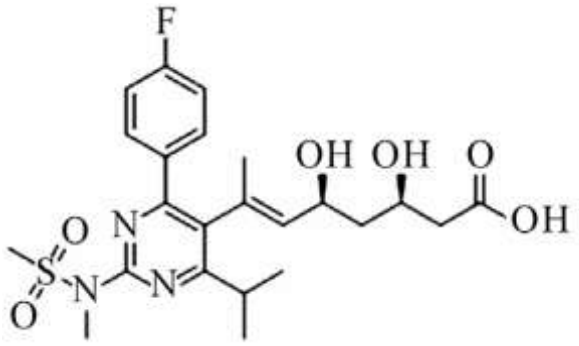

Figure I: chemical structure of Rousuvastatin calcium (ROS)

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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.

Direct compression is the easiest way of manufacturing tablets. The biggest advantages are the low manufacturing cost, high mechanical property of the tablets and it is the ideal method for moisture and heat-labile medications. The purpose of this study was to prepare rousavastatin tablets with enhanced solubility and stability.

MATERIALS AND METHODS

Materials: Rousavastatin (generously gifted by Epico Co., Egypt); Polyethylene glycols 6000 (Fluka AG Buchs SG, Switzerland); Avicel PH 101: microcrystalline cellulose, (FMC Corporation, Pennsylvania, USA); Aerosil 200: colloidal silicon dioxide (DeguROSa-Huls Ltd., FranROSurt, Germany); Explotab: sodium starch glycolate and Ac-di-sol: croROScarmellose sodium(FMC corporation, Philadelphia ,USA); magnesium stearate, (Prolabo, France); granular mannitol (spray-dried NF, Fast Flo; Foremost Farms, Baraboo, WI).

Tablet preparations: ROS tablets were prepared by direct compression technique. ROS was formulated as solid nanoemulsion to increase the dissolution (unpublished data). A full factorial design (2^3) was applied for the screening study in which three factors were used at two levels. These factors were the concentration of superdisintegrants either at low concentration (3%w/w) or at a high level (5%w/w), the type of both the superdisintegrants (Ac-di-sol or Explotab) and binder (Avicel PH-102 % or PEG6000).

All the ingredients of the tablets of Rousvastatin were weighed and mixed in a mortar and pestle, finally magnesium stearate (1mg) was added for a good lubrication characteristics. The blended material was slightly compressed on the flat–faced punch (7mm) using a single punch machine (Erweka type, GmbH, Germany).

Pre compression evaluation (evaluation of the powder blends)

Determination of flow ability for the eight formulae (F1- F8) would be achieved through the determination of angle of repose, tapped density Carr's index, Hausner's ratio and bulkiness for all the prepared ROS tablet formulations.

Angle of repose: Angle of repose that measures frictional forces between the particles was determined by funnel method .Accurately weighed blends were taken into a funnel and allowed to flow freely through the funnel .The height of the funnel was adjusted in a way that tip of the funnel just touched the apex of the heap of powder blends. The diameter of the powder cone was measured and angle of repose was calculated through *(equation1).*

$\tan \theta = h/r$ (equation1)

Where h is the height of the heap; r is radius of the base of the heap, θ is angle of repose. The test was performed in triplicate for each formula powder blend [8].

Bulk and Tapped density: A mass of about 10gm (blend) is carefully introduced in a 100ml graduated cylinder, then dropped onto a hard surface three times from a height of 2.5 cm at two second interval. The tapping was continued until no further change in volume was noticed then bulk and tapped densities were calculated from dividing the mass to the cross ponding volume [9].

Hausner's ratio

Hausner's ratio can be calculated mathematically from equation2.

$HR = \text{Tapped density} / \text{Bulk density} = (\rho_t)/(\rho_b)$ *(equation2).*

, Where HR is Hausner´s ratio.

Carr's index (Compressibility index)

Carr's index = (Tapped density- Bulk density)/(Tapped density)x 100 (equation) [10].

Evaluation of the prepared tables

Weight variation: Twenty tablets were selected randomly from each formula and individual tablet weight was calculated and then compares tablet weight with average weight for each formula. The result presented as mean value ± S.D.

Uniformity of Tablet Diameter and Thickness: The diameter and thickness of ten tablets were measured using Vernier caliber at two different positions. The average value was then calculated.

Uniformity of ROS content: Ten tablets from each formula were accurately weighed and crushed in glass mortar to a fine powder. A quantity equivalent to 20 mg of ROS from each formula was

transferred to a 50 mL volumetric flask containing distilled water to dissolve the drug. The solution was filtered and the drug content was calculated specrophotometrically using standard calibration curve at λ_{max} 241[11].

Tablet Hardness: The crushing strength, which is the load in Kg applied on the diameter of the tablet, was measured 72 hours after compression to allow for any stress relaxation. Ten tablets from each formula were tested for their hardness, using Erweka hardness tester, then, the mean hardness in kg of each formula was determined [12].

Friability: The test was done using Roche friabilator (ERWEKA, Germany) by weighing twenty tablets from each formula then placed in friabilator and rotated for 100 revolutions at 25 rpm. After that the tablets were dedusted and reweighed. The percentage loss in weight should not exceed 1% [13].

In-vitro disintegration time: The test was done by disintegration apparatus using six tablets from each formula and the results are expressed as mean value ± S.D (n=6) [14, 15].

Moisture Content using Karl Fischer Apparatus: The moisture content of all formulae was determined using Karl Fischer apparatus as described in the USP. 20µL of water were introduced into the flask of the apparatus containing dry methanol HPLC grade, and were automatically titrated with Karl Fischer reagent till consumed. Consumption of the water stops titration automatically. The reading of the monitor was recorded, then the previously weighted tablets were inserted into the flask and the previous steps were repeated. The amount of humidity contained in the tablets was calculated based on the reading given by water [16]. The experiment was carried out in triplicate for each formula and the average values were tabulated

The percent humidity = Weight of the humidity/ Weight of the tablets X100 (equation 4).

In- vitro dissolution studies: Dissolution studies were done for all eight formulae in USP Paddle (apparatus II). The dissolution medium was phosphate buffer pH 6.8 (50 mL) at a rotation speed 100 rpm and temperature 37 ± 0.5 ˚C. The samples of 1ml were withdrawn at time interval 5, 10, 15, 30, 45, 60, 90 and 120 minutes min then filtered and measured by UV spectrophotometer at 241 nm**.** The dissolution data obtained from the dissolution test of the prepared ROS loaded FDSTs were fitted to various mathematical models (zero order, first order and Higuchi) to determine the kinetics of drug release [17].

Accelerated stability study: In order to determine the change in vitro release profile on Storage, stability study of selected formulae was carried out at 40^{o} C in a Humidity chamber having 75% RH. Sample was withdrawn at various time intervals and the study was conducted for 13 weeks. The sample was evaluated for change in vitro drug release pattern, hardness, percent drug content and disintegration time, and moisture content [18, 19].

Analytical Procedure for Determination of ROS in the Stored Tablets: High performance liquid chromatography method of assay was adopted [20] for the determination of the drug actually present in the formulations rather than any degradation form.

Chromatographic condition: The HPLC apparatus consisted of: Isocratic pump LC-10 AS and a UV/VIS detector SPD-10A connected to a C-R6A Integrator (Shimadzu, Koyoto, Japan). The analytical column was Ponapak C18 HPLC column, 4.6 × 250 I.D mm, particle size 125 ºA (Waters Associates, Ireland). The mobile phase consisted of filtered and degassed mixture of methanol HPLC, water: acetonitrile in a ratio of 30:70. The mobile phase was filtered and degassed daily by passing it through a 0.45 µm membrane filter (Millipore). The mobile phase was delivered into the HPLC apparatus at a flow rate 1.2 mL per minute and the injection volume was 20µL. The liquid chromatograph is equipped with a 242 nm U.V. detector.

RESULTS AND DISCUSSION

Evaluation of powder blends: All formulae showed good flow properties as indicated by the values of angle of repose (22.36–34.75). Carr's index was from 7.69 to 12.28 which indicated that all formulae had excellent to good flow ability. Regarding Hausner's ratio powder with low inter-particle friction such as coarse spheres had ratios approximately 1.2, whereas less free flowing particles such as flakes had Hausner's ratios greater than 1.6. All formulae had Hausner's ratio values ranged from 1.08 to 1.14 which indicated excellent to good flow ability (Table 3).

Evaluation of the prepared tablets: Table 4, shows the data obtained from the evaluation of tablets. All the ROS formulae in the factorial design complied with the compendia standards for the weight variation and content uniformity tests (all tablet formulae were found to conform to pharmacopoeial limit 85% - 115%) of the label claim. The prepared tablets showed a uniformity of diameter and thickness.

Tablet hardness: Table (4), show that all the formulae evaluated had hardness values within the acceptable range. All the tablets maintained hardness in the range of 3.97 to 6.11kg. The statistical analysis revealed that all factors; superdisintegrant type, superdisintegrant concentration and binder type, had no significant effect on the hardness of the prepared formulae ($p \leq 0.05$). The two-way interactions on the examined different factors were found to be non-significant at $p \leq 0.05$ (figure 1). It is worthy to say that the different hardness values were obtained because of the fact that the pressure of the tableting machine was adjusted at the least hardness sufficient to form a suitable tablet. Also high hardness values didn't necessarily lead to long disintegration times [22], from table (4) formulae F2 and F6 had lower hardness. It was worthy to note that both of formulae had combined effect of the higher concentration of the superdisintegrant with 30% Avicel PH101 as binder, this was expected as both additives act as disintegrants in the concentration ranges used and according to Shangraw, et al [21] who proved that most disintegrating agents have negative effect on compressibility. On the other hand, none of the formulae was above the acceptable range.

Tablet Friability: According to compendial standards of the British pharmacopoeia, the tablets comply with the friability test if the weight loss during the test was less than 1% of the given weight. The tablets should not break or show any capping or cracking during the test. Table 4 shows that the tablets formulated with the different excipients showed low percentage of fines within the acceptable range.

In-vitro disintegration test: The shortest disintegration time were observed from F4 and F6. This might be due to the synergistic effect of both of Avicel PH101 and the higher concentration of the superdisintegrants either Ac -di-sol or Explotab in those formulae. ANOVA test at $p \leq 0.05$ was carried out followed with Fischer's PLSD test (pair-wise least significant difference) to test the significance of the difference between the tested factors and their effects on tablet disintegration time at 95% confidence limits which, found that all factors under study, namely, superdisintegrant type, superdisintegrant concentration and binder types had significant effects on the disintegration time of the prepared FDSLTs ($p<0.05$) , the results were graphically illustrated in (table 4). The interaction lines of the combined effects of the tested additives on the mean disintegration time were illustrated graphically in figure (2) which revealed that the interaction between superdisintegrant type and superdisintegrant concentration was significant. On the other hand, super disintegrant concentration either 3% or 5% had no significant interaction at $p \leq 0.05$ with the binder type.

In- vitro dissolution studies: The dissolution profiles of ROS within 120 minutes from the formulae are shown in figures (3, 4). The maximum percent of ROS release noticed for formula F6, prepared by (5% Ac-di-sol and 30% Avicel-PH 101) was 100±2.6, while the Crestor® tablet was 54.71±2.56 %**.**

Accelerated stability study: The stability study shows that there was no significant physical or chemical change in the selected formula during the storage period. The results are shown in (table 5).

CONCLUSION

The development of ROS tablets containing nanoemulsion with different excipients is a promising formula resulted in higher dissolution of ROS. The best *in-vitro* drug release observed in formulation F6 was found to be 100% which contain the drug Rosuvastatin calcium in the form of nanoemlsion and Ac-di-sol as superdisintegrant agent with other excipients.

Table 1: Factorial plane 2^3 for preparing ROS tablets.

Variable	**Level**	
	-	+
Type of superdisintegrants	Ac-di-sol	Explotab
concentration of superdisintegrants	Low	High
Binder type	Avicel PH101	PEG600

Table 2: Formulations of ROS basic tablets**.**

Formula code	F1	F2	F3	F4	F5	F6	F7	F8
ROS	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg
Avicel PH 101	15 mg	30mg	-	-	15 mg	30mg	-	-
PEG 6000	-	-	15 mg	30mg	-	-	15 mg	30mg
Explotab	3mg	5 mg	3mg	5 mg	-	-	-	-
Ac-di-sol	-	-	-	-	3mg	5 mg	3mg	5 mg
Magnesium stearate	1	1	1	1	1	1	1	1
Mannitol up to	100	100	100	100	100	100	100	100

Table 3: Evaluation of the powder Blends of the different tablets formulae.

Formula	Angle of Repose (Ɵ)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Hausner's Ratio	Carr's Index %	Bulkiness
F1	25.41	0.62	0.67	1.08	7.69	1.6
F2	27.53	0.86	0.94	1.08	7.69	1.16
F3	31.45	0.8	0.90	1.12	10.34	1.25
F4	22.36	0.73	0.80	1.10	9.09	1.37
F5	31.8	0.64	0.72	1.12	10.71	1.56
F6	29.53	0.89	0.99	1.12	10.91	1.12
F7	30.11	0.71	0.81	1.14	12.28	1.41

Table 4: Characterization of the prepared tablet.

Formula	Average Weight (mg)	Mean Diameter (mm)	Mean Thickness (mm)	Drug content (%)	Hardness (Kg)	In-vitro D.T (second)	Friability (%)	Moisture content (%)
F1	100.19±4.2	7.04 ±0.01	2.19 ±0.16	99.62±2.46	6.11±0.24	92.17±6.3	0.74	0.25±0.12
F2	101.85±6.2	7.02±0.04	2.03±0.08	98.61±1.4	3.97±0.51	71.46±5.1	0.63	0.19±0.09
F3	103.36±5.6	7.2 ±0.03	2.02±0.02	102.71±2.5	5.9±0.41	88.33 ±1.37	0.89	0.24±0.1
F4	99.13±7.69	7.09 ±0.02	2.02 ±0.13	97.25±4.9	4.5±0.35	51.33±5.2	0.71	0.16±0.17
F5	100.33±4.3	7.11±0.01	2.15±0.02	101.62±3.6	4.4±0.71	81.32±1.5	0.59	0.17±0.11
F6	102.29±3.51	7.07±0.03	2.12±0.19	103.55±5.7	3.97±0.21	45.5±4.92	0.85	0.11±0.13
F7	102.77 ±5.5	7.05 ±0.06	2.06 ±0.12	100.36±5.3	5.26±0.14	76.83 ±0.75	0.92	0.24±0.08
F8	105.03±3.5	7.14 ±0.09	2.12 ±0.14	101.05±5.7	4.27±0.21	63.5±4.92	0.88	0.14±0.17

* D.T: Disintegration time,

Table 5: Physical characteristics of the prepared formula (F6) tablets at 40° C and 75% relative Humidity for (13 Weeks).

Storage Time (weeks)	Weight (mg)	Mean Thickness (mm	Mean Diameter (mm)	Content Uniformity (%)	Friability (%)	Hardness (Kg)	D.T (S)	Moisture content (%)
0	102.29±1.98	2.12 ±0.08	7.14 ±0.21	103.55	0.850	3.97±0.7	27.80±2.09	0.11
1	100.25±1.57	2.09 ±0.05	0.713 ±0.11	99.361	0.850	3.62±0.9	26.23±3.31	0.152
2	100.10±1.79	2.08±0.07	0.709 ±0.07	97.059	0.882	3.41±0.6	25.34±3.8	0.195
3	100.35±1.58	2.08 ±0.06	0.722 ±0.08	96.365	0.921	3.37±0.7	22.08±2.9	0.229
4	100.57±2.28	2.12±0.15	0.712 ±0.09	94.716	0.954	3.11±0.4	20.15±2.5	0.330
6	100.69±2.09	2.13 ±0.12	0.705 ±0.01	93.829	0.982	3.18±0.9	19.17±3.6	0.388
9	100.32±2.21	2.03 ±0.04	0.709 ±0.06	91.513	1.103	3.14±0.8	17.56±2.7	0.407
13	99.79±2.26	2.08±0.06	0.719 ±0.04	87.692	1.142	3.11±0.9	16.01±1.9	0.411

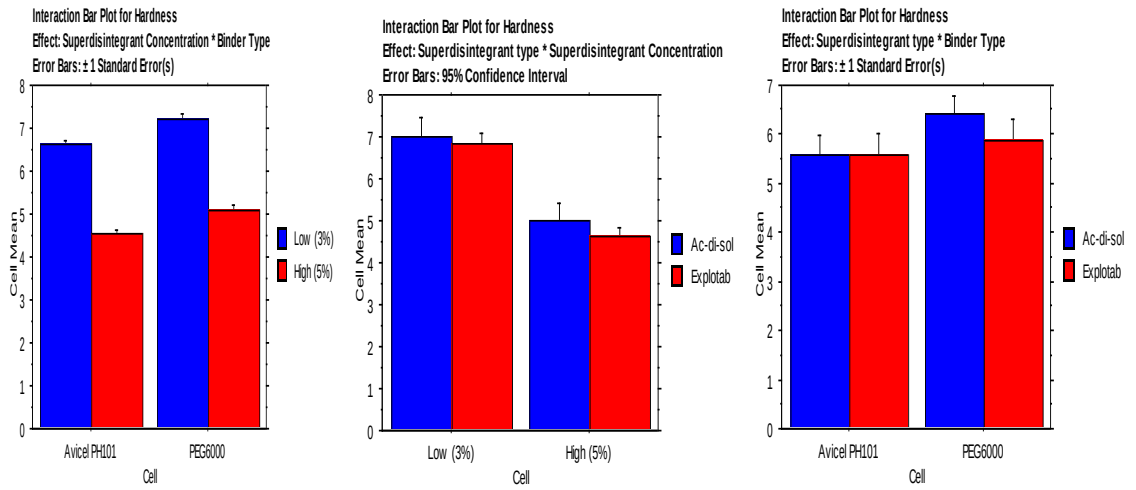

Figure (1): Interaction Bar Plot for the mean effect of tablets hardness of different formulation From ROS Tablets.(a) Superdisintegrant type*Superdisintegrant concentration (b) Superdisintegrant type*Binder type and (c) Superdisintegrant concentration*Binder type

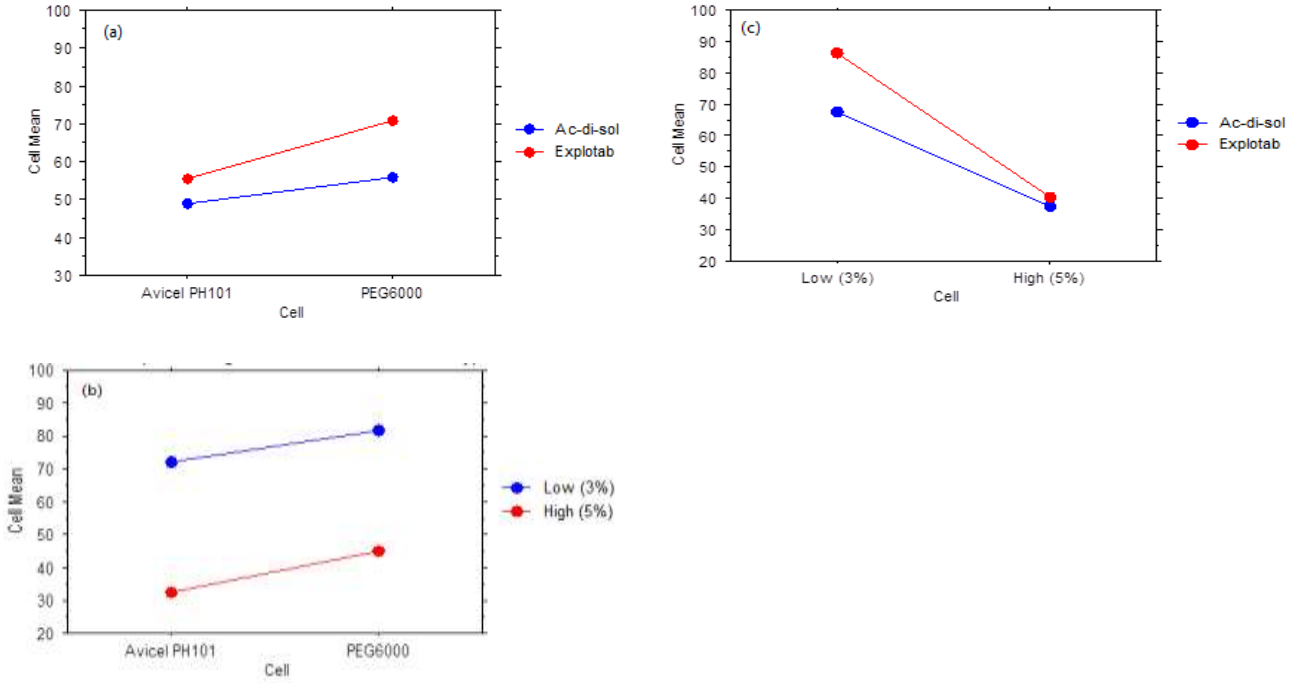

Figure (2): interaction line plots for the combined effects of different factors on ROStablets (a) Superdisintegrant type* Superdisintegrant concentration (b) Superdisintegrant type*Binder type (c) Superdisintegrant concentration*Binder type

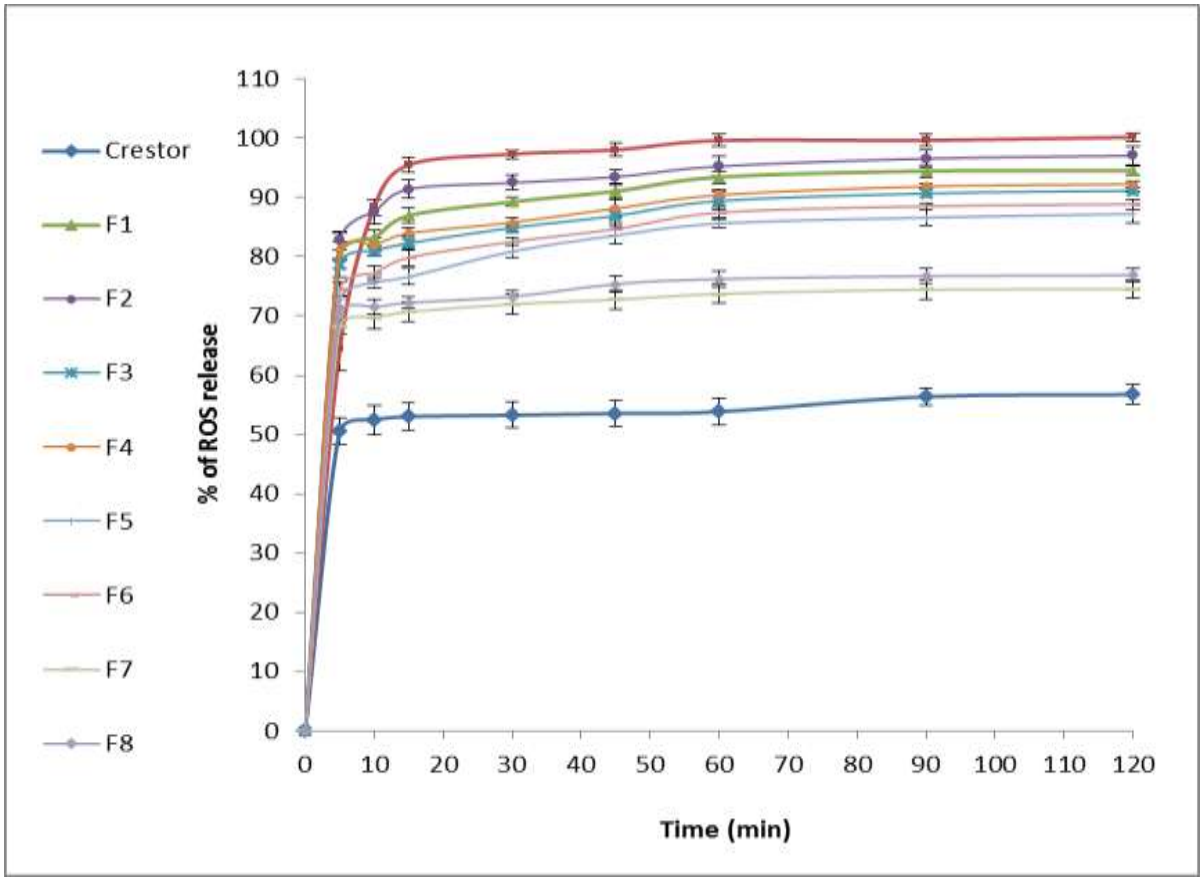

Figure (3): Dissolution of ROS from different prepared formulations compared to Crestor® tablet (PH 6.8)

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