ejpmr, 2016,3(3), 351-358

SJIF Impact Factor 3.628

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 3294-3211

EJPMR

FORMULATION, DEVELOPMENT AND EVALUATION OF ROSUVASTATIN CALCIUM IMMEDIATE RELEASE TABLETS

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Article Received on 12/01/2016 **Article Revised on 04/02/2016** **Article Accepted on 24/02/2016**

ABSTRACT

Rosuvastatin calcium is a synthetic lipid lowering agent which inhibits the enzyme 3-hydroxy-3-methylglutaryl-coenzymeA to mevalonate, a precursor of sterols, including cholesterol. It comes under class II of Biopharmaceutical Classification System. The purpose of this study was to develop and evaluate Rosuvastatin calcium immediate release tablets by wet granulation method using different proportions of superdisintegrants and binder. Pre-formulation studies were done initially and the results were found to be within the limits. All the mentioned batches were prepared and granules were evaluated for pre-compression parameters such as loss on drying, bulk density, tapped density and compressibility index. Tablets were evaluated for weight variation, thickness, hardness, friability; disintegration time and assay were found to be within the limits. In vitro dissolutions were performed in 0.05M 6.8 PH phosphate buffer and effect of various superdisintegrants was explored. Final selection of formulation was based on dissolution profile, from dissolution studies formulation 11 showed 80% drug release within 15 minutes. Similarity and difference factors which revealed that formulation (F11) containing 1.5% polyplasdone XL 10 and polyplasdone XL 100 each and 20% binder are most successful as it exhibited in vitro drug release. In vitro drug release profile reveals that with increased concentration of polyplasdone XL 10 and polyplasdone XL 100 (1.5%) and decreased binder concentration (20%) there was increased in drug release. Accelerated stability studies were performed for the optimized batch which indicated that there were no changes in drug content and in vitro dissolution.

KEYWORDS: Biopharmaceutical Classification System, pre-compression parameters, Polyplasdone XL 10, Rosuvastatin calcium, superdisintegrants,

INTRODUCTION

The need for new oral drug delivery system continues, due to poor patient acceptance for invasive methods, need for exploration of new market for drugs and coupled with high cost of disease management. Developing new drug delivery techniques and utilizing them in product development is critical for pharma companies to survive this century.

Immediate release dosage form is those which disintegrate rapidly and get dissolved to release the medicaments. Immediate release may be provided for by way of an appropriate pharmaceutically acceptable diluent or carrier, which diluent or carrier does not prolong, to an appreciable extent, the rate of drug release and/or absorption. This term excludes formulations which are adapted to provide for "modified", "controlled", "sustained", "prolonged", "extended" or "delayed" release of drug.[1, 2,3]

Immediate release solid oral dosage forms are classified as either having rapid or slow dissolution rates. Immediate release dosage forms are those for which ≥85% of labelled amount dissolves within 30 min. For immediate release tablets, the only barrier to drug release is simple disintegration or erosion stage, which is generally accomplished in less than one hour. To enhance dissolution and hence bioavailability of any drug from immediate release tablets, disintegration is one of the important process. Few Super-disintegrants are available commercially as Croscarmellose sodium, Crospovidone and SSG.[4,5]

Several Technologies are available to manufacture immediate release tablets. The most common preparation methods are moulding, lyophilisation or freeze drying, direct compression, spray drying and sublimation. Direct compression, is one of the techniques that requires the incorporation of a superdisintegrants into the formulation. Direct compression does not require the use of water or heat during the formulation procedure and is very sensitive to changes in the type and proportion of excipients and the compression forces, when used to

achieve tablets of suitable hardness without compromising the rapid disintegration characteristics.[6]

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

MATERIALS AND METHODS

Rosuvastatin calcium was obtained as gift sample from MSN laboratories, Hyderabad.

Microcrystalline Cellulose 101 (Avicel 101) grade was obtained from Accent Microcell Industries. Starch 1500 & Maize Starch Ashland obtained from Aqualon functional ingredients. Poly plasdone XL 10 Crospovidone & Poly plasdone XL 100 Crospovidone were obtained from FMC Biopolymer. Remaining all other chemicals was obtained from S.D. Fine Chemicals. Pvt Ltd, Mumbai, India. All chemicals and solvents used were of analytical grade.

Drug- Excipient Compatibility Study

Compatibility studies conducted to investigate and predict physicochemical interaction between drug substance and excipients were performed by preparing compatibility blends at different ratios of different excipients with drug based on tentative average weight. These blends were stored at accelerated conditions at 40^0 c, 75%RH for one month. The ratio of drug and excipient varies from 1:1 to 1:10. . Samples were evaluated for any change in physical characteristics with reference to controlled sample stored at 4^oc for 7, 14 and 30 days. Chemical compatibility is tested by FTIR spectrometry, which is most powerful technique to identify functional groups of the drug. In the present study potassium bromide disc (pellet) method was employed.

Preparation of Rosuvastatin Calcium Tablets[7,8]

Rosuvastatin Calcium, Lactose Monohydrate and Microcrystalline Cellulose (Accel- 101) was co-sifted through # 40 sieve and mixed thoroughly in a poly bag. Transferred the sifted material into the RMG and mixed for 15 minutes. Binder solution was prepared by dissolving Starch in purified water. Binder solution was added slowly to dry mix in Fluid Bed Drier bowl. Dried the wet granulate in fluid bed dryer at an inlet temperature of 35° - 40°C till the desired LOD of 2.0 –3.0 %w/w was achieved. Sifted the dried granules through # 20 sieves. Polyplasdone XL was sifted through # 40 sieve and geometrically mixed and collected in a polybag. Load the dried, sized granules in to the Octagonal blender and Blended for 20 minutes. Magnesium stearate was sifted through # 60 sieve, added to the blend and mixed for 5 minutes. Granules were compressed using compression machine with lubricated blend, employing appropriate punch tooling.

Evaluation of Flow properties of Prepared Granules[9,10,11,12,13]

Angle of repose: The angle of repose of API powder was determined by funnel method. Angle of Repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. The accurately weighed powder blend was taken in the funnel. The height of the funnel was adjusted in a way that, it measures 2.5 cm from the surface level. The powder blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and the same procedure is done for triplicate, the average value is taken. The angle of repose is calculated by using equation.

$$\text{Angle of Repose } (\theta) = \text{Tan}^{-1} (h/r)$$

Where, h = height of pile
r = radius of the base of the pile
θ = angle of repose

Bulk density determination

Weighed quantity of the powder (W) is taken in a graduated measuring cylinder and volume (V_0) is measured and bulk density is calculated using the formula.

Bulk density (BD) = W/ V_o
W=Weight of the powder
V_O=Volume of powder

Tapped density determination

The powder sample under test was screened through sieve No.18 and the weight of the sample equivalent to 25 gm was filled in a 100 mL graduated cylinder. The mechanical tapping of cylinder was carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume Vo was noted. The difference between two tapping volume was less than 2%, Vf is considered as a tapped volume. The volume of blend was used to calculate the tapped density, Hausner's ratio and Carr's Index.

Tapped density (TD) = W/ V_f g/ml
W=Weight of the powder
V_f=Volume of powder

Carr's index

Carr's index is also known as compressibility. It is indirectly related to the relative flow rate, cohesiveness and particle size.

Carr's index was calculated by using the formula

$$\text{Carr's Index}(\%) = \frac{\text{(Tapped Density – Bulk Density)}}{\text{Tapped Density}} \times 100$$

Hausner's ratio

Hausner's ratio indicates the flow properties of the powder and measured by the ratio of tapped density to bulk density.

Hausner's Ratio = Tapped density / Bulk density.

Evaluation of post compression parameters of Prepared Tablets[14,15,16]

1) Thickness

The thickness of tablets was determined by using digital vernier calipers. Ten individual tablets from each batch were used and the results averaged. It should be in a range of ±5% variation of a standard value. The results were expressed in mm.

(2) Weight variation

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation were calculated. The test for weight variation is passed only if not more than two of the individual tablet weights deviate from the average weight by more than the allowed percentage deviation and none deviate by more than twice the percentage shown.

(3) Hardness: Ten tablets from each batch were selected and hardness was measured using Digital hardness tester to find the average tablet hardness or crushing strength.

Hardness should be in between 3-6 kg/cm^2.

(4) Friability: The friability values of the tablets were determined using a Roche friabilator. It is expressed in %. 20 tablets were initially weighed (initial weight) and transferred to friabilator. Friabilator was operated at 25 rpm for 4 min. Percentage friability was calculated using the following equation. Friability of tablets less than 1% was considered acceptable**.**

$$\% \text{ Friability} = \frac{\text{initial weight - final weight} \times 100}{\text{Initial weight}}$$

5) Disintegration Time: Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets, which is repeatedly immersed 30 times per minute into a thermostatically controlled fluid at 37°C and observed over the time described in the individual monograph. To fully satisfy the test the tablets disintegrate completely into a soft mass having no palpably firm core. Immediate release tablet should be able to release the drug with in 3 min.

***6. In vitro* dissolution test:** The dissolution studies of the prepared tablets were carried using Electro lab apparatus II. Dissolution was performed in 900 ml phosphate buffer of pH 6.8 at 37 ± 0.5°C at 100 rpm. An auto sampler, coupled to the dissolution apparatus was programmed to withdraw and replace 10 ml of the dissolution media at 0, 5, 10, 15, and 30 min. About 80% of the drug should be released within 15 min.

Dissolution parameters

Medium : Phosphate buffer, pH 6.8
Volume : 900 ml
Apparatus (paddle) : Dissolution apparatus type II of USP
Rotation speed : 75 rpm
Temperature : 37 ±0.5°C

6. Drug Release Kinetics (Dependent Model Method)

The mathematical models are used to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation coefficient (r) value in various models. The model that gives high 'r' value is considered as the best fit of the release data.

Mathematical models are
1) Zero order release model
2) First order release model
3) Hixson-crowell release model
4) Higuchi release model
5) Korsmeyer – peppas release model

RESULTS AND DISCUSSION

Twelve formulations of Rosuvastatin tablets were prepared by wet granulation method using two superdisintegrants and binder each. Superdisintegrants used were Polyplasdone XL 10 and Polyplasdone XL 100 in the concentration ranging 1% to 4%. The concentration of binder used was ranging 5% and 30%.
Results of drug excipient compatibility study indicated that the selected excipients are compatible with the drug. Hence, the selected set of excipients can be conveniently chosen in the formulation development of generic version of Crestor.

Evaluation of Granules: The granules of all the formulations were evaluated for angle of repose, LBD, TBD, compressibility index and hausner's ratio. The Bulk densities of the granules were found to be in the range of 0.439 to 0.486 g/ml. Tapped densities in the range of 0.519 to 0.555 g/ml. Carr's index 11.259 to 20.036 and Hausner's ratio was 1.126 to 1.24.From the above studies, the results of compressibility index (<15), also hausner's ratio (<1.25) indicate good flow properties of the granules. All these results indicate that the granules having free flowing nature.

Table No: 1. Formulation table of Rosuvastatin calcium tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Rosuvastatin calcium	20	20	20	20	20	20	20	20	20	20	20	20
Lactose monohydrate	--	--	--	--	--	--	--	--	50	50	50	50
Microcrystalline cellulose 101	--	--	--	--	--	--	204	201	145	137	154	151
Microcrystalline cellulose 102	195	237	219	201	180	207	--	--	--	--	--	--
Starch 1500	15	30	45	60	90	--	--	--	15	40	60	--

Maize starch	60	--	--	--	--	60	60	60	60	40	--	60
Meglumine	05	05	05	05	05	05	05	05	05	05	05	05
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Polyplasdone XL10	03	06	09	12	--	--	--	--	1.5	03	4.5	06
Polyplasdone XL100	--	--	--	--	03	06	09	12	1.5	03	4.5	06
Magnesium stearate	02	02	02	02	02	02	02	02	02	02	02	02
Total	300	300	300	300	300	300	300	300	300	300	300	300

Table No: 2. Preformulation studies

S. No	Test	Specifications	Result
a.	Description	White to off white colored crystalline powder	White powder
b.	Solubility	Freely soluble in methanol, slightly soluble in ethanol, very slightly soluble in water and acetonitrile and insoluble in aqueous solutions of pH 4 and below	Complies
c.	Loss on drying	Not more than0. 5%	0.37%
d.	Melting point	157-161 $^{\circ}$C	160.2 $^{\circ}$C
e.	Water content by KF	3.0-7.0%	3.05%
f.	Specific optical rotation	-6.0 and -12.0°	-7.27°
g.	Drug identification	Performed by FTIR	Functional groups identified
h.	Identification of λmax	Based on highest peak	Found at 248 nm

Table No: 3. Evaluation of Pre compression parameters

Batch No.	Bulk density	Tapped Density	Carr's Index (%)	Hausner's ratio
F1	0.444	0.543	18.239	1.223
F2	0.439	0.549	20.036	1.249
F3	0.464	0.529	12.287	1.140
F4	0.468	0.533	12.195	1.138
F5	0.453	0.545	16.880	1.203
F6	0.459	0.540	15.000	1.176
F7	0.459	0.529	13.232	1.1522
F8	0.465	0.524	11.259	1.126
F9	0.486	0.571	14.886	1.174
F10	0.448	0.519	13.680	1.1584
F11	0.481	0.555	13.333	1.1538
F12	0.476	0.548	13.138	1.1512

Table No: 4. Evaluation of post compression parameters

Batch No.	Average weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	D.T (min)	Assay (%)
F1	298.75±1.44	5.51±0.01	4.260±0.271	0.23	1.1	98.1
F2	299.70±1.38	4.54±0.06	5.52±0.268	0.21	1.15	99.5
F3	300.60±1.35	4.12±0.03	4.23±0.36	0.20	45sec	98
F4	299.50±1.43	4.35±0.09	6.13±0.361	0.17	53sec	99
F5	301.80.±1.43	5.42±0.02	4.0±0.213	0.19	1.05	97.2
F6	300.70±1.49	4.58±0.08	5.4±0.301	0.20	1.09	98.5
F7	298.55±1.39	4.31±0.19	4.2±0.310	0.23	44sec	98.7
F8	299.90±1.41	4.47±0.11	6.1±0.213	0.21	49sec	99.9
F9	300.75±1.44	4.49±0.14	4.36±0.403	0.20	1.3	99.8
F10	301.70±1.44	4.67±0.17	4.50±0.415	0.17	1.8	101.4
F11	299.70±1.44	4.64±0.15	4.40±0.353	0.19	43sec	99.9
F12	300.32±1.44	4.8±0.11	5.52±0.347	0.19	48sec	100.2

Evaluation of Tablets

The average weights of the tablets were found to be in the range of 301.80±1.43 to 298.55±1.39 mg. Thickness in the range of 4.12±0.03 to 5.51±0.01 mm, Hardness 4.0±0.310 to 6.13±0.361kg/cm2 and Friability was 0.17 to 0.23 %. The disintegrating time of the tablets were found to be in the range 43 sec to 1.8 min and assay in the range of 97.2 to 101.4 %.From the above results, all

the formulations showed uniform thickness, hardness of the tablets were satisfactory and the percentage friability for all the formulations was below 1% indicating that friability is within the prescribed limits. Good and uniform drug content (>98%) was observed within the batches of different tablet formulations.

***In vitro* Dissolution Studies**

Tablet blends were prepared and micromeritic studies were carried out for those blends. Pre-compressional parameters such as bulk density, tapped density, compressibility index, and Hauser's ratio for physical mixtures of immediate release formulations (F1 – F12) were evaluated. The calibration curve was constructed having regression value of 0.999. Assay values of the formulations were observed in the range of 98 to 102%. Compatibility studies were performed and it was observed that all the ingredients used were compatible with the drug. Formulation (F11) was formulated by including 1.5% polyplasdone XL 10 and polyplasdone XL 100 each and 20% binder. The results showed disintegration was within limits and 100% drug release was found in 30 min .So, formulation (F11) was taken as optimized formulation. Accelerated stability studies were performed for this batch. Assay and dissolution studies were performed for the optimized formulation (F-11) at different time intervals. All the parameters were found to be satisfactory, dissolution studies were performed and it was found that formulation F11 have shown best results. The formulations F11, followed first order kinetics, Krosmeyer-Peppas exponential coefficient 'n' > 1 indicates that the release was governed by Super case II transport.

Table No: 5. Dissolution profile of different formulations (F1 to F4)

Time (min)	F1	F2	F3	F4
5	21.59±0.14	19.63±0.76	30.8±0.27	27.5±0.73
10	36.73±0.61	34±0.45	50.2±0.26	44.9±0.26
15	42.3±0.48	39.72±0.79	57.7±0.38	52.5±0.36
20	48.2±0.46	44.63±0.54	64.8±0.72	59.7±0.38
30	51.8±0.62	48.95±0.73	79.21±0.16	72.18±0.92
45	56.7±0.45	53.8±0.24	82.8±0.82	75.6±0.28
60	81.2±0.37	77.5±0.62	92.8±0.24	83.15±0.82

Table No: 6. Dissolution profile of different formulations (F5 to F8)

Time (min)	F5	F6	F7	F8
5	22.86±0.54	19.99±0.65	32.02±0.65	28.03±0.26
10	38.54±0.24	35.91±0.06	53.71±0.27	45.61±0.38
15	42.034±0.66	40.53±0.35	58.5±0.38	52.62±0.37
20	48.66±0.56	45.63±0.73	67.11±0.32	62.38±0.93
30	52.92±0.48	49.86±0.37	80.92±0.27	74.81±0.38
45	57.85±0.59	54.62±0.43	85.41±0.49	82.04±0.47
60	81.05±0.37	78.46±0.27	93.11±0.86	91.46±0.54

Table No: 7. Dissolution profile of different formulations (F9 to F12)

Time (min)	F9	F10	F11	F12
5	23.53±0.26	20.43±0.87	32.47±0.56	27.64±0.62
10	37.95±0.83	32.669±0.35	64±0.69	46.173±026.
15	44.82±0.46	40.64±0.88	82±0.65	59.93±0.38
20	48.82±0.58	45.95±0.35	91±0.41	68.82±0.15
30	54.32±0.26	50.64±0.78	99±0.93	80.62±0.32
45	58.5±0.47	55.99±0.34	100±0.23	83.85±0.15
60	82.66±0.27	79.16±0.31	---	91.11±0.17

Table No: 8. Drug Release Kinetics & Mechanisms

Formulations	Correlation coefficient				K value (mg/hr)
	Zero order	First order	Higuchi	Peppas	
F1	0.9362	0.9888	0.8758	0.9880	6.9122
F2	0.9518	0.9925	0.8838	0.9909	5.8946
F3	0.9626	0.9922	0.8830	0.9920	4.9423
F4	0.9839	0.9959	0.8989	0.9945	3.8055
F5	0.9953	0.9977	0.9233	0.9935	2.9874
F6	0.9918	0.9942	0.9197	0.9900	2.5232
F7	0.9311	0.9881	0.8728	0.9818	6.7358

F8	0.9366	0.9858	0.8691	0.9824	5.4095
F9	0.9674	0.9902	0.8809	0.9828	5.2566
F10	0.9841	0.9958	0.9007	0.9837	3.9971
F11	0.9868	0.9945	0.9014	0.9813	3.0827
F 12	0.9841	0.9903	0.9011	0.9761	2.6472

Table No: 9. Accelerated stability studies of optimized formulation (F11) At 40±2°C & 75±5% RH

S.No	Time period	Description (color)	Friability (%)	Hardness (Kg/cm^2)	Assay (%)
1	Initial	White to off - white	0.19±0.05	4.30±0.02	99.9
2	1st month	White to off - white	0.21±0.04	4.22±0.05	99.8
3	2nd month	White to off - white	0.21±0.05	4.20±0.03	99.8
4	3rd month	White to off - white	0.21±0.05	4.20±0.03	99.8

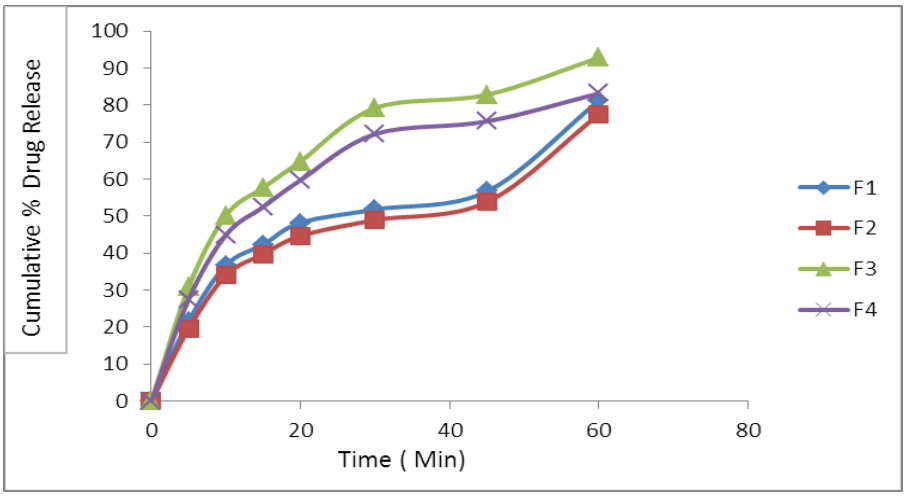

Fig No:1. In vitro drug Release Profiles of F1-F4 Formulations

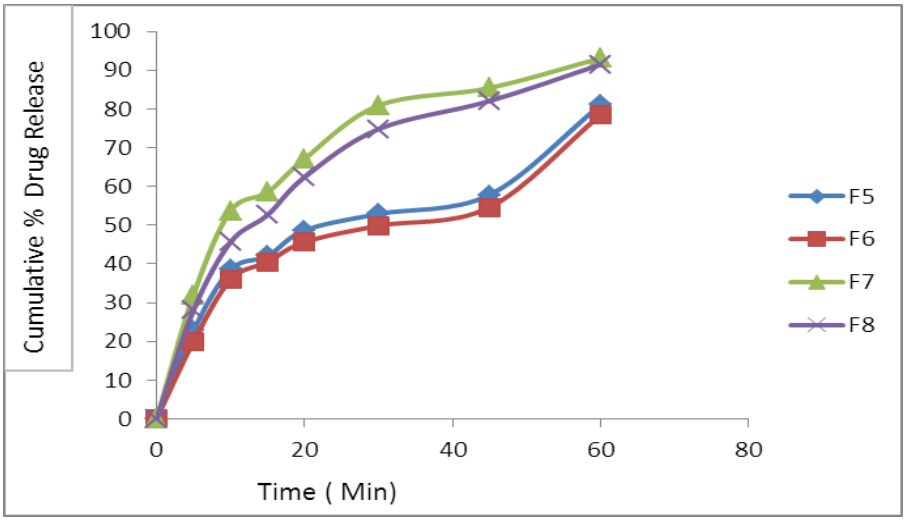

Fig No: 2. In vitro drug Release Profiles of F5-F8 Formulations

Table No: 10. Dissolution profile of optimized batch (F11) after Accelerated stability studies at 40±2°C & 75±5% RH

S. No	Time period	% drug release			
		Time (min)			
		10	15	20	30
1	Initial	64±0.24	82±0.37	91±0.27	99±0.31
2	1st month	63.8±0.56	81.7±0.83	91±0.50	98.8±0.15
3	2th month	63.4±0.24	81.1±0.35	90.6±0.78	98.6±0.43
4	3rdmonth	63.2±0.37	80.9±0.24	90.5±0.45	98.4±0.53

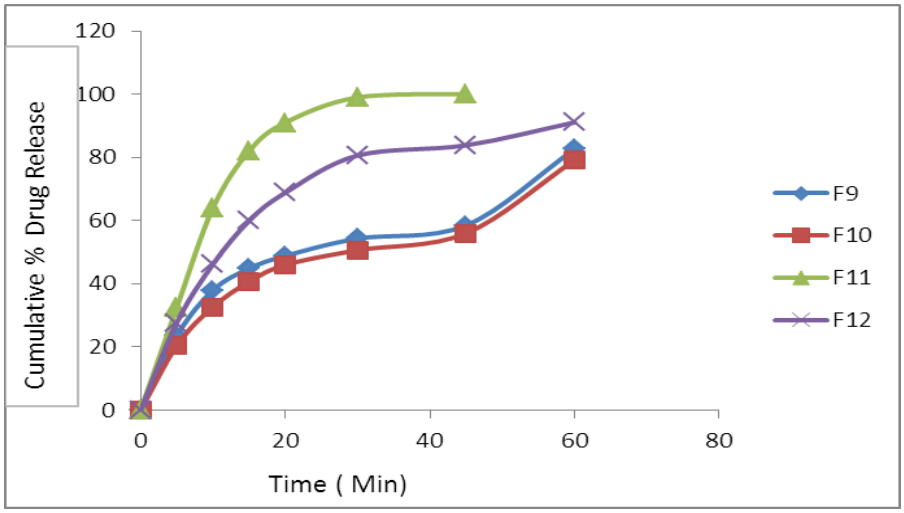

Fig No: 3. In vitro drug Release Profiles of F9-F12 Formulations

Stability Studies

The selected formulation (F11) was subjected to stability testing as per ICH guidelines. Indicated that the tablets did not show any physical changes i.e. color change, friability, and hardness during the study period. The drug content was found to be above 97% at the end of 30 days. This indicates that the formulation F11 tablets were fairly stable at accelerated storage conditions. However real time for stability studies 2years required to establishing the developed product.

CONCLUSION

From the above experimental results it can be concluded that immediate release tablets of Rosuvastatin calcium can be prepared by using different proportion & combination of superdisintegrants and binder and we selected F11 as best formulation based on dissolution profile and physical characteristics. Formulation (F11) showed total drug release in 30 min when compared to other formulations and showed fair flow properties. The formulations F11, followed first order kinetics, Krosmeyer-Peppas exponential coefficient 'n' > 1 indicates that the release was governed by Super case II transport.

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