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Original Article

Formulation and evaluation of rosuvastatin solid dispersions

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ABSTARCT

The present study was to investigate the technique in enhancement of dissolution rate of Rosuvastatin using solid dispersion method. Development of solid dispersion compacts is one such technology to enhance dissolution rate of poorly soluble drugs, thereby improving efficacy of drug molecules. For this study PEG 4000 and Polaxomer were used as carriers in different rations and solid dispersions were prepared. Tablets of solid dispersions were prepared using Polyplasdone XL as super disintegrate. All formulations were evaluated for pre and post compression studies and those results were found to be within limits. Dissolution studies revealed that F2 formulation which had Drug and PEG4000 in the ratio of 1:2 along with a super disintegrate was an optimised formulation based on its fastest drug release. The optimised formulation was compared with F9 formulation which does not contain super disintegrate. That comparison data revealed that drug release was high when it contains super disintegrate.

Keywords: Rosuvastatin, Solid dispersion, PEG 4000, Polaxomer, Polyplasdone XL.

INTRODUCTION

The main objective of this study was to enhance the aqueous solubility of Rosuvastatin by suitable solid dispersion technique. Development of solid dispersion compacts is one such technology to enhance dissolution rate of poorly soluble drugs, thereby improving efficacy of drug molecules. One of the major challenges in drug development nowadays is poor solubility, as estimated 40% of all newly developed drugs are poorly soluble or insoluble in water. In addition, up to 50% of orally administered drug compounds suffer from formulation problems related to their low solubility and high lipophilicity. Bioavailability of poorly water-soluble drugs is inadequate by their solubility and dissolution rate. Especially for class II substances according to the Bio pharmaceutics Classification System (BCS), the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids. The term "water-insoluble drugs" includes those drugs that are "sparingly water-soluble" (1 part solute into 30 to 100 parts of water), "slightly water-soluble" (1 part solute into 100 to 1000 parts of water), "very slightly water-soluble" (1 part solute into 1000 to 10,000 parts of water), and "practically water-insoluble" or "insoluble" (1 part solute into 10,000 or more parts of water).[1]

Techniques for Dissolution Enhancement[2]

There are various techniques available to improve the solubility subsequently improves dissolution rate of poorly soluble drugs. Some of the approaches to improve the solubility and dissolution rate are:

1. Micronization.
2. Nanonization.
3. Salt Form.
4. Use of Surfactants.
5. Use of Co-Solvents.
6. Use of Metastable Polymorphs.
7. Drug Dispersion in Carriers:

a) Solid Solutions.
b) Eutectic Mixtures.
c) Solute–Solvent Complexation Reactions.
d) Solid Dispersion.
e) High Pressure Homogenization.
f) Nanomorph Technology (Nt).
g) Evaporative Precipitation.

Solid dispersion method allows the preparation of physically modified forms of the drug that are much more rapidly soluble in water than the pure compound. The most regularly used hydrophilic carriers for solid dispersions include polyvinyl pyrrolidone, polyethylene glycols, and plasdone-S630. Surfactants may also be used in the

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formation of solid dispersions. Surfactants like Tween-80, Myrj-52, Pluronic-F68 and sodium lauryl sulfate are used as water-soluble polymer, as an excellent universal carrier for improving the dissolution rate and oral absorption of water-insoluble drugs. Various methods are used in preparation of solid dispersion like fusion (melting), solvent evaporation, lyophilization (freeze drying), melt agglomeration, extrusion, spray drying, surfactant use, electrostatic spinning, and super critical fluid technology. In the preparation, the use of vast amount of organic solvent may cause environment and safety concern. The surface solid dispersions were introduced to overcome this limitation. But still there are limitations for this technique which be positioned with the use of solvents for preparation of surface solid dispersions. Finding an appropriate solvent to dissolve the drug and carrier is difficult. Complete removal of solvent is complicated and residual solvent cause toxicity.

MATERIALS AND METHODS

Materials: Rosuvastatin drug was procured from Sura Labs, Hyderabad as a gift sample. PEG 4000, Polaxomer and Mannitoln was procured form Nihar chemicals Ltd. All other excipients used were of analytical grade.

Methodology:

Preformulation Studies [3]: Pre formulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substance are characterized with the goal of designing optimum drug delivery system.

Drug-Excipients compatibility studies: Drug Excipients compatibility studies were carried out using FTIR by mixing the drug with various excipients in different proportions.

Analytical method development for Rosuvastatin:

a) Determination of Absorption maxima: A spectrum of the working standards was obtained by scanning from 200-400nm against the reagent blank to fix absorption maxima. The λmax was found to be 239nm. Hence all further investigations were carried out at the same wavelength.

b) Preparation of standard graph in pH 6.8 medium: 10 mg of Rosuvastatin was dissolved in 10 ml methanol (Primary stock). From this primary stock 1 ml was transferred to another volumetric flask made up to 10ml with Phosphate buffer of pH 6.8 (Secondary stock). From this secondary stock was taken to produce 4, 8, 12, 16 and 20µg/ml respectively. The absorbance was measured at 239 nm by using a UV spectophotometer.

Formulation Development: Solid dispersions were prepared by solvent evaporation method. Methanol was used as solvent. Water soluble polymers such as PEG 4000 and Polaxomer were selected as carriers. Drug and Carriers were taken in different ratios stated in the formulation table no.1. The prepared solid dispersions were passed through the sieve no 20 to get uniform sized particles. The solid dipersions were mixed with required quantities of super disintegrate, diluent, lubricant and glidant as mentioned in table no.2. The blend was evaluated for precompression parameters.

Evaluation of tablets:[4,5,6]

Pre compression parameters: Measurement of Micromeritic Properties of Powders

Angle of repose: The angle of repose of API powder is determined by the funnel method. The accurately weight powder blend are taken in the funnel. The height of the funnel is adjusted in a way that, the tip of the funnel just touched the apex of the powder blend. The powder blend is allowed to flow through the funnel freely on to the surface. The diameter of the powder cone is measured and angle of repose is calculated using the following equation.

$$\tan \theta = h/r \quad \ldots\ldots\ldots\ldots \quad (1)$$

Where, h and r are the height and radius of the powder cone.

Bulk density: The powder sample under test is screened through sieve No.18 and the sample equivalent to 25 gm is weighed and filled in a 100 ml graduated cylinder and the power is leveled and the unsettled volume, V_0 is noted. The bulk density is calculated in g/cm^3 by the formula.

$$\text{Bulk density} = M/V_0 \quad \ldots\ldots\ldots \quad (2)$$

M = Powder mass

V_0 = apparent unstirred volume

Tapped density: The powder sample under test is screened through sieve No.18 and the weight of the sample equivalent to 25 gm filled in 100 ml graduated cylinder. The mechanical tapping of cylinder is carried out using tapped density tester at a nominal rate for 500 times initially and the tapped volume V_0 is noted. Tappings are proceeded further for an additional tapping 750 times and tapped volume, V_b is noted. The difference between two tapping volume is less the 2%, V_b is considered as a tapped volume V_f. The tapped density is calculated in g/cm^3 by the formula.

$$\text{Tapped density} = M/V_f \quad \ldots\ldots\ldots\ldots \quad (3)$$

M =weight of sample power taken

V_f =tapped volume

Compressibility Index: The Compressibility Index of the powder blend is determined by Carr's compressibility index to know the flow character of a powder. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD) /TD] x100 …….. (4)

Hausner's ratio: The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hasner's ratio. It is calculated by the following equation.

H = ρT / ρB …….. (5)

Where ρT = tapped density, ρB = bulk density

Post compression parameters:

a) Thickness: The thickness of tablets was determined by using Digital micrometer. Ten individual tablets from each batch were used and the results averaged.

b) Weight variation: Ten tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation three batches were calculated. It passes the test for weight variation test 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. It was calculated on an electronic weighing balance.

c) Friability [7]: The friability values of the tablets were determined using a Roche-type friabilator. Accurately weighed ten tablets were placed in Roche friabilator and rotated at 25 rpm for 4 min. Percentage friability was calculated using the following equation.

Friability = ([w_O – w] /w_O) × 100

Where; w_O = weight of the tablet at time zero before revolution.

w = weight of the tablet after 100 revolutions.

d) Assay: The content of drug carried out by take five randomly selected tablets of each formulation. The five tablets were grinded in mortar to get powder; this powder was dissolved in pH 6.8 phopshate buffer by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at 239 nm using UV spectrophotometer and calculated.

e) Disintegration test [8,9]: Six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 10 minutes and the basket was lift from the fluid, observe whether all of the tablets have disintegrated.

f) Dissolution Studies: The dissolution study of was performed over a 1 hr period using USP type II (paddle) Dissolution Testing Apparatus (Lab india) 900ml of pH 6.8 Phosphate buffer was used as dissolution medium agitated at 50 RPM, at temperature of 37º± 0.5ºC. 5 ml samples were withdrawn at 5, 10, 15, 20, 30, 45 and 60 min to estimate the drug release. The samples were analyzed by UV Spectrophotometry at their respective λ max value.

RESULTS AND DISCUSSION

Determination of λ max: The prepared stock solution was scanned between 200-400 nm to determine the absorption maxima. It was found to be 239 nm.

Calibration curve of Rosuvastatin: The standard graph of Rosuvastatin was obtained and good correlation was obtained with R^2 value of 0.999. The medium selected was pH 6.8 phosphate buffer. The standard graph values of Rosuvastatin are tabulated in table no.3. and the graph obtained is mentioned in fig.No.1.

Drug – Excipient Compatibility: Drug and excipients compatibility Studies were performed By using FTIR and results confirmed the compatibility of the drug with the used excipients. The FTIR spectra of pure drug and the final formulation blend of the optimised formula is depicted in fig.No. 2.

Characterization of Precompression Blend: The precompression blend of Rosuvastatin solid dispersions were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio**.** Angle of repose was less than 28^0, Carr's index values were less than 11 for the precompression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties (table No.4).

Evaluation of Tablets:

Physical Evaluation of Rosuvastatin solid dipersion tablets: The results of the weight variation, hardness, thickness, friability, and drug content of the tablets are given in Table 5. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 2.2±0.31 to 2.8±0.26 kg/cm^2 and the friability values were less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged from 2.1±0.15 to 2.4±0.16 mm. All the formulations satisfied the content of the drug as they contained 95-100% of Rosuvastatin and good uniformity in drug content was observed. Thus all the physical attributes of the

prepared tablets were found to be practically within control limits.

In vitro release studies: The drug release rate was studied using the USP type II dissolution test apparatus. The dissolution medium was 900 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 1 hr and analysed after appropriate dilution by using UV Spectrophotometer at 239 nm. Results were depicted in table No.6, fig no.3&4. From the dissolution data, Formulations containing PEG 4000 as carrier was shown good drug release compared to formulations containing Polaxomer as carrier. F5 to F8 formulations were not shown maximum drug release within 60 min. Hence those formulations were not taken into consideration.

Among all formulations F2 formulations containing Drug and PEG 4000 in the ratio of 1:2 was shown maximum drug release at 10 min. Hence F2 formulation was concluded as optimised formulation. After getting the optimised formulation, that was compared with F9 formulation which does not contain Polyplasdone XL as super disintegrate. (F2 – drug, PEG4000 and Polyplasdone XL, F9- drug and PEG 4000 only). From the comparison graphs revealed that Formulation F9 (without Super disintegrate) was shown maximum drug release at 30 min (fig.No.5). Hence Among all formulations F2 was considered as optimised formulation.

CONCLUSION

Solid dispersions were prepared using PEG 4000 and Polaxomer as carriers in different rations. Tablets of solid dispersions were prepared using Polyplasdone XL as super disintegrate. All formulations were evaluated for pre and post compression studies and those results were found to be within limits. Dissolution studies revealed that F2 formulation which had Drug and PEG4000 in the ratio of 1:2 along with a super disintegrate was an optimised formulation based on its fastest drug release. The optimised formulation was compared with F9 formulation which does not contain super disintegrate. That comparison data revealed that drug release was high when it contains super disintegrate.

Table no: 1 Formulation of solid dispersion showing various compositions

	SD1	SD2	SD3	SD4	SD5	SD6	SD7	SD8
Rosuvastatin	100	100	100	100	100	100	100	100
PEG 4000	100	200	300	400				
Polaxomer					100	200	300	400

Table no: 2 Formulation of fast dissolving tablet by using solid dispersion

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rosuvastatin equivalent to 5mg	SD1	SD2	SD3	SD4	SD5	SD6	SD7	SD8	SD2
Polyplasdone XL	10	10	10	10	10	10	10	10	-
Mg.stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
MCC	QS	QS	QS	QS	QS	QS	QS	QS	QS
Total weight	150	150	150	150	150	150	150	150	150

Table no: 3 Standard Graph values of Rosuvastatin at 239 nm in pH 6.8 phosphate buffer

Concentration (µg/ml)	**Absorbance**
0	0
4	0.184
8	0.336
12	0.521
16	0.68
20	0.85

Table no: 4. Physical properties of precompression blend

Formulation Code	Angle of repose (Θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio
F1	25.10	0.53	0.59	10.16	1.11
F2	25.43	0.54	0.64	15.62	1.18
F3	25.41	0.54	0.58	6.89	1.07
F4	26.40	0.51	0.61	16.39	1.19
F5	27.12	0.58	0.63	7.93	1.08
F6	25.31	0.59	0.64	7.81	1.08
F7	26.11	0.56	0.63	11.11	1.12
F8	26.15	0.53	0.58	8.62	1.09
F9	26.10	0.54	0.61	11.47	1.12

Table No. 5: Physical Evaluation of Rosuvastatin tablets

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Content uniformity(%)
F1	150±1.24	2.1±0.15	2.5±0.24	0.42	99.44
F2	148±1.63	2.4±0.13	2.2±0.31	0.34	100.84
F3	151±1.11	2.2±0.18	2.6±0.19	0.36	96.09
F4	149±1.52	2.1±0.16	2.8±0.13	0.56	98.34
F5	145±1.16	2.3±0.13	2.8±0.26	0.48	95.23
F6	152±0.91	2.4±0.12	2.4±0.29	0.51	97.35
F7	147±1.24	2.4±0.16	2.5±0.33	0.41	98.94
F8	149±1.82	2.1±0.17	2.6±0.28	0.43	99.48
F9	150±1.13	2.4±0.16	2.5±0.19	0.51	100.03

Table No: 6: Invitro drug release results for all formulations

TIME(Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	42.34	69.85	20.36	14.82	16.38	13.92	10.84	8.71	19.46
10	67.14	99.63	39.61	28.67	30.62	22.87	19.63	15.93	32.51
15	98.62		61.82	41.71	36.31	31.66	27.32	23.86	58.17
20			84.66	50.12	43.29	39.45	36.18	31.94	79.64
30			95.63	63.46	56.91	51.63	48.26	40.68	96.82
45			95.63	75.14	72.63	69.48	59.72	51.34	96.82
60				88.62	91.62	83.47	74.18	63.56	

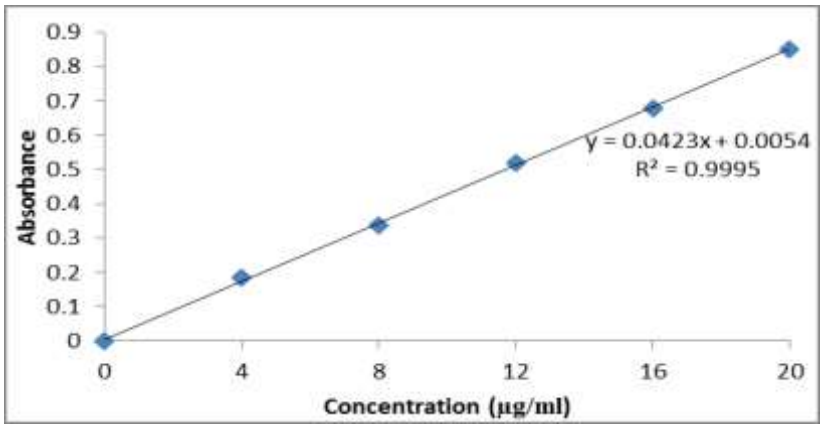
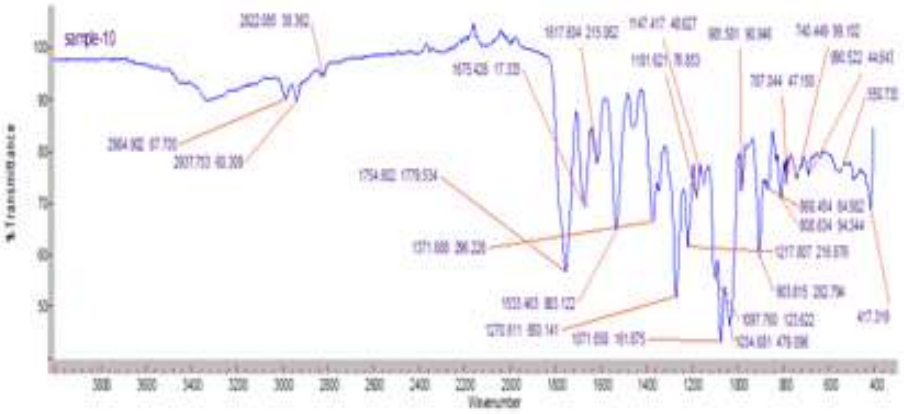
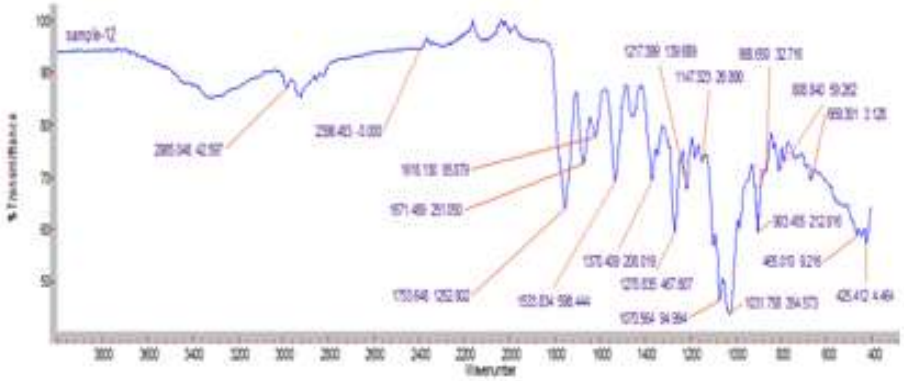


Fig No 1: Standard Curve of Rosuvastatin.



FTIR SPECTRA OF PURE DRUG



FTIR SPECTRA OF OPTIMISED FORMULA

Fig.No.2: FTIR spectra for Drug – Excipient Compatibility studies.

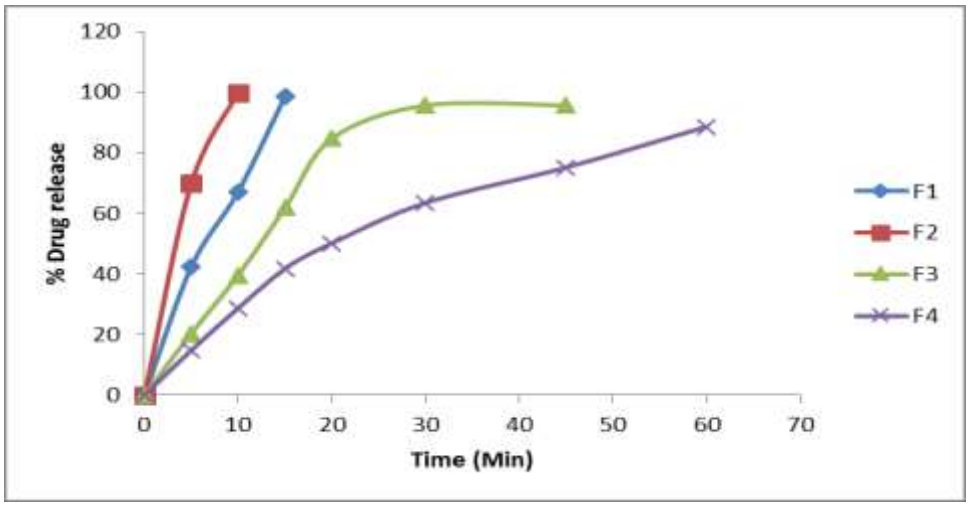


Fig no: 3. Invitro dissolution data for formulations F1-F4 containing PEG 4000 as carrier.

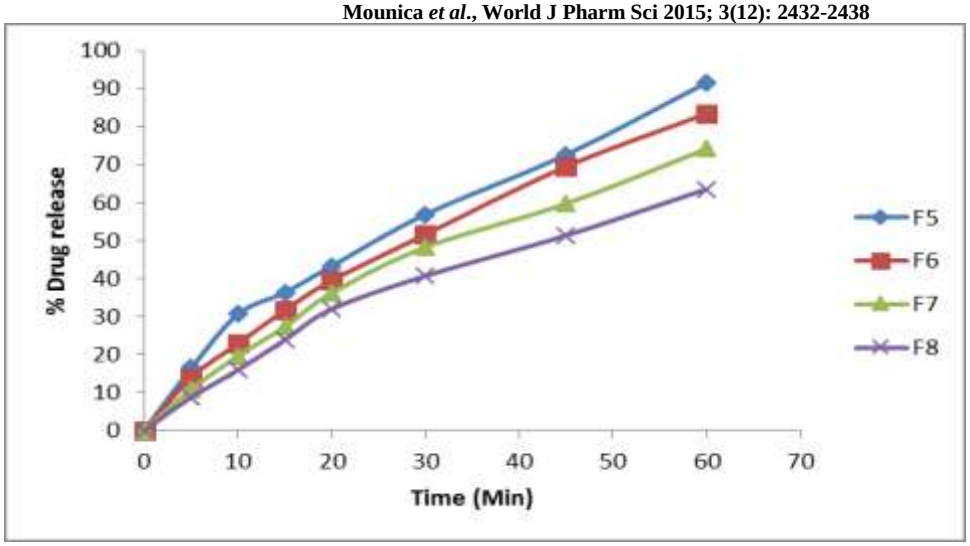


Fig No: 4. Invitro dissolution data for formulations F5-F8 containing Polaxomer as carrier.

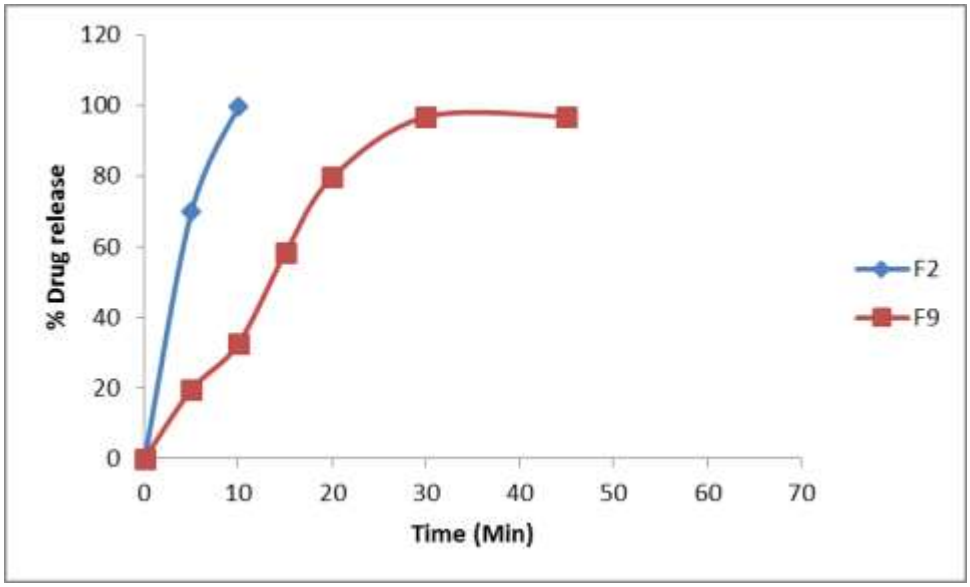


Fig No: 5. Comparison dissolution data for formulations F2 and F9 containing PEG 4000 as carrier

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