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SOLUBILITY ENHANCEMENT OF POORLY WATER SOLUBLE DRUG RIVAROXABAN BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

Solid dispersions in water soluble carriers have attracted considerable interests as a mean of improving the dissolution rate & hence possibly bioavailability range of hydrophobic drugs. The poor solubility of rivaroxaban leads to poor dissolution & hence variation in bioavailability. In present study solid dispersion using various carriers like mannitol & lactose in different ratios were prepared by solvent evaporation method. The prepared solid dispersions were characterized for drug content, asolubility & dissolution rate. The dissolution rate substantially improved for rivaroxaban from its solid dispersions compared with pure drug. Dissolution rate increased with increase in carrier content. The dissolution rate was increased 3 folds with solid dispersions containing 1:4 of drug: lactose. The granules of rivaroxaban solid dispersion containing 1:4 of drug: lactose ratio was prepared by wet granulation method using polymer such as ethyl cellulose & HPMC. The prepared granules were evaluated to preformulation studies such as angle of repose, bulk density, tapped density, compressibility index & hausner's ratio. All the parameters shows that the granules having good flow properties. These granules had converted into the capsule forms. Then the formulated capsules were taken to the evaluation studies. We can conclude that all the parameters were within the acceptable limits.

KEYWORDS: Solid dispersion, Rivaroxaban, Dissolution rate, Solvent evaporation, Solubility.

INTRODUCTION

Solubility is an important determinant in drug liberation and hence drug absorption, which plays a key role in oral bioavailability of formulations. The dissolution rate of a drug directly depends upon its solubility. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure Most of the new drugs have poor water solubility; there by pose a difficulty in formulating into drug delivery systems.[1] solubility enhancement of poorly water soluble drugs is one of the necessary Preformulation steps in the pharmaceutical product development research. The poor solubility & low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. Especially for class II (low solubility & high permeability) substances according to the BCS, the bioavailability may be enhanced by increasing the solubility & dissolution rate of the drug in the gastrointestinal fluids. As for BCS class II drugs rate limiting step is drug release from the dosage form & solubility in the gastric fluids & not the absorption, so increasing the solubility in turn increases the bioavailability for BCS class II drugs. Many methods are available to improve these characteristics including salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of these methods and involved a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting solvent method.[1,2,3]

EXPERIMENTAL

Materials

Rivaroxaban was obtained as a gift sample from Megafine Pharma Pvt Ltd. (Mumbai), Mannitol, Lactose, Hydrochloric acid, Cetyl alcohol, Ethyl cellulose, HPMC, Sodium Bicarbonate, starch & Talc were procured from Pallav Chemicals (Mumbai). All materials used were of analytical grade.

Method estimation

Stock solution was prepared by dissolving 100 mg of accurately weighed Rivaroxaban in 100 ml of Dimethyl sulfoxide to get 1 mg/ml solution. Further 10 ml of this solution was pipette out into 100 ml volumetric flask and made up to 100 ml with Dimethyl sulfoxide to get 100µg/ml solution. Further 10 ml of this solution was pipette out into 100 ml volumetric flask & made up to 100 ml Dimethyl sulfoxide to get 10 µg/ml solutions. From this 0.1, 0.2, 0.4, 0.6, 0.8, 1.0 ml solution was pipette out into a series of 10 ml volumetric flask and were made

up to 10 ml with Dimethyl sulfoxide respectively. The absorbance of resulting solution was measured at 270 nm[4] against the blank.

Preliminary solubility studies

Solubility measurements of Rivaroxaban were performed according to publish method.[5] Solubility measurements of Rivaroxaban were performed. An excess amount of Rivaroxaban was added to 10 ml of aqueous solution of water soluble carriers like Mannitol & Lactose in the various ratios such as 1:1, 1:2 and 1:4 in screw capped bottles. Samples were shaken in an orbital shaker for 24 hrs at room temperature. Subsequently, the suspensions were filtered through a whatman filter paper grade no. 1. Filtered solution diluted properly with Methanol. The diluted solution analyzed for the Rivaroxaban in UV 270 nm.

Preparation of solid Dispersion

Solid dispersion is one of the most commonly used techniques to improve the solubility of water insoluble drugs which in turn improves the bioavailability. Rivaroxaban solid dispersions were prepared by using carriers (i.e. D-Mannitol & Lactose) in proportions viz. 1:1, 1:2, and 1:4 (Drug : Carrier) by solvent evaporation method. The drug and carrier was dissolved in Dichloromethane & triturated dry mortar until the solvent evaporated and clear film of drug & carrier was obtained. The resultant solid dispersion was scraped out with a spatula. Dispersions were pulverized in a mortar and pestle and passed through a sieve no 80. Then the prepared formulations were stored in desiccators until further use.[6]

Table no. 1: Formulation plan of rivaroxaban solid dispersion.

Sr. No.	Formulation	Composition	Drug : Polymer
1	SDM1	Rivaroxaban + Mannitol	1:1
2	SDM2	Rivaroxaban + Mannitol	1:2
3	SDM4	Rivaroxaban + Mannitol	1:4
4	SDL1	Rivaroxaban + Lactose	1:1
5	SDL2	Rivaroxaban + Lactose	1:2
6	SDL4	Rivaroxaban + Lactose	1:4

Evaluation of solid dispersion

Drug content

Solid dispersion equivalent to 10 mg of rivaroxaban were weighed accurately & dissolved in the 10 ml of Dimethyl sulfoxide. The solution was filtered, diluted suitably & drug content was analyzed at 270 nm by UV spectrophotometer. The actual drug content was calculated using the following equation as follows;

% Drug content (DC) = (Mact/Mt) X 100

Mact = Actual amount of drug in solid dispersion

Mt = Theoretical amount of drug in solid dispersion.

Determination of flow properties

Bulk density & tapped density

Accurately weighed amount of solid dispersions were transferred to a 100 ml graduated cylinder to measure the apparent volumes or bulk volume (Vb). The measuring cylinder was tapped for fixed period of time & tapped volume (Vt) occupied in the cylinder was measured. The bulk density & tapped/ true density were calculated in gram per milliliter by the following formula:

Bulk Density (BD) = Mass/Volume = M/Vb

Tapped Density (TD) = Mass/Tapped Volume = M/Vt

Carr's Index (CI) & Hausner's ratio (HR)

Carr's index & Hausner's ratio are calculated by using following formulae

$$CI = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} X\ 100$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of repose

A funnel was fixed in the stand in such a way that the top of the funnel was at the height of 6 cm from the surface. The solid dispersions were passed from the funnel was at height of 6 cm from the surface. The height & radius of the heap were measured & the angle of repose was calculated using the equation.[11]

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

h = Height of the heap,

r = Radius of the heap

In Vitro release study

In vitro dissolution studies were performed for prepared solid dispersion. The following conditions were maintained for the dissolution process.[12]

1. Instrument: Dissolution test apparatus.

2. Apparatus: paddle type.
3. Temperature: 37 ± 0.5^0C.
4. RPM: 75.
5. Dissolution medium: Acetate buffer pH 4.5
6. Volume of medium: 900 ml.
7. Sampling intervals: 60, 120, 180, 240, 300 and 360 minutes.
8. Sample volume: 5 ml withdrawn and replace with 5 ml of Acetate buffer.

Preparation of granules

Rivaroxaban solid dispersions, Ethyl cellulose, HPMC, Cetyl alcohol and Sodium bicarbonate were weighed by electronic balance and mixed well in a mortar. Required amount of starch was taken in a beaker. Small amount of water was taken in it and stirred until thick past was formed without lumps. Excess water was boiled in a separate beaker for 15 min and then added to the paste when stirring to form the mucilage. The mucilage was slowly added to the powder mix to form a damp mass that breaks with a snap when pressed between thumb and index finger. The damp mass was passed through the sieve and the granules were collected on a dry tray. The granules were dried in a hot air oven at 60°C for 2 hrs. Then the dried granules were passed through sieve. The granules were filled in the empty gelatin capsule shell by hand filling capsule machine.[7,8]

Evaluation of granules flow characteristics[13,14,15]

Bulk density

A known quantity of granules was poured into the measuring cylinder carefully level the granules without compacting, if necessary & read the unsettled apparent volume (V), to the nearest graduated unit. Calculate the bulk density, in gm per ml, by the formula m/v.

Tapped density

A known quantity of granules were taken in a measuring cylinder & tapped on mechanical tapping apparatus for 5 minutes. The initial 7 final volumes were noted.

$$\textbf{Tapped density} = \frac{\textbf{volume of granules}}{\textbf{Final volume after tapping}}$$

Angle of repose

The frictional forces in a loose powder or granules can be measured by angle of repose. This is maximum angle possible between the surface of pile of powder or granules & the horizontal plane. The value of angle of repose are calculated by using the following formula,

$$\tan\theta = \frac{h}{r}$$

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

Where θ = Angle of repose, h = Height of the heap and r = Radius of the heap.

Composition of solid dispersion capsules.

Table no. 2: Composition of rivaroxaban solid dispersion capsules.

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Solid dispersion equivalent to Rivaroxaban	100	100	100	100	100	100
Cetyl alcohol	q.s…	q.s...	q.s...	q.s...	q.s...	q.s...
Ethyl cellulose	125	100	75	50	25	-
HPMC	-	25	50	75	100	125
Starch	15	15	15	15	15	15
Sodium bicarbonate	25	25	25	25	25	25
Talc	2.5	2.5	2.5	2.5	2.5	2.5

Determination of In-Vitro dissolution study

Dissolution study was carried out in USP-II type dissolution apparatus (Paddle type). Dissolution study was performed at 75rpm in 900 ml Acetate buffer 5 ml of sample was withdrawn at a predetermined interval and the volume of dissolution medium was maintained by adding same volume of dissolution medium. Absorbance of these solutions were measured using a UV-visible spectrophotometer.[16]

RESULT AND DISCUSSION

Method of estimation

Rivaroxaban was estimated by UV spectrophotometric method by measuring the absorbance at 270 nm. The method was validated for linearity, accuracy, precision, and interference. The method obeyed beers Law in the concentration. (R^2 = 0.998).

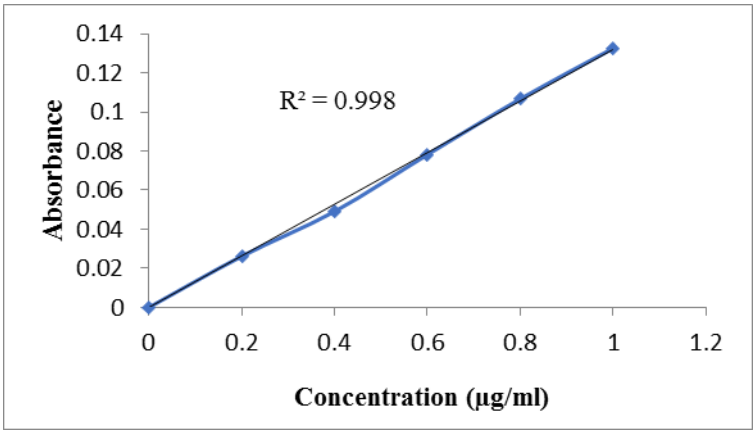

Fig. no. 1: Calibration Curve of Rivaroxaban.

Preliminary solubility study

Table no. 3: Preliminary solubility studies of drug.

Sr. No.	Drug : Carrier	Solubility (µg/ml)
1	Pure drug	4.7
2	Rivaroxaban + Mannitol (1:1)	9.57
3	Rivaroxaban + Mannitol (1:2)	11.41
4	Rivaroxaban + Mannitol (1:4)	14.53
5	Rivaroxaban + Lactose (1:1)	20.51
6	Rivaroxaban + Lactose (1:2)	27.23
7	Rivaroxaban + Lactose (1:4)	31.89

In case of solid dispersions initially preliminary solubility analysis were carried out to select the appropriate water soluble carriers for the preparation of solid dispersion in which pure drug solubility found to be 4.7 mcg/ml. From this Mannitol & Lactose in the ratio of 1:1, 1:2, 1:4 was selected for the preparation of the solid dispersion. Complete composition of six formulations showed. The preliminary solubility study of Rivaroxaban was carried out for pure form as well as for drug: carrier mixture forms as shown in Table no. 8.1. The solubility of pure Rivaroxaban was found to be 4.7 mg/ml. the preliminary solubility for drug: mannitol ratios 1:1, 1:2, 1:4 was observed 9.57 mg/ml, 11.41 mg/ml, 14.53 mg/ml respectively. On another hand, drug : lactose ratios 1:1, 1:2, 1:4 respectively showed 20.51 mg/ml, 27.23 mg/ml, 31.89 mg/ml preliminary solubility. The drug: lactose ratio 1:4 showed higher solubility as compared to drug : mannitol ratio 1:4 as showed in fig. no.2.

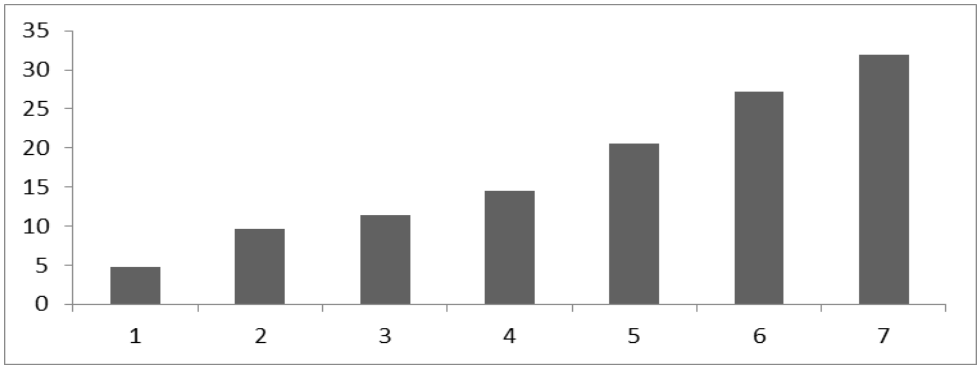

Fig. no. 2: Preliminary Solubility studies of Rivaroxaban.

Solid dispersion solubility study

Solid dispersions were prepared by solvent evaporation method with their respective carriers. All the SDs prepared was found to be fine and free flowing powders. After preparation of solid dispersion solubility analysis were carried out and compared with pure drug. The formulation with lactose in the ratio of 1:4 (Drug to carrier) which had increased the solubility almost 8 fold compared to that of pure drug. The solid dispersion solubility study of rivaroxaban was carried out as shown in table no. 8.2. The solid dispersion solubility for SDM1, SDM2, SDM4, SDL1, SDL2, and SDL4 was found to be 11.49 mg/ml, 12.97 mg/ml, 16.57 mg/ml, 28.51 mg/ml, 33.22 mg/ml, and 41.92 mg/ml respectively. The SDL4 showed higher solubility as compared to SDM4 as shown in fig no. 3.

Table No. 4: Solubility studies of Rivaroxaban solid dispersions.

Sr. No.	Drug : Carrier	Solubility (µg/ml)
1	SDM 1	11.49
2	SDM 2	12.97
3	SDM 4	16.57
4	SDL 1	28.51
5	SDL 2	33.22
6	SDL 4	41.92

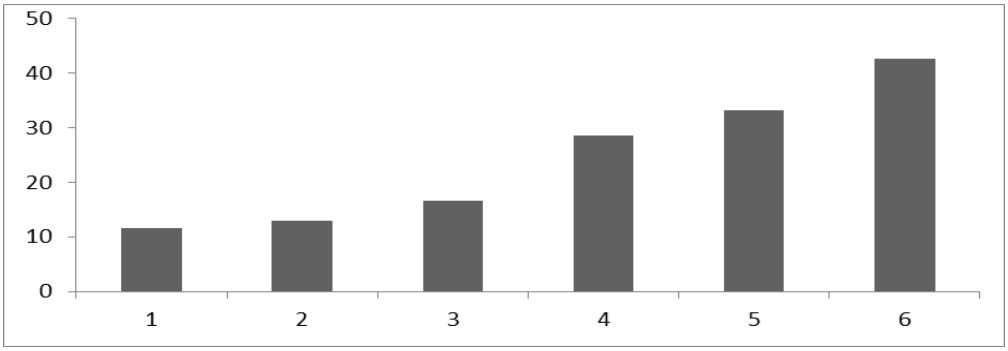

Fig. no. 3: Solubility studies of Rivaroxaban solid dispersion (on X-axis: 1.SDM1; 2.SDM2; 3.SDM4; 4.SDL1; 5.SDL2; 6.SDL4).

Micromeritic & morphological study of solid dispersions

Table no. 5: Drug content, Micromeritics properties, Solubility & Dissolution efficiency of rivaroxaban & its solid dispersion.

Sample	Drug content (%)	Carr's index	Hausner's ratio	Angle of repose (Θ)	Aqueous Solubility (µg/ml)
Pure drug	100	39.45	1.67	45	4.7
SDM 1	92.45	16.45	1.195	29.32	12.52
SDM 2	93.57	16.26	1.191	28.72	13.71
SDM 4	92.08	15.82	1.187	28.04	17.67
SDL 1	96.89	15.75	1.184	27.85	29.01
SDL 2	94.08	14.33	1.164	27.69	34.23
SDL 4	93.96	13.98	1.161	26.58	42.61

Flow ability of Rivaroxaban (Pure drug) and its solid dispersions was assessed by determination of Carr's Index (CI), Hausner's Ratio (HR) & angle of repose. Micromeritics behaviors of the untreated Rivaroxaban powder & all prepared solid dispersions are listed. Table no. 5 shows that the flow ability represented in terms of Carr's Index, Hausner;s Ratios & angle of repose was much improved compared to those of original powders (Untreated Rivaroxaban). In case of pure Rivaroxaban, powder could not pass through the funnel during the angle of repose experiment. The poor flow of Rivaroxaban could be due to the irregular shape & high fineness of the powder, which posed hurdles in the uniform flow from the funnel. These results are significantly different from those of untreated Rivaroxaban. Actual drug contain of all six formulations are shown in table no. 5 The drug content of the prepared SDs was found to be in the range of 92.08 to 96.89%.

In Vitro dissolution study of solid dispersion

Table no. 6: Cumulative % drug release of Rivaroxaban solid dispersion.

Time (Min)	PD	SDM 1	SDM 2	SDM 4	SDL 1	SDL 2	SDL 4
5	2.77	18.96	27.53	38.53	51.56	63.68	77.63
10	4.94	39.65	46.23	51.56	62.50	75.15	82.41
15	11.80	52.89	61.23	69.87	71.23	84.39	87.35
20	18.54	69.14	76.96	73.20	80.23	87.22	92.96
30	29.60	80.61	82.52	84.37	88.91	93.76	97.07
45	36.20	84.23	87.85	89.23	91.52	96.78	99.68
60	39.56	87.85	91.23	92.56	97.05	99.21	---
90	42.21	90.84	95.96	98.97	99.03	---	---

The dissolution rate study was carried out for pure Rivaroxaban as well as for Rivaroxaban solid dispersion. The cumulative % drug release has showed in table no.6 The % drug release of pure form was found to be 42.21% at 90 minutes. The SDM4 showed 98.97% drug release

at 90 minutes as showed in fig no. 4. The SDL4 showed 99.68% drug release at 45 minutes as showed in fig no 5. which is higher than % drug release of SDM4.

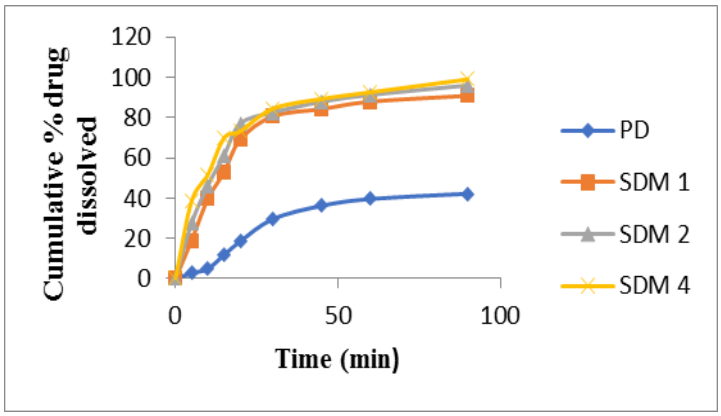

Fig. no. 4: Cumulative % drug dissolved Vs Time plots of Rivaroxaban solid dispersion containing Mannitol.

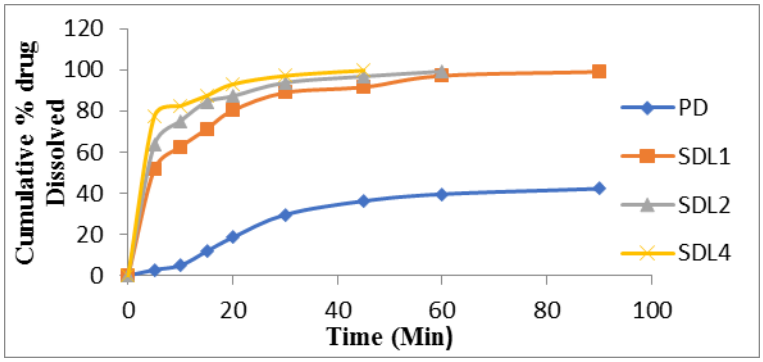

Fig. no. 5: Cumulative % drug dissolved Vs Time plots of Rivaroxaban solid dispersion containing Lactose.

Evaluation of solid dispersion granules

In the present study, Rivaroxaban capsules were prepared by using polymer such as ethyl cellulose (EC) and HPMC. A total number of six formulations were prepared by wet granulation method. Angle of repose for F1-F6 is between 18.41θ to 24.22θ, bulk density is between 0.392 – 0.398, tapped density is between 0.442 – 0.450, compressibility index is between acceptable limits (Table No. 8.5). The above values of pre compression parameters show the prepared granules having good flow property. From the preformulation studies for drug excipients compatibility, it was observed that no physical incompatibility existed between the drugs & excipients. The weight variation was within ± 5%, it was within the acceptable limit.

Table no. 7: Evaluation of Rivaroxaban + Lactose solid dispersion granules (Ratio = 1:4).

Formulation	Angle of repose (Θ)	Bulk density (gm/cc)	Tapped density (gm/cc)	Compressibility index (%)	Hausner's ratio
F1	18.41	0.392	0.442	11.312	1.127
F2	23.19	0.395	0.445	11.235	1.126
F3	17.35	0.390	0:447	12.751	1.146
F4	20.22	0.393	0:444	11.486	1.129
F5	22.30	0.395	0:449	11.026	1.136
F6	24.22	0.398	0:450	11.555	1.130

In Vitro dissolution study of formulated capsules

In-vitro drug release showed (Fig no.6) that the variation of release pattern of different batches (F1-F6) of the Rivaroxaban in 6 hrs study period. In-vitro dissolution study was carried out for Rivaroxaban solid dispersion capsules. The F6 Showed 53.86% drug release at 360 minutes, which is higher than % drug release of others. Formulation F6 Showed higher solubility profile.

Table no. 8: In-vitro dissolution study of Rivaroxaban + Lactose solid dispersion capsules (Ratio = 1:4).

Time (Minutes)	F1	F2	F3	F4	F5	F6
60	21.01	22.86	24.56	27.86	29.32	31.58
120	22.56	24.86	28.96	30.45	32.56	36.34
180	24.81	27.61	31.56	35.68	37.96	43.08
240	26.56	29.76	35.07	39.05	42.63	46.89
300	28.82	31.45	36.89	41.56	46.03	49.89
360	29.98	34.89	39.91	45.63	49.05	53.86

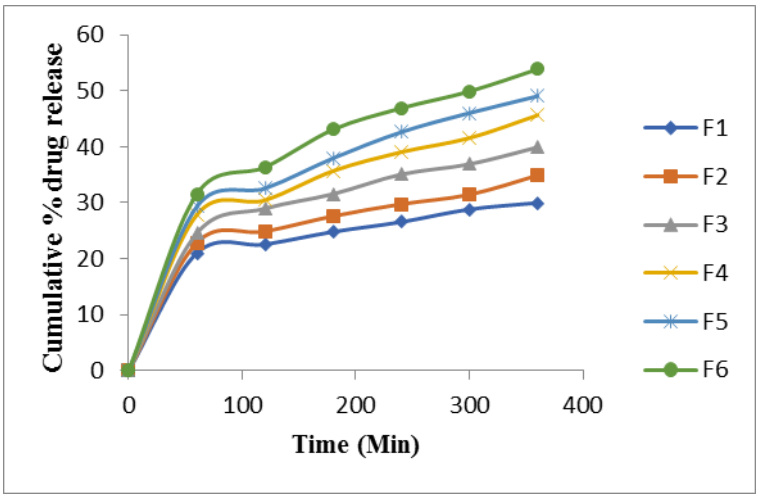

Fig. no. 6: In-vitro dissolution study of Formulated capsules.

CONCLUSION

Solid dispersions prepared from hydrophilic polymers like Mannitol & Lactose using the solvent evaporation technique was effective in improving drug dissolution. These solid dispersions were analyzed for solubility & in-vitro dissolution profile. Dissolution of drug increased with an increase in carrier content. Solid dispersions prepared with lactose had shown enhanced solubility with improved dissolution rate. Controlled release capsules of Rivaroxaban & different carriers can increase the gastric residence time as well as bioavailability and better patient compliance can be achieved.

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