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Research Article

Enhancement of solubility and dissolution rate of Rifampicin by melt granulation technique

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ABSTRACT

This work describes a melt granulation technique to improve the solubility and dissolution characteristics of a poorly water-soluble drug, rifampicin. Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable polymers and surfactants. The advantage of this technique compared to a conventional granulation is that no water or organic solvents is needed. Because there is no drying step, the process is less time consuming and uses less energy than wet granulation. Granules were prepared by using polymer like different grades of polyethylene glycol and surfactant like different grades of poloxomers. The granules were characterized using powder XRD, DSC and FTIR techniques. A significant enhancement in the in vitro dissolution profiles of the melt granules was observed compared to the pure drug and drug excipient physical mixtures. Besides the remarkable enhancement of drug dissolution rate of the granulates in comparison to physical mixtures and pure drug, no significant differences were found between the dissolution profiles of the melted granulates containing lactose or crospovidone. XRD data confirmed crystalline drug in the melted granules. DSC results indicated change in internal energy of Rifampicin with polymers and surfactant in the melted granulated. In conclusion, the results of this work suggest that melt granulation is a useful technique to enhance the solubility and dissolution rate of poorly water-soluble drugs, such as, Rifampicin.

Key words:Rifampicin, surfactants, melts granulation, Dissolution enhancement, polyethylene glycol.

INTRODUCTION

A melt granulation technique is a process by which pharmaceutical powders can be efficiently agglomerated by the use of molten polymers or additives at relatively low temperature (about 60^0C)[1]. This process can be used for the preparation of sustained released dosage forms by using lipophilic polymers, such as glycerol monostearate [2] , a combination of a hydrophobic material such as a starch derivative [3] and stearic acid [4]or a combination of hydroxypropyl methyl cellulose and hydrophobic polymers [5]. It also can be used to prepare fast release melt granules by utilizing water-soluble polymers and surfactants, such as PEG and poloxomers.[6] PEG has been widely used in melt granulation because of its favorable solution properties, low-melting point, rapid solidification rate, low toxicity, and low cost. Another commonly used binder is Gelucire®, which is a mixture of glycerides and fatty acid esters of PEGs. Gelucire® has been shown to further increase the dissolution rate of poorly water-soluble drugs, attributed to the surface active and self-emulsifying properties of this excipient.[7]

In recent years, the interest in melt granulation has increased due to the advantage of this technique over traditional wet granulation, that is, elimination of water or organic solvents from the melt granulation process. This negates any risk originating from residual solvents; moreover, in melt granulation the drying step is not necessary, thus the process is less consuming in terms of time and energy as compared to wet granulation [8] .The apparatus of choice for melt granulation are the high shear mixers, where the product temperature is raised above the melting point of the binder either by using a heating jacket or via the heat of friction generated by the impeller blades, when the impeller speed is high enough.

In recent years, melt granulation technique has been successfully employed to improve the solubility and dissolution rate of poorly soluble compounds and the technique has proved that melt granulation can be used to enhance the in vitro dissolution rate of ibuprofen, employing poloxamer 188 as a

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melting binder which is mostly used as surfactant.

The objective of this work was to evaluate the feasibility of the melt granulation technique to improve the dissolution characteristics of a poorly water-soluble drug, rifampicin.

Rifampicin, a complex semi-synthetic macrocyclic antibiotic derived from Streptomyces mediterranei, is a member of the rifamycin class of antibiotics used for the treatment of tuberculosis and other infectious diseases. As rifampicin is a BCS class II drug, solubility and rate of dissolution are the rate limiting step in its absorption.[9]

In the present work, the feasibility of fast-release rate granules by melt granulation has been considered. Rifampicin was chosen as a water-insoluble model drug and PEG, poloxamer as a hydrophilic polymer and surfactant. Polyethylene glycol (PEG) and poloxamer were employed as a melting binder, in consideration of its favourable solution properties, low melting point, rapid solidification rate, low toxicity and low cost. Along with these binders effect of lactose and crosspovidone were also studied. In-vitro release of the drug from the granules was investigated and compared to that of the pure drug and drug excipient physical mixtures. Differential scanning calorimetry and X-ray powder diffraction were utilized to investigate the crystallinity of the system.

MATERIALS AND METHODS:

Materials

Rifampicin was supplied as a gift sample from Lupin Ltd, (Aurangabad, India). Poloxamer (Pluronic F-68), crosspovidone and Polyethylene glycol were procured from Alembic (Vadodara, India). Hydrochloric acid (HCL), lactose and were of S. D. Fine (Mumbai, India).

Preparation of the granules, physical mixtures

Granules were prepared in a porcelain dish. Firstly, the mixture of rifampicin and polymer (Polyethylene glycol) or surfactant (poloxamer-F68) with different excipients (mentioned in Table:1) was dry blended for 10 min .Then, this mixture was then placed in hot porcelain dish and supply the heat around 60^{0}C on temperature controlled water bath so as to melt the polymers or surfactant in which the drug was dispersed . The formed molted mass is then cooled to room temperature and at the end of the granulation process the granules were allowed to solidify at room temperature by spreading them out in thin layers on trays. Pass the melted granules through sieve no # 20 so as to form uniform granules. The cooled granules were stored in sealed bags for their evaluation.

Prepared the physical mixtures of the same formulation and compared the solubility and dissolution rate with the melt granules.

Yield and Drug Content

The prepared melt granules were weighed after drying, and process yield was calculated. Melted granules (300mg) were powdered, from which powder equivalent to 100 mg rifampicin was weighed and extracted using three portions of 100 ml 0.1 N HCL. Each portion was filtered through a G-4 sintered glass filter and volume was adjusted to 100 ml. After sufficient dilution with 0.1 N HCL, samples were analyzed spectrophotometrically at 475 nm. Rifampicin content was calculated by comparison with standard solution.

Saturation solubility studies

Saturation solubility studies were carried out using deionized water as a solvent. Each excessive quantity (200 mg) of Rifampicin and equivalent prepared melt granules were taken in seven screws capped test tubes with fixed volume (20 ml) of deionized water. The resultant suspension was treated at 37 ^{0}C with 100 rpm in incubator shaker. After 24 h samples were withdrawn and filtered through 0.2µ filters (Millipore, Pall Life sciences, Mumbai, India). The filtrate was suitably diluted with deionized water and analyzed at 475 nm by UV-visible spectrophotometer (Pharma spec 1700, Shimadzu Corporation, Kyoto, Japan).

In-Vitro Dissolution Studies

A LABINDIA Disso 2000 (Mumbai) dissolution test apparatus type I (Basket) at rotation speed of 100 rpm was used for the study. Dissolution of the drug and samples was carried out on an equivalent of 450 mg of the RIF. As per USP XXVI, 0.1 N HCL was used as dissolution media. The volume and temperature of the dissolution media were 900 ml and 37 ± 0.2 ^{0}C, respectively. After fixed time intervals, 5 ml of samples were withdrawn and sink condition was maintained. These samples were assayed through ultraviolet absorbance measurement at 475 nm using UV-Visible Spectrophotometer (Shimadzu UV-1700, Japan) by an analytically validated method (r^2 = 0.9995). To increase the reliability of the observations, the dissolution studies were performed in triplicate.

Fourier Transforms Infrared Spectroscopy

FTIR spectra of prepared formulation were recorded on Shimadzu FTIR-8400 spectrophotometer (Shimadzu Corporation, Kyoto, Japan). Potassium bromide pellet method was employed and background spectrum was collected under identical situation. Each spectrum was derived from single average scans collected in the region 400 – 4000 cm^{-1} at spectral resolution of 2 cm^{-2} and ratio against background interferogram. Spectra were analyzed by software supplied by Shimadzu.

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Powder X-Ray Diffraction (PXRD)

Crystallinity of the drug and the samples was determined using the Philips Analytical X-RD (Model: PW 3710, Holland) with copper target. The conditions were: 40 kV voltages; 30 mA current; at room temperature. The samples were loaded on to the difffractometer and scanned over a range of 2? values form 5 to 60 ^{0} at a scan rate of 0.02 ^{0}/min.

Differential Scanning Calorimentry (DSC)

Thermal properties of the untreated drug and the samples were analyzed by DSC (TA Instruments, USA, Model: SDT 2960). The samples were heated in a hermetically sealed aluminum pans. Heat runs for each sample were set from 30 to 350 ^{0}C at a heating rate of 10 ^{0}C/ min, using nitrogen as blanket gas.

Stability studies

Stability studies for the samples were carried out as per ICH guidelines. The samples (each 10mg, n=3) were kept for stability studies at 40 ± 2 ^{0}C and 75 ± 5% RH for a period of 3 months in environmental test chamber (HMG INDIA, Mumbai). The samples were kept in glass vials sealed with rubber plugs. After 30, 60 and 90 days, the samples were taken out and analyzed for appearance, drug content and dissolution study.

Flow Properties

Flow properties of the drug and prepared melt granules were studied by determining the bulk density (s_b), tap density (s_t), Carr's Index and Hausner ratio. A weighed quantity of the samples was taken to determine the bulk and tap density. The properties were determined using following equations

Bulk density (s_b) = Mass / Poured volume (1)

Tap density (s_t) = Mass / Tapped volume (2)

Carr's Index = $[(s_t - s_b) / s_t] \times 100$ (3)

Hausner ratio = $(s_t / (s_b)$ (4)

Wettability/ powder bed hydrophilicity study

The untreated drug, prepared melt granules were placed (1 g) on a sintered glass disk forming the bottom of glass tube on which methylene blue crystals were placed. The whole device was brought into contact with water. The time taken for the capillary rising of water to the surface so as to dissolve methylene blue crystals was noted.

RESULTS AND DISCUSSION:

Solid-state analysis of the granulates

XRD analysis

The physical characterization was firstly carried out by means of XRD analysis. The diffraction pattern (Fig: 1) of the prepared melt granules was compared to the RIF .The diffractograms of the granules indicated that the polymorphic form of the drug was maintained substantially unchanged after melt granulation process, and only a little reduction of the degree of crystallinity was detected in comparison with the corresponding Drug.

DSC analysis

Fig. 2 reports the DSC scans of the raw RIF material and prepared melt granules. Thermal analysis completely reconfirmed the previously reported XRD findings. The thermogram of granules conducted at 10 ^{0}C/min. RIF shows a melting endotherm peak onset at 187^{0}C comparative to RIF-PEG (183 ^{0}C) and RIF-POL (178 ^{0}C). The DSC study revealed that slightly decrease in melting endotherm peak comparative to RIF.

FTIR analysis

FTIR spectra of the drug and samples are given in Fig. 3. The FTIR spectra of the prepared melt granules showed no change occur in the chemical nature and do not present great fingerprint difference comparative to RIF.

Solubility study

The solubility of prepared melt granules were significantly improved (** P<0.01) compared to RIF raw crystals and physical mixtures (PM). The solubility data is mentioned in Table 3. The melted granules prepared by incorporating of water-soluble polymers PEG and surfactant Poloxomer can improve solubility due to its hydrophilic nature and adsorbed on drug surface to improve wettability. The addition of the excipients like lactose and crosspovidone does not show significant (ns P>0.05) improvement in solubility.

In vitro dissolution of the granules

The in vitro dissolution rate of all prepared granulates (Fig. 4) was increased compared to the corresponding physical mixtures (Fig. 5) and the drug alone, because of the higher hydrophilic character of the systems due to the carriers and the slight reduction of RIF crystallinity. No significant differences were attested by the analysis of variance (ns P> 0.05) between the samples with different amount of PEG, nor with the incorporation of lactose and crosspovidone into the formulation.

Technological characterization of the granules:

According to the literature data, powders with a Compressibility Index (CI) between 5 and 15 % and a Hausner ratio below 1.25 are suitable for producing tablets. The prepared melt granules formulations had a CI ranging between 12 and 14 while their Hausner ratio was below 1.15. As for the rheological properties, the prepared melt granules revealed a good

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Table 1: Product coding of melt granules prepared with polymers, surfactants and excipients

Sr. No:	Drug:Excipeint	Ratio	Coding
1	Rifampicin (Drug)	———	RIF
2	Rifampicin:PEG	1:1	RIF-PEG
3	Rifampicin:PEG:Lactose	1:1:0.5	RIF-PEG L
4	Rifampicin:PEG:Crosspovidone	1:1:0.5	RIF-PEG C
5	Rifampicin:Poloxomer	1:1	RIF-Pol
6	Rifampicin: Poloxomer:Lactose	1:1:0.5	RIF-Pol L
7	Rifampicin: Poloxomer:Crosspovidone	1:1:0.5	RIF-Pol C

Table 2: Product coding of physical mixture prepared with polymers, surfactants and excipients

Sr. No.	Drug:Excipeint	Physical mixture ratio	Coding
1	Rifampicin:PEG	1:1	RIF-PEG(PM)
2	Rifampicin:PEG:Lactose	1:1:0.5	RIF-PEG L(PM)
3	Rifampicin:PEG:Crosspovidone	1:1:0.5	RIF-PEG C(PM)
4	Rifampicin:Poloxomer	1:1	RIF-Pol(PM)
5	Rifampicin: Poloxomer:Lactose	1:1:0.5	RIF-Pol L(PM)
6	Rifampicin: Poloxomer:Crosspovidone	1:1:0.5	RIF-Pol C(PM)

Table 3: Saturation solubility studies of prepared melt granules and physical mixture

Sr. No.	Dispersion Code	Solubility (mg/ml)
1	RIF	0.256±0.027
2	RIF-PEG	1.486±0.089
3	RIF-PEG(PM)	0.468±0.086
4	RIF-PEG L	1.481±0.067
5	RIF-PEG L(PM)	0.435±0.065
6	RIF-PEG C	1.467±0.048
7	RIF-PEG C(PM)	0.398±0.065
8	RIF-Pol	8.190±0.070
9	RIF-Pol(PM)	0.345±0.035
10	RIF-Pol L	7.990±0.095
11	RIF-Pol L(PM)	0.407±0.058
12	RIF-Pol C	7.880±0.065
13	RIF-Pol C (PM)	0.453±0.098

* Mean ± S.D. (n = 3)

Table 4: Technological characterizations of RIF and prepared melt granules

Characteristics	RIF	RIF-PEG	RIF-POL
Bulk density (gm/ml)	0.525±0.056	0.575±0.023	0.585±0.028
Tap density (gm/ml)	0.655±0.085	0.655±0.026	0.665±0.065
Compressibility Index(CI)	19.85±0.23	12.21±0.07	14.16±0.05
Hausner ratio	1.25±0.05	1.14±0.08	1.14±0.08
Flow time 100 ml/s	28.56±0.07	21.54±0.01	20.88±0.04
Angle of repose (?)	34.9±0.3	23.5±0.4	24.7±0.6
Wettability study (Water raising time-hrs)	8.0±0.6	4.0±0.7	4.5±0.6

* Mean ± S.D. (n = 3)

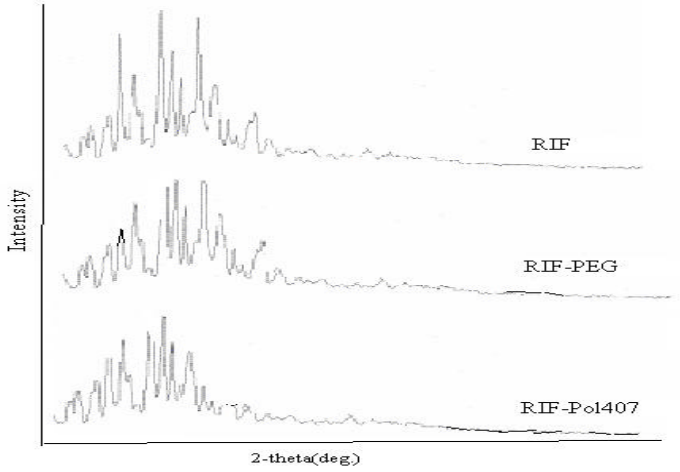

Figure 1: X-ray diffraction pattern of RIF, RIF-PEG and RIF-POL granules

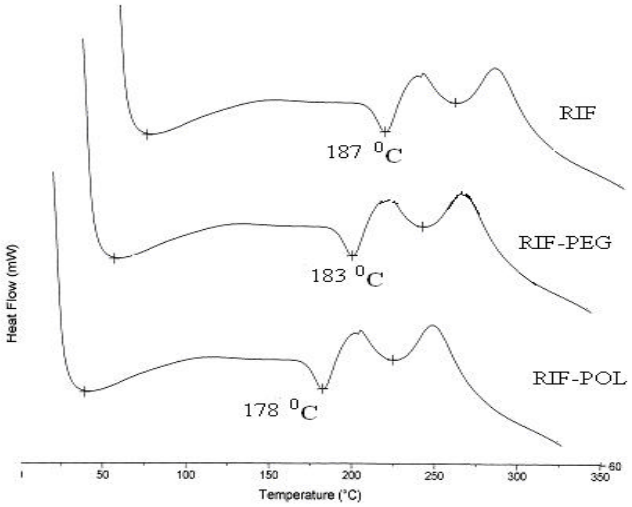

Figure 2: DSC thermograms of RIF, RIF-PEG and RIF-POL granules

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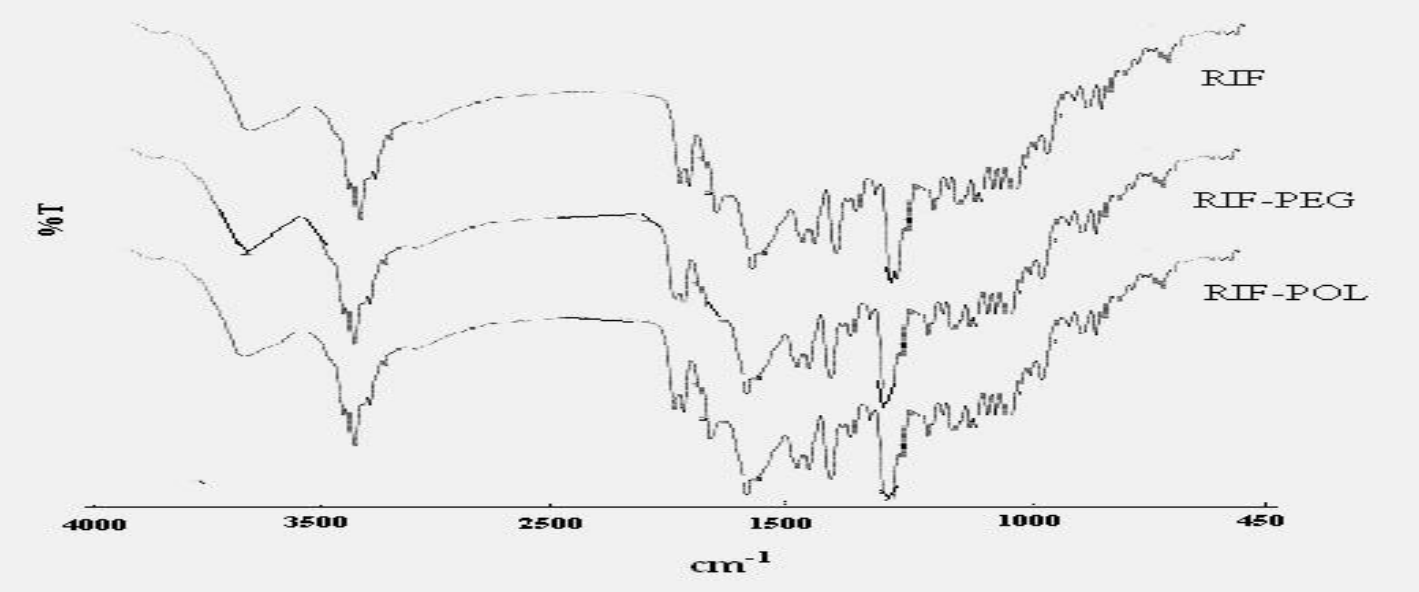

Figure 3: FTIR spectra of RIF, RIF-PEG and RIF-POL granules

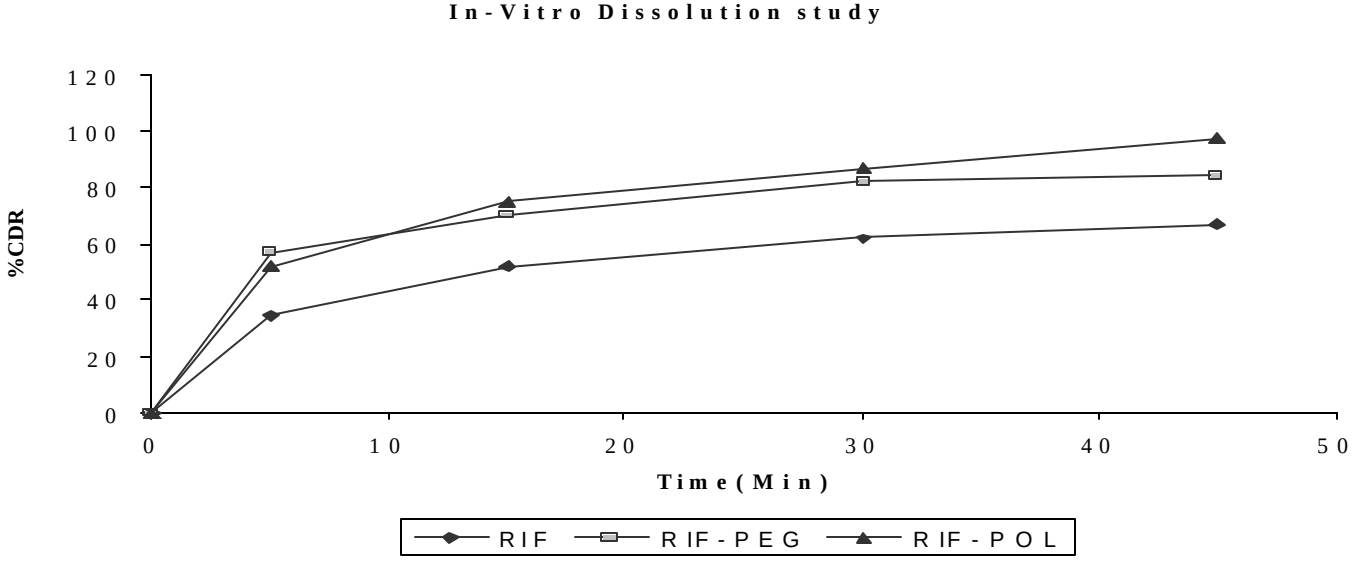

Figure 4: In-vitro dissolution study of RIF and prepared melt granules

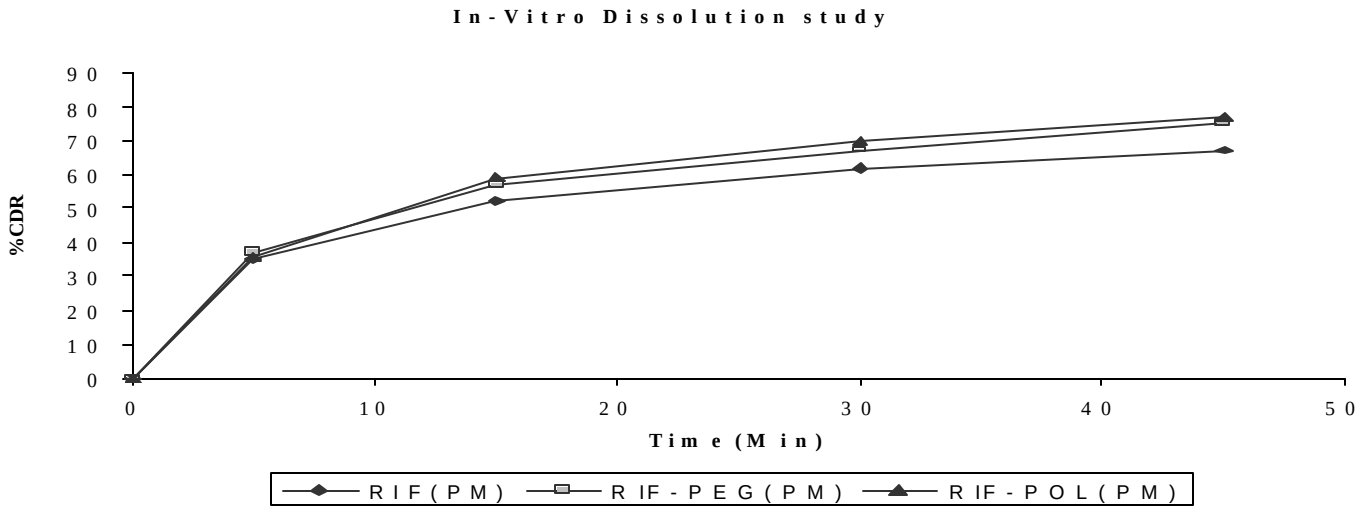

Figure 5: In-vitro dissolution study of RIF and prepared physical mixture

flowability because of their granular size which reduces the surface area and increases the flow rate.

Powder bed hydrophilicity study:

Table 4 indicates powder bed hydrophilicity study of RIF and their melted granules. The melt granules showed significantly shortest rising time ($_{**}$ P<0.01) of water to its surface as compared to raw RIF crystals represent better wattability of prepared granules as compared to raw RIF. The order of wettability RIF-PEG> RIF-POL>RIF. The reason for the superior wettability with PEG is due to adsorption of polymers on the raw crystals of RIF during preparation.

CONCLUSIONS:

In conclusion, melt granulation technique has been proved to be a important process to increase the solubility, dissolution and other techniqual characteristics of RIF using PEG and Poloxomer as a melt binder, without using any solvents. Solid-state analysis indicated slightly reduction in crystallinity of the drug and no changes in its polymorphic form. The granules displayed a significant improvement in vitro drug dissolution behavior. The dissolution profiles of granules containing PEG and Poloxomer were found to be superimposable to RIF and physical mixture. However, the intragranular addition of lactose and crosspovidone were not found significant improvement in solubility and dissolution comparative to melt granules without lactose and crosspovidone.

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