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A COMPARATIVE SOLUBILITY ENHANCEMENT AND DISSOLUTION STUDY OF RANOLAZINE USING DIFFERENT TECHNIQUES

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ABSTRACT: The aim of the present study was to enhance the solubility of the poorly soluble drug Ranolazine. Solid dispersions were prepared using PVP K-30 and PEG 4000 & 6000 by melting, solvent evaporation using varying polymer ratios (1:1, 1:2, 1:3, 1:4). The prepared formulations were characterized for saturation solubility, IR, PXRD, SEM. The aqueous solubility of Ranolazine was favored by the presence of polymers. In contrast to the very slow dissolution rate of pure Ranolazine, amorphous solid dispersions considerably improved the dissolution rate. PXRD, DSC, SEM studies confirmed the amorpicity of Ranolazine. The saturation solubility of pure drug RN was found to be 0.142mg/ml, whereas that of SD4 was found to be 0.77mg/ml. The drug release of the pure drug was 28.70% at the end of 3 hours and the drug release was found to be enhanced in SD4 that is 96.44% and SD8 is 84.85%. The formulations SD4 and SD8 showed the highest solubility and dissolution rate. This can be attributed to the increased wettability and dispersibility of Ranolazine in polymeric matrix as well as decreased crystallinity and increase in amorphicity. Stability study confirmed that there is no recrystallinity of drug over storage for a specific period.

INTRODUCTION: One of the most common and convenient route for the administration of drug formulation is oral route [1]. The drug needs to get dissolved in GI fluids for its absorption through GI membrane. In the current scenario, most of the drug molecules discovered are lipophilic and exhibit poor aqueous solubility, which in turn results in low bioavailability and poses a challenge in developing optimum oral solid dosage form. Nearly 40% of the new chemical entities currently being discovered are poorly water-soluble drugs. If the drug has good permeability, then the rate-limiting step in absorption is the drug dissolution.

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This is a characteristic of compounds that belong to the biopharmaceutical classification system II (BCS class II). Drugs in this class are expected to have a variable dissolution profile due to the formulation and *in-vivo* variables. The aqueous solubility lesser than 1 µg/mL creates the problem of bioavailability.

Alteration of the solid-state at the particle or molecular level involves a physical change in the drug can be used as an option to improve the drug solubility. Physical modification of lipophilic drugs is done by using several carriers like cyclodextrins, carbohydrates, hydrotropes, dendrimers, poly-glycolized glycerides, and other methods by use of superdisintegrants, solid dispersions, and surfactants melt granulation, particle size reduction. Conversion of a crystalline form of drug to amorphous is one of the strategies which improve the drug solubility [2].

Solid dispersion is defined as the dispersion of one or more active ingredients (hydrophobic) in an inert carrier or matrix (hydrophilic) at solid-state prepared by melting, solvent, or melting-solvent method. It basically includes a solid product that consists of two components, a hydrophilic matrix and a hydrophobic drug [3].

Ranolazine (RN), approved as a second-line agent in the management of chronic stable angina pectoris, is an acetanilide and piperazine derivative that acts by inhibiting late sodium current during ventricular depolarization, which assists in controlling exertional angina. It is effective in the treatment of chronic angina as it also reduces the calcium influx through sodium/calcium exchanger by blocking late sodium currents. It has anti-anginal & antineoplastic activities. It belongs to BCS class II, having a low solubility (0.118mg/mL) [4, 5].

The hydrophilic polymer Polyvinyl pyrrolidone K30 (PVP K30), PEG4000, and PEG 6000 are used as carriers in the preparation of solid dispersions. These polymers show good water solubility, low toxicity, low melting point, rapid solidification rate, physiological tolerance, and economic cost. These properties ensure that the polymers are good carrier polymer s for preparing solid dispersion [6].

Several methods are used to characterize the solid dispersions. The characterization methods include Infrared spectroscopy, Differential scanning calorimetry, Powder X-Ray Diffraction [6, 7].

In the present study, Solid dispersions are prepared using the melting method and solvent evaporation method. The solid dispersions were prepared using hydrophilic polymers that are PVP K-30 and PEG 4000 & 6000. The formulations were prepared with varying ratios of polymers. The formulations were characterized using IR, DSC, PXRD, SEM, and dissolution studies. The results were compared with that of the pure drug.

MATERIALS AND METHODS:

Materials: Ranolazine is obtained as a gift sample from Apotex Pvt. Ltd., Banglore, PVP K30 and PEG 4000 & 6000 by SD Fine Chem. Ltd, Mumbai. All other chemicals and solvents used in this study were of analytical grade reagents.

Methods:

Preparation of Solid Dispersions:

Solid Dispersion by Hot Melt Method: [8] Solid dispersions of RN in different ratios of drug to polymer ratio (1:1, 1:2, 1:3, and 1:4) were prepared by hot-melt method as follows. Accurately weighed polymers (PEG 4000& PEG 6000 in equal quantity) were melted on a water bath at 70 °C. The accurately weighed drug was added to the molten mass in the respective ratios & stirred to form a homogeneous dispersion. The mixture is allowed to cool to room temperature. The solid dispersions formed were scrapped using a spatula & ground in mortar & pestle. The ground mixture was passed through sieve no. 80 and the samples were stored in desiccator for further studies.

Solid Dispersion by Solvent Evaporation Method: [8] Solid dispersions of RN in different ratios of drug to polymer ratio (1:1, 1:2, 1:3, and 1:4) were prepared by solvent evaporation method as follows. Accurately weighed drug was dissolved in 10 ml methanol, and weighed quantity of polymer PVP K-30 in the respective ratios was dissolved in 10mL of ethanol. Both the solutions were stirred to form clear solutions. Further, the drug solution was added to the polymer solution. The clear solution obtained was transferred to the petri-dish and dried in an oven at 60 °C for 20 min. The sample is allowed to cool to room temperature. The solid dispersions formed were scrapped using a spatula & ground in mortar & pestle. The ground mixture was passed through sieve no. 80 and the samples were stored in desiccator to remove traces of solvents and till used for further studies.

Compatibility Studies by Infrared Spectroscopy: Compatibility studies were carried out for pure drug (RN), (PVPK30), (PEG 4000 & 6000), physical mixtures of polymers (RN+PVPK30, RN +PEG mixture), and solid dispersions prepared by melting and solvent evaporation methods. Infrared spectroscopic analysis was done for the same. Fourier transform infrared spectra of moisture-free powdered samples were obtained by using a spectrophotometer (FT-IR Shimadzu Co., Japan) by potassium bromide (KBr) pellet method (2 mg of sample in 200 mg of KBr). The scanning range was 400-4000 $cm^{-1,}$ and the resolution was 1 cm^{-1} [9].

Saturation Solubility: An excess amount of drug or solid dispersion was added to an adequate amount of distilled water and stirred on a magnetic stirrer for 24 h at 37 °C. Samples were then filtered, suitably diluted, and analyzed spectrophotometrically at 271nm [9, 10].

Scanning Electron Microscopy (SEM): Using SU 9000 field emission scanning electron microscope, the surface morphology of RN and the solid dispersions were observed. Samples were mounted on double-faced adhesive tapes and coated with gold (200Å) under reduced pressure (0.001 torr) for 5 min. using an ion sputtering device. The gold coated samples were observed under the SEM, and photomicrographes of suitable magnifications were obtained [10].

Differential Scanning Calorimetry (DSC) Analysis: DSC scans of the samples were recorded by using DSC Shimadzu-60. The samples were hermetically sealed in aluminium pans and heated at a constant rate of 10°C/min under dry nitrogen flow (100mLmin) between 50 to 200 °C [10, 11].

Powder X-Ray Diffraction (PXRD) Analysis: X-Ray powder scattering measurements were carried out with a D2 Phaser Difractometer at room temperature using the monochromatic CuKa-radiation at 34 mA and at 38 Kv over a range of 2θ angles from 5-90 ° with an angular increment of 0.05 °/s [9, 10, 11].

Dissolution Studies: The dissolution studies were performed using USP XXIII type 2 apparatus (electrolab India) for 3 h. Samples of pure RN and solid dispersions equivalent to 10 mg of the drugs were added to the 900 mL of phosphate buffer (pH 6.8) as dissolution medium maintained at 37±0.5 ºC, which was stirred at 100 rpm. At suitable intervals, 5mL samples were withdrawn, filtered (0.22µm), diluted and analyzed at 271 nm using a UV spectrophotometer. An equal volume of fresh medium at the same temperature was replaced into the dissolution medium after each sampling to maintain its constant volume throughout the test. Each test was performed in triplicate (n=3), and calculated mean values of cumulative drug release were used for plotting curves [8, 9, 11].

Stability Studies: The accelerated stability of SD 4 and SD 8 were checked as per ICH guidelines at 40 °C/75% RH upto 3 months. Periodically (15days, 1 month and 3 months), samples were removed and checked for *in-vitro* drug release and presence of crystallinity using PXRD studies [12].

RESULTS AND DISCUSSION:

Compatibility Studies: The spectra of all the samples are shown in **Fig. 1**. The spectra of pure RN presented characteristic peaks at 3562.52 cm^{-1} (N-H stretching), 3442.94 cm^{-1} (OH stretching), 1685.79 cm^{-1} (carbonyl stretching), 1633.71 cm^{-1} (COOH stretching), 1496.76 cm^{-1} (aromatic C=C), 1458.18 cm^{-1} (C=C), 1253.73 cm^{-1} (C-O stretching), 1124.50 cm^{-1} (C-N stretching) respectively. The spectrum of PVPK 30 showed the band at 2947.16 cm^{-1} (C-H stretching) and 1678 $cm^{-1,}$ indicating stretching vibration of the carbonyl group. This is the most distinct peak in the IR spectrum of PVPK30. The broad peak at 3000-3300 cm^{-1} (OH stretching vibrations), which was attributed to the presence of water. The spectrum of PEG showed bands at 2879.72 cm^{-1} (C-H stretching), 1109 cm^{-1} showing C-O stretching.

By comparing the spectra of solid dispersions by Hot melt method (RN-PEG) and physical mixtures, no difference was seen in the position of absorption bands. The spectra can be simply regarded as the superimposition of those of RN and PEG. However, it could be expected to have hydrogen bonding between the hydrogen atom of the drug and one of the lone pairs of the oxygen atom in PEG.

Upon comparison, the spectra of solid dispersions by Solvent evaporation (RN-PVPK30) and physical mixtures; in contrast to the physical mixtures, solid dispersions presented the possibility of hydrogen bonding between RN and PVPK30. Each pyrrolidone moiety of PVP has two groups (=N- AND C=O) that can potentially form a hydrogen bond with the drug at the molecular level in solid dispersion formulation. Significant broad peaks at 2954 cm^{-1} and 1685 cm^{-1} suggested hydrogen bonding interaction between the free O-H group of RN and carbonyl group of PVPK30.

Preparation of Solid Dispersions: The solid dispersions were optimized by varying a number of variables like drug: polymer ratio, processing variables such as temperature, the composition of

polymers, and solvent selection. Based on drug content, saturation solubility, and powder characteristics, the formulations are considered optimum formulations. The formulations showed good flow properties; further increase in polymer concentration will affect the flow properties, which will create problems during the processing of solid dispersions. The composition of Solid Dispersions (SD) is shown in **Table 1**.

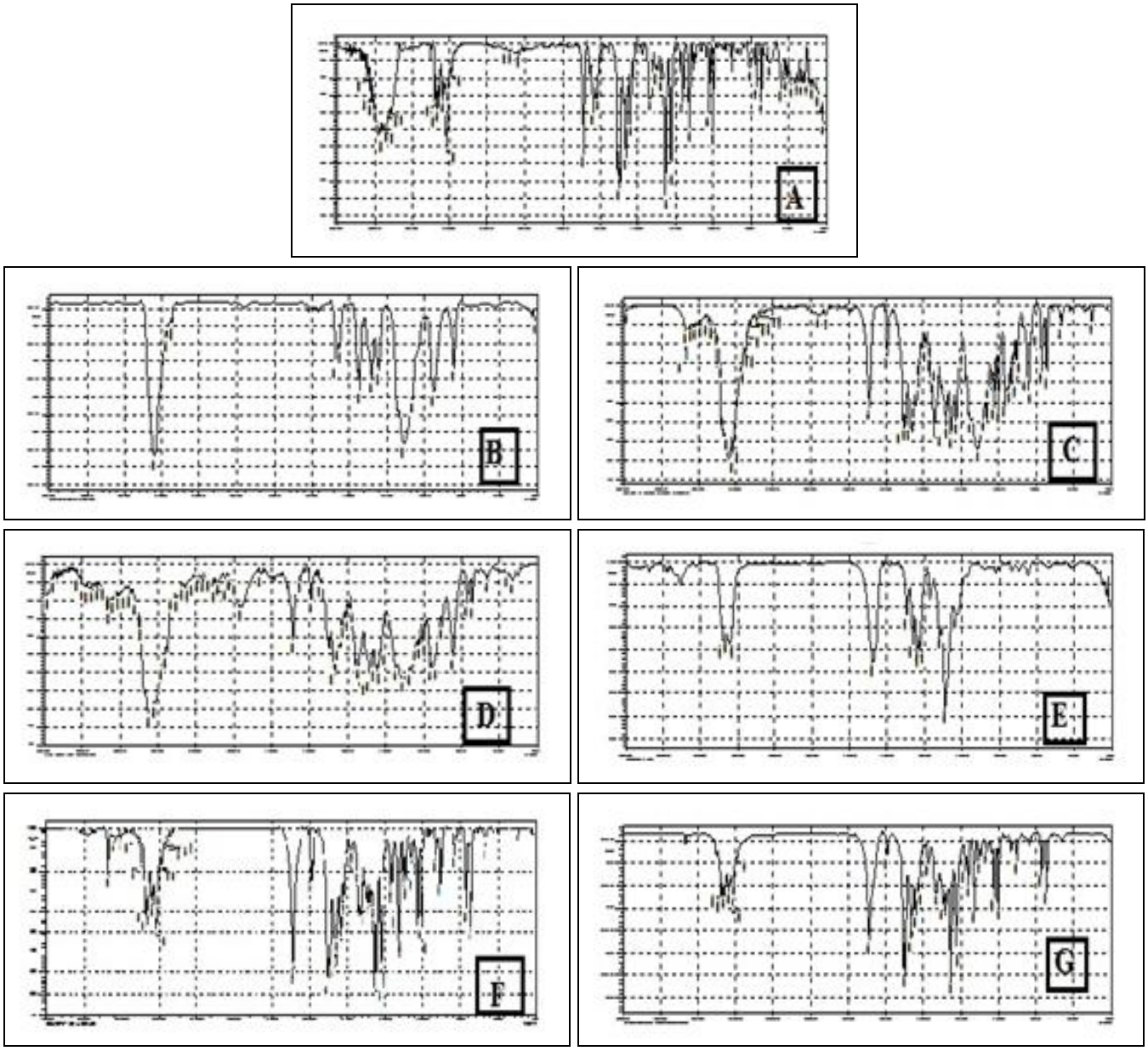

FIG. 1: FTIR SPECTRA OF A. RANOLAZINE B. PEG MIXTURE C. PHYSICAL MIXTURE MELT METHOD D. SD4 E. PVPK30 F. PHYSICAL MIXTURE SOLVENT EVAPORATION METHOD G. SD8

TABLE 1: COMPOSITION OF SOLID DISPERSION AND PHYSICAL MIXTURE

Type of Formulation	Composition (parts by weight)		
	RN	PEG 4000& 6000	PVPK 30
SD1	1	1	-
SD2	1	2	-
SD3	1	3	-
SD4	1	4	-
SD5	1	-	1
SD6	1	-	2
SD7	1	-	3
SD8	1	-	4

TABLE 2: SATURATION SOLUBILITIES OF SOLID DISPERSIONS

Formulation	Solubility (mg/mL)
Pure drug	0.142
SD 1	0.293
SD 2	0.402
SD 3	0.567
SD 4	0.77
SD 5	0.265
SD 6	0.32
SD 7	0.430
SD 8	0.594

Saturation Solubility: The saturation solubilities are given in **Table 2**. The saturation solubility of pure RN is 0.142mg/mL. The saturation solubility of SD increased compared to pure RN. This may be due to increased drug wettability.

SEM: The microphotographs of pure RN and optimized formulations are shown in **Fig. 2**. The images reveal that there is a formation of amorphous dispersions of RN and the polymers. The pure drug is consisting of a mixture of small and bigger crystalline particles. In contrast, the particles in SD4 and SD8 show porous amorphous particles of drug dispersed uniformly throughout the polymer matrix.

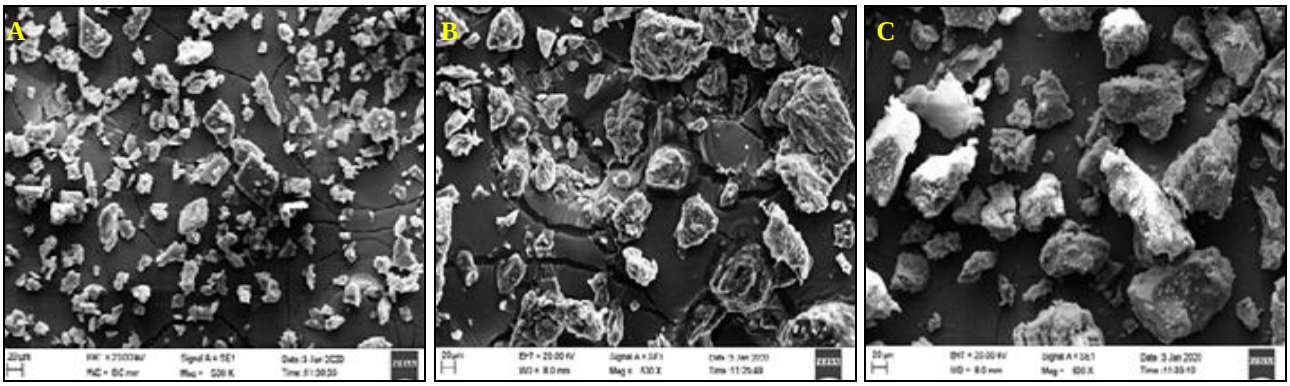

FIG. 2: SEM PHOTOMICROGRAPHS OF A. RN B. SD4 C. SD8

DSC: The thermal behaviour of pure drug RN and solid dispersions was studied by DSC. The DSC curves are shown in **Fig. 3**. The pure RN shows melting endotherm at 121 ºC with enthalpy of fusion (ΔH) of -279mJ/g. DSC scan of SD4 (melting method), shows a sharp peak at 64.9 ºC along with the drug RN peak at 102 ºC, which is shifted to the lower melting region. DSC scan of SD8 (solvent evaporation), shows a peak at 90-140 ºC due to loss of water which corresponds to PVPK30 along with drug RN peak at 121 ºC. This confirms the amorphicity of RN in solid dispersion or the existence of drug as a solid solution inside the polymer matrix.

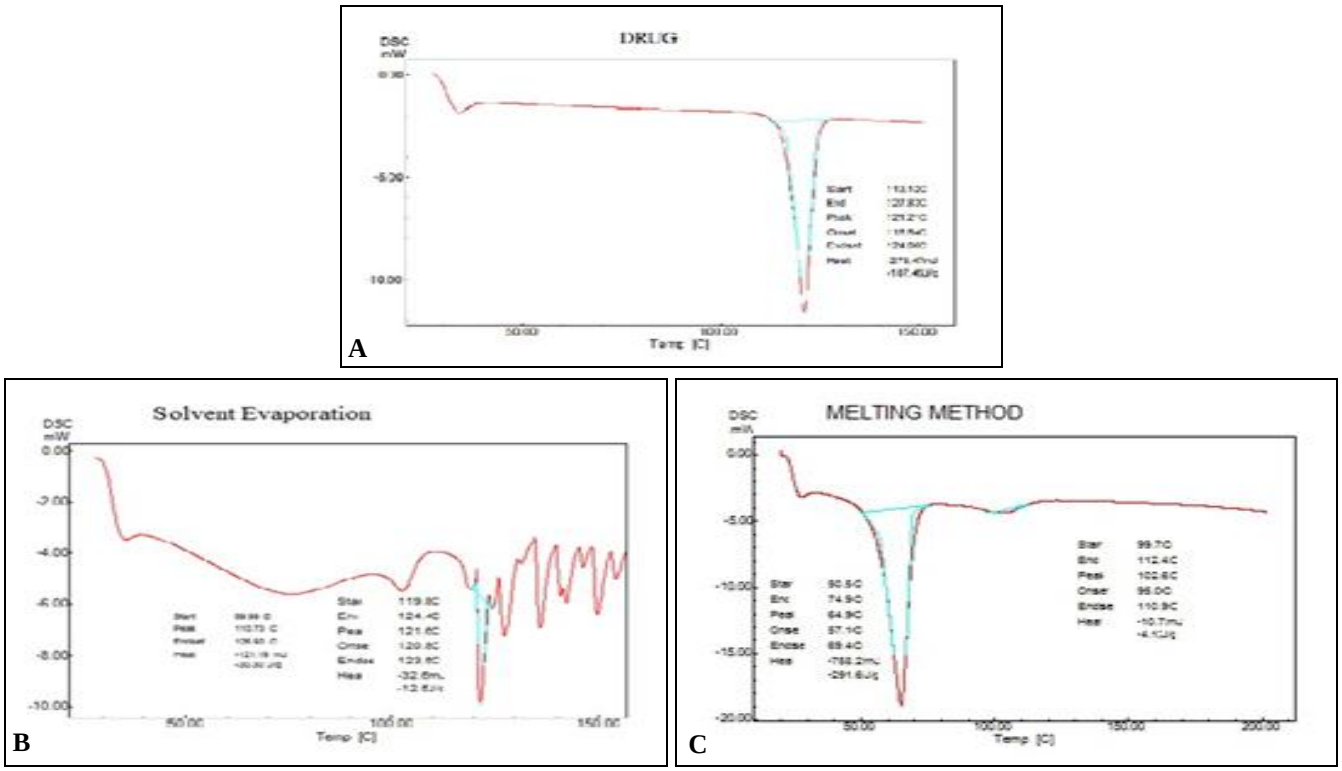

FIG. 3: DSC THERMOGRAPHS OF A. PURE DRUG B. SD8 AND C. SD4

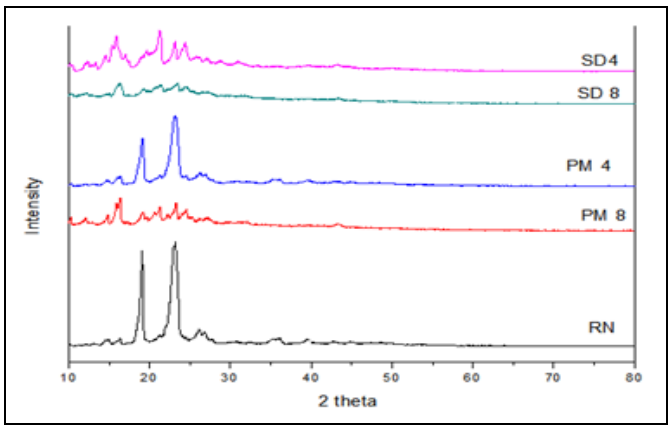

FIG. 4: POWDER X-RAY DIFFRATOGRAM OF RN, PHYSICAL MIXTURES AND SD4 AND SD8

PXRD: PXR diffractogram of Pure RN and optimized formulation are shown in **Fig. 4**. The diffractogram of Drug RN shows numerous peaks between 5°- 40° at 2Θ with characteristic peaks at 18.5°, 18.98°, 19.08°, 19.2° with high intensity reflecting drug's crystalline nature. Diffractograms PM of physical mixture showed decreased number of peaks with reduced intensity in comparison with pure RN. The decreased number of peaks might be due to partial amorphization of the drug. Diffratogram of SD4 and SD8 exhibited few peaks with reduced intensity with a lesser number of peaks. Thus, the overall PXRD results indicate that there is a reduction in the crystalline form, and amorphization of RN is observed in dispersions.

Dissolution Studies: Dissolution profiles of pure RN and solid dispersions over 3 h period are shown in **Fig. 5**. The dissolution rate of pure RN is low that is 28.70%. Solid dispersions of RN showed a significant increase in the dissolution rate of RN. For SD formulations, the dissolution rate was increased with the increasing ratio of drug and polymer.

The dissolution rates were ranged from 71-96%, depending on the polymer used and drug: polymer ratio. There was 7-9 fold increase in percentage drug release compared to pure RN. The highest drug release was shown by SD4 with PEG that is 96.44%. This improved drug release is due to the presence of amorphous form of RN, as confirmed by IR, SEM, DSC, and PXRD studies.

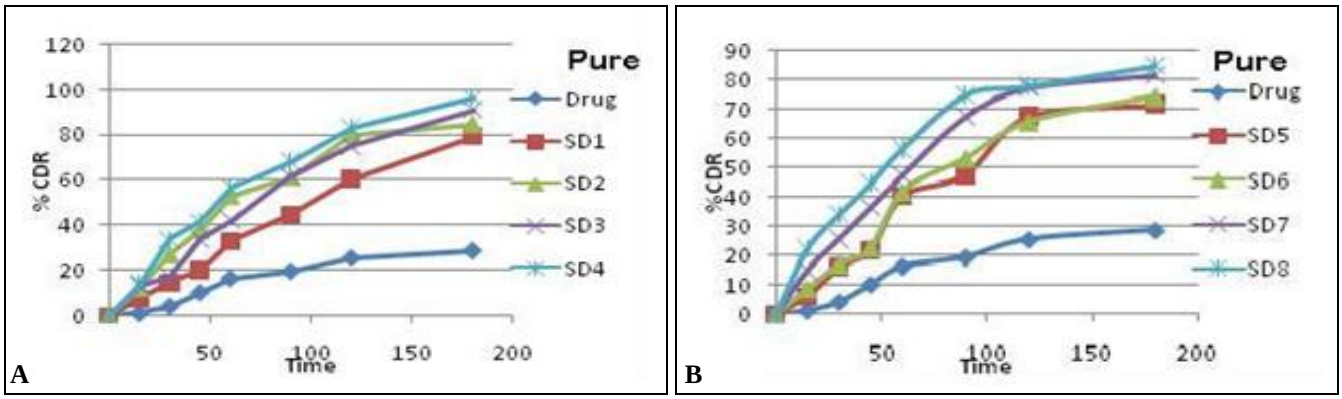

FIG. 5: *IN-VITRO* DISSOLUTION PROFILES OF RN PURE DRUG AND SOLID DISPERSIONS A. HOT MELT METHOD B. SOLVENT EVAPORATION

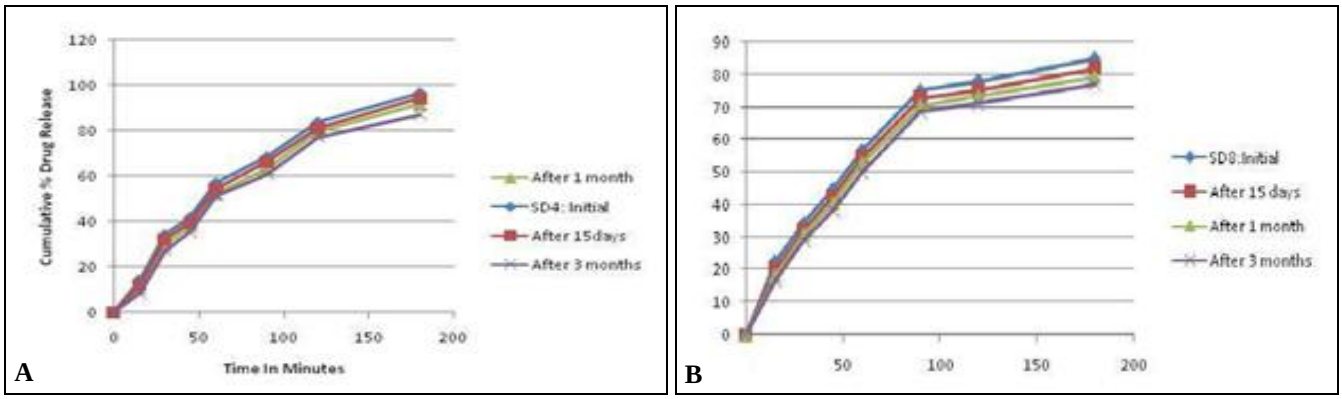

FIG. 6: *IN-VITRO* DISSOLUTION PROFILES OF A. SD4 AND B. SD8 DURING STABILITY AT DIFFERENT TIME INTERVALS

Stability Studies: Previous studies conducted on solid dispersions reported that there is a tendency of recrystallinity of drug in solid dispersions at higher temperatures and relative humidity. Hence there is a need for stability studies to test recrystallinity upon storage. Stability studies were conducted as per ICH guidelines. When SD4 and SD8 were subjected for dissolution; at a specific time interval (15 days, 1 month and 3 months), the decrease in *in-vitro* drug release was found to be insignificant, which is shown in **Fig. 6**. Also, PXRD observations indicated that the presence of amorphicity at a specific time interval of 3 months period. There were no changes found in the powder x-ray diffractograms, which is shown in **Fig. 7**. This could be attributed to the entrapment of drug molecules in the polymer matrix, which prevents further recrystallization upon storage.

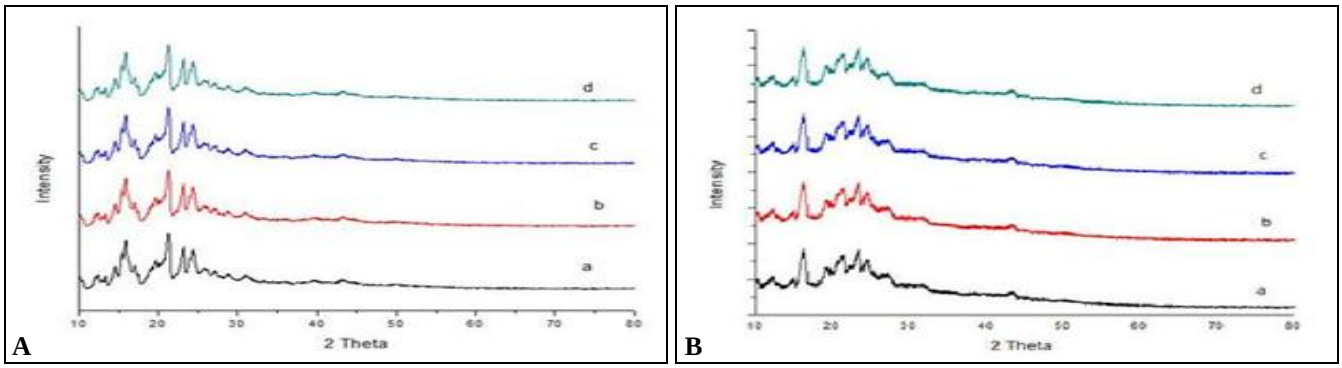

FIG. 7: POWDER X-RAY DIFRACTOGRAMS OF A. SD4 AND B. SD8 DURING STABILITY STUDY AT DIFFERENT TIME INTERVALS. (A) INITIAL (B) 15 DAYS (C) 1 MONTH (D) 3 MONTHS

CONCLUSION: The solubility and dissolution can be enhanced by solid dispersions of RN with PEG and PVP K30. In the case of PEG polymers, there is uniform dispersion of drug RN in the polymer matrix leading to amorphization. IR studies confirmed that there is hydrogen bonding between the drug RN and polymer PVP K30 at the molecular level in SDs, which could be the reason for enhanced solubility. Conversion of crystalline to amorphous form of RN is confirmed by IR, DSC, PXRD, SEM, and dissolution studies. Stability study results confirm the absence of recrystallinity upon storage over a period of 3 months. Hence, the present study suggests that the hot melt method and solvent evaporation method can be successfully used to prepare solid dispersions. However, the hot-melt method shown the highest percentage of drug release than solvent evaporation. Also, this method does not utilize organic solvent, suggesting an efficient and economical method of preparation of solid dispersion.

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CONFLICTS OF INTEREST: Authors declare no conflict of interest.

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