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Enhanced solubility and bioavailability of ranolazine by solid dispersion method in vitro and in vivo evaluation: A potential novel approach for cardiovascular diseases

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Abstract---Objective: This study aims to formulate solid dispersions incorporating ranolazine to enhance its aqueous solubility. Methodology: The poor aqueous solubility and permeability of BCS class II drug hamper their bioavailability when orally or topically administered. The present research study focused on formulating amorphous solid dispersions of ranolazine. The hydrophilic polymeric carriers like, HPMC, PEG 6000 and PVPK 30K, Soluplus were used in different ratio. Solid dispersions were prepared by employing modified solvent evaporation method. The prepared physical mixtures and solid dispersions were physico-chemically characterized using fourier transform infrared spectroscopy, scanning electron microscopy, powder x-ray diffractometry, drug content estimation by UV-spectrophotometric method. Result: Functional evaluation of ranolazine solid dispersions was carried out by solubility analysis, in-vitro dissolution studies and pharmacokinetics study. According to solubility studies, Soluplus showed the highest solubility profile among the polymers tested. An optimized ranolazine containing solid dispersions formulation composed of Soluplus at 1:2.5 ratio had 10

fold ($41.21 \pm 0.35 \mu\text{g/mL}$) higher solubility and dissolution over that of pure ranolazine ($\sim 3.92 \pm 0.06 \mu\text{g/mL}$) and physical mixture ($\sim 4.51 \pm 0.32 \mu\text{g/mL}$). In-vitro dissolution studies revealed that there was increase in solubility of drug and enhanced dissolution rate in solid dispersions compared to physical mixtures respectively. Polymeric carrier based 12 amorphous solid dispersion formulations were prepared, out of these (F1-F12) formulation 11 (SD-R-S-2) is considered as best formulation as it has shown highest drug release. Conclusion: The studies depicted the enhanced solubility with dispersion of Soluplus, polymer, thus ranolazine amorphous solid dispersion could be promising approach for enhanced dissolution rate.

Keywords---ranolazine, solubility, BCS class, hydrophilic carriers, solid dispersion, solvent evaporation method.

Introduction

In drug development and discovery process most of the compounds are associated with dissolution problems leading to limited bioavailability.^[1] To resolve this pharmaceutical challenge, numerous solubilization nano-strategies have been established including nanocrystals, amorphous polymeric solid dispersions, supra molecular inclusion system and lipid carrier formulations etc. ^[2] Dissolution and solubility of poorly water soluble pharmaceuticals may be improved by the use of amorphous solid dispersions (ASDs).^[3] Modern drug delivery technologies have enhanced drug solubility and stability, as well as their kinetics and dynamics. They have also increased bioavailability and decreased toxicity.^[2] As a result, the ability to generate and maintain a supersaturated condition has made amorphous solid dispersions more appealing. ^[4] It's a new anti-anginal drug that belongs to the piperazinacetamide family: Ranolazine is a 2-[2-hydroxy-3-(2-methoxyphenoxy) propyl piperazine-1-yl]acetamide.^[5] It's used for those with chronic angina who haven't responded well to other anti-anginal medications.^[6] It controls myocardial ischemia through intracellular metabolic changes, hence beneficial in chronic angina and other cardio metabolic disorders. Moreover, it is categorized as BCS class II drug low aqueous solubility as the rate limiting step.^[7, 8]

Using amorphous solid dispersions, researchers hoped to boost the super saturation of ranolazine solution, resulting in increased oral bioavailability. Because of this, certain formulation techniques have been developed to increase the drug's physicochemical characteristics and bioavailability.^[9] For the production of solid dispersions, hydrophilic polymers such as HPMC, PEG 6000, and PVPK 30K, Soluplus were used. Physiological toleration, fast solidification, and strong water solubility are all shown by these polymers.^[1] Polymers with these characteristics may be used to make solid dispersions.^[10] Since these carriers may be used in varied proportions, the result is amorphous solid dispersions. Soluplus (polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (PCL-PVAc-PEG)) is a new pharmaceutical excipient designed originally for preparing solid solutions of poorly water-soluble drugs by hot-melt extrusion technology. Soluplus is a water-soluble copolymer with the average molecular

weight ranging from 90,000 to 140,000 g/mol, and it is capable of solubilizing poorly water-soluble drugs. Analysis of ranolazine amorphous solid dispersions was carried out utilising PXRD, scanning electron microscopy, FTIR, and dissolution investigations, among other techniques. Ranolazine, a BCS class II medication, was being studied to see whether it could be made more soluble in water using a hydrophilic carrier. [10]

Materials and Methods

Veeprho Laboratories Pvt. Ltd. in Pune, Maharashtra, India provided the ranolazine as a free sample. S.D. Fine-Chem Ltd, Mumbai, India, supplied all of the analytical-grade solvents and chemicals utilised in this study. Analytical-grade of purity and quality polymers (HPMC, PEG 6000 and PVPK 30K, Soluplus), chemicals and solvents were employed in this study. These all materials are procured from SD fine Chem Ltd, Mumbai, India. Double distilled water made in-house was utilised in the experiment.

Preparation and optimization of solid dispersions of ranolazine Solvent evaporation method

In order to make water-insoluble medications more soluble, one of the most prevalent methods is solid dispersion. Ranolazine solid dispersions were prepared by using four carriers i.e. HPMC, PEG 6000 and PVP 30K, Soluplus in proportions viz. 1:1, 1:2.5 and 1:5 (Drug: Carrier) by solvent evaporation method.[5] So, total 12 formulations were prepared using 3 formulations of each polymer. Methanol was added to the mixture after the drug and polymers were weighed according to the method. Evaporation was carried out at 40°C under decreased pressure using an evaporation flask that had been transferred from the round bottom flask. The dried and ground-up solid dispersions were the final product. The last step was to keep the created formulations in desiccators until they could be used again. [11] Table 1 lists the ingredients in each of the 12 formulations.

Characterization of ranolazine solid dispersions Solubility studies

Solubility Studies of pure drug ranolazine, solid dispersion and physical mixture (PM) were performed according to the published method.[12] For this, individual sample an excess amount of individual sample weighed and then transferred in stoppered conical flask in an orbital shaker. Over the course of 24 hours, at 37°C, the aqueous dispersion was stirred constantly using an industrial-grade rotary shaker (RS-24 BL, Remi House, Mumbai, India). Membrane filter, 0.45µm was used to filter the solution, and the resultant solution was adequately diluted. [13]

Fourier transform infrared spectroscopy

Pure ranolazine, HPMC, PEG 6000, and PVPK 30K, Soluplus were examined by acquiring infrared scans of the formulation components using an FTIR spectrophotometer (Model: Shimadzu IRAffinity-1). Individual samples were mixed with FTIR-grade potassium bromide (KBr) in a mortar and pestle to create the homogeneous mixture for the FTIR analysis. In order to get the best results, the

samples were scanned in a range of 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1} .^[14]

Differential scanning calorimetry

The thermograms of pure ranolazine, physical mixture, and solid dispersion were recorded by heating the samples from 50°C to 350°C per minute (model -Perkin-Elmer Instruments, USA). Individual samples (2.0 ± 0.2 mg) were weighed and sealed in an aluminium pan with a lid and crimper before DSC analysis.^[14]

Powder X-ray diffraction (XRD) study

PXRD spectra of pure drug ranolazine, physical mixture, and solid dispersion were obtained using a powder X-ray diffractometer (Analytical technologies limited, Model 3010). PXRD spectra describe shift of crystalline to amorphous nature of ranolazine at 30 kV and 15 mA. The samples were evaluated in the 3°–40° range, using a step size of 0.020° (2θ) and a scan speed of 2° per minute.^[15]

Shape and surface morphology (scanning electron microscope)

The surface morphology of nanoformulation was evaluated using a scanning electron microscope. SEM provides an image of a sample by scanning its surface with a low-energy electron beam (usually 1 to 30 keV), with resolutions in the nanometre range. The SEM images were obtained by a scanning electron microscope (Analytical technologies limited, Model- SEM 3000). The accelerating voltage is 15 kV at 200x. A little quantity of material was weighed and spread thinly on double-faced carbon tape. The samples were then sputter coated with a thin coating of gold. The images were then collected using instrument software at appropriate magnification.^[5]

Particle size and zeta potential analysis

PCCS (photon cross-correlation spectroscopy) was used to measure the particle size of pure ranolazine, a physical mixture, and a solid dispersion. A 10mg/ml solid dispersion of ranolazine in deionized water was produced and deposited in the sample chamber of the analyzer (model: Litesizer 500, Anton Paar). In order to optimise the count rate of the loaded sample, the optimal optimising count rate position was adjusted.^[16] The manufactured ranolazine dispersion was also used to analyse the zeta potential using a nanoparticle analyzer (Litesizer 500, Anton Paar) with DLS configuration. The sample solution was tested from -200 to +200 mV. The whole analysis was carried out at 25°C.^[17]

Estimation of drug content

Choudhary et al. employed UV-visible spectrophotometry to measure ranolazine concentration in the produced solid dispersion.^[18] The aqueous solution for ranolazine spectrum analysis was generated by dissolving about 10mg of ranolazine solid dispersion in 100ml of phosphate buffer (pH 6.8) and stirring well. Filtration of produced solution by 0.45 μm membrane filter, the filtered solution was diluted and measured for absorbance at 270nm using a Shimadzu UV Spectrophotometer 1800. To prevent interference, a polymer blank solution

was created and compared to the sample solution.^[5] The percent ranolazine in the solid dispersion was determined using Eq. (1):

$$(\%)\text{Yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Dissolution studies

In this study, a paddle-based dissolving apparatus (model: TDT-08LX, Electrolab India Pvt. Ltd., Mumbai, India) was used to evaluate the in-vitro dissolution performance of the pure drug ranolazine, a physical combination, and a solid dispersion, in comparison to each other. The dissolving investigations were carried out in accordance with the technique that had previously been published in the scientific literature.^[5] For the sake of simplicity, the testing samples, which consisted of pure ranolazine (10mg) or a produced physical combination (equivalent to 10mg of ranolazine) and solid dispersion (10mg), were dispersed in 900ml of dissolution fluid (phosphate buffer-pH 6.8) in a dissolution flask containing the dissolution media. After mixing the samples, the flask's contents were agitated at a speed of 100 rpm throughout the experiment. The temperature of the medium was kept at $37 \pm 0.5^\circ\text{C}$ throughout. The dissolution investigation was carried out for 120 minutes in total. Every 10 minutes, the samples were removed, filtered (membrane filter, $0.45\mu\text{m}$), diluted, and evaluated using a UV-visible spectrophotometer (model: Shimadzu UV Spectrophotometer- 1800) at a maximum wavelength of 270nm in comparison to a blank solution using the absorbance of the resultant solution. The recorded absorbance readings of each sample were used to calculate the percentage cumulative quantity of ranolazine released and the amount of solid dispersion released from each sample. It was possible to estimate the release kinetic analysis of solid dispersion by fitting the release data into several kinetic models, such as zero-order, first-order, and Higuchi models, using the release data.^[12]

In vivo studies

Albino wistar rats were used in experiments on the oral bioavailability of ranolazine solid dispersion. Rats that weighed $200 \pm 20\text{gm}$ were split into two groups, each consisting of three rats. Groups of rats are fasted overnight before the experiment begins, but they have free access to drinking water throughout that time. Using halothane inhalation, the animals were sedated and 2ml of blood was taken from the retro-orbital sinus. Blood samples for the kinetic studies were obtained at various times according to approved protocol [The institutional animal ethical committee of Columbia Institute of Pharmacy, Raipur, reviewed and sanctioned the protocol (CIP/IAEC/2018/127), dated November 11, 2018]. The blood was fractionated at 10,000rpm for 10min and the serum was separated for analysis by using HPLC (model: Shimadzu i-series LC-2050C)[18]. When it comes to pharmacokinetic characteristics, the maximum plasma concentration (C_{max}) and time it takes to reach that concentration (T_{max}) were directly derived from the plasma concentration-time profiles. Calculation of AUC (area under the plasma concentration curve).

Results and Discussion

Preparation and optimization of solid dispersion

An easy and practical way for making solid dispersions in the laboratory is the solvent-evaporation method. HPMC, PEG 6000, and PVP 30K, Soluplus were used to generate ranolazine-containing ASD formulations. The solubility profiles of drug from solid dispersion were explored as indicated in Table 1 in order to understand the impact of drug/carrier ratio on created solid dispersion. Compared to the pure drug, all of the formulations had a far greater solubility rate. Formulation F₁₁, on the other hand, had a much greater solubility profile at the drug/carrier ratio of 1:2.5(SD-R-S-2). Formula F₁₁ was identified as the best formulation for future research.

Saturation Solubility studies

Table 1 includes results of analyses of solubility in water in the aqueous phase. For the determination of ranolazine solubility profiles in PMs and solid dispersions, the following ratios were used: 1:1, 1:2.5, and 1:5. Because of its poor water solubility and the high permeability profile of the BCS class II category, pure ranolazine only dissolved in $3.94 \pm 0.06 \mu\text{g/ml}$. Compared to the pure medication, physical mixtures of ranolazine with various polymers showed somewhat greater solubility in water and their solubility ranged from 3.98 ± 0.10 to $4.51 \pm 0.32 \mu\text{g/ml}$. Polymer-ranolazine strong association may have led to the development of slightly changed ranolazine particles that have greater water solubility and wettability properties, explaining the moderate increase in aqueous solubility of all PMs tested. Aqueous solubility of ranolazine, except for the physical combination of ranolazine and Soluplus PM-R-S-3, decreased further when the drug and polymer ratios increased (i.e. 1:5). In addition, the aqueous solubility of ranolazine in solid dispersion was enhanced between 18.30 ± 0.20 and $41.21 \pm 0.35 \mu\text{g/ml}$. Ranolazine water solubility was greatly improved by the optimised (SD-R-S-2) formulation₁₁ [a drug to carrier ratio of 1:2.5]. When compared to the water solubility of pure ranolazine and any physical combination with the drug, the resulting value demonstrates a ten-fold increase. In the solid dispersion, the complexation of carrier with ranolazine particles was most likely the cause of the improved water solubility. [19] Ranolazine water solubility may be improved due to the drug's amorphous form in this carrier.

Fourier transform infrared spectroscopy

The FT-IR study confirms the interaction between the functional groups of different formulation components. Fig.1 (a,b,c,d) depicts the FT-IR spectrum of pure ranolazine, as well as mixtures of ranolazine polymer and solid dispersion formulations. Figure 1a shows the FT-IR spectra of ranolazine in its purest form. The N-H stretching (primary aliphatic amine), C-H stretching, C=C stretching, C-H bending, and C-O stretching vibrations are represented by the absorption peaks seen at 3328.5cm^{-1} , 2829.0cm^{-1} , 1684.8cm^{-1} , 1591.6cm^{-1} , 1461.1cm^{-1} , 1330.7cm^{-1} , and 1252.4cm^{-1} in this figure. Asymmetric and symmetric C-H 278cm^{-1} stretching occurred at 2923cm^{-1} and 2857cm^{-1} , respectively, in the soluplus spectra, as did ester carbonyl stretching at 1733cm^{-1} 1279cm^{-1} and

C=O stretching for tertiary amide at 1628cm^{-1} . These were the most prominent absorption bands [5]. Fig.1b. It was found that PM (1:2.5) displayed absorption peaks at 3322.1cm^{-1} , 2451.4cm^{-1} , 13611.1cm^{-1} , 1230.7cm^{-1} and 11522.4cm^{-1} that had additive features of pure ranolazine, as demonstrated by the FT-IR spectra in Fig.1c. This formulation, as shown in Fig.1d by FT-IR spectra, has absorption peaks at 3322.1cm^{-1} , 2451.4cm^{-1} , 1584.8cm^{-1} , 1739.1cm^{-1} , and 1528.2cm^{-1} in the spectrum. The FT-IR study confirms the interaction between the functional groups of different formulation components. Additional peaks might be seen in the SD-R-S-2-F₁₁ formulation for solid dispersion. There is a substantial physico-chemical interaction between the pure medication and the carrier, as seen by this additive peak. There seems to be a molecular interaction between ranolazine and the carrier polymer, which might be evidence for the creation of a solid dispersion of ranolazine with soluplus, according to the changing absorption peaks.^[20]

Powder X-ray diffraction (XRD) study

Fig 2 shows the PXRD analysis of pure ranolazine, a physical combination, and a solid dispersion. Diffractograms of pure ranolazine exhibited many sharp-pointed peaks detected at 3.93° , 9.31° , 11.22° , 13.92° , 14.42° , 17.42° , 19.27° , 22.37° , 23.39° , and 24.60° on a 2θ scale, showing the crystalline form of the substance. Because of the interaction between the drug carrier and the improved formulation, these peaks were reduced while the amorphous nature increased. XRD examination indicated that the crystalline character of the material had changed to an amorphous form, which increases the solubility and dissolution rate, and hence improves the bioavailability.^[21] Amorphous material exhibits higher free energy as compared to crystalline compounds. Solubility and dissolution rates of drug molecules may be improved by nanosizing their crystalline structure, which will lead to an increase in their bioavailability.

Differential scanning calorimetry

DSC thermograms of pure ranolazine, physical combination, and solid dispersion formulations are showed in Fig. 3. The thermogram of pure ranolazine revealed a single endothermic peak at 123.12°C , which is the melting temperature of pure ranolazine. This peak's enthalpy of fusion (H) was measured to be $\sim 77.22\text{ J/g}$. The substance showed three faint intensity peaks between ~ 221.72 and $\sim 322.70^\circ\text{C}$ ($\Delta H \sim 5.87\text{ J/g}$). This may be related to the drug phase shift from crystalline to anhydrous. Moreover, compared to pure drug spectra, PM and solid dispersion had lower peak intensities. This indicates that the physical mixture has less ranolazine than the formulation (SD-R-S-2-F₁₁), and that the pure ranolazine and carrier polymer melted together, forming a partial mixture, resulting in weaker peaks than the pure ranolazine and formulation (SD-R-S-2-F₁₁). Based on the aforementioned comparison, it is determined that pure ranolazine and polymeric carrier establish strong interactions, resulting in amorphous solid ranolazine dispersion.

Shape and surface morphology (scanning electron microscope)

Fig. 4 shows SEM images of pure ranolazine, physical combination and produced

solid dispersion. Pure ranolazine appeared as clumps of granules with a rough surface. Physical mixture exhibited larger, non-uniform particles with non-defined morphology. The produced solid dispersion formulation emerged as aggregates of pure ranolazine. This interaction between pure ranolazine and the polymeric carrier Soluplus was validated by these aggregates. It is also possible that these aggregates formed owing to solvent evaporation.

Particle size and zeta potential analysis

Fig. 5 shows the particle size and zeta potential of developed ranolazine solid dispersion formulations. The physical stability of submicron particles distributed in liquid media is determined by particle size and zeta potential. The present study's solid dispersion formulation has an average particle size of 83.76 nm, demonstrating tiny particle size. This smaller particle size formulation has better dispersibility, increasing drug release rate. Also, particles less than 500nm are deemed acceptable for absorption through biological membranes. Moreover, the identical formulation's PDI was found to be 25.0%. The PDI data represents the carrier's maximal dispersion of pure ranolazine. The zeta potential measures the surface charges of particles. The zeta potential may also be used to characterise particle behavior in oral formulations. Generally, zeta potentials between -30 and +30 mV are suitable for multiparticulate systems.^[19] The prepared solid dispersion formulation has a zeta potential of 0.7 mV, which is satisfactory and confirms the formulation's stability.^[22]

Estimation of drug content

The formulation SD-R-S-2 (F₁₁) had the greatest drug concentration at 97.40 ± 0.19 percent w/w, whereas the other formulations F2, F6, and F9 had lesser drug content at ~89.40 ± 0.19 percent, 92.40 ± 0.39 percent, and 94.40 ± 0.89 percent, respectively. The SD-R-S-2 (1:2.5) formulation was chosen for further study.

Dissolution studies

Pure ranolazine and optimized solid dispersion formulation evaluated in distilled water for 120 min. After 120 minutes, pure ranolazine dissolved at ~4.63 ± 4.125 percent. Table 2 shows dissolution data. The PMR-S showed a small increase in ranolazine dissolution rate and extent (18.27 ± 3.146 after 120 min) compared to pure ranolazine. This may be due to 1) converting ranolazine to amorphous form, which is more soluble than its crystalline form, and 2) particle size reduction to nano range, which increases interfacial surface area and therefore wettability and surface free energy. All of these elements work together to speed up drug breakdown. The dissolving investigation further revealed that solid ranolazine retained particle size and did not agglomerate.^[23]

Furthermore, tiny particle size solid dispersion boosts cell membrane adhesiveness, increasing bioavailability of weakly water-soluble medicines. Dissolution is the rate-limiting phase for BCS class II medicines. As a result, low water solubility of BCS-II medicines must be addressed, hence increasing ranolazine bioavailability. The weakly water-soluble ranolazine demonstrated better dissolution rate, indicating improved bioavailability. In comparison to pure

ranolazine and a physical mixing, the optimised solid dispersion formulation demonstrated the maximum dissolving efficiency, with $85.14 \pm 1.242\%$ percent of ranolazine released in distilled water (Table 2). The enhanced solid dispersion dissolving rate may be related to the solvent evaporation process. Solvent evaporation, for example, changes crystalline drugs into partly amorphized powders, which boosts the dissolving rate of poor solubility drugs. [24] The results from solid dispersion formulations were evaluated using first-order, zero-order, Higuchi, and Korsmeyer-Peppas kinetic models. Given the greater correlation coefficient value ($R^2 = 0.998$) compared to the zero-order ($R^2 = 0.985$) and first-order ($R^2 = 0.998$) models, the first order model is the best-fit kinetic model for solid dispersion formulations. The release exponent (n) for optimum solid dispersion formulations was determined to be 0.49, showing that diffusion is the main mechanism responsible for ranolazine release (Table 3).

***In vivo* studies**

Ranolazine formulation pharmacokinetic characteristics compared to pure drug in rats. Table 4 summarizes pharmacokinetic parameters (C_{max} , T_{max} , AUC, K_{el} , $t_{1/2}$). Compared to the pure medication, the solid dispersion formulation had greater plasma concentration. The solid dispersion group had greater C_{max} ($4.24 \pm 0.40 \mu\text{g/ml}$) and AUC ($148.01 \pm 33.96 \mu\text{g/ml}$) than the pure drug group. Oral bioavailability of ranolazine in solid dispersion may be owing to improved dissolution and subsequent absorption in rats. [25]

Conclusion

Solid dispersion (SD-R-S-2-F11) was studied in order to improve ranolazine water solubility. An amorphous solid dispersion of ranolazine (SD-R-S-2-F11) was prepared using the solvent evaporation method. The solid dispersion was confirmed using physico-chemical (SEM, DSC, FT-IR, and PXRD) and functional characterization tests (solubility study, *in vitro*, and pharmacokinetics). When compared to pure ranolazine and a physical combination, the SD-R-S-2-F11 formulation improved aqueous solubility (10-fold), rate, and extent of ranolazine dissolution. Improved ranolazine dissolution is aided by increased surface area, drug conversion to amorphous form, increased dispersibility, improved wettability, and reduced agglomeration and aggregation among drug particles. The results demonstrate that employing soluplus as a polymeric carrier to improve overall biopharmaceutical properties for ranolazine and other drugs with limited water solubility is a strong prospect. Thus ASDs is a novel and promising approach for improve physiochemical and functional properties of BCS Class II drugs.

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Authors' contributions

Monika bhairam performed the analysis, reported the results and prepared the first draft. The corresponding author Ravindra kumar pandey revised the calculations and prepared the final manuscript. Shiv Shankar shukla and Beena gidwani guided and proof read. All authors have read and approved the manuscript.

Conflict of interest

The authors declare that they have no competing interests.

Abbreviations

Biopharmaceutical Classification System (BCS), Amorphous solid dispersions (ASDs), Powder X-ray diffraction (PXRD), Scanning electron microscopy (SEM), Fourier transform infrared (FTIR), Hydroxypropyl Methylcellulose (HPMC), Polyethylene glycol (PEG), Ranolazine (R), Polyvinylpyrrolidone (PVP), Soluplus (S), Solid dispersion (SD), Physical mixture (PM), Area under curve (AUC), polydispersity index (PDI), Differential scanning calorimetry (DSC).

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List of Table

Table 1
Composition of the prepared ranolazine solid dispersion and their aqueous solubility

S.No.	Sample Code of Formulation	Drug-Polymer Ratio	Aqueous Solubility (µg/ml) ^a
Drug	Pure drug (Ranolazine)	-	3.91 ± 0.06
PM-1	PMR-HPMC	-	3.98 ± 0.10
PM-2	PMR-PVP	-	4.20 ± 0.15
PM-3	PMR-PEG	-	4.30 ± 0.12
PM-4	PMR-S	-	4.51 ± 0.32
F ₁	SD- R-HPMC-1	1:1	11.54 ± 0.03
F ₂	SD- R-HPMC-2	1:2.5	18.30 ± 0.20
F ₃	SD- R-HPMC-3	1:5	13.20 ± 0.32
F ₄	SD- R-PVP-1	1:1	19.10 ± 0.12
F ₅	SD- R-PVP-2	1:2.5	21.10 ± 0.32
F ₆	SD- R-PVP-3	1:5	27.20 ± 0.25
F ₇	SD- R-PEG-1	1:1	29.20 ± 0.52
F ₈	SD- R-PEG-2	1:2.5	31.10 ± 0.32
F ₉	SD- R-PEG-3	1:5	35.90 ± 0.42
F ₁₀	SD- R-S-1	1:1	36.78 ± 0.32
F ₁₁	SD- R-S-2	1:2.5	41.21 ± 0.35
F ₁₂	SD- R-S-3	1:5	39.13 ± 0.35

*All results are expressed as mean \pm Std. Dev. (n = 3),
 Abbreviation: Ranolazine (R), Hydroxypropylmethylcellulose(HPMC),
 Polyvinylpyrrolidone (PVP), Polyethylene glycol (PEG), Soluplus® (S),
 Solid dispersion (SD), Physical mixture (PM).

Table 2
 Data for *In-vitro* dissolution study for solid dispersion formulations

Time (min)	Cumulative Percentage Release of Drug (%)					
	Pure drug	Physical mixture (R+S)	Formulation F ₂ SD-R - HPMC 2	Formulation F ₆ SD-R -PVP-3	Formulation F ₉ SD-R - PEG-3	Formulation F ₁₁ SD-R-S-2
0	0	0	0	0	0	0
10	1.33 \pm 2.113	2.54 \pm 2.045	6.15 \pm 1.457	9.93 \pm 1.761	5.43 \pm 1.429	6.29 \pm 1.259
20	1.79 \pm 3.255	3.72 \pm 1.251	12.68 \pm 2.332	15.12 \pm 2.720	11.16 \pm 1.734	11.57 \pm 1.077
30	2.69 \pm 2.156	3.94 \pm 2.345	15.75 \pm 3.674	19.93 \pm 1.703	16.10 \pm 1.159	18.55 \pm 2.323
40	2.89 \pm 1.135	4.91 \pm 5.467	20.26 \pm 4.455	24.59 \pm 2.704	19.28 \pm 1.044	21.84 \pm 2.396
50	3.14 \pm 2.047	5.47 \pm 3.345	22.36 \pm 2.688	28.11 \pm 4.619	21.87 \pm 1.720	26.49 \pm 2.051
60	3.37 \pm 6.025	5.77 \pm 4.345	27.89 \pm 2.271	31.69 \pm 3.217	26.53 \pm 1.069	32.60 \pm 2.685
70	3.54 \pm 1.345	6.77 \pm 0.264	29.16 \pm 2.916	33.20 \pm 3.986	29.99 \pm 1.242	40.19 \pm 1.749
80	3.79 \pm 2.345	8.95 \pm 2.345	31.53 \pm 3.521	35.38 \pm 0.739	34.54 \pm 1.134	49.61 \pm 2.453
90	3.89 \pm 2.145	10.23 \pm 2.567	35.32 \pm 1.345	37.48 \pm 3.493	38.39 \pm 1.345	67.73 \pm 2.051
100	4.27 \pm 4.378	12.58 \pm 1.416	37.19 \pm 1.652	39.20 \pm 7.833	42.76 \pm 1.562	72.89 \pm 2.813
110	4.40 \pm 1.321	14.89 \pm 5.132	38.53 \pm 3.863	41.85 \pm 3.635	46.05 \pm 1.114	79.60 \pm 1.186
120	4.63 \pm 4.125	18.27 \pm 3.146	39.92 \pm 1.946	42.97 \pm 3.955	55.48 \pm 4.838	85.14 \pm 1.242

*All results are expressed as mean \pm Std. Dev. (n = 3)

Table 3
Kinetic model analysis of in vitro release data of solid dispersion formulation

Formulation Code	Zero Order Model		First Order Model		Hixon crowell Model		Higuchi Model		Korsmeyer peppas Model		
	R ²	K(mg ⁻¹)	R ²	K(mg ⁻¹)	R ²	K(mg ⁻¹)	R ²	K(mg ⁻¹)	R ²	n	K(mg ⁻¹)
F ₂	0.989	2.111	0.993	-0.014	0.983	-0.039	0.967	13.121	0.986	0.771	0.734
F ₆	0.980	2.049	0.989	-0.012	0.979	-0.040	0.960	12.687	0.991	0.540	0.873
F ₉	0.984	2.558	0.991	-0.017	0.989	-0.053	0.956	15.779	0.984	0.378	0.891
F ₁₁	0.985	2.133	0.998	-0.013	0.983	-0.041	0.985	13.207	0.982	0.490	0.966

Table 4
Pharmacokinetic study of ranolazine in pure drug and optimized solid dispersion formulation

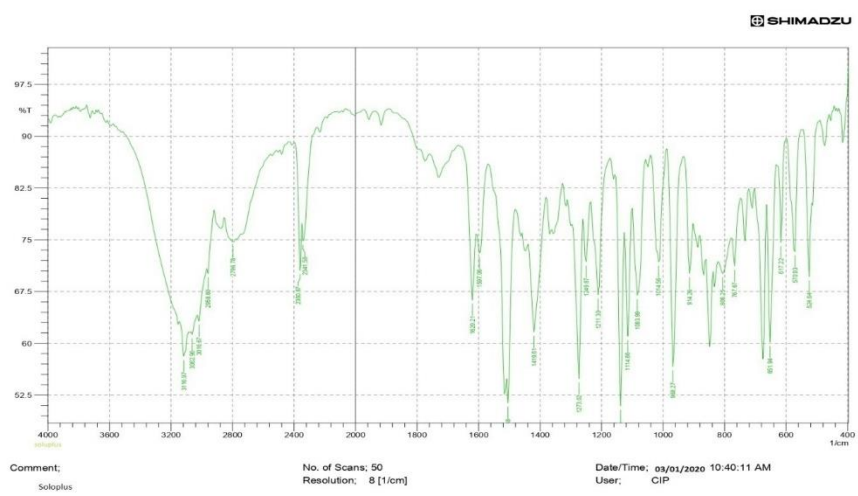
S.No.	Parameters	Pure drug	Optimized solid dispersion formulation (SD-R-S-2-F ₁₁)
1	C _{max} (µg/mL)	3.91 ± 0.73	12.25 ± 0.40
2	T _{max} (h)	4.00 ± 2.00	5.00 ± 0.00
3	AUC (h.µg/mL)	82.01 ± 24.56	148.01 ± 33.96
4	K _{el} (h ⁻¹)	0.036 ± 0.002	0.028 ± 0.004
5	t _{1/2} (h)	19.37 ± 1.16	25.16 ± 3.26

List of Figure

Figure 1. FT-IR spectra of (a) pure ranolazine, (b) soluplus (c) the physical mixture of ranolazine and soluplus, and (d) prepared solid dispersion (SD-R-S-2-) formulation (F₁₁)

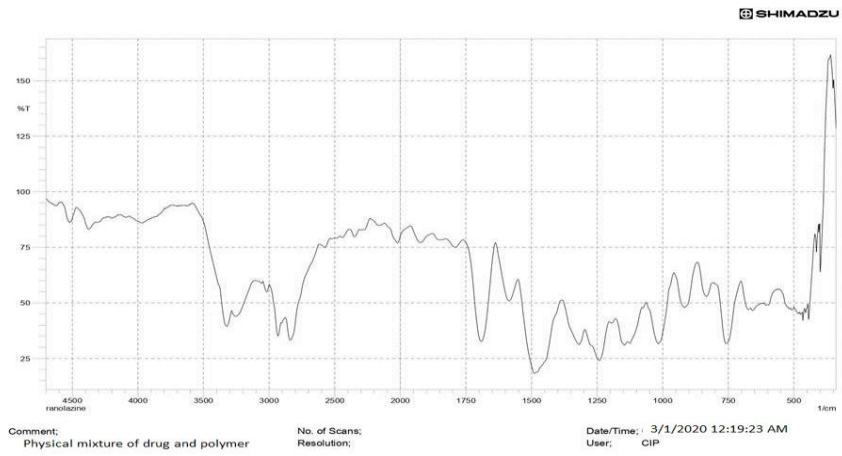


1(a)

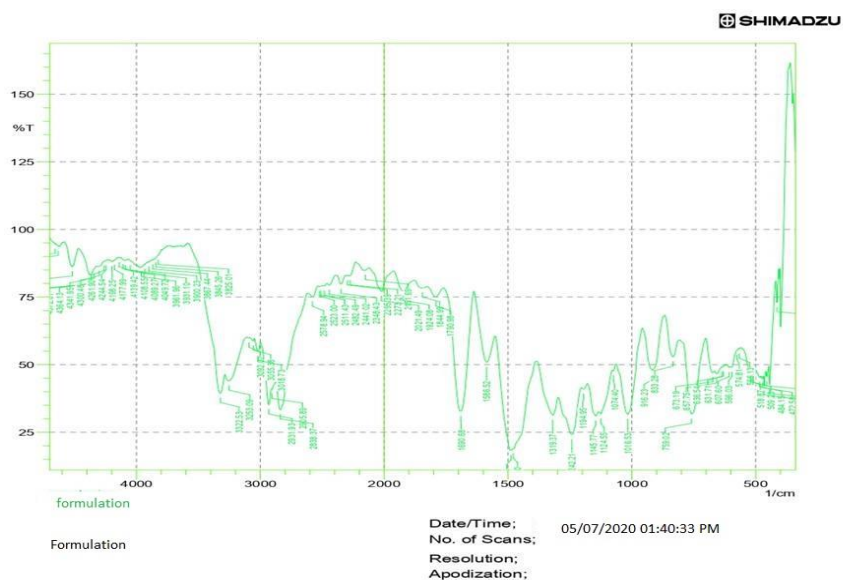


1(b)

3744



1(c)



1(d)

Figure 2. The powder x-ray diffractograms of (a) pure ranolazine, (b) the physical mixture of ranolazine with soluplus, and (c) prepared solid dispersion (SD-R-S-2) formulation (F₁₁)

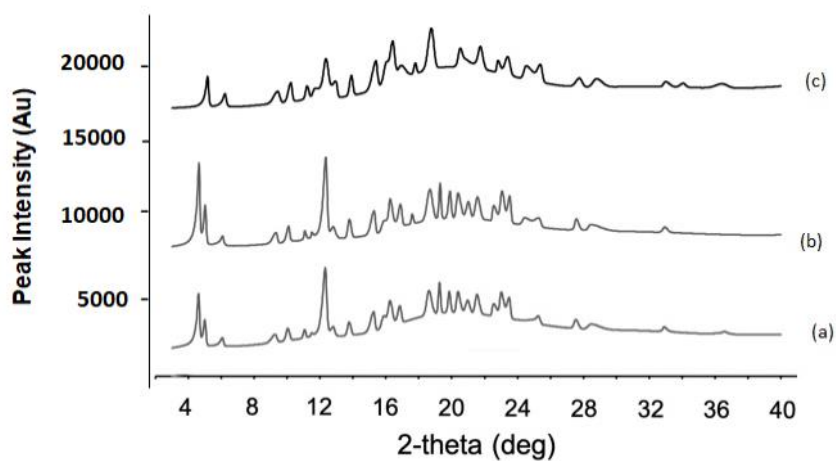


Figure 3. DSC thermograms of (a) pure ranolazine, (b) the physical mixture of ranolazine and soluplus, and (c) prepared solid dispersion (SD-R-S-2) formulation (F₁₁)

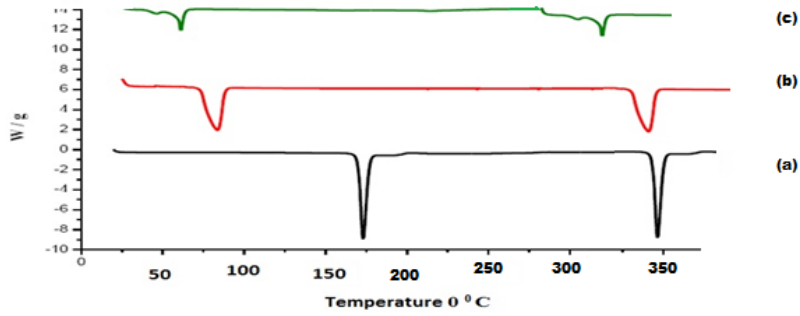
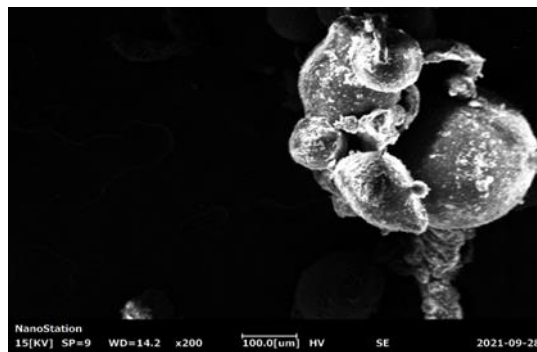
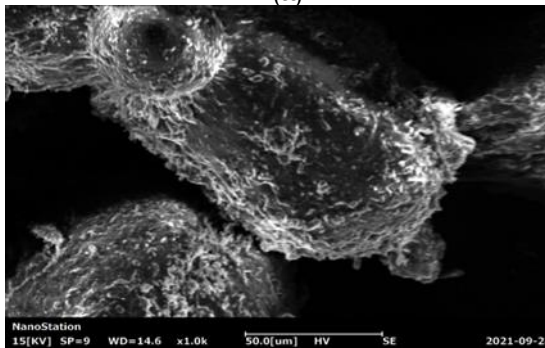


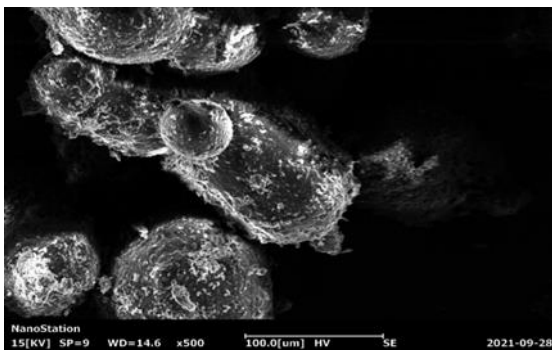
Figure 4. SEM images of (a) pure ranolazine, (b) the physical mixture of ranolazine and soluplus, and (c) prepared solid dispersion (SD-R-S-2) formulation (F₁₁)



4(a)

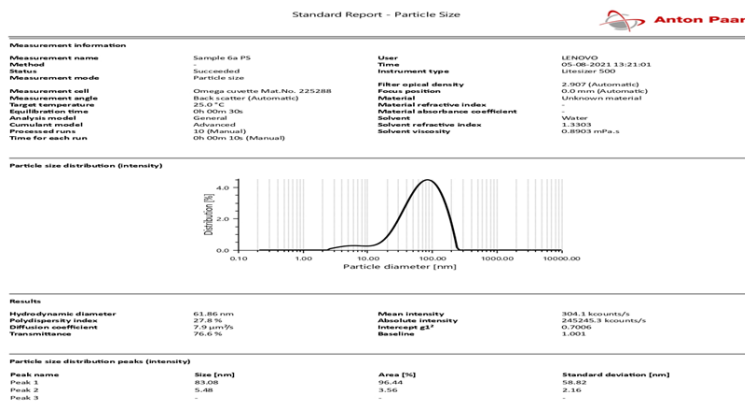


4(b)

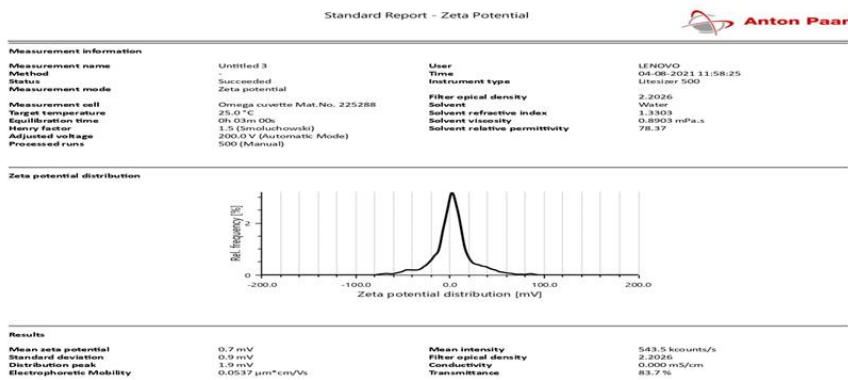


4(c)

Figure 5: (a) Particle size and (b) zeta potential of the prepared optimized solid dispersion formulation(F₁₁)



5(a)



5(b)

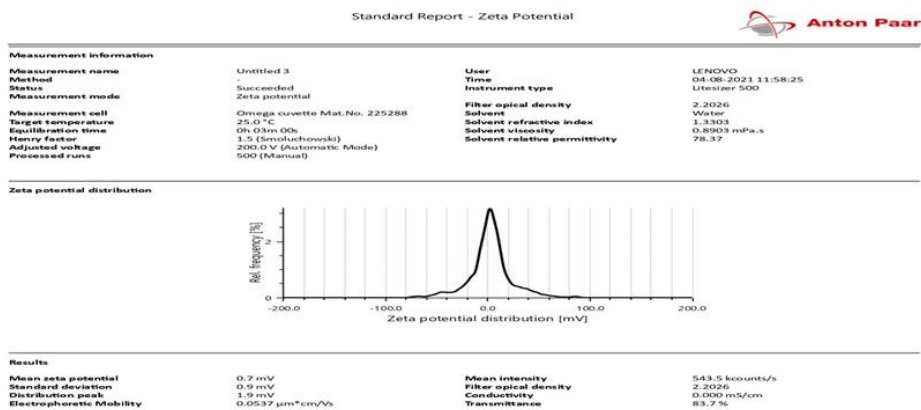


Figure 6. *In vitro* dissolution profiles of pure ranolazine, the physical mixture and the prepared optimized solid dispersion (SD-R-S-2) formulation (F₁₁).

