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ORIGINAL ARTICLE

LIPOID SPC-3-Based Coprecipitates for the Enhancement of Aqueous Solubility and Permeability of Ranolazine

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Abstract

Purpose The study was aimed at exploring the feasibility of LIPOID SPC-3 as a coprecipitate carrier to enhance the aqueous solubility and permeability of ranolazine, a BCS class II drug.

Methods LIPOID SPC-3-based coprecipitates of ranolazine (RNZ-SPC-CP) were developed using the solvent method. The developed formulation was physico-chemically characterized using scanning electron microscopy (SEM), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FT-IR), powder x-ray diffractometry (PXRD), and drug content. Functional evaluation of RNZ-SPC-CP formulations was carried out by solubility analysis, in vitro dissolution studies, fed vs. fasted state dissolution comparison, and ex vivo permeation studies.

Results The SEM studies revealed dissimilar morphological characteristics of pure ranolazine, LSPC-3, and RNZ-SPC-CP formulations. The physico-chemical analysis confirmed the formation of the coprecipitate. Optimized RNZ-SPC-CP1 demonstrated a noteworthy increase (~18-fold) in water solubility (~92.23 ± 1.02 μg/mL) over that of pure ranolazine (~4.94 ± 0.06 μg/mL) and physical mixture (PM) (~30.21 ± 2.12 μg/mL). Optimized RNZ-SPC-CP1 appreciably enhanced the rate and extent of ranolazine dissolution (~85%), compared with that of pure ranolazine (~21%) and PM (~35%). Similarly, the permeation rate of ranolazine from optimized RNZ-SPC-CP1 formulation was found to be enhanced significantly (~83%) over that of pure ranolazine (~19%) and PM (~32%). In the fed state, the RNZ-SPC-CP1 improved the rate and extent of ranolazine dissolution, compared with those of fasted state dissolution.

Conclusions The results conclude that RNZ-SPC-CP could be used as a promising approach for enhancing the aqueous solubility and permeation rate of ranolazine.

Keywords Coprecipitates · Dissolution · Permeability · Phospholipids · Solubility

Introduction

Ranolazine (IUPAC name: *N*-(2,6-dimethyl phenyl)-2-[4-[2-hydroxy-3-(2-methoxy phenoxy) propyl]-propyl piperazine-acetamide]), a piperazine derivative, is used predominantly for the management of chronic stable angina pectoris (CSAP). It is a selective sodium channel blocker, which inhibits the late phase of Na^+ current in ischemia [1]. Upon oral administration, ranolazine produces a low and variable pharmacokinetic profile, resulting in poor oral bioavailability (i.e., ~35 to 50%). This is mainly attributed to its shorter half-life (~2 to 6 h), rapid clearance (>70%), and rapid hepatic first-pass metabolism by cytochrome P-450 3A (CYP3A) and CYP2D6, respectively [2–4]. Moreover, it is categorized as a Biopharmaceutics Classification System (BCS) class II drug, which exhibits low solubility and high permeability [5]. Earlier published reports have also shown that ranolazine plasma concentration is highly undesirable and fluctuate following oral administration [2]. Therefore, a unique formulation approach is strongly needed to improve the solubility, dissolution rate, permeability, and oral bioavailability of ranolazine.

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Previous reports showed that a very few formulations have been developed and explored by scientists for improving the solubility and permeability of ranolazine. These include sustained-release tablets [2], extended-release tablets [6], microparticles [7], floating microsphere [8], and extended-release tablets [9]. Following a review of these reports, it was found that the author only reduced the dosing frequency and improved patient compliance without investigating the solubility, permeability, and systematic evaluation of ranolazine. Hence, to address this significant issue, we employed a novel and suitable formulation strategy and/or approach to improve the biopharmaceutical attributes of ranolazine.

Among all formulation approaches, the phospholipid-based coprecipitate approach is found to be a distinctive one for improving the solubility and permeability of BCS class II drugs. Previous literature has evidenced that the coprecipitate strategy significantly improved the solubility and dissolution rate of probenecid [10], indomethacin [11], carbamazepine [12], and ibuprofen [13]. Moreover, the combination of phospholipids, i.e., LIPOID SPC-3, and solvent evaporation method physico-chemically modifies the particles of the drug into coprecipitates, leading to enhancement of the biopharmaceutical properties of ranolazine. Coprecipitates are amorphous solid dispersion prepared by the solvent evaporation method [14]. This approach has created tremendous interest among scientists due to multiple benefits like controlled and rapid release, increased therapeutic efficacy, prevention of thermal decomposition of the drug and carrier, improved particle size and their composition, simple and easy preparation, and improved dissolution rate of BCS class II drugs in a lower concentration of phospholipids. LIPOID SPC-3 (free flow and non-sticky lipid) phospholipids are used in the present study, and these are reported to enhance the biopharmaceutical properties of plant bioactive and/or drug molecules [15]. The amphiphilic property of this lipid (both water- and lipid-soluble portions) entraps the drug within itself, forming a complex, and thereby improves the aqueous solubility, dissolution rate, and permeability of the drug via facilitating its transportation across the biological membrane (6. 1). The complex is also reported to enhance the poor bioavailability of drugs by inducing the alteration in the target cell membrane structure and by changing the polarity of drug molecules [16]. The liposome- and phytosome-forming ability of phospholipids entraps and/or sequesters the drug molecules within the bilayer structure during the dissolution process and further improves drug dissolution by transporting the drug to the diffusion layer, then to the bulk solution, and then to the site of absorption for rapid release of the drug to the blood circulation [17, 18]. Moreover, the phase transition (Tc) temperature of these phospholipids being lower than the experimental temperature, i.e., 37 °C, makes them disperse spontaneously when coming in contact with water, which results in an increase in the dissolution rate of the drug. Also, the phospholipids containing a negative charge of the phosphate group can make a strong electrostatic complex with the positive charge of drug molecules, resulting in an increase of the dissolution rate of drugs with poor bioavailability [9, 10]. Besides these advantageous effects, these phospholipids also exhibit high compatibility, biodegradability, metabolic activity, and low toxicity over other lipids, representing them as the most appropriate carrier for the development of coprecipitates. This approach has been successfully used and explored for the only liposome-forming phospholipids such as L-α-dimyristoyl phosphatidylcholine (DMPC), L-α-dimyristoyl phosphatidylglycerol (DMPG), L-α-distearoyl phosphatidylcholine (DSPC), and egg phosphatidylcholine (EPC); however, the same approach is found to be lacking and unexplored for phytosome-forming phospholipids, i.e., LIPOID SPC-3, and small molecules with poor aqueous solubility like ranolazine. Additionally, the previous reports are also found to lack a systemic and comprehensive evaluation of physicochemical and functional characterization of coprecipitate formulations. According to this, the current work was undertaken, to explore the feasibility of LIPOID SPC-3 as a coprecipitate carrier for enhancing the solubility and permeability of ranolazine.

The present research is a "proof-of-concept" type of work, in which we explore the feasibility of LIPOID SPC-3 as a coprecipitate carrier for improving the solubility and permeability of ranolazine. Coprecipitate formulations of ranolazine with LIPOID SPC-3 (RNZ-SPC-CP) were prepared using the solvent evaporation method. The prepared coprecipitates were physically evaluated by particle size, zeta potential, SEM, DSC, FT-IR, powder x-ray diffractometry (PXRD), and drug estimation. Functional characterization was carried out by solubility and in vitro dissolution and ex vivo permeation studies. Moreover, the coprecipitate formulation was also tested for preliminary stability study under the influence of controlled temperature and relative humidity for 6 months.

Materials and Methods

Materials

Ranolazine (purity more than 99.86%) was obtained from Alkem Laboratories Ltd., Mumbai, India. LIPOID SPC-3 was obtained from Lipoid GmbH, Ludwigshafen, Germany. Absolute ethanol, acetone, chloroform, dichloromethane, diethyl ether, and 1,4-dioxane were purchased from Loba Chemicals Pvt., Ltd., Mumbai, India. The remaining ingredients such as potassium bromide, potassium chloride, potassium dihydrogen phosphate, sodium hydroxide, sodium dihydrogen phosphate, and sodium chloride were purchased from Sigma-Aldrich Corporation, St. Louis, MO.

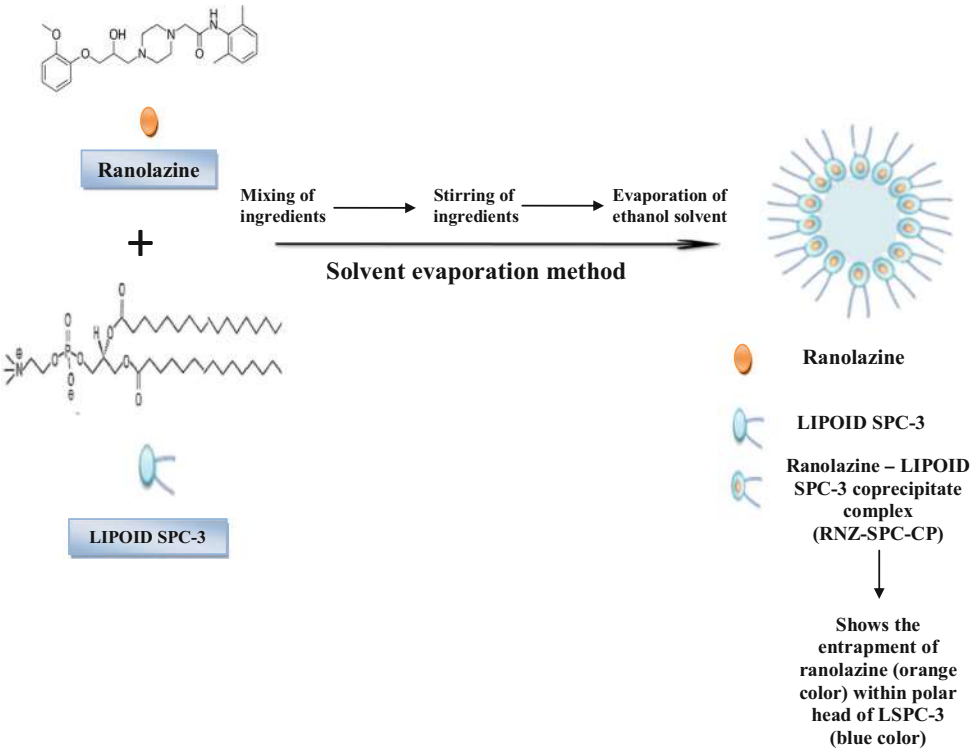

Fig. 1 Schematic diagram representing the entrapment of pure ranolazine within the polar head of LSPC-3 resulting in formation of the RNZ-SPC-CP complex

Preparation of Ranolazine-LIPOID SPC-3 Coprecipitate

The RNZ-SPC-CP was prepared according to stoichiometric ratios (1:1, 1:2, 1:3, 1:4, and 1:5) using a method reported previously [10]. Briefly, the required quantity of ranolazine and LIPOID SPC-3 (LSPC-3) was accurately weighed and transferred into a 50 -mL beaker. The weighed ingredients were mixed and then dissolved in 10 mL of absolute ethanol using a magnetic stirrer until a homogenous solution was achieved. The prepared solution was allowed to evaporate at room temperature, resulting in the formation of a solid mass of RNZ-SPC-CP. The obtained solid mass was collected from the beaker and dried under vacuum at 40 °C for 24 h. The dried RNZ-SPC-CP formulation was sieved and placed into a light-resistant amber-colored glass bottle, flushed with N_2, and finally kept in desiccators for further characterization. The composition of the formulation is shown in Table 1.

Physico-chemical Characterization of Ranolazine-LIPOID SPC-3 Coprecipitate

Scanning Electron Microscopy

The surface characterization of samples such as ranolazine, LSPC-3, and RNZ-SPC-CP was carried out on SEM (model: Supra® 55, Carl Zeiss NTS Ltd., Germany). Briefly, an approximate amount of samples (~ 50 mg) was weighed and then spread as a very thin layer on double-faced carbon tape. The prepared samples were then loaded into a sputter coater and then coated with a thin layer of gold. After this, the images were captured at suitable magnification using instrument-associated software (SmartSEM®, TV mode). The accelerating voltage throughout the scanning was maintained at 10 kV.

Particle Size and Zeta Potential Analysis

Particle size analysis of RNZ-SPC-CP formulations was carried out by photon cross-correlation spectroscopy (PCCS) with the support of dynamic light scattering (DLS) technology setup as per the method reported by our laboratory [19]. Briefly, the RNZ-SPC-CP formulation with a concentration of ~ 500 μg/mL in deionized water was prepared and placed into the sample chamber of the analyzer (model: NANOPHOX, Sympatec GmbH, Clausthal-Zellerfeld, Germany). The loaded sample was analyzed for particle size within the sensitivity range of 1 nm to 10 μm via adjusting its suitable optimizing

Table 1 Composition of the prepared ranolazine-LIPOID SPC-3 coprecipitate formulations

Coprecipitates	Drug (mg)	LIPOID SPC-3 (mg)
RNZ-SPC-CP1	100	100
RNZ-SPC-CP2	100	200
RNZ-SPC-CP3	100	300
RNZ-SPC-CP4	100	400
RNZ-SPC-CP5	100	500

count rate position. The results were read by the instrument-associated software.

The prepared dispersion of RNZ-SPC-CP formulations was also employed for the zeta potential analysis using Nano Particle Analyzer (model: NanoPlusTM-2, particulate system, Norcross, GA, USA) equipped with a DLS setup. The sample solution was analyzed in the sensitivity range of − 200 to + 200 mV. The temperature during the entire analysis was set to 25 °C.

Differential Scanning Calorimetry

Samples of formulation components such as ranolazine, LSPC-3, physical mixture (PM) of ranolazine and LSPC-3 (1:1), and prepared RNZ-SPC-CP were analyzed to study their thermal interaction as well as performance using a differential scanning calorimeter (model: DSC-1821e, Mettler Toledo AG, Analytical, Schwerzenbach, Switzerland) as per the procedure described earlier by our groups [20]. Briefly, the individual samples (~ 2.0 ± 0.2 mg) were accurately weighed and then sealed in an aluminum pan covered with a lid and crimper. After this, the weighed samples were loaded into the DSC instrument that had been previously calibrated concerning heat flow and capacity using standard indium (In). The sample-analyzing chamber was constantly purged with dried nitrogen gas (N_2) at a flow rate of (50 mL/min) to avoid any interference from entrapped moisture. The tested samples were allowed to be heated at a temperature range of 0 to 400 °C at a heating rate of 10 °C/min. DSC thermograms along with their associated heating parameters were read by the instrument-accompanied software (Universal Analysis 2000, V4.5A, build 4.5.0.5).

Fourier Transform Infrared Spectroscopy

An FT-IR spectrophotometer (model: FTIR-8300, Shimadzu, Kyoto, Japan) was used to analyze and understand the molecular-level functional group interaction between the samples of ranolazine, LSPC-3, PM, and RNZ-SPC-CP, respectively. Briefly, the homogenous mixture for the FT-IR analysis was prepared by mixing of individual samples with FT-IR-grade potassium bromide (KBr) in an agate mortar and pestle. The individual mixture was compressed into thin and uniform transparent discs using a mini handpress machine (model: MHP-1, P/N-200-66747-91, Shimadzu, Kyoto, Japan). The prepared discs were scanned under a wave number region of 4000 to 400 cm^{-1}, with the resolution set to 4 cm^{-1}. The instrument-received FT-IR spectra for a single sample were compared and interpreted using the FT-IR software (IRSolution FT-IR control software, version 1.10). The detailed procedure for FT-IR analysis has been followed as per earlier published literature [21].

Powder X-ray Diffractometry

The crystalline performance of ranolazine, LSPC-3, PM, and RNZ-SPC-CP was evaluated in terms of their PXRD spectra using a powder x-ray diffractometer (model: D8 Advance, Bruker AXS, Inc., Madison, WI, USA). The detailed procedure regarding the sample preparation, their evaluation, and interpretation of the spectrum was followed according to the literature reported earlier [22].

Estimation of Drug Content

A UV-visible spectrophotometry–based procedure earlier described by Choudhary et al. was used to estimate the content of ranolazine in the prepared RNZ-SPC-CP formulations [23]. Briefly, an aqueous solution for the spectral analysis of ranolazine was prepared by dissolving the approximate amount of RNZ-SPC-CP formulations (~ 100 mg of ranolazine) in 100 mL of phosphate buffer (0.05 M, pH 6.8) and stirred well. The developed solution was then filtered through a membrane filter (0.45 μm). The filtered solution was diluted suitably and analyzed for absorbance on a UV-visible spectrophotometer (model: V-630, JASCO International Co., Ltd., Tokyo, Japan) at 270 nm. Moreover, the blank solution of LSPC-3 was also prepared and compared against the sample solution to avoid the interference from the added phospholipid carrier. The content of ranolazine (%) in the RNZ-SPC-CP was calculated according to Eq. (1) described below:

$$\text{RNZ content}\ (\%) = \frac{\text{total RNZ}\ (\text{mg}) - \text{free drug}\ (\text{mg})}{\text{total RNZ}\ (\text{mg})} \times 100 \quad (1)$$

Functional Characterization of Ranolazine-LIPOID SPC-3 Coprecipitate

Aqueous Solubility Analysis

The samples of pure ranolazine, PM of ranolazine, and LSPC-3 and RNZ-SPC-CP formulations were analyzed for aqueous solubility using the procedure reported earlier elsewhere [24]. Briefly, an individual sample in an excess amount was weighed and then transferred into clean screw-capped glass vials containing 10 mL of distilled water. The aqueous dispersion was stoppered carefully and agitated using a rotary shaker (model: RS-24 BL, REMI Laboratory Instruments, Remi House, Mumbai, India) at 37 °C for 24 h. After agitation, the mixture was filtered (membrane filter, 0.45 μm), collected, and diluted appropriately. The resulting solution was assayed for recording the

absorbance using a UV-visible spectrophotometer (model: V-630, JASCO International Co., Ltd., Tokyo, Japan) at a maximum wavelength of 272 nm against a blank. The entire study was carried out at room temperature.

In Vitro Dissolution Studies

A paddle (USP type II)–based dissolution apparatus (model: TDT-08LX, Electrolab India Pvt. Ltd., Mumbai, India) was employed for the comparative evaluation of in vitro dissolution performance of pure ranolazine and ranolazine from the prepared RNZ-SPC-CP formulation, respectively. The dissolution studies were carried out as per the procedure previously reported in the literature [10, 11]. Briefly, the testing samples, i.e., pure ranolazine (~ 100 mg) or prepared RNZ-SPC-CP (~ 100 mg of pure ranolazine), were dispersed in a dissolution flask containing 900 mL of distilled water. After dispersing the samples, the contents of the flask were stirred at a speed of 100 RPM and the temperature of the media was maintained at 37 ± 0.5 °C throughout the study. The dissolution study was performed for 120 min. At designated time intervals (10 min), the samples were withdrawn, filtered (membrane filter, 0.45 μm), diluted, and analyzed for measuring the absorbance of the resulting solution on a UV-visible spectrophotometer (model: V-630, JASCO International Co., Ltd., Tokyo, Japan) at a maximum wavelength of 270 nm against the blank. The recorded absorbance values of each sample were used for calculation of the percentage cumulative amount of release of ranolazine and RNZ-SPC-CP formulations.

Kinetic Model–Fitting Analysis The release kinetic analysis of RNZ from RNZ-SPC-CP was estimated by the fitting of the release data into different kinetic models such as zero order, first order, and Higuchi models. The zero-order model represents the cumulative amount of drug released vs. time, and it is represented by the following equation:

$$C = K_0 t$$

where K_0 describes the zero-order rate constant that is expressed in units of concentration/time and t represents the time in minutes. A graph of concentration of vs. time would yield a straight line with a slope equal to K_0 and the intercept at the origin of the axis.

The first-order model shows the release as a cumulative percentage of the drug remaining vs. time, and it is described in the following equation:

$$\log C = \log \mathrm{C0} - Kt/2.303$$

where C0 is the initial concentration of the drug, K is the first-order rate constant, and t is the time in minutes.

The Higuchi model equation shows the release as a cumulative percentage of drug released vs. the square root of time, and it is calculated using the described equation below.

$$Qt = Kt^{1/2}$$

where Qt represents the amount of drug released in time t, K is the kinetic constant, and t is the time in minutes.

Mechanism of Drug Release The RNZ release mechanism from optimized RNZ-SPC-CP was determined by subjecting the release data to the Korsmeyer-Peppas equation as shown below; it describes the release as a cumulative percentage of drug released vs. time.

$$Mt/M_\infty = Kt^n$$

where Mt/M_∞ describes the fraction of drug released, K is the rate constant, t is the time for drug release, and n is the diffusional exponent for drug release. The diffusional exponent (n) value describes the release mechanism of formulations. For example, when $n = 1$, the release can be considered zero order (case II transport), and $n = 0.5$ indicates a Fickian diffusion release; $0.5 < n < 1.0$ indicates diffusion and non-Fickian diffusion. Finally, if $n > 1$, then the apparent mechanism is super case II transport.

Fasted vs. Fed State Dissolution Comparison

The comparative release pattern of pure ranolazine or ranolazine from RNZ-SPC-CP formulations was also studied under the effect of fasted (FaSSIF) or fed state (FeSSIF) in a USP type II (paddle) dissolution apparatus (model: TDT-08LX, Electrolab India Pvt. Ltd., Mumbai, India). Dissolution studies were carried out in FaSSIF (fasted state simulated intestinal fluid) and FeSSIF (fed state simulated intestinal fluid) media, and the procedure for the preparation of this media was followed according to the procedure reported earlier [25]. Briefly, ranolazine (~ 100 mg) or ranolazine from RNZ-SPC-CP formulations (~ 100 mg of pure ranolazine) was dispersed in dissolution media of FaSSIF (500 mL) or FeSSIF (1000 mL), respectively. The media were stirred continuously at a speed of 50 RPM, with the temperature maintained at 37 ± 0.5 °C for 120 min. During the study, the small samples were removed using a micropipette and replaced with fresh dissolution media for maintaining the sink conditions. The removed samples were diluted and assayed for absorbance using a UV-visible spectrophotometer (model: V-630, JASCO International Co., Ltd., Tokyo, Japan) at a wavelength of 271 nm for FaSSIF or 270 nm for FeSSIF against blank absorbance. Sample

absorbance values were calculated and represented in the form of a percentage cumulative release.

Ex Vivo Permeability Studies

The testing samples of pure ranolazine or prepared RNZ-SPC-CP formulations were analyzed for permeation across the biological membrane using the *everted rat intestine method* described earlier in the literature [26]. The studies were performed as per the literature earlier reported by our group [19, 27]. The Institutional Animal Ethical Committee of Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, reviewed and sanctioned the protocol (*SKBCOP/IAEC/201819, dated August 19, 2018*). The study was performed under the supervision of guidelines suggested by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). Briefly, the prepared everted rat intestine membrane was fixed between the two tapered ends of the apparatus. After that, the apparatus was filled with freshly prepared Krebs solution and then immersed into a 250-mL beaker containing testing solutions of pure ranolazine (~ 100 μg/mL) or RNZ-SPC-CP formulations (~ 100 μg/mL) in Krebs solution. The entire assembly was placed on a magnetic stirrer, and the contents were stirred at a speed of 25 RPM, with the temperature of the media maintained at 37 ± 0.5 °C for 120 min. The permeation media (inside and outside of the apparatus) was continuously aerated using carbogen (95% O_2 and 5% CO_2 mixture). At predetermined time intervals, the small samples were removed from the apparatus, filtered, diluted, and analyzed for absorbance at 271 nm on a UV-visible spectrophotometer (model: V-630, JASCO International Co., Ltd., Tokyo, Japan) against the blank, and the absorbance values of the samples were reported as percentage cumulative permeation release.

Preliminary Stability Assessment Studies

The preliminary stability assessment studies on the optimized formulation, i.e., RNZ-SPC-CP1, were carried out to study the influence of storage conditions, i.e., controlled temperature (25 ± 5 °C) and relative humidity (60 ± 5% RH), on the dissolution and permeation rate of RNZ from the abovementioned formulations. This study was carried out as per the literature reported earlier [28]. Briefly, the RNZ-SPC-CP1 formulation was packed in a screw-capped container, with high-density polyethylene (HDPE) amber-colored bottles. The packed samples were stored in a stability chamber (model: TS00002009, Mumbai, Maharashtra, India) for 6 months. At the end of the study, the samples were removed and tested for functional characterization.

Results and Discussion

Physico-chemical Characterization of Ranolazine-LIPOID SPC-3 Coprecipitate

Scanning Electron Microscopy

The SEM analysis of pure ranolazine, LSPC-3, and prepared RNZ-SPC-CP formulations are depicted in Fig. 2 a, b, and c, respectively. Pure ranolazine (Fig. 2a) appeared as clusters of small and larger particles, with a heterogeneous surface. LSPC-3 particles (Fig. 2b) are exhibited as larger and non-uniform particles with ill-defined morphology. The prepared RNZ-SPC-CP formulations (Fig. 2c) appeared as aggregates with characteristics of small particles of pure ranolazine and large particles of LSPC-3. The formation of these aggregates confirmed that pure ranolazine and LSPC-3 physically interact with each other. Results agreed with earlier published reports [28]. Moreover, the formation of such types of aggregates was possibly due to the solvent evaporation method. These findings were found to be consistent with an earlier published report which suggests that SPC-based carriers using the solvent evaporation method produce the same types of particles following their interaction with drugs [29, 30]. Moreover, different types and grades of phospholipids may also have different effects on the shape and surface morphology of phospholipid-based formulations [29].

Particle Size and Zeta Potential Analysis

The particle size and zeta potential analysis of prepared RNZ-SPC-CP formulations are shown in Fig. 3 a and b, respectively. Particle size and zeta potential are the basic parameters used for the determination of the physical stability of submicron particles dispersed in the liquid media. In general, the particle size of the pharmaceutical excipients is found to be inversely proportional to their surface area/volume ratio (SA/*V*) [31]. In the current study, the prepared RNZ-SPC-CP formulation (Fig. 3a) showed an average particle size of ~ 95.76 ± 0.20 nm, indicating the small particle size of the formulations. This lower particle size formulation shows a higher SA/*V*, which in turn results in increase in the release rate of drugs from coprecipitate formulations through the mechanisms of diffusion and erosion. Moreover, a particle with a size smaller than 500 nm is considered a suitable particle size for its transportation across the biological membrane via endocytosis, whereas a particle size greater than 5 mm is particularly absorbed through the lymphatic system [32, 33]. Additionally, the polydispersity index (PDI) value of the same formulation was observed to be ~ 0.29 ± 0.10. An obtained lower PDI value indicates a narrow distribution of pure ranolazine within the carrier. Zeta potential (ζ) is another valuable indicator used particularly for the determination of

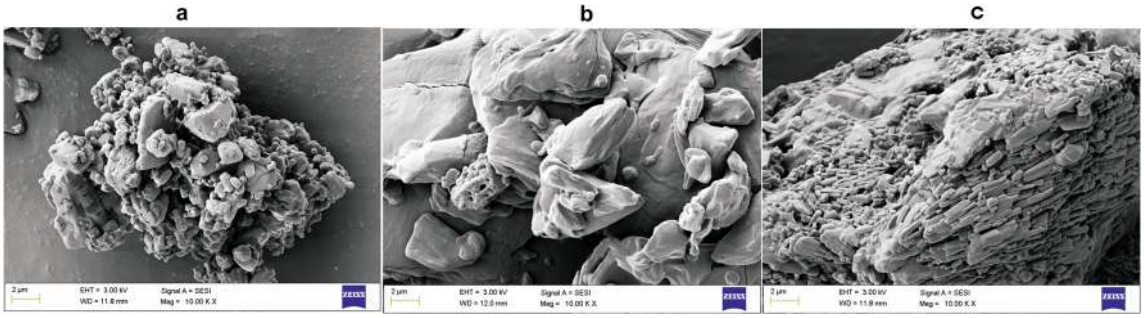

Fig. 2 SEM photomicrographs of **a** pure ranolazine, **b** LSPC-3 and **c** prepared RNZ-SPC-CP formulations

surface charges distributed around the particles. Moreover, zeta potential can also provide useful information about the behavior of particles following an oral administration [34]. Generally, the zeta potential values in the range of − 30 to + 30 mV can be considered acceptable values for the physical stability of multiparticulate systems. Prepared RNZ-SPC-CP formulations (Fig. 3b) showed zeta potential values as ~− 24.31 ± 0.19 mV, indicating that it lies in between the acceptable range and, thus, confirming that the prepared formulation is physically stable. Moreover, this acceptable zeta potential value was likely due to a large portion of LSPC-3 contributing to the complexation process and generating negative charges in the aqueous environment with a neutral pH value. This possible mechanism provides sufficient negative charges on the surface of the RNZ-SPC-CP complex and makes the complex stable in the aqueous state. Additionally, the phospholipid composition and its type may also have a strong impact on the zeta potential values. Findings were found to be consistent with earlier published reports [21, 34]. Therefore, based on this discussion, it is suggested that zeta potential plays a significant role in the stabilization of the phospholipid-based coprecipitate complex.

Differential Scanning Calorimetry

DSC is a valuable analytical tool used often in the quantitative determination of the interaction (physical and solid state) between the ingredients of the formulations. The thermograms of pure ranolazine, LSPC-3, the PM of ranolazine and LSPC-3 (ratio 1:1), and optimized RNZ-SPC-CP1 formulations are presented in Fig. 4 a, b, c, and d, respectively. The thermograms of pure ranolazine (Fig. 4a) showed a single and sharp

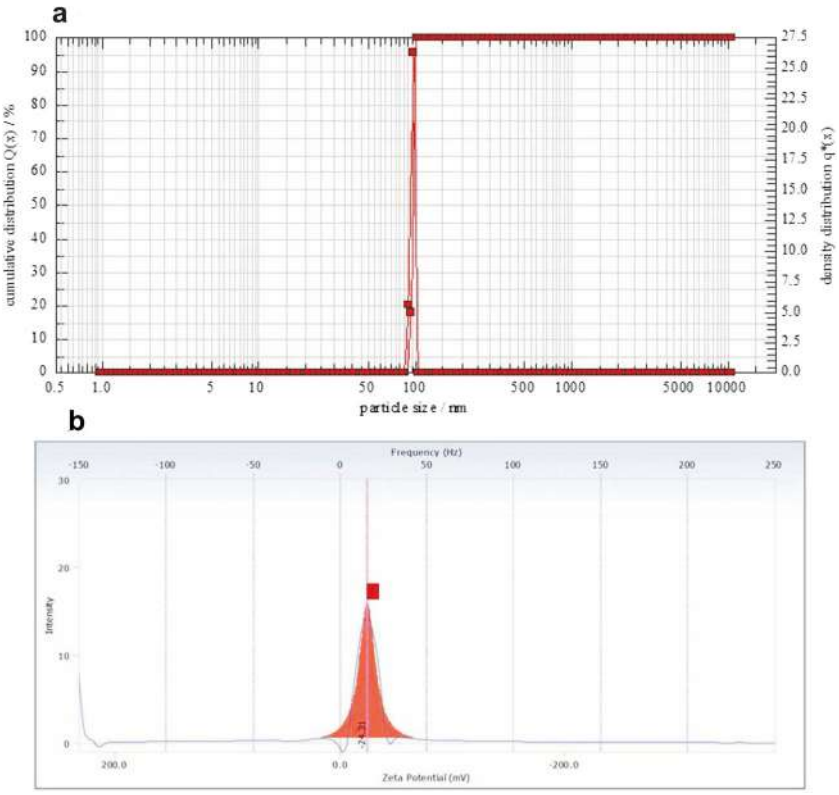

Fig. 3 **a** Particle size and **b** zeta potential of the prepared RNZ-SPC-CP formulations

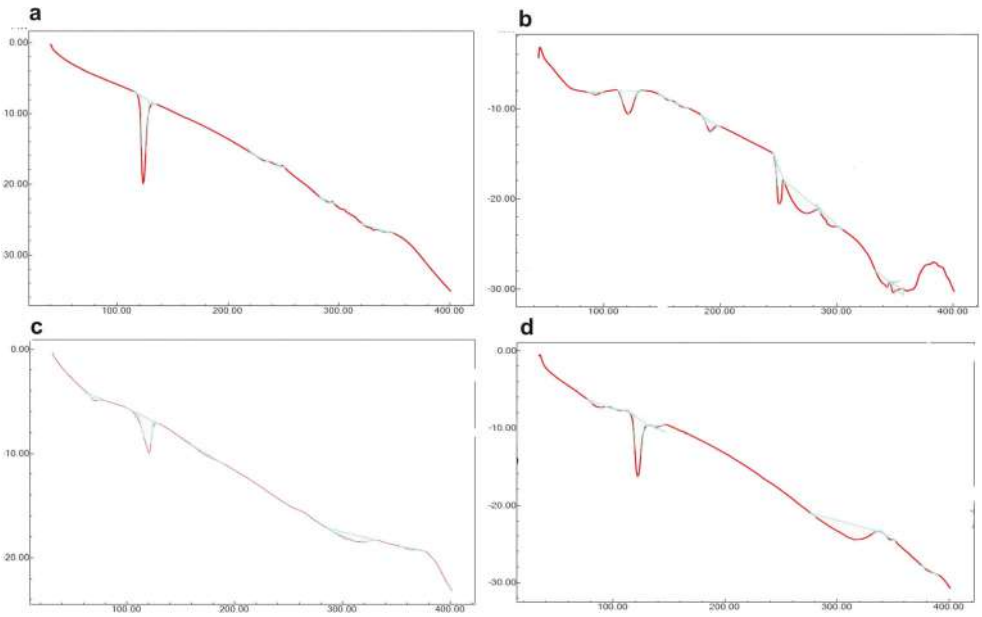

Fig. 4 DSC thermograms of **a** pure ranolazine, **b** LSPC-3, **c** the physical mixture of ranolazine and LSPC-3 (1:1), and **d** prepared RNZ-SPC-CP formulations

endothermic peak at ~ 124.13 °C; this peak signifies the melting point of pure ranolazine. The enthalpy of fusion (ΔH) for this peak was found to be ~ 79.26 J/g. Additionally, the same drug also displayed four very small intensity peaks in the region between ~ 222.78 and ~ 321.71 °C (ΔH ~ 6.97 J/g). This may be likely due to the phase transition of ranolazine from its crystalline to anhydrous form. The results are well supported with earlier published reports [6]. The LSPC-3 thermograms (Fig. 4b) exhibited six dissimilar endothermic peaks. First, four small intensity peaks appeared at ~ 93.36 °C, 121.46 °C, 161.72 °C, and 191.95 °C, indicating the melting of the polar element of LSPC-3 as a function of increasing temperature. The remaining two peaks at ~ 250.90 °C and ~ 274.45 °C appeared to be mild, fused, and diffused ones compared with the initial four peaks. These peaks may be attributed to the physical transformation of the carbon-hydrogen part of LSPC-3 from the gel to the liquid crystalline state. Findings were consistent with those of phospholipids published earlier [20, 35]. The DSC thermograms of PM (1:1) (Fig. 4c) showed a combination of endothermic peaks at ~ 62.53 °C (ΔH ~ 6.02 J/g), 120.65 °C (ΔH ~ 38.99 J/g), 158.73 °C (ΔH ~ 4.86 J/g), and 318.92 °C (ΔH ~ 22.44 J/g) that correspond to pure ranolazine and LSPC-3 of the formulation. Moreover, the PM spectra showed the predominant peak of ranolazine with a small intensity compared with the peak observed for pure ranolazine; this indicates that a low amount of ranolazine is present in the PM as compared with LSPC-3 as well as possible physico-chemical interaction between them, suggesting that as the thermal temperature was achieved to a favorable position, the pure ranolazine and LSPC-3 were both melted, formed a partial mixture, and, thus, showed the peaks with low intensities, compared with pure ranolazine and LSPC-3 [35, 36]. Moreover, the last phase transition peak of ranolazine also appeared at ~ 318.92 °C with broad and low-intensity characteristics indicating possible interaction of ranolazine with LSPC-3. Compared with the thermograms of PM, the thermograms of RNZ-SPC-CP1 formulations (Fig. 4d) displayed new endothermic peaks at ~ 89.28 °C and 122.68 °C. The overall appearance of these peaks was similar to that of PM; however, based on the endothermic peak position, the obtained peaks in these thermograms were found to be different from that of the peak position for pure ranolazine and PM. Moreover, the new peak at 122.68 °C appeared parallel to that of PM and pure ranolazine; however, it could be formed due to complete dispersion of pure ranolazine into the LSPC-3 matrix, reducing the sharp crystalline nature of the drug (i.e., partial amorphization) and converting it into an LSPC-3-based coprecipitate complex with broad and low-intensity peaks. Findings were consistent with earlier published literature [20]. Likewise, the enthalpy of fusion for major peaks of pure ranolazine, PM, and RNZ-SPC-CP1 formulations was found to be different, i.e., ~ 79.26 J/g, 38.99 J/g, and ~ 43.37 J/g. Therefore, based on the above comparative discussion, it is concluded that pure ranolazine and LSPC-3 forms strong interaction with each other, resulting in the formation of an amorphous RNZ-SPC-CP complex with different endothermic peak characteristics compared with those of the pure drug and PM.

Fourier Transform Infrared Spectroscopy

The interaction between the functional groups of various components of the formulation is confirmed by the FT-IR analysis. The FT-IR spectrum of pure ranolazine, LSPC-3, PM (1:1), and prepared RNZ-SPC-CP1 formulations are shown in Fig. 5a–d, respectively. The units are represented as cm^{-1}.

The FT-IR spectrum of pure ranolazine is displayed in Fig. 5a. In this figure, the absorption peaks observed at ~3328.5, 2829.0, 1684.8, 1591.6, 1461.1, 1330.7, and 1252.4 represent the N–H stretching (primary aliphatic amine), C–H stretching, C=C stretching, C–H bending, and C–O stretching vibrations. The FT-IR spectrum of LSPC-3 (Fig. 5b) shows absorption peaks at 3362.1, 2914.8 and 2847.7, 1736.9, 1237.5, 1092.3, and 902.0, representing the O–H stretching, C–H stretching (for the long fatty acid chain), C=O stretching (fatty acid ester), P=O and P–O–C stretching, and [$-N^+(CH_2)_3$] [37]. The FT-IR spectrum of PM (1:1), as shown in (Fig. 5c), exhibited absorption peaks at ~3332.2, 2851.4, 2918.5, 1684.8, 1461.1, 1330.7, and 1252.4, indicating that these peaks had additive characteristics of pure ranolazine and LSPC-3. This additive peak suggests that both pure drug and LSPC-3 show strong physico-chemical interactions. As compared with the FT-IR spectrum of PM, that of RNZ-SPC-CP1 formulations (Fig. 5d) displayed lower absorption peaks at ~3328.5, whereas compared with pure ranolazine, RNZ-SPC-CP1 showed complete disappearance of the absorption peak at ~2829.0. Moreover, the absorption peak at ~3362.1 due to the O–H stretching vibration of LSPC-3 was found to disappear completely in the coprecipitate complex formulation. Likewise, the low absorption peak at ~902.0 in LSPC-3 appeared at a higher frequency at ~969.1 in the coprecipitate complex formulation. The peak frequencies' change observed in the spectrum of the RNZ-SPC-CP1 formulation for broadening, shifting, and appearance and/or disappearance of primary aliphatic amine (N–H stretching), O–H stretching, C–H stretching, and [$-N^+(CH_2)_3$] peaks to lower and higher frequencies compared with those of PM, pure ranolazine, and LSPC-3 could be explained on the basis that pure ranolazine molecularly interacted with the polar part of LSPC-3 through weak interactions, i.e., H-bonding, ion-dipole forces, and van der Waals forces, thus leading to the formation of stable RNZ-SPC-CP. Therefore, the shifting of absorption of peaks in the formulation concludes that there is a molecular interaction between ranolazine and LSPC-3, and this could be the evidence for the formation of RNZ-SPC-CP.

Powder X-ray Diffractometry

Figure 6 a, b, c, and d display the diffractogram spectra of pure ranolazine, LSPC-3, PM (1:1), and prepared RNZ-SPC-CP1 formulations on a 2θ scale, respectively. Pure ranolazine (Fig. 6a) diffractograms showed a chain of multiple numbers of sharp-pointed peaks observed at ~4.95°, 10.31°, 12.22°, 14.92°, 16.42°, 16.42°, 19.27°, 21.37°, 23.39°, and 24.60° on a 2θ scale, indicating the crystalline nature of pure ranolazine. Moreover, the intensity (Lin counts on the *y*-axis) of these peaks appeared as ~490, 400, 240, 300, 750, 250, 480, 550, and 350 counts, respectively, also confirming the crystalline nature of pure ranolazine. The PXRD spectrum of LSPC-3 (Fig. 6b) exhibited two dissimilar peaks. The first sharp and small-intensity peak developed at ~5.92° (650 counts), whereas a second broad and large-intensity peak was found at ~21.57° (2050 counts) on a 2θ scale. Two very miniature peaks also developed at 3.80° and 9.93°. Results were found to be similar to those of phospholipid literature published earlier [38]. Diffractograms of PM (Fig. 6c) displayed several combined peaks associated with small and large intensities, indicating that pure ranolazine and LSPC-3 were both physically mixed in the ratio 1:1, and

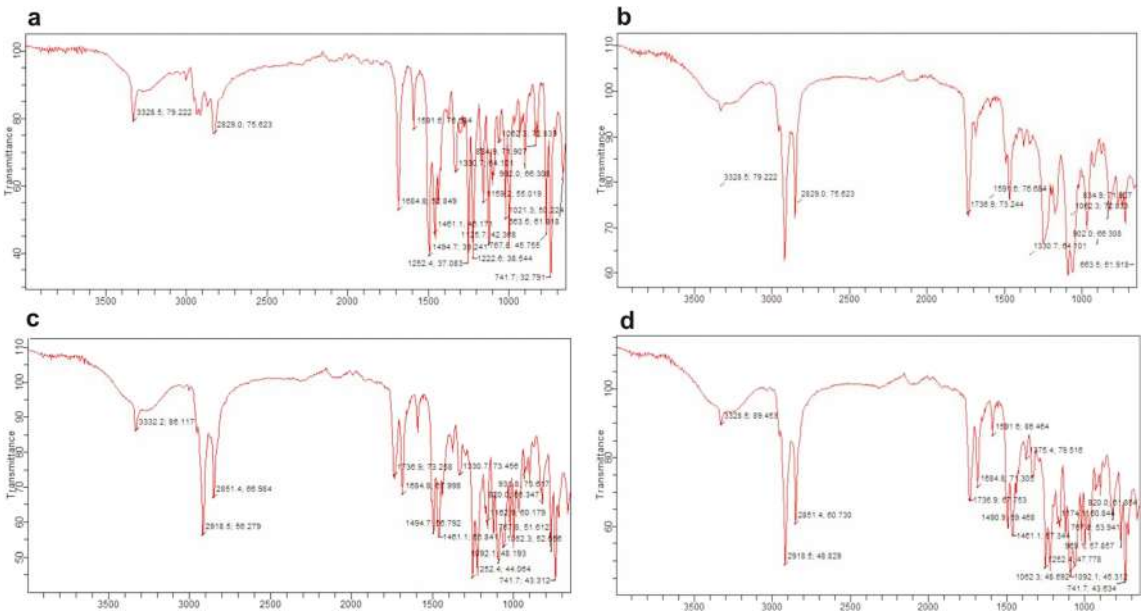

Fig. 5 FT-IR spectra of **a** pure ranolazine, **b** LSPC-3, **c** the physical mixture of ranolazine and LSPC-3 (1:1), and **d** prepared RNZ-SPC-CP formulations

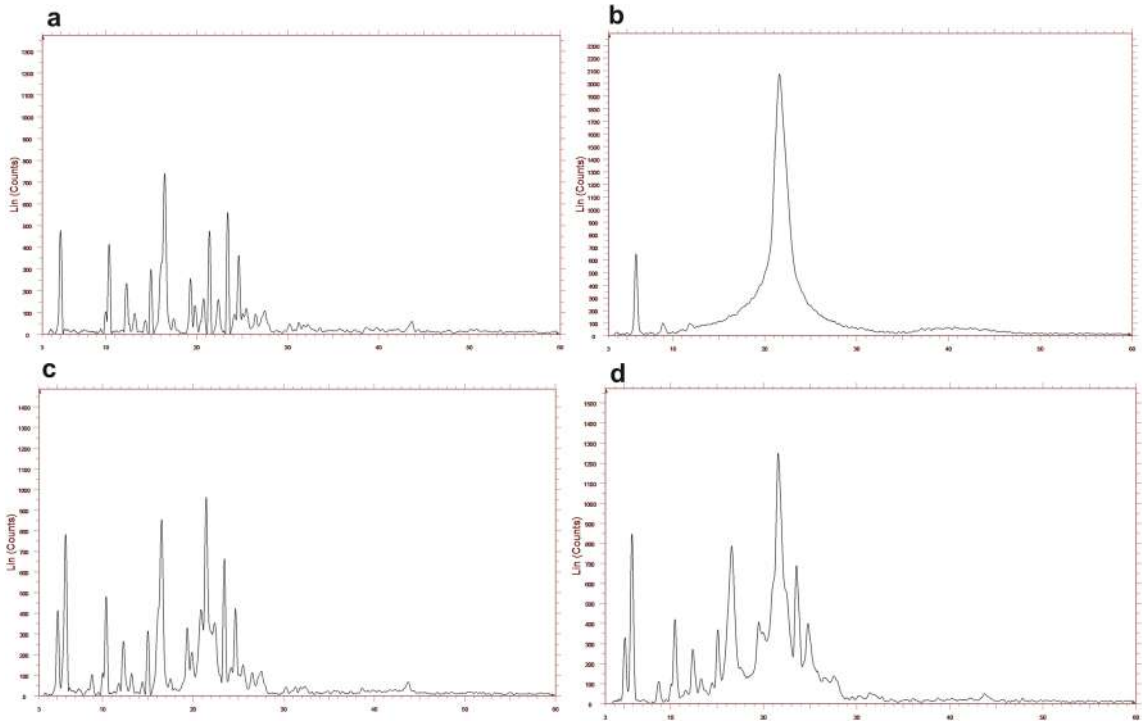

Fig. 6 The powder x-ray diffractograms of **a** pure ranolazine, **b** LSPC-3, **c** the physical mixture of ranolazine and LSPC-3 (1:1), and **d** prepared RNZ-SPC-CP formulations

therefore, the resulting peaks appeared in a combination of ranolazine as well as LSPC-3. Also, in this spectrum, the peak height/intensity of ranolazine in between the region of ~ 3 and 18° was found to be nearly similar to the peak height of the PXRD spectrum of pure ranolazine, whereas in the region of ~ 19 to 28°, the PM demonstrated a narrow range of LSPC-3-dominated peak along with the appearance of sharp peaks of pure ranolazine, and the complete appearance of these peaks was found to be parallel to that of the peak height of LSPC-3, indicating interaction between ranolazine and LSPC-3, and this was likely due to formation of in situ partial aggregates with equal contribution of both formulation components. PXRD diffractograms of optimized RNZ-SPC-CP1 formulation (Fig. 6d) exhibited few peaks of ranolazine with small, broad, and fused characteristics in the region between 3 and 20°, and their peak intensity was found to be lowered in this spectrum to around 300, 400, and 800 counts compared with higher counts, i.e., 400, 470, and 850, in PM, whereas in the region between 10 and 30°, the same formulation showed a broad range of LSPC-3-dominated peaks with a low intensity accompanied with reduction and/or disappearance of peaks as compared with PM and pure ranolazine. Formation of this spectrum could be explained that while the formulation of the pure ranolazine firstly mixed with LSPC-3 in the ratio 1:1 and then dispersed into the matrix of LSPC-3, this dispersion resulted in the partial reduction of the crystal nature of pure ranolazine, which was finally converted into RNZ-SPC-CP formulation accompanied with amorphous characteristics [39]. Hence, the observed significant difference in the formation of a broad range of LSPC-3-dominated peaks with lower-intensity peaks in RNZ-SPC-CP compared with a narrow range of LSPC-3 peaks with a higher intensity in PM confirms that there were molecular association and interaction between ranolazine and LSPC-3, and this could be the basis for the development of RNZ-SPC-CP.

Drug Content

The analyzed ranolazine content in the prepared RNZ-SPC-CP formulations is shown in Table 2. As seen in Table 2, the formulation RNZ-SPC-CP in the ratio 1:1 exhibited the highest percentage of incorporation efficiency of ranolazine of ~ 96.40 ± 1.19% w/w, whereas the other formulations in the ratios 1:2, 1:3, 1:4, and 1:5 showed lower percentages of ranolazine efficiency of ~ 94.80 ± 1.40%, 93.47 ± 0.70%, 93.11 ± 1.36%, and 92.07 ± 1.41%, respectively. Among all formulations, the RNZ-SPC-CP (1:1) formulation was considered to be an optimized one for further analysis. Moreover, based on this analysis, it was found that the phospholipid carrier and solvent evaporation method could be a suitable and robust approach for the preparation of RNZ-SPC-CP with high ranolazine content.

Table 2 Drug content of ranolazine in prepared coprecipitate formulations

Coprecipitates	Drug content (%, w/w)*
RNZ-SPC-CP1	96.40 ± 1.19
RNZ-SPC-CP2	94.80 ± 1.40
RNZ-SPC-CP3	93.47 ± 0.70
RNZ-SPC-CP4	93.11 ± 1.36
RNZ-SPC-CP5	92.07 ± 1.41

*All results are expressed as mean ± Std. Dev. ($n = 3$)

Functional Characterization of Ranolazine-LIPOID SPC-3 Coprecipitate

Aqueous Solubility Analysis

Table 3 displays the aqueous solubility analysis of pure ranolazine, PM (1:1), and prepared RNZ-SPC-CP formulations. Pure ranolazine showed low aqueous solubility of ~ 4.94 μg/mL, and this was likely due to its low solubility and the high permeability profile of the BCS class II category. PM formulations displayed somewhat higher aqueous solubility, and their solubility range was found to be between ~ 24 and ~ 30 μg/mL. The value corresponds to a nearly 6-fold increase in aqueous solubility. PM containing phospholipid ratios increasing from 1:1 to 1:3 showed significant enhancement in the solubility, and thereafter, further increasing ratios of phospholipids, i.e., 1:4 and 1:5, lowered the aqueous solubility of pure ranolazine. The modest increase in aqueous solubility of all PM was possibly attributed to the close association of the amphiphilic nature of phospholipids with ranolazine resulting in the formation of slightly modified ranolazine particles with higher aqueous solubility and wettability characteristics.

Table 3 Aqueous solubility of pure ranolazine, the physical mixture of ranolazine and LIPOID SPC-3, and ranolazine-LIPOID SPC-3 coprecipitate formulations

Coprecipitates	Aqueous solubility (μg/mL)*
Pure ranolazine	4.94 ± 0.06
PM1	30.20 ± 0.04
PM2	28.41 ± 0.07
PM3	27.50 ± 0.02
PM4	25.07 ± 0.08
PM5	24.27 ± 0.03
RNZ-SPC-CP1	92.23 ± 0.08
RNZ-SPC-CP2	90.07 ± 0.01
RNZ-SPC-CP3	87.46 ± 0.05
RNZ-SPC-CP4	84.39 ± 0.08
RNZ-SPC-CP5	80.12 ± 0.03

*All results are expressed as mean ± Std. Dev. ($n = 3$)

Apart from this, the higher amount of phospholipids in PM formulations, i.e., PM 1:4 and 1:5, may restrict the access of ranolazine particles into the aqueous media and, thus, reduces their solubility in water [11]. Moreover, the higher amount of phospholipids may also impart higher viscosity to formulations, which further reduced the solubility of the drug into the aqueous media [40]. RNZ-SPC-CP formulations improved the aqueous solubility in the range between ~ 80 and ~ 92 μg/mL. Among all formulations, the optimized RNZ-SPC-CP1 formulations (a drug to carrier ratio of 1:1) significantly ($p < 0.01$) enhanced the aqueous solubility of ranolazine to ~ 92.23 μg/mL. The obtained value shows an 18-fold increase in aqueous solubility as compared with those of pure ranolazine and all PM. The possible reason for the enhancement of this aqueous solubility was likely attributed to the complex formation and partial amorphization of ranolazine particles within the formulations [41, 42]. The amphiphilic character of LSPC-3 and the amorphous state of the drug within this carrier could have the possibility of increasing the aqueous solubility of ranolazine [43]. Moreover, the phospholipids are known to form self-assembly of amphiphilic structures like micelles, liposomes, and phytosomes with high incorporation of hydrophobic drug particles, resulting in the increase in the aqueous solubility of the drug via formation of a complex between the drug and phospholipids. The wetting nature of these phospholipids can also contribute to increasing the water solubility of the hydrophobic drug via surface coating [44]. The amphiphilic nature, wetting, and lowering of the interfacial tension between the drug and water functions of LSPC-3 may also contribute to increasing the hydrophilicity of drugs [40].

In Vitro Dissolution Studies

Figure 7 describes the comparative dissolution pattern of pure ranolazine, PM (1:1), and optimized RNZ-SPC-CP1 formulations tested in distilled water for 120 min. As seen in the figure, the pure ranolazine exhibited only ~ 21% dissolution by the end of 120 min. The low solubility and high permeability profile of ranolazine are considered to be the main reason for its low dissolution in distilled water. The PM (1:1) demonstrated a modest increase in the rate and extent of ranolazine dissolution compared with pure ranolazine. By the end of dissolution, the rate and extent of ranolazine dissolution from PM were found to be only ~ 35%. From this observation, it is found that the PM pursued the same dissolution fashion as observed in the solubility studies. As compared with pure ranolazine and PM (1:1), the optimized RNZ-SPC-CP1 exhibited the highest dissolution efficiency, and by the end of the dissolution period, ~ 85% of ranolazine was found to be released in the distilled water. The improved dissolution rate of RNZ-SPC-CP1 formulation could have been possibly due to the solvent evaporation method, LSPC-

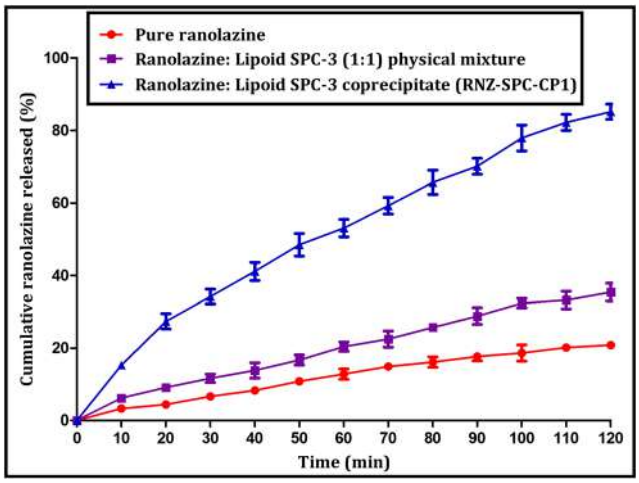

Fig. 7 The in vitro dissolution profiles of pure ranolazine, the physical mixture of ranolazine and LSPC-3 (1:1), and the prepared optimized RNZ-SPC-CP1 formulations

3 carrier, and ethanol solvent. Solvent evaporation, a well-known method, transforms the crystalline drug into a partially amorphized form and, finally, converts it into the high–energy state powder, which increases the dissolution rate of low-solubility drug particles [45]. The shorter fatty acid chain length, as well as the phase transition temperature (Tc) of LSPC-3 being lower than the experimental temperature (37 °C), may cause to increase the dissolution rate of ranolazine because of its more amorphous nature as well as the spontaneous dispersibility of LSPC-3 when coming in contact with distilled water [10, 11]. Moreover, the LSPC-3 structure was found to be similar to those of earlier used phospholipids, i.e., DMPC and DMPG. The combined impact of this phospholipid exhibits a dual effect; the first one is the complex formation between the negative charge of the phosphate group of phospholipids and positive charge of ranolazine, and the second one is liposome and phytosome formation ability, which in turn increases the dissolution rate of ranolazine in distilled water [11, 12]. Ethanol, a non-toxic and class III solvent, may remain as a trace solvent even after the vacuum drying. This trace amount of solvent can form hydrogen bonding with ranolazine and LSPC-3, resulting in the formation of the coprecipitate complex, which can increase the rate and extent of ranolazine dissolution. Moreover, ranolazine forms a strong chemical association with LSPC-3 via intermolecular bonding, and this interaction could change the physico-chemical properties of both of these compounds, resulting in a significant enhancement of the dissolution rate of ranolazine from the prepared coprecipitate complex. Results were found to be consistent with earlier published reports [13].

The obtained release data from RNZ-SPC-CP formulations were analyzed using various kinetic models such as first-order, zero-order, Higuchi, and Korsmeyer-Peppas models. Following analysis, the obtained higher correlation coefficient value ($R^2 = 0.9731$) compared with the small value of the zero-order ($R^2 = 0.9322$) and first-order ($R^2 = 0.9550$) models suggests the Higuchi model as a best-fit kinetic model describing the dissolution of RNZ-SPC-CP formulations. Moreover, the release exponent value (n) was found to be ~0.48, indicating that diffusion is the principal mechanism responsible for the release of ranolazine from RNZ-SPC-CP formulations. Moreover, based on the Korsmeyer-Peppas model, the release mechanism of the ranolazine from the optimized RNZ-SPC-CP1 complex was found to be a two-step diffusion process. First, the ranolazine molecule dissociates from the RNZ-SCP-CP complex, and second, the dissociated ranolazine molecule diffuses out from the LSPC-3 matrix into the dissolution media.

Fasted vs. Fed State Dissolution Comparison

The fasted vs. fed state dissolution profile comparison between the pure ranolazine and optimized RNZ-SPC-CP1 formulation is shown in Fig. 8. Pure ranolazine in the FaSSIF state showed a lower rate and extent of dissolution of ~22% at the end of 2 h of dissolution study. Compared with this, in the FeSSIF state, the pure ranolazine showed an increase in dissolution rate of ~30% over the same dissolution period. The optimized RNZ-SPC-CP1 formulation enhanced the dissolution rate of pure ranolazine in the FaSSIF state as well as in the FeSSIF state. However, the dissolution rate of optimized formulation in FeSSIF state was found to be increased drastically, i.e., ~78%, as compared with only ~60% in the FaSSIF state over the same dissolution period. This enhanced rate and extent of dissolution of pure ranolazine and RNZ-SPC-CP1 formulation in the fed state could be attributed to positive food effects on enhancing the solubility and dissolution rate of BCS class II drugs [25, 46]. Moreover, in the fed state, the generation of taurocholate-ranolazine micelles as well as

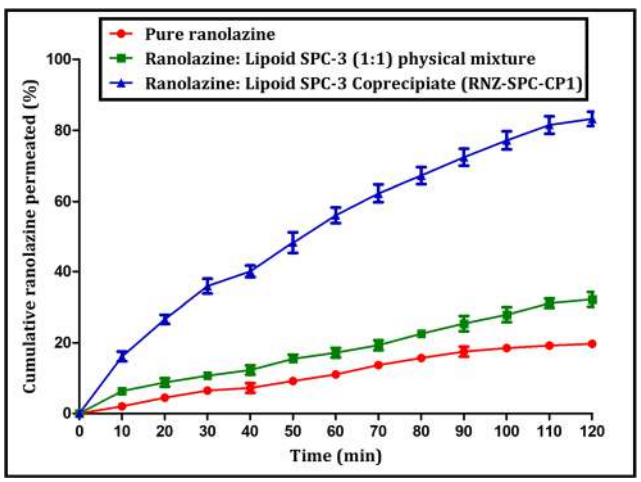

Fig. 8 The ex vivo permeation profiles of pure ranolazine, the physical mixture of ranolazine and LSPC-3 (1:1), and the prepared optimized RNZ-SPC-CP1 formulations

taurocholate-phospholipid-ranolazine micelles during dissolution could have possibly enhanced the dissolution rate of ranolazine. The results are found to be consistent with previously published reports [47].

Ex Vivo Permeability Studies

The comparative permeation efficiency of pure ranolazine and ranolazine from the optimized RNZ-SPC-CP1 formulation is depicted in Fig. 9. As seen in this figure, the pure ranolazine permeated only ~ 19% at the end of 2 h of the dissolution period, likely due to low permeability characteristics of pure ranolazine. The PM in a ratio of 1:1 fairly enhanced the permeation rate of ranolazine, and by the end of the permeation period, it was found to be ~ 32%. This was possibly attributed to a close association of the amphiphilic nature of LSPC-3. The optimized RNZ-SPC-CP1 formulation, after 1 h of study, showed ~ 56% permeation, and by the end of 2 h, the permeation rate was increased and found to be ~ 83%, compared with that of pure ranolazine and PM (1:1). This was likely attributed to amphiphilic and wetting characteristics of LSPC-3 that was used in the current study. Moreover, the amphiphilic phospholipid bilayers are also the component of the biological membrane, and therefore, the prepared phospholipid-based coprecipitate formulation shows higher miscibility with the biological membrane, resulting in the increase of the permeability of the drug across the membrane [48]. Additionally, LSPC-3 like a class of phospholipids exhibits beneficial advantages such as biocompatibility, biodegradability, metabolic activity, and low toxicity [49, 50]. These advantages of LSPC-3 serve it as an excellent carrier for the transportation of drugs across the biological barrier. Therefore, based on the biocompatible nature and safety profile in animal studies without any sign of inflammation and other negative effects [51, 52], the LSPC-3 carrier was selected and used in the preparation of the ranolazine coprecipitate complex. Overall, the results conclude that LSPC-3 improved the permeation rate of ranolazine and its permeation pattern was found to be similar to that of solubility and in vitro dissolution studies.

Preliminary Stability Assessment Studies

The preliminary stability evaluations under the influence of controlled temperature and relative humidity on the comparative in vitro dissolution and ex vivo permeation profile of ranolazine from the optimized RNZ-SPC-CP1 formulation are depicted in Figs. 10 and 11, respectively. The comparative in vitro dissolution patterns of optimized RNZ-SPC-CP1 at day 0 and day 180 (sixth month) are shown in Fig. 10. As seen in the figure, the dissolution pattern of the stored RNZ-SPC-CP1 formulation at day 180 was found to be parallel to that of the dissolution pattern of the initial formulation on day 0. Both dissolution patterns did not show any significant difference. However, the rate and extent of dissolution of ranolazine from stored RNZ-SPC-CP1 at day 180 was found to be decreased over that of the initial release formulation at day 0. Figure 11 shows the comparative ex vivo permeation profile of the optimized RNZ-SPC-CP1 formulation at day 0 and day 180. The permeation profile of initial RNZ-SPC-CP1 on day 0 and stored RNZ-SPC-CP1 formulation at day 180 was found to be parallel without any significant differences between them. However, the stored RNZ-SPC-CP1 formulation after the sixth month of the study demonstrated lower permeation efficiency compared with that of the initial formulation on day 0. Obtained results confirmed that the optimized formulation is robust and stable. Conversely, the shifting of the dissolution and permeation profile from that of original may be attributed to the influence of relative humidity and other unclear factors. Therefore, additional characterization studies must be warranted to understand the behavior of stored samples under the impact of stability parameters.

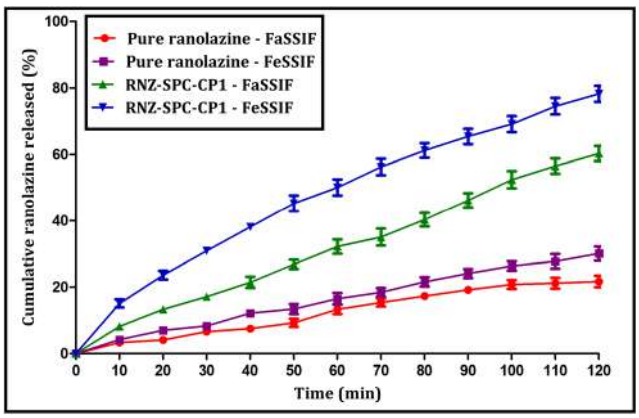

Fig. 9 The influence of fasted and fed state conditions on the dissolution behavior of pure ranolazine and the prepared optimized RNZ-SPC-CP1 formulations

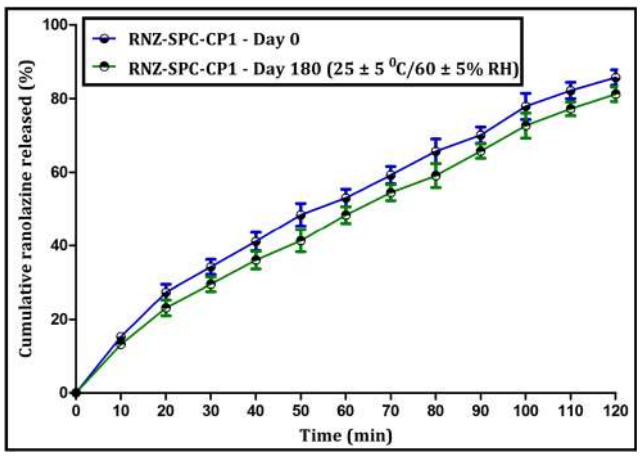

Fig. 10 Comparison of the in vitro dissolution profiles of the optimized RNZ-SPC-CP1 formulation before and after 6-month (day 180) storage at 25 ± 5 °C/60 ± 5% RH

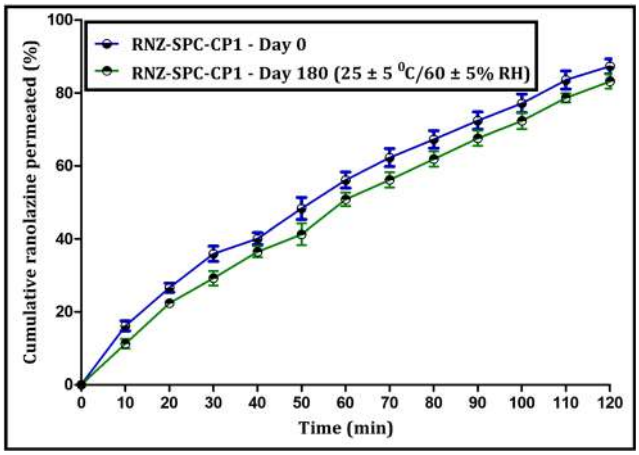

Fig. 11 Comparison of the ex vivo permeation profiles of the optimized RNZ-SPC-CP1 formulation before and after 6-month (day 180) storage at 25 ± 5 °C/60 ± 5% RH

Conclusions

In this study, we explored the feasibility of LIPOID SPC-3 as a coprecipitate carrier for improving the aqueous solubility and permeability of ranolazine. The coprecipitate of ranolazine with increasing ratios of LIPOID SPC-3 was prepared using the solvent method. Formation of the RNZ-SPC-CP formulation was confirmed by physico-chemical (i.e., SEM, DSC, FT-IR, and PXRD) and functional (solubility analysis, in vitro dissolution, and ex vivo permeation) characterization studies. Optimized RNZ-SPC-CP1 formulations significantly improved the aqueous solubility (18-fold), the rate and extent of dissolution, and the permeation of ranolazine as compared with those of pure ranolazine and PM. Moreover, the same optimized formulation also increased the rate and extent of dissolution of ranolazine under the influence of food effects. Optimized RNZ-SPC-CP1 was found to be stable and robust at the end of 6-month stability studies; however, the modest impact of storage conditions appeared on the in vitro dissolution and ex vivo permeation of either the drug and/or formulations. The mechanism of this influence is still under investigation, and therefore, additional characterization studies must be required on the stability samples. Finally, the obtained appreciable results display the excellent feasibility of LIPOID SPC-3 as a coprecipitate carrier to improve the overall biopharmaceutical attributes of ranolazine and other similar drugs with poor water solubility.

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CRediT Authorship Contribution Statement Darshan Telange: conceptualization, investigation, methodology, writing—original draft, writing—review and editing. Sarita Ukey: methodology, investigation, data curation. Atul Hemke: validation, data curation. Milind Umekar: project administration, resources. Anil Pethe: conceptualization, supervision, investigation, visualization. Prashant Kharkar: investigation, methodology, writing—original draft.

Compliance with Ethical Standards

The Institutional Animal Ethical Committee of Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, reviewed and sanctioned the protocol (*SKBCOP/IAEC/201819, dated August 19, 2018*). The study was performed under the supervision of guidelines suggested by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

Conflict of Interest The authors declare that they have no conflict of interest.

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