RESEARCH PAPER

Development And Characterization Of Ranolazine Liquisolid Compacts For Enhanced Dissolution

Ishwar S Vaishnav[1], Ramdas T. Dolas[2]

[1,2] Department Of Pharmaceutics, School Of Pharmaceutical Sciences, Sandip University, Mahiravani, Nashik, Maharashtra, India.

Corresponding Author: Ishwar S Vaishnav, Email: ishwar258@gmail.com

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Abstract

Background: Ranolazine, a drug for chronic stable angina, is classified as a bcs class ii compound, meaning it has high permeability but critically poor aqueous solubility. This low solubility significantly limits its dissolution rate and leads to variable oral bioavailability. This study, therefore, leveraged liquisolid technology—a simple, scalable alternative—to enhance ranolazine's dissolution performance.

Method: Liquisolid compacts of ranolazine were prepared using a non-volatile solvent (e.g., propylene glycol) to form the liquid medication. This solution was converted into a free-flowing, compressible powder by blending it with microcrystalline cellulose (mcc) (carrier) and colloidal silicon dioxide (coating). The resulting compacts were evaluated for flow and tablet properties. Critical solid-state analysis using ftir, dsc, pxrd, and sem confirmed the drug's physical state and excipient compatibility.

Results: The liquisolid technique proved to be an effective, simple, and scalable method. The optimized liquisolid tablets achieved a significant enhancement in dissolution performance, releasing more than 90% of the ranolazine within 45 minutes. Solid-state characterization supported these findings, indicating successful conversion of the drug into an optimized state, and confirming excipient compatibility. The improved drug release is fundamentally driven by enhanced drug wetting and increased surface area exposed to the dissolution medium.

Conclusion: The development of ranolazine liquisolid compacts successfully addressed the drug's solubility limitations. This method offers a promising, scalable, and stable approach to significantly enhance the dissolution rate and potentially improve the oral bioavailability of this bcs class ii drug.

Keywords: Ranolazine, Liquisolid Compacts, Bcs Class Ii, Dissolution Enhancement.

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1. Introduction:

Oral drug delivery remains the most preferred route for therapeutic administration due to patient compliance, convenience, and cost-effectiveness. However, a significant proportion of newly developed drugs exhibit poor aqueous solubility, which limits dissolution and absorption in the gastrointestinal tract, thereby reducing oral bioavailability [1,2]. Ranolazine, a late sodium current inhibitor widely used in the management of chronic stable angina, is classified as a BCS Class II drug, characterized by low solubility and high permeability [3,4]. The solubility of Ranolazine in water is extremely limited (<0.03 mg/mL), whereas it demonstrates higher solubility in organic solvents such as DMSO and ethanol [5]. This poor solubility results in slow dissolution rates in vivo, leading to variable plasma concentrations and suboptimal therapeutic effects [6].

Several formulation strategies have been explored to overcome Ranolazine’s solubility challenges. Solid dispersions, nanosuspensions, inclusion complexes, and lipid-based carriers have been reported to enhance dissolution and bioavailability [7,8]. For example, Ranolazine solid dispersions with hydrophilic polymers increased the wettability and dispersion of the drug, thereby improving dissolution [9]. Nanostructured lipid carriers demonstrated enhanced entrapment efficiency, reduced particle size, and improved systemic absorption [10]. Despite these advancements, many of these methods face limitations such as poor mechanical properties,

complex manufacturing processes, high cost, and limited scalability [11,12].

Liquisolid technology presents a promising, cost-effective approach for enhancing the dissolution of poorly soluble drugs. In this system, the drug is first dissolved or suspended in a non-volatile liquid vehicle and then converted into a free-flowing, compressible powder by adsorption onto porous carriers and coating with fine excipients [13,14]. This approach enhances surface area, improves wetting, and may induce partial or complete amorphization of the drug, leading to significant improvement in dissolution rate [15]. Additionally, liquisolid compacts maintain good compressibility and mechanical strength, making them suitable for large-scale tablet manufacturing [16].

Previous studies have shown that liquisolid compacts can improve the dissolution and bioavailability of BCS Class II drugs such as Rosuvastatin, Ezetimibe, and Ramipril [17–19]. For Ranolazine, limited studies have explored the use of liquisolid systems for enhancing solubility. These studies indicate potential improvements in drug release profiles but highlight the need for systematic optimization of liquid load factor, carrier-to-coating ratio, and excipient selection to achieve ideal pre- and post-compression properties [20]. Furthermore, comprehensive solid-state characterization (FTIR, DSC, PXRD, SEM) is necessary to understand the physical state of the drug and the mechanisms underlying enhanced dissolution.

The present study aims to develop and optimize liquisolid compacts of Ranolazine to overcome its solubility limitations. The specific objectives are: (1) to evaluate solubility of Ranolazine in various non-volatile liquid vehicles, (2) to prepare liquisolid formulations with optimized liquid load factor and carrier–coating ratio, (3) to assess pre- and post-compression characteristics including flow, hardness, friability, and disintegration, (4) to characterize the solid state of the drug using FTIR, DSC, PXRD, and SEM, (5) to compare in vitro dissolution profiles of liquisolid compacts versus conventional tablets, and (6) to evaluate short-term stability under accelerated conditions. The ultimate goal is to develop a stable, mechanically robust, and dissolution-enhanced Ranolazine liquisolid system suitable for potential clinical application.

2. Materials and Methods:

2.1 Materials:

The model drug selected for this study was Ranolazine, obtained as a pure sample from Sun Pharmaceutical Industries Ltd. (India). The carrier material Avicel PH 102 (microcrystalline cellulose) and coating agent Aerosil 200 (colloidal silicon dioxide) were procured from S.D. Fine Chemicals, Mumbai. Propylene glycol (non-volatile solvent) and sodium starch glycolate (disintegrant) of analytical grade were also supplied by S.D. Fine Chemicals, Mumbai. All chemicals and reagents used in this study were of analytical grade, and double-distilled water was used throughout the experiments.

2.2 Preparation of Liquisolids:

2.2.1 Formulation of Liquisolids Trial batches:

Based on data obtained from preliminary experiments, trial batches were formulated. Compositions of trial batches containing drug from F1 to F9 as shown in table.

Table 1: Formulation of Liquisolids Trial batches

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ingredient	gm (w/w)								
Ranolazine	250	250	250	250	250	250	250	250	250
Avicel PH 102	200	200	200	350	350	350	500	500	500
Aerosil 200	10	20	30	10	20	30	10	20	30
Propylene glycol	0.247	0.247	0.247	0.247	0.247	0.247	0.247	0.247	0.247

2.2.3 Preparation of Liquisolid Systems

Calculated amounts of Ranolazine and propylene glycol were accurately weighed and heated in a glass beaker until complete dissolution. The resulting drug solution was gradually incorporated into the pre-weighed carrier and coating powders. The blending process was carried out in three stages:

i. **Initial Mixing:** The drug–solvent solution was blended with the powder at approximately one rotation per second for 1 minute to ensure uniform distribution.
ii. **Absorption Stage:** The admixture was spread evenly on a mortar surface and allowed to stand for 5 minutes to facilitate absorption of the drug solution into the interior of the carrier particles.
iii. **Final Blending:** The powder was scraped from the mortar surfaces using an aluminum spatula and mixed with sodium starch glycolate for 30 seconds to achieve homogeneity [21].

3. Preformulation Studies:

Preformulation studies are essential in the development of Ranolazine liquisolid systems to understand the drug's physicochemical properties and guide formulation design. These studies involve characterization of

solubility, particle size, crystallinity, hygroscopicity, and pKa of Ranolazine. Additionally, potential carriers are evaluated for compatibility, surface area, porosity, melting point, and safety to ensure effective adsorption of the drug–lipid or drug–solvent solution [14,22].

Thorough investigations of drug–lipid–carrier interactions, including phase behavior and optimal drug loading, are conducted to prevent instability and enhance dissolution efficiency. Accelerated stability studies at elevated temperatures and humidity are performed to predict long-term stability and ensure that the liquisolid formulation remains efficacious and safe under storage conditions [14,21].

The physical characteristics of Ranolazine were also determined: the drug appeared as a white to crystalline powder. The melting point was assessed using a digital melting point apparatus. The standard melting point of Ranolazine is 118–120 °C, while the observed melting point in this study was 116–118 °C, indicating slight variation within acceptable limits [22].

4.1 Optimization of Liqusolids:

4.1.1 Factorial Design:

For the present work 3^2 full factorial design was selected. It has been summarized in Table. In this design, 2 factors were evaluated each at 3 levels and experimental trials were performed at all 9 possible combinations as reflected in the table. The two independent variables selected were

Table 2: Factors and their levels

Variables	Code	Factor
Independent	X1	Carrier
	X2	Coating material
Dependent	Y1	Solubility
	Y2	% CDR

4.1.2 Experimental Design as per 3^2 Full Factorial Design:

The experimental data explores the impact of two pharmaceutical excipients, Avicel PH 200 (Factor 1) and Aerosil 200 (Factor 2), on a formulation's Solubility and % Cumulative Drug Release (% CDR). A clear and consistent trend is evident: increasing the amount of either factor generally leads to an improvement in both performance responses. For instance, when the Aerosil amount is fixed, raising Avicel from 300 mg to 500 mg progressively boosts solubility from 76% to 87% and % CDR from 76% to 85%. Similarly, at a medium Avicel level (400 mg), increasing Aerosil from 18 mg to 22 mg results in a significant jump in solubility from 81% to 91% and % CDR from 79% to 96%. The strongest performance is achieved in Run 9, using the highest quantities of both components (500 mg Avicel and 22 mg Aerosil), which yields the maximum observed solubility (97%) and % CDR (98%). This pattern suggests a synergistic or additive positive effect from both Avicel and Aerosil, indicating that within the tested range, increasing these components is effective for enhancing the dissolution and release characteristics of the final drug product.

Table 3: Details of the nine formulations in 3^2 the factorial design

		Factor 1	Factor 2	Response 1	Response 2
Group	**Run**	**A: Avicel PH 200**	**B: Aerosil 200**	**Solubility**	**% CDR**
		mg	**mg**	**%**	**%**
1	1	300	18	76	76
1	2	400	18	81	79
2	3	500	18	87	85
2	4	300	20	79	86
3	5	400	20	84	90
4	6	500	20	89	92
4	7	300	22	88	94
5	8	400	22	91	96
5	**9**	**500**	**22**	**97**	**98**

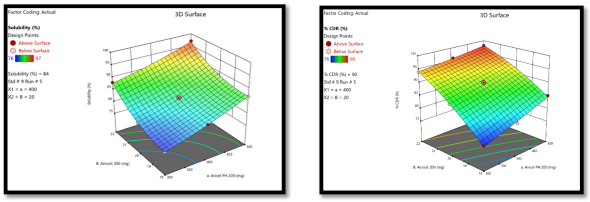

Figure 1: 3D Response Surface plot (Based on Solubility & Based on % CDR)

5. Characterization of Liquisolid Systems:

The characterization of liquisolid compacts is essential to establish their quality, performance, and the underlying mechanisms responsible for improved solubility and dissolution.

5.1 UV- Visible Spectroscopy:

5.1.1 Preparation of working standard drug solution:

Standard Ranolazine 100 mg was weighed and transferred to a 100 ml volumetric flask and dissolved in methanol. The flask was shaken and volume was made up to the mark with methanol to give a solution containing 1000 µg / ml. From this stock solution, pipette out 10 ml and placed into 100 ml volumetric flask. The volume was made up to mark with methanol to give a working stock solution containing 100 µg /ml[24].

The present study focused on the development of liquisolid compacts of Ranolazine to enhance its solubility and dissolution characteristics. UV–visible spectrophotometric analysis revealed the absorption maxima (λmax) of Ranolazine in methanol at **272.26 nm**, aligning with earlier reports for similar BCS Class II drugs. The calibration curve exhibited excellent linearity over the concentration range of 20–100 µg/mL with a correlation coefficient (**R^2**) of **0.9902**, confirming the accuracy and reliability of the methd as per ICH Q2(R1) guidelines.

Concentration	Absorbance
20	0.2132
40	0.4873
60	0.6623
80	0.8143
100	0.9967

Table 4: Concentration and Absorbance of standard formulations of UV

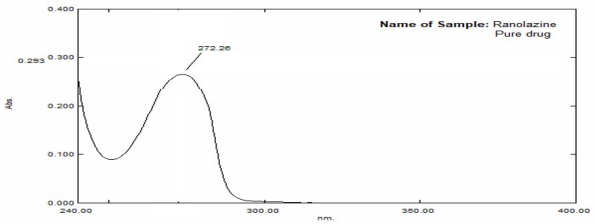

Figure 2: UV absorbance of Ranolazine

The liquisolid technique employs a non-volatile solvent system and appropriate carrier–coating material ratios to convert liquid medications into free-flowing, compressible powders. Spireas et al. and Javadzadeh et al. demonstrated that this method improves drug wettability, surface area, and molecular dispersion, enhancing dissolution rates. Our study used propylene glycol as the liquid vehicle, reported to enhance solubility and bioavailability. Optimized formulations ensured uniform drug content, satisfactory flow properties, and tablet integrity, indicating suitability for large-scale production.

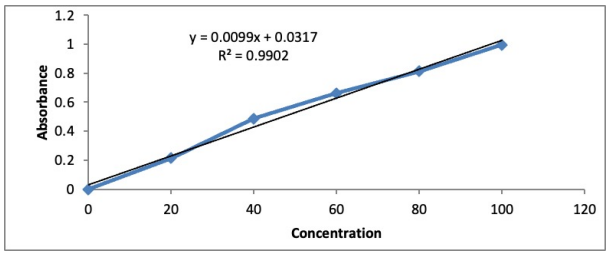

Figure 3: UV calibration curve of Ranolazine

Overall, the results corroborate previous findings that liquisolid compacts significantly enhance solubility and dissolution of poorly soluble drugs. Future investigations should focus on in vivo bioavailability and stability to establish clinical applicability.

5.2 In Vitro Dissolution Studies:

Dissolution testing remains the most important tool for evaluating liquisolid systems. Using USP dissolution apparatus, drug release profiles are compared against pure drug and directly compressed formulations. Liquisolid tablets typically exhibit enhanced dissolution rates, attributed to improved wetting and surface area exposure of drug particles [25].

Solubility studies were performed in order to analyze solubility enhancing properties of liquisolids. Solubility studies gave the basis for selection of best ratio that is to be forwarded for formulation. The results of the same are shown in Table.

Above results, indicate F6 batch shows 7.59 folds rise in solubility of ranolazine which indicates formation of liquisolids.

Table 5: Solubility of Ranolazine liquisolids

Sr. No.	Batch	Solubility (mg/ml)	Increase in Solubility (folds)
1	**Pure Drug (Ranolazine)**	0.49	-
2	**F1**	1.13	2.30
3	**F2**	1.36	2.77
4	**F3**	1.56	3.18
5	**F4**	2.01	4.10
6	**F5**	2.48	5.06
7	**F6**	3.72	7.59

5.3 Differential Scanning Calorimetry (DSC):

DSC is employed to detect changes in drug crystallinity. The disappearance or shifting of characteristic endothermic peaks indicates transformation of the drug into an amorphous or molecularly dispersed state within the liquisolid matrix [26].

The DSC (Differential Scanning Calorimetry) graph for Ranolazine provides valuable information about its thermal properties. The sharp, deep endothermic peak

observed at 118.99°C is characteristic of a substance undergoing a first-order phase transition, specifically melting. This peak's location is in excellent agreement with the reported melting point of 120°C, confirming the identity and purity of the Ranolazine sample. The narrowness and intensity of the peak indicate a highly crystalline material with a uniform melting process. This suggests the sample is free from significant impurities that would typically cause a broader, less defined endothermic transition.

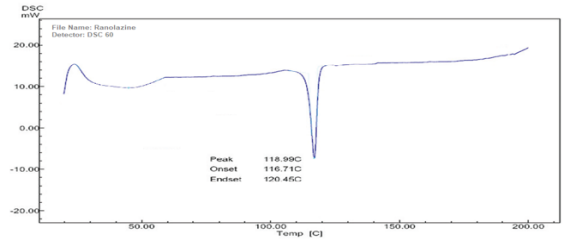

Figure 4: DSC graph for Ranolazine

5.4 X-Ray Diffraction (XRD):

XRD complements DSC by confirming changes in crystallinity. Sharp diffraction peaks observed in pure drug samples often diminish or disappear in liquisolid formulations, further indicating reduced crystallinity [27]. The powder X-ray diffraction (PXRD) graph for Ranolazine indicates the high purity and crystalline nature of the drug. The sharp, well-defined diffraction peaks at specific two-theta (2θ) angles, such as those at **5.2°, 6.9°, 18.4°, 21.13°, 22.7°, 25.6°, 27.2°**, and **28.1°**, are characteristic of a crystalline solid. Amorphous substances, on the other hand, would exhibit a broad halo instead of sharp peaks. The presence of these distinct peaks confirms that the drug substance exists in a highly ordered, three-dimensional crystalline lattice, a critical quality attribute for many pharmaceutical products.

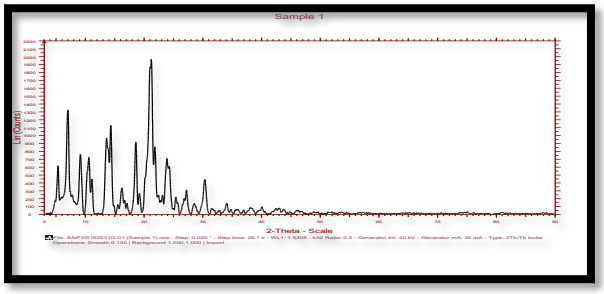

Figure 4: X-ray diffraction (PXRD) graph for Ranolazine

5.5 Fourier Transform Infrared Spectroscopy (FTIR):

FTIR analysis is performed to evaluate possible drug–excipient interactions. The absence of significant peak shifts or disappearance of characteristic functional group signals indicates compatibility and absence of chemical interaction [28].

The FT-IR (Fourier-transform infrared) spectrum of Ranolazine serves to confirm its chemical structure through the presence of key functional groups. The analysis reveals several characteristic absorption bands: the peak at 3327 cm−1 corresponds to the stretching vibration of the -NH group, with its bending vibration appearing at 1589 cm−1. The prominent band at 1681 cm−1 indicates the presence of the carbonyl group (-C=O). Additionally, the peaks observed at 2922 cm−1 and 1465 cm−1 are assigned to the stretching and bending of aliphatic (-C-H) bonds. The collective presence of these bands confirms the identity and chemical integrity of the pure Ranolazine sample.

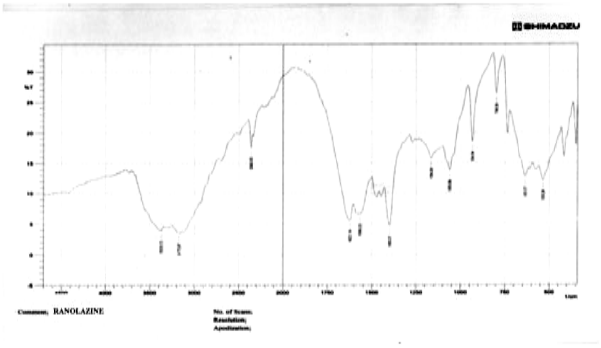

Figure 5: FTIR of ranolazine

Together, these characterization techniques confirm the physicochemical transformation achieved through liquisolid technology, establishing its ability to enhance dissolution and provide stable dosage forms suitable for industrial development.

6. Results and Discussion:

The study successfully developed and characterized Ranolazine liquisolid compacts to improve the drug's solubility and dissolution. The findings confirm that liquisolid technology is an effective method for enhancing the oral bioavailability of this BCS Class II drug.

The UV-Visible spectrophotometric analysis confirmed the maximum absorption of Ranolazine at 272.26 nm in methanol. The calibration curve showed excellent linearity (R2=0.9902), validating the analytical method

for quantitative analysis. The solubility studies demonstrated a significant improvement, with the T6 batch achieving a 7.59-fold increase in solubility compared to the pure drug, which had a solubility of 0.49 mg/mL.

A 3^2 full factorial design was used to optimize the formulation, evaluating the impact of Avicel PH 200 and Aerosil 200. The results revealed a positive correlation, where increasing the amounts of both excipients led to higher solubility and % Cumulative Drug Release (% CDR). The best performance was achieved with the highest levels of both factors (500 mg Avicel and 22 mg Aerosil), resulting in 97% solubility and 98% % CDR. Solid-state characterization confirmed the drug's properties: DSC showed a sharp endothermic peak at 118.99∘C, consistent with the melting point of a crystalline material. PXRD analysis further supported this, with well-defined diffraction peaks at specific angles, indicating a highly ordered crystalline structure. FT-IR spectroscopy confirmed the chemical structure of Ranolazine, identifying key functional groups such as the -NH group (3327 cm−1) and the -C=O group (1681 cm−1).

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