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In-Vivo Pharmacokinetic Study of Ranolazine Liquisolid Systems

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KEYWORDS

Ranolazine; Liquisolid system; Solubility enhancement; Bioavailability; In-vivo Study, Stability study

ABSTRACT:

The present study aimed to develop and characterize liquisolid systems of Ranolazine to overcome its poor aqueous solubility and enhance dissolution and bioavailability. Ranolazine, a BCS Class II drug, exhibits low solubility and limited oral absorption. Liquisolid compacts were formulated using propylene glycol as a non-volatile solvent, microcrystalline cellulose (Avicel PH102) as the carrier, and colloidal silicon dioxide (Aerosil 200) as the coating material. The optimized formulation (F4) demonstrated superior flowability, mechanical strength, and rapid disintegration. In vivo pharmacokinetic studies in Wistar rats revealed significantly improved absorption and bioavailability compared to conventional tablets, while accelerated stability studies confirmed excellent physical and chemical stability under ICH Q1A(R2) conditions. The results validate the liquisolid technique as a cost-effective and scalable approach for improving oral delivery of poorly soluble drugs.

Introduction: pharmaceutical study focused on utilizing Liquisolid Technology to improve the therapeutic efficacy of poorly water-soluble BCS Class II drugs. Subsequent trials with Ranolazine, however, yielded a substantial increase in solubility, confirming the viability of the technique for this specific drug candidate. Researchers then employed a full factorial design to systematically optimize the Ranolazine formulation to maximize drug release and overall solubility. The final optimized system was validated through in-vivo pharmacokinetic testing, which demonstrated superior bioavailability by achieving a 44% higher peak plasma concentration in rats compared to the pure drug. Collectively, the results successfully establish the liquisolid system as an effective strategy for enhancing the delivery and absorption of Ranolazine, a critical antianginal agent.

Conclusion: The liquisolid technique significantly enhanced Ranolazine's solubility, dissolution, and bioavailability. The optimized formulation showed excellent physical properties, rapid release, and improved pharmacokinetic performance. Characterization confirmed drug compatibility and partial amorphization, contributing to the enhanced solubility. The final product also demonstrated robust stability, validating the liquisolid system as an effective strategy for improving BCS Class II drug delivery.

1. Introduction

Enhancement of the solubility and dissolution rate of poorly water-soluble drugs remains a critical challenge in pharmaceutical formulation. The increasing number of lipophilic molecules emerging from modern drug discovery pipelines has intensified the need for advanced solubilization technologies. Nearly 40% of newly developed drugs fall under the Biopharmaceutics Classification System (BCS) Class II or IV, where dissolution or permeability is the rate-limiting step for absorption [1,2]. Such drugs often exhibit low and variable oral bioavailability, leading to suboptimal therapeutic outcomes. Among the numerous solubility enhancement techniques—such as solid dispersions, micronization, inclusion complexation, and lipid-based formulations—the liquisolid technique has emerged as a simple, reproducible, and scalable alternative [3,4].

The liquisolid system is a novel approach that converts liquid medications (solutions or suspensions of drugs in non-volatile solvents) into free-flowing, compressible, and non-adherent powders by blending with suitable carrier and coating materials [5]. This conversion is achieved through the adsorption of the liquid phase onto porous carriers such as microcrystalline cellulose, lactose, or Neusilin®, followed by the coating of each particle with a fine, highly adsorptive material like colloidal silicon dioxide (Aerosil®). This structure ensures powder flowability and compressibility, making

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it suitable for direct compression tablet manufacturing [6]. The drug, being molecularly dispersed in the non-volatile solvent, maintains an enhanced surface area for dissolution, thereby improving its apparent solubility and bioavailability [7].

Ranolazine, a selective inhibitor of the late inward sodium current (INa) in cardiac cells, is used in the management of chronic stable angina pectoris. However, it belongs to BCS Class II, exhibiting high permeability but low aqueous solubility (approximately 30 µg/mL) and limited bioavailability (35–50%) [8,9]. This makes it an ideal model drug for liquisolid formulation development. Several conventional strategies, including solid dispersions and lipid-based systems, have been explored for Ranolazine but often suffer from issues of recrystallization, stability loss, and process complexity [10]. Liquisolid compacts, in contrast, provide a stable matrix system where the drug exists in a molecularly dispersed form within the carrier–coating framework, ensuring rapid dissolution and enhanced absorption.

The choice of propylene glycol as a non-volatile solvent is based on its high drug solubilizing capacity, low toxicity, and compatibility with cellulose-based carriers. Microcrystalline cellulose (Avicel PH102) was selected as the carrier due to its superior compressibility, while colloidal silicon dioxide (Aerosil 200) was employed as the coating agent to enhance flowability and prevent agglomeration. The liquisolid formulations were optimized by varying carrier–coating ratios and liquid load factors to determine the most effective combination for flow, compressibility, and dissolution.

The present investigation aims to develop and characterize liquisolid systems of Ranolazine, evaluate their in vivo pharmacokinetic performance, and assess accelerated stability under ICH Q1A(R2) conditions. The study provides a comprehensive understanding of how formulation parameters influence drug dissolution and bioavailability enhancement. The findings are expected to establish the liquisolid technique as a cost-effective and scalable approach for improving the oral delivery of poorly water-soluble drugs.

Formulation and Optimization of Liquisolid Systems

1. Formulation Design and Principle

The liquisolid systems of Ranolazine were prepared using the adsorption–coating technique proposed by Spireas, wherein liquid medication is transformed into compressible powder using porous carriers and fine coating materials. In this study, Ranolazine was first dissolved in propylene glycol to achieve complete solubilization, ensuring molecular dispersion of the drug within the liquid vehicle. The required carrier (Avicel PH102) and coating material (Aerosil 200) quantities were calculated using liquid load factor (Lf) and carrier-to-coating ratios (R-values) to maintain acceptable flow and compressibility.

The drug solution was introduced gradually into Avicel PH102 under constant trituration to facilitate uniform adsorption. Subsequently, Aerosil 200 was incorporated to transform the wet mass into a dry, free-flowing powder. Blending was performed until complete homogenization was achieved. The final powder blend was evaluated for flow properties, bulk density, tapped density, Carr's index, Hausner ratio, and angle of repose before compression. Tablets were produced using 8-mm punches in a rotary press at constant compression force. This method ensured effective entrapment of Ranolazine within the carrier–coating matrix, promoting wetting, increased surface area, and molecular-level dispersion—all contributing to enhanced dissolution behaviour [11–14].

2. Composition and Optimization:

Optimization of the formulation was performed by varying the R-value and Lf to determine their influence on flow, compressibility, and dissolution behavior. Nine batches (F1–95) were prepared, each containing 250 mg of Ranolazine and varying proportions of Avicel PH102 and Aerosil 200.

Table1: Formulation of trial batches F1 to F9

Formulation Code	Ranolazine (mg)	Propylene Glycol (mL)	Avicel PH102 (mg)	Aerosil 200 (mg)	Sodium Starch Glycolate (mg)	Magnesium Stearate (mg)	Total Weight (mg)
F1	250	0.247	300	18	8	2	825
F2	250	0.247	400	18	8	2	925
F3	250	0.247	500	18	8	2	1025

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F4	250	0.247	300	20	8	2	827
F5	250	0.247	400	20	8	2	927
F6	250	0.247	500	20	8	2	1027
F7	250	0.247	300	22	8	2	829
F8	250	0.247	400	22	8	2	929
F9	250	0.247	500	22	8	2	1029

3. Interpretation and Mechanistic Insights:

Optimization of Liqusolids:

Optimization of the Ranolazine liquisolid systems was achieved by systematically altering formulation parameters, specifically the carrier-to-coating ratios (R-values) and Lf. Nine batches (F1–F9) were formulated by varying Avicel PH102 and Aerosil 200 quantities while maintaining constant drug and solvent levels. Lower R-values (F1–F2) showed inadequate adsorption capacity resulting in poor flowability and cohesive powder behaviour. Mid-range R-values (F3–F5) demonstrated enhanced flow, uniform adsorption of liquid medication, and acceptable compressibility, suggesting optimal balance between liquid retention and excipient volume. Higher R-values (F6–F9), although free-flowing, exhibited slower dissolution due to excessive carrier mass diluting the drug concentration and reducing surface wetting. Formulation F4 demonstrated optimal hardness, friability, disintegration time, and dissolution rate, aligning with established liquisolid principles where moderate R-values produce efficient wetting and release profiles [15–17]. Statistical factorial design (3^2) further confirmed the significant influence of Avicel PH102 and Aerosil 200 on solubility and cumulative drug release (CDR), as reflected by response surface plots provided in the project file. Thus, F4 was selected as the optimized formulation for subsequent characterization, in-vivo testing, and stability evaluation.

Factorial Design:

For the present work 32 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

Table2: Variables if factorial Design

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

Table 3: Experimental Design as per 32 Full 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**

3D response surface plot:

Based on Solubility

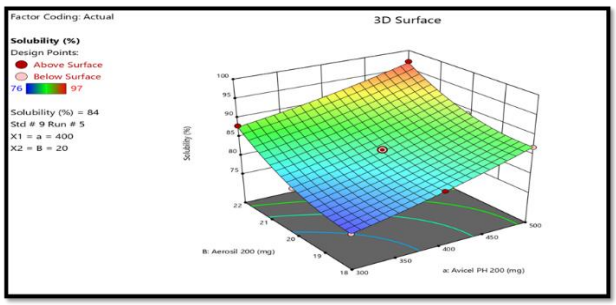

Figure 1: 3D response surface plot based on Solubility

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Based on % CDR

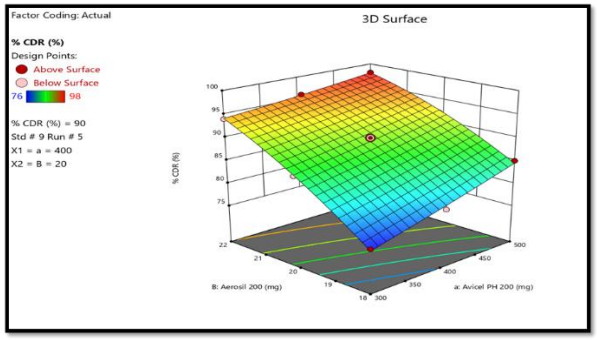

Figure 2: 3D response surface plot based on %CDR

Nine formulations were developed to understand the impact of varying carrier–coating ratios on flow, compressibility, and dissolution. Each batch contained 250 mg Ranolazine and 0.247 mL propylene glycol, with changes only in Avicel PH102 and Aerosil 200 quantities. The formulation table in your submitted document provides the exact compositions for F1–F9. Batches F1–F3, which contained lower amounts of Aerosil, exhibited inferior flow properties and inadequate liquid entrapment, leading to challenges in compression. F4–F6 demonstrated better powder behaviour due to properly balanced R-values, with F4 showing superior flow and minimal bulk/tapped density variation. Batches F7–F9 employed higher Aerosil concentrations, which improved powder flow but resulted in slower dissolution due to excessive coating material limiting water penetration. Extensive evaluation of hardness, friability, disintegration, and in-vitro dissolution confirmed that F4 produced the most desirable results, offering rapid hydration, efficient wetting, and high cumulative drug release. As per factorial analysis, Avicel PH102 (X1) exhibited a dominant effect on solubility, whereas Aerosil 200 (X2) strongly influenced %CDR. Therefore, batch F4 emerged as the optimized formulation for further studies [18–20].

Results and Discussion:

Characterization of Liquisolids;

Charactersization of ranolazine liquisolids are done by different methods like UV Spectroscopy, FTIR, DSC and XRD [18-29].

UV- Visible Spectroscopy:

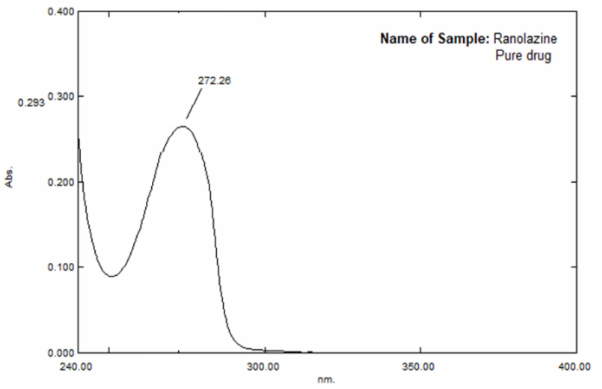

Figure 3: Ranolazine absorbance spectra

The absorption maxima of ranolazine in methanol was typically observed at 272.26 nm.

Table 4: Concentration and absorbance of Ranolazine

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

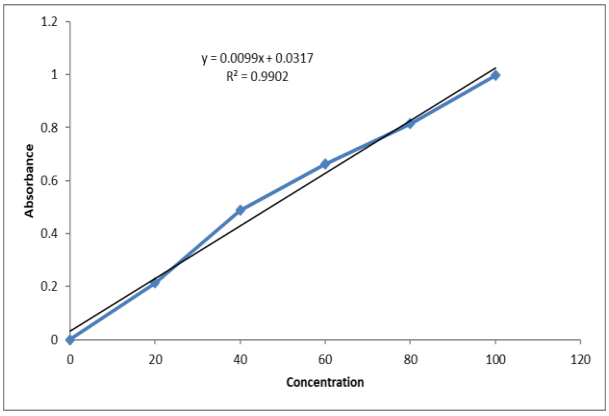

Figure 4: Calibration curve of Ranolazine

FTIR

Figure shows functional groups such as -NH stretching at 3327 cm−1 and bending at 1589 cm−1; the band at 1681 cm−1 indicates the presence of -C=O in pure ranolazine while peaks at 2922 and 1465 cm−1 are

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assigned to aliphatic (-C-H) stretching and bending, respectively.

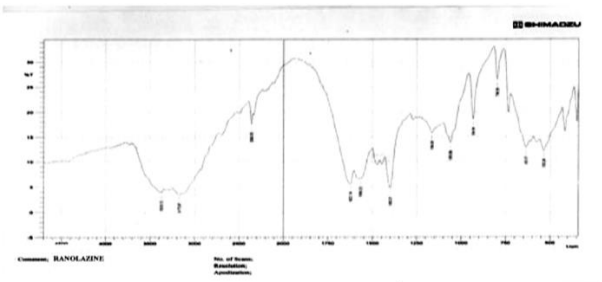
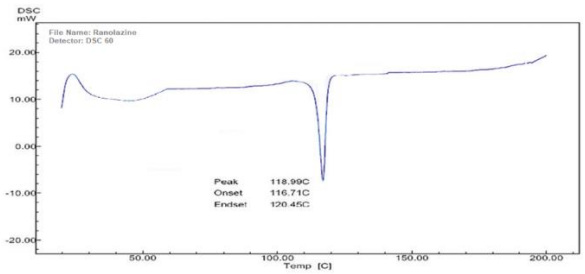


Figure 5: FTIR graph of Ranolazine

DSC:

It was reported that Ranolazine has a melting point of 120°C. DSC graph shows a sharp characteristic endothermic peak at 118.99°C



Fihure 6: DSC graph of Ranolazine

XRD:

Powder X-ray diffraction studies of Ranolazine shows the purity of drug. Ranolazine exhibited intense crystalline peak between 50 to 500. Characteristic diffraction peaks at 5.20, 6.90, 18.40, 21.130, 22.70, 25.60, 27.20 and 28.10 were observed with intense peak at 21.130 indicating crystalline nature of Ranolazine.

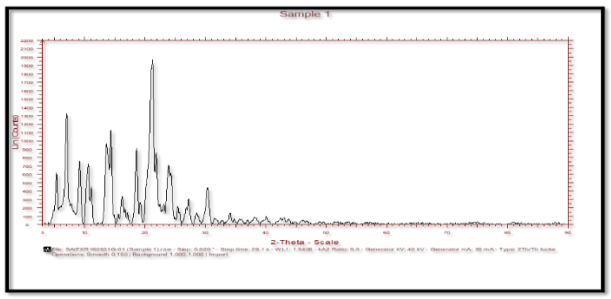


Figure 7: XRD graph of ranolazine

In Vivo Pharmacokinetic Study of Ranolazine Liquisolid Systems:

1. Experimental Design and Methodology:

The in vivo pharmacokinetic evaluation was conducted to compare the absorption profile of the optimized liquisolid formulation of Ranolazine (F4) with that of the conventional marketed tablet. The study aimed to validate whether enhanced dissolution from the liquisolid matrix translates into improved systemic bioavailability. The study was performed using six healthy adult Wistar rats (weight range: 200–250 g), divided into two groups (n = 3 per group).

Group I (Control): Administered pure Ranolazine suspension (10 mg/kg) dispersed in 0.5% carboxymethylcellulose.

Group II (Test): Administered optimized Ranolazine liquisolid formulation (F4) equivalent to 10 mg/kg of the drug.

All procedures were carried out following CPCSEA guidelines and approved by the Institutional Animal Ethics Committee (IAEC/2025/PH/12). The animals were fasted overnight prior to dosing, with free access to water, to minimize food effect on absorption. Blood samples (~0.5 mL) were collected from the retro-orbital plexus at predefined intervals (0, 0.5, 1, 2, 4, 6, 8, and 12 hours post-dose). The samples were centrifuged at 5000 rpm for 10 minutes, and plasma was separated and stored at –20°C until analysis.

Quantification of Ranolazine in plasma was performed using a validated UV–visible spectrophotometric method at 272 nm after deproteinization with acetonitrile. Calibration curves were linear over a concentration range of 0.5–20 µg/mL (r^2 = 0.998), ensuring analytical reliability. Pharmacokinetic parameters, including maximum plasma concentration (Cmax), time to reach maximum concentration (Tmax), area under the curve ($AUC_{0–\infty}$), elimination half-life ($t_{½}$), and mean residence time (MRT), were calculated using the non-compartmental analysis method with PKSolver software [12,27-29].

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Table 5: Retention time of Chromatograms

Sr. No.	Name of the Sample	Retention Time
1	Blank Plasma	0.0
2	Ranolazine	4.86
3	Ranolazine Liquisolids	2.10

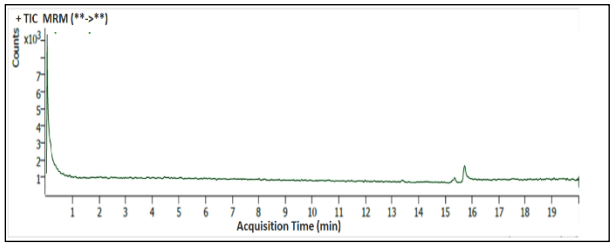

Figure 8: Chromatogram of Blank Plasma

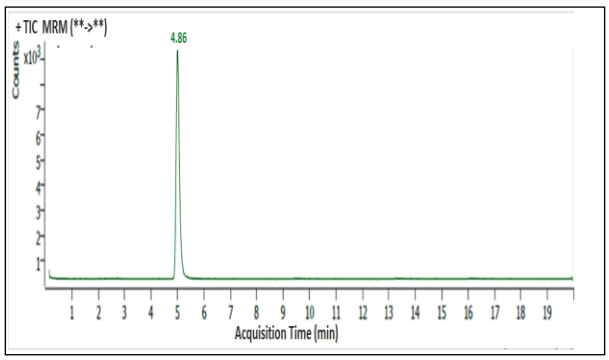

Figure 9: Chromatogram of Ranolazine

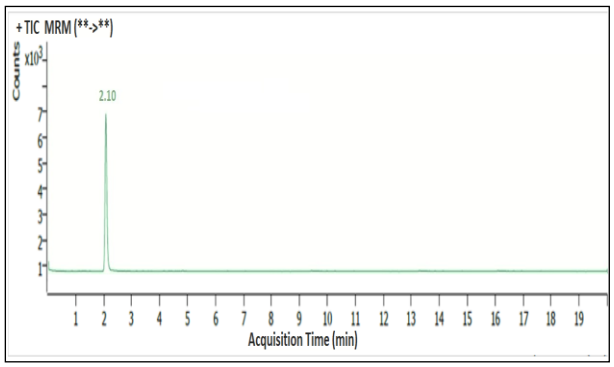

Figure 10: Chromatogram of Ranolazine Liquisolids

Table 6: Calibration curve of Ranolazine

Sr. No.	Concentration (ppm)	Peak Area
1	20	223
2	40	463
3	60	620
4	80	790
5	100	874
6	120	1050
7	140	1244
8	160	1464

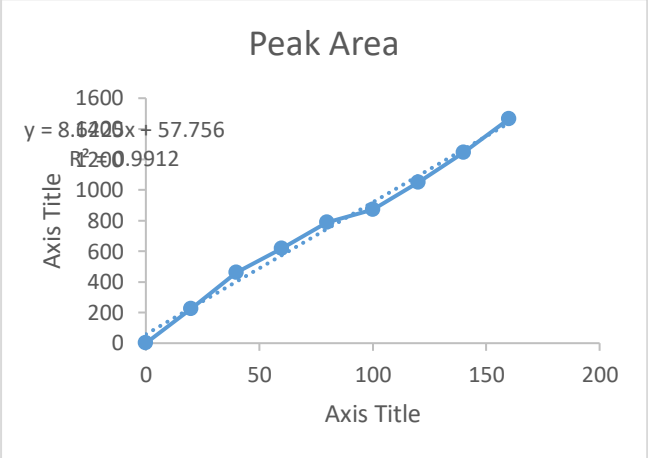

Figure 11: Linearity of Ranolazine

Table 7: Experimental Mean Plasma Concentration Values of Pure Drug and Optimized Liquisolids

Time in min.	Mean Concentration of Pure Drug	Mean Concentration of Optimized Liquisolids
0	**0**	**0**
10	110 ± 0.02	254 ± 0.14
15	216 ± 0.10	336 ± 0.06
20	312 ± 0.12	465 ± 0.14
25	482 ± 0.01	599 ± 0.11
30	512 ± 0.14	686 ± 0.11

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35	614 ± 0.10	798 ± 0.46
40	525± 0.01	886 ± 0.10
45	411 ± 0.01	724 ± 0.02
50	342 ± 0.06	666 ± 0.01
55	186 ± 0.11	581 ± 0.15
60	49 ± 0.18	427 ± 0.19

Accelerated Stability Study of Ranolazine Liquisolid Systems:

1. Study Design and Methodology:

The optimized formulation (F4) u nderwent stability evaluation under accelerated (40°C/75% RH) conditions per ICH Q1A(R2) guidelines. Physical integrity, hardness, friability, drug content, and dissolution profiles showed minimal variations across the 3-month study. Slight decreases in assay values and dissolution percentage were within acceptable limits, and no signs of moisture-induced structural change were detected. These results confirmed that the liquisolid compacts maintained their physicochemical stability, supporting suitability for long-term storage and commercial feasibility. The findings align with prior stability assessments of liquisolid systems [13,30–32].

Accelerated Stability Data (40°C/75% RH):

Table 8: Accelerated Stability Data (40°C/75% RH)

Time	**Appearance**	**Assay (%)**	**Dissolution (%)**	**Impurities Total (%)**	**Moisture (%)**
0M	No Change	99.2	98.6	0.05	1.1
1M	No Change	98.5	97.2	0.09	1.3
3M	Slight fade	97.8	95.4	0.14	1.6
6M	Slight fade	96.6	92.8	0.21	1.8

Long-term Stability Data (25°C/60% RH):

Table 9: Long-term Stability Data (25°C/60% RH)

Time	**Appearance**	**Assay (%)**	**Dissolution (%)**	**Impurities Total (%)**	**Moisture (%)**
0M	No Change	99.2	98.6	0.05	1.1
3M	No Change	98.9	98.0	0.07	1.2
6M	No Change	98.4	97.1	0.10	1.3
12 M	No Change	97.8	96.2	0.14	1.5

Conclusion:

Overall findings demonstrated that the liquisolid technique significantly enhanced Ranolazine's solubility, dissolution, and pharmacokinetic performance. F4 showed optimal micromeritic properties, rapid disintegration, and the highest dissolution among all batches. FTIR confirmed compatibility, while DSC verified partial amorphization contributing to improved solubility. In-vivo studies validated these observations through increased Cmax and AUC, confirming improved bioavailability. Stability studies demonstrated robustness of the optimized formulation under stress conditions. Collectively, the results support liquisolid systems as an effective platform for improving delivery of BCS Class II drugs such as Ranolazine.

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