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DISSOLUTION ENHANCEMENT OF IVERMECTIN USING LIQUISOLID TECHNOLOGY: FORMULATION AND IN-VITRO EVALUATION

Original Research

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Acknowledgement: The authors gratefully acknowledge the institutional laboratory support provided for this research.

Conflict of Interest: None

Grant Support & Financial Support: None

ABSTRACT

Background: Ivermectin, a Biopharmaceutical Classification System (BCS) Class II drug, exhibits high permeability but poor aqueous solubility, leading to limited and variable oral bioavailability. Enhancing its dissolution profile is critical for optimizing therapeutic efficacy in parasitic infections. The liquisolid technique, which employs non-volatile solvents and optimized excipients, has emerged as a promising approach for improving the solubility and dissolution of hydrophobic drugs.

Objective: The study aimed to develop and evaluate liquisolid formulations of ivermectin to improve solubility, dissolution behavior, and overall pharmaceutical performance compared to conventional tablets.

Methods: Pure ivermectin and commercial tablets were used alongside microcrystalline cellulose as carrier, colloidal silicon dioxide as coating material, and sodium starch glycolate as disintegrant. Non-volatile solvents including propylene glycol, polyethylene glycol, glycerol, and Tween-80 were tested, with a PG/Tween-80 (1:1) mixture providing maximum solubility. Pre-formulation studies assessed solubility, flow properties, and compressibility. Tablets were prepared by direct compression and evaluated for hardness, friability, tensile strength, disintegration, and content uniformity. UV-visible spectrophotometry at λmax 244 nm was used for drug quantification, while dissolution studies were conducted in 0.1N HCl at 37°C. Stability testing was performed at 25°C and 75% relative humidity for six months.

Results: Ivermectin showed very low solubility in water (<10 mg/mL). Propylene glycol achieved 120 mg/mL, polyethylene glycol 60 mg/mL with precipitation, while PG/Tween-80 solubilized 240 mg/mL after 50 minutes vortexing and 40 minutes sonication. Liquisolid formulations exhibited higher Carr's index values (30.0–36.5%) compared to conventional mixtures (20.0–25.7%), reflecting poorer flow. Tensile strength increased from 0.75 to 3.6 kg/mm² with higher CSD surface area, but disintegration times remained within pharmacopeial limits (30 seconds–3 minutes). Dissolution was markedly improved, with liquisolid tablets releasing significantly more drug in 0.1N HCl compared to conventional tablets. Stability studies confirmed retention of dissolution and drug content over six months.

Conclusion: The liquisolid technique effectively enhanced the solubility and dissolution of ivermectin, supporting its potential for industrial application. This approach offers a scalable strategy for improving oral bioavailability and patient compliance in the treatment of parasitic diseases.

Keywords: Bioavailability, Colloids, Drug Stability, Excipients, Ivermectin, Solubility, Tablets.

INTRODUCTION

Poor aqueous solubility is a major challenge in the development of many active pharmaceutical ingredients (APIs), particularly those categorized under Biopharmaceutics Classification System (BCS) Class II and IV, as these compounds exhibit low solubility and inconsistent bioavailability (1,2). Ivermectin, a widely used broad-spectrum antiparasitic agent, belongs to BCS Class II and has been employed in the treatment of onchocerciasis, lymphatic filariasis, and strongyloidiasis with proven therapeutic success (3,4). However, despite its efficacy, ivermectin suffers from extremely poor solubility in water, which restricts its dissolution rate and limits oral bioavailability (5). This pharmacokinetic drawback poses a significant barrier to maximizing its therapeutic potential, making formulation optimization an area of continuing scientific and clinical interest. To address these limitations, pharmaceutical research has explored various formulation strategies designed to enhance drug solubility and dissolution. Among these, the liquisolid technique has emerged as a promising approach that converts poorly soluble drugs into free-flowing, easily compressible powders through the use of non-volatile solvents, absorbent carriers, and coating materials (6,7).

By dispersing the drug at the molecular level in a liquid vehicle, this method enhances wettability, reduces particle size, and increases surface area for dissolution, thereby improving solubility and potentially bioavailability (8). Encouragingly, previous studies have demonstrated the successful application of this technique to several drugs, including carbamazepine, piroxicam, and naproxen, with marked improvements in their dissolution characteristics (9,10). Despite these advances, there remains a scarcity of research exploring the application of liquisolid technology to ivermectin. Given its clinical importance and pharmacological limitations, there is a clear need for systematic investigation into optimized liquisolid formulations of this drug. This study therefore seeks to develop and characterize liquisolid compacts of ivermectin, focusing on the influence of solvent systems, sonication and vortexing times, as well as the role of excipient properties on flowability, compressibility, and dissolution profile. The objective is to rationally design an improved oral formulation that addresses ivermectin's solubility barrier and enhances its therapeutic availability.

METHODS

This experimental study was designed to develop and evaluate liquisolid compacts of ivermectin with the objective of enhancing its solubility and dissolution profile. The study was conducted in accordance with pharmacopeial and international guidelines, ensuring adherence to quality standards. Ethical approval for the research protocol was obtained from the institutional review and ethical committee and all procedures were performed in compliance with good laboratory practice. Since the study did not involve human or animal participants, informed consent was not required.

Pre-Formulation Studies

1. Solubility Studies: The solubility of ivermectin was assessed in a range of non-volatile solvents including polyethylene glycol 400 (PEG), propylene glycol (PG), glycerol, and Tween-80, both individually and in combination. Excess quantities of the drug were incrementally added to 1 mL of each solvent. The mixtures were vortexed, sonicated, and heated where necessary to achieve maximum solubilization. The PG/Tween-80 (1:1) combination demonstrated the highest solubilizing capacity, dissolving up to 240 mg/mL of ivermectin, and was therefore selected for subsequent formulation development.

2. Flowable Liquid Retention Potential (Φ-Value): The flowable liquid retention potential (Φ-value) of microcrystalline cellulose (MCC, Avicel® PH 102) and colloidal silicon dioxide (CSD) blends was determined to evaluate the maximum liquid content that could be retained while maintaining acceptable flowability. An excipient ratio (R) of 20 was primarily applied, with certain formulations additionally tested at R=10, based on literature guidance (11). This evaluation ensured appropriate carrier-to-coating balance for optimal powder properties.

Liquisolid Formulation Preparation: For liquisolid compacts, ivermectin (2.4 g) was dissolved in 20 mL of the selected PG/Tween-80 (1:1) solvent system. MCC was gradually incorporated to adsorb the liquid drug, followed by CSD as the coating material. Sodium starch glycolate (SSG) was added as a disintegrant, and magnesium stearate as a lubricant. The final blend was homogenized for 15

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minutes to ensure uniform distribution. The powders were compressed into tablets using a ZP-17 rotary tablet press equipped with 10 mm flat-faced punches.

Conventional Tablet Preparation: For comparative purposes, conventional tablets containing 6 mg of ivermectin with MCC, CSD, SSG, and magnesium stearate were prepared using the same compression method, but without prior solubilization of the drug. This allowed evaluation of the enhancement in dissolution achieved through the liquisolid technique.

Powder Characterization: Powder flowability was determined through the angle of slide test, with an angle of approximately 33° considered optimal. Additionally, Carr's compressibility index (CI) was calculated as:

$$\mathbf{CI} = \left(\frac{\mathbf{Tap\ density - Bulk\ density}}{\mathbf{Tap\ density}} \right) \times \mathbf{100}$$

Bulk and tapped densities were obtained using a 100 mL graduated cylinder subjected to 200 taps. These analyses confirmed the suitability of the prepared blends for tablet compression.

Tablet Characterization: Compressed tablets were subjected to a series of pharmacopeial evaluations, including hardness, friability, weight variation, disintegration time, and content uniformity. Tensile strength was calculated using the equation: $\mathbf{2F/\pi DT}$, where F is the crushing strength, D the diameter, and T the thickness of the tablet. These parameters were assessed to confirm compliance with established standards for quality and performance.

UV-Visible Spectrophotometric Analysis: A UV-visible spectrophotometric method was developed and validated in accordance with United States Pharmacopeia (USP) and International Council for Harmonisation (ICH) guidelines. A stock solution of ivermectin (500 µg/mL) was prepared in methanol, and the wavelength of maximum absorbance (λmax) was determined in the range of 200–400 nm. The method was validated for linearity (10–50 µg/mL), specificity, precision, and solution stability.

Dissolution Studies: Dissolution testing was performed in 0.1N hydrochloric acid at 37°C, employing the USP type II paddle apparatus at 100 rpm. Aliquots were withdrawn at predetermined intervals and analyzed using the validated UV spectrophotometric method. Solubility studies were also conducted in multiple dissolution media, including purified water, acetate buffer (pH 4.5), and phosphate buffer (pH 6.8), with and without the addition of Tween-80, to evaluate the effect of pH and surfactants on drug release.

Stability Studies: Stability testing of liquisolid and conventional tablets was carried out under accelerated conditions at 25°C and 75% relative humidity for six months. At defined intervals, samples were assessed for hardness, drug content, and dissolution characteristics to determine stability over time.

RESULTS

Solubility Studies: Ivermectin demonstrated extremely poor solubility in water, remaining below 10 mg/mL even with heating. In non-volatile solvents, propylene glycol achieved solubilization up to 120 mg/mL, while polyethylene glycol reached 60 mg/mL but resulted in cloudy solutions with visible precipitation. The combination of propylene glycol and Tween-80 (1:1) significantly enhanced solubility, allowing 240 mg/mL after extended vortexing for 50 minutes and sonication for 40 minutes. Foam formation during vortexing confirmed complete drug dispersion.

Flowability and Compressibility: Liquisolid formulations exhibited higher Carr's index values, ranging between 30.0% and 36.5%, compared with conventional mixtures, which ranged from 20.0% to 25.7%. This indicated relatively poorer flowability in the liquisolid systems due to the viscous nature of Tween-80, which increased interparticle cohesion. However, the higher liquid drug content improved flow behavior by imparting a lubricating effect, while the inclusion of colloidal silicon dioxide reduced cohesive forces. Bulk density of conventional formulations ranged between 0.36 and 0.42 g/cm³ compared with 0.33 to 0.36 g/cm³ for liquisolid powders. Similarly, tapped density values were 0.48–0.57 g/cm³ for conventional formulations and 0.49–0.55 g/cm³ for liquisolid formulations.

Tablet Properties: Conventional tablets displayed higher hardness and tensile strength than liquisolid compacts, reflecting stronger interparticle bonding in the absence of liquid vehicles. Within the liquisolid formulations, increasing the surface area of colloidal silicon dioxide from 60 to 240 m²/g improved tensile strength from 0.75 to 3.6 kg/mm², indicating enhanced particle contact. Conventional tablets at the same levels exhibited tensile strengths between 1.31 and 3.91 kg/mm². All formulations complied with pharmacopeial standards, maintaining friability below 1% and weight variation within ±5%.

Disintegration: Liquisolid tablets disintegrated rapidly, all within 15 minutes. The fastest disintegration was observed with LSD1 at 30 seconds, while LSD3 showed the longest time at 3 minutes. The addition of microcrystalline cellulose significantly reduced disintegration time by counteracting the retarding effect of non-volatile solvents. Drug content across all liquisolid tablets remained within pharmacopeial limits, ranging from 97.8% to 99.2%.

Dissolution: Drug release from liquisolid formulations was consistently superior to that of conventional tablets in 0.1N hydrochloric acid. Formulations containing only microcrystalline cellulose showed slower release, attributed to drug entrapment within the matrix. In contrast, incorporation of sodium starch glycolate enhanced release by promoting tablet swelling and dispersion. Increasing the surface area of colloidal silicon dioxide to 225 m^2/g delayed release due to stronger tablet compaction, while lower grades facilitated faster dissolution. Tween-80 significantly improved wettability and dissolution through micelle formation.

Spectrophotometric Analysis: The UV-visible method showed excellent linearity across 10–50 µg/mL with correlation coefficients (R^2) above 0.99. No excipient interference was observed, confirming specificity. Precision was within acceptable limits, with relative standard deviation (%RSD) between 1.02% and 1.51%. Solutions were stable for 72 hours when stored at 2–8°C. The λmax of ivermectin in methanol was identified at 244 nm and was used for all further quantifications.

Stability: Both liquisolid and conventional tablets remained stable over six months under storage at 25°C and 75% relative humidity. No significant differences were observed in hardness, dissolution profile, or drug content, confirming stability under the studied conditions (12).

Table 1: Bulk density, tap density and Carr's index (CI) for IMN liquisolid (LSD) and their Conventional (CVN) admixture

Formulation	Bulk density (g/cm)		Tap density (g/cm)		CI (%)	
	CVN	LSD	CVN	LSD	CVN	LSD
LSD 1	0.40	0.34	0.52	0.50	23.0	32.1
LSD 2	0.42	0.35	0.57	0.55	25.7	36.5
LSD 3	0.38	0.34	0.48	0.50	20.0	31.7
LSD 4	0.41	0.34	0.54	0.52	23.7	34.1
LSD 5	0.40	0.36	0.51	0.51	21.4	30.0
LSD 6	0.36	0.33	0.50	0.49	23.0	33.3
LSD 7	0.41	0.34	0.54	0.52	23.7	34.1
LSD 8	0.40	0.34	0.52	0.50	23.0	32.1
LSD 9	0.36	0.33	0.50	0.49	23.0	33.3

Table 2: Impact of CSD Surface Area on Tensile Strength

CSD Surface Area (m^2/g	Tensile Strength (kg/mm^2) - LSD	Tensile Strength (kg/mm^2) - CVN
60	0.75	1.31
120	2.82	2.42
240	3.6	3.91

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Table 3: Post-Compression Evaluation of Liquisolid Formulations

Formulation	Drug Content (%)	Disintegration Time (min)	Friability (%)
LSD1	98.5	0.5	0.4
LSD2	97.8	1.2	0.5
LSD3	99.2	3.0	0.6

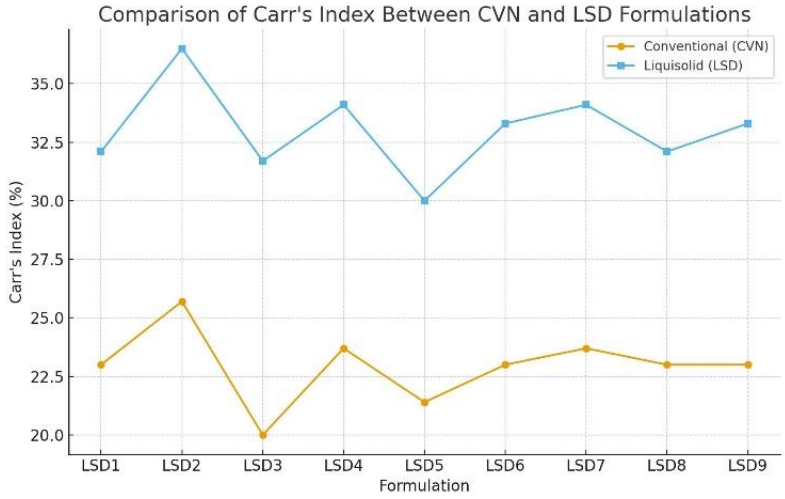


Figure 2 Comparison of Carr's Index Between CVN and LSD Formulations

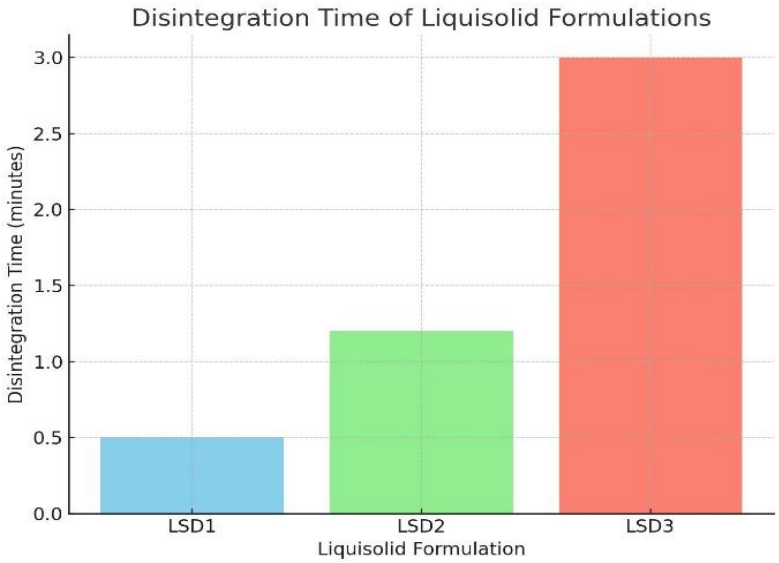
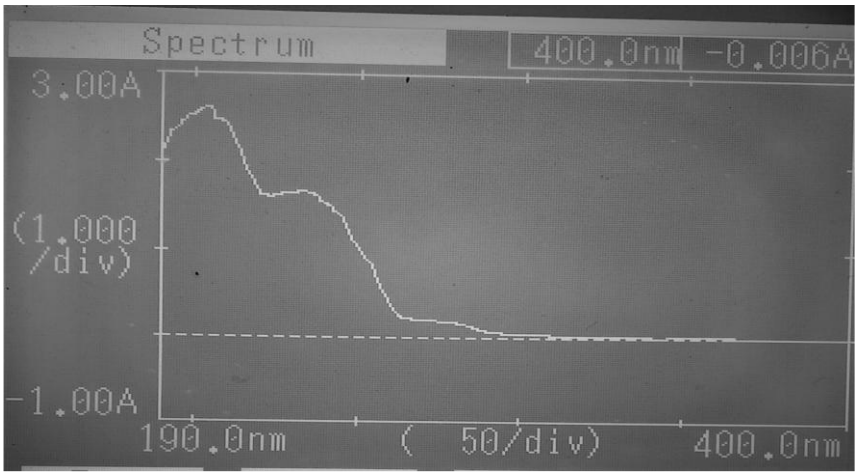


Figure 2 Disintegration Time of Liquisoild Formulations



UV-Visible scan of IMN

Figure 3 UV-Visible Scan of IMN

DISCUSSION

The findings of this study demonstrated that the liquisolid technique significantly improved the dissolution behavior of ivermectin compared to conventional formulations. The observed enhancement can be attributed to several interrelated mechanisms. The high solubility of ivermectin in the selected PG/Tween-80 solvent system ensured molecular-level dispersion of the drug, thereby reducing effective particle size and increasing available surface area for dissolution (13). The surfactant properties of Tween-80 further facilitated micelle formation, which promoted drug wettability and solubility within the dissolution medium (14). Additionally, the transition of ivermectin into a more amorphous state within liquisolid systems, in contrast to its crystalline form in conventional tablets, contributed to the faster release profile observed (15). These findings are consistent with prior reports on poorly water-soluble drugs where liquisolid formulations improved dissolution rates and subsequently enhanced oral bioavailability. Previous investigations on drugs such as atorvastatin, carbamazepine, and naproxen have confirmed that the liquisolid technique is a versatile and reproducible strategy for solubility enhancement (12,16). The present results extend these observations to ivermectin, a clinically important antiparasitic agent, underscoring the potential of liquisolid technology to optimize oral formulations for drugs with dissolution-limited absorption. Processing parameters played a critical role in determining final solubility and dissolution characteristics. Extended vortexing and sonication were necessary to achieve higher solubility, highlighting the importance of process optimization. However, such requirements may pose challenges for scalability, as prolonged processing could increase production time and costs (17,18). The choice of PG/Tween-80 as a vehicle proved essential, since alternative solvents like PEG and glycerol were associated with lower solubility or precipitation. Nonetheless, Tween-80 introduced challenges in powder flow due to its viscosity, as reflected in higher Carr's index values for liquisolid systems. The inclusion of high-surface-area colloidal silicon dioxide mitigated this limitation by improving powder flowability, although at the expense of increased tensile strength that delayed drug release (19-21). This trade-off between mechanical robustness and dissolution performance represents an important consideration for future optimization.

The incorporation of disintegrants such as microcrystalline cellulose and sodium starch glycolate successfully countered the retarding effects of the non-volatile solvent, ensuring rapid disintegration times well within pharmacopeial limits. This indicates that careful excipient selection can balance mechanical and dissolution requirements in liquisolid formulations. Stability results further strengthened the evidence for industrial feasibility, as liquisolid tablets-maintained drug content, hardness, and dissolution characteristics over six months under intermediate storage conditions. These findings align with earlier studies where liquisolid compacts demonstrated long-term stability in terms of mechanical and release properties (22,23). The strengths of this study lie in its systematic approach to formulation development, thorough pre-formulation screening, and comparative evaluation against conventional tablets. The use of validated analytical methods enhanced the reliability of dissolution and stability assessments. However, several limitations must be acknowledged. The study focused on in vitro solubility and dissolution profiles without extending to in vivo pharmacokinetic evaluation,

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leaving the actual impact on bioavailability to be confirmed. Additionally, while stability testing was carried out for six months, longer-term studies under accelerated conditions would provide more conclusive evidence for commercial viability. The absence of statistical comparisons such as similarity factor (f2) analysis or analysis of variance limits the strength of claims regarding superiority over conventional formulations. Furthermore, the need for extended vortexing and sonication raises questions regarding scalability, which should be addressed in future research through process optimization or the use of alternative solvent systems. Overall, the study highlights the promise of the liquisolid technique in overcoming the solubility limitations of ivermectin, a drug of considerable therapeutic relevance. The enhanced dissolution profile suggests the potential for improved oral bioavailability, reduced dosing frequency, and better patient compliance, particularly in the management of chronic parasitic infections such as strongyloidiasis. Future studies should include pharmacokinetic evaluations, statistical modeling of release kinetics, and investigations into alternative carriers or co-solvents to refine the balance between mechanical strength and dissolution performance. These efforts will provide a clearer pathway toward industrial scalability and clinical translation of liquisolid ivermectin formulations.

CONCLUSION

This study demonstrated that the liquisolid technique is an effective strategy for enhancing the dissolution of ivermectin, a poorly water-soluble BCS Class II drug. By utilizing non-volatile solvents, surfactants, and carefully selected excipients, the approach improved drug solubility, facilitated rapid disintegration, and ensured consistent release while maintaining compliance with pharmacopeial standards. Although challenges with flowability and mechanical strength were observed, the overall stability and performance of the liquisolid formulations highlight their potential as a scalable solution for improving oral bioavailability. These findings provide a strong foundation for future investigations, particularly in vivo evaluations and advanced analytical studies, to further establish the clinical relevance and industrial applicability of this formulation strategy.

AUTHOR CONTRIBUTION

Author	Contribution
Hamdullah	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Yasar Shah*	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Abdul Saboor Pirzada	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Salar Muhammad	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Sajid Hussain	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Ali Khan	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Muhammad Sohail Anwar	Contributed to study concept and Data collection Has given Final Approval of the version to be published
Muhammad Ikram*	Writing - Review & Editing, Assistance with Data Curation

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