To Improve Solubility and Dissolution Rate of BCS Class-II Drug using Herbal Ingredient

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Abstract: The present study demonstrates that co-crystallization is a promising method for enhancing the solubility and dissolution rate of poorly water-soluble drugs, specifically Macitentan. Utilizing a range of analytical techniques such as UV-Visible spectroscopy, solubility testing, dissolution profiling, FTIR, DSC, and SEM, the research confirmed that co-crystals formed with Glycyrrhizic acid, Quercetin, and Saponin substantially improved the physicochemical properties of the parent drug. The incorporation of selected herbal excipients proved effective in enhancing the solubility and dissolution rates of this BCS Class II drug. A comparative analysis with conventional formulations underscored the superior performance of herbal-based systems in enhancing dissolution behavior. Furthermore, the natural origins, biocompatibility, biodegradability, and low toxicity of these materials bolster their applicability in pharmaceutical contexts. Overall, the study concludes that co-crystallization with chosen coformers significantly enhances the solubility, dissolution, and structural properties of Macitentan, with Saponin identified as the most effective coformer. Thus, herbal excipients present a viable alternative to traditional methods of solubility enhancement, offering multifunctional properties, a favorable safety profile, and sustainability, making them particularly well-suited for improving the dissolution characteristics of poorly soluble drugs. The findings provide valuable insights for the application of natural excipients in drug delivery and highlight new research opportunities in the development of eco-friendly and patient-compliant pharmaceutical formulations.

Keyword: Co-crystallization, Macitentan, BCS Class II, Sustainability, Coformer.

1. Introduction

Oral drug delivery is the most convenient, economical, and patient-compliant route of drug administration. However, the therapeutic performance of many orally administered drugs is hampered by their poor aqueous solubility. It is estimated that more than 40% of new chemical entities and nearly 60% of drugs under development suffer from low water solubility, leading to inadequate dissolution, incomplete absorption, and reduced bioavailability.[1] Poor aqueous solubility is a major limitation for BCS Class-II drugs (high permeability, low solubility) and often results in slow dissolution, variable absorption and reduced oral bioavailability. Classical pharmaceutical strategies to overcome poor solubility include particle size reduction, solid dispersions, complexation, surfactant systems and lipid-based formulations. [2]

Challenges in BCS Class-II Drugs The formulation of BCS Class-II drugs poses several challenges:

- Low aqueous solubility restricts dissolution in gastrointestinal fluids.
- Variable absorption leads to inconsistent therapeutic outcomes.
- Dose escalation is often required to achieve therapeutic levels, which may increase side effects.
- Food effect dependency, since solubility may increase in fed state due to bile salts.
- Poor correlation between in-vitro dissolution and in-vivo absorption unless dissolution is significantly enhanced. Thus, overcoming dissolution limitations of BCS-II drugs is a key objective in modern drug delivery research. [3]

Herbal Approaches for Solubility Enhancement Recently, herbal ingredients have gained significant attention as natural alternatives to synthetic excipients. They offer advantages of safety, biocompatibility, biodegradability, cost effectiveness, and wide acceptability in herbal and nutraceutical formulations. Commonly studied herbal agents include: [4] [5]

- Saponins (from fenugreek, liquorice, soapnut) act as natural surfactants and solubilizes.
- Flavonoids (quercetin, naringin, and hesperidin) modify permeability and enhance solubility via hydrogen bonding.
- Alkaloids (e.g., piperine) act as bioenhancers by inhibiting drug-metabolizing enzymes and efflux transporters.
- Plant mucilages and gums (e.g., tragacanth, isabgol, hibiscus, fenugreek mucilage) hydrophilic carriers that improve wettability and dispersion.
- Essential oils (peppermint, clove, black cumin oil) act as lipidic solubilizers and self-emulsifiers. 5 These herbal based excipients are eco-friendly and align with the “green pharmacy” concept. [6] [7]

2. Formulation and Evaluation of Macitentan Cocrystals:

Preparation of Co-crystals:

Step 1: Weighing

- Take the equimolar amount of Macitentan and coformer in 1:1 ratio, the required quantities of Macitentan and coformer were calculated based on their respective molecular weights.
- For Macitentan=100mg, to maintain a 1:1 molar ratio, we need:

Herbal Ingredient	MW (g/mol)	Required Amount (mg)
Saponin	1223.3	207
Glycyrrhyzic acid	822.9	140
Quercetin	302.23	51

Step 2: Dissolution in Solvent

- Transfer both to a 100 mL beaker and add 15 mL of methanol.
- Stir the mixture at 40–50 °C on Hot Plate and stirrer until a clear solution is achieved (about 30 minutes).

Step 3: Evaporation

- After complete solvent evaporate, dry the powder.

Step 4: Collection

- After complete evaporation, collect the solid crystals with a spatula.

Step 5: Drying

- Place the crystals in a hot air oven at 40 °C for 1-2 hours to remove residual solvent.

Step 6: Storage

Store the dried Macitentan–coformer co-crystals in an airtight container in a desiccator for further characterization.

Characterization of Co-Crystals

A. Quantitative Analysis:

- UV Spectrophotometric Analysis
- Solubility studies
- Dissolution studies

B. Qualitative Analysis

- Fourier Transform Infrared Spectroscopy (FTIR) Analysis
- Differential Scanning Calorimetry (DSC)
- X-Ray Diffraction (XRD)
- Scanning Electron Microscopy (SEM)

3. Result and Discussion

A. Quantitative Analysis

1. UV Spectrophotometry Analysis

Table No-1: Maximum Wavelength of Drug and Co-crystals

Formulation	Absorbance	Interpretation
Pure Macitentan	0.281	Baseline :Low Solubility
Macitentan+ Glycyrrhyzic acid	0.382	Lowest absorbance; suggests weak interaction or minimal effect on electronic transitions.
Macitentan+ Quercetin	0.697	Highest absorbance; indicates enhanced interaction, possibly due to π–π stacking.
Macitentan +Saponin	0.921	Increased absorbance over pure drug; suggests effective molecular interaction, possibly via hydrogen bonding.

Table No-2: Solubility Test for Macitentan and Co-crystals

Sample	Solubility
Macitentan	11.59
Macitentan + Glycyrrhyzic acid	16.05
Macitentan + Quercetin	26.75
Macitentan + Saponin	34.95

The **dissolution profiles** of pure Macitentan and its co-crystals with Glycyrrhyzic acid, Quercetin, and Saponin were assessed over 60 minutes. Results showed a marked increase in dissolution rate for Macitentan when combined as co-crystals, with the highest rate noted for the Saponin co-crystal, followed by Quercetin and Glycyrrhyzic acid.

FTIR analysis of Macitentan with salicylic acid, benzoic acid, and succinic acid indicated significant spectral changes due to intermolecular interactions. Pure Macitentan showed distinct peaks associated with N–H, C–H, and C=O stretches, confirming its crystalline nature. Co-crystals with Glycyrrhyzic acid, Quercetin, and Saponin exhibited broadened peaks and shifts in C=O regions, suggesting strong hydrogen bonding and new crystalline phases.

DSC analysis revealed Macitentan's sharp melting point (130.19 °C), indicating purity and stability, while the other compounds displayed multiple melting events.

Morphologically, Macitentan's structure is highly porous, while its co-crystals varied from plate-like formations to rough flakes, demonstrating how processing affects material properties and performance.

4. Summary and Conclusion

The results of this study demonstrate that co-crystallization significantly enhances the physicochemical properties of Macitentan. UV spectrophotometric analysis revealed changes in absorbance and minor shifts in λmax, indicating successful interaction between Macitentan and the selected coformers—Glycyrrhyzic acid, Quercetin, and Saponin. The co-crystals exhibited improved solubility, with the highest solubility observed in the Saponin Macitentan–co-crystal, followed by Quercetin and Glycyrrhyzic acid co-crystals, in comparison to the pure drug. Dissolution studies further confirmed enhanced drug release from all co-crystals, particularly the Macitentan–Saponin formulation, which showed the greatest improvement in dissolution rate over 60 minutes. FTIR analysis confirmed molecular interactions through characteristic peak shifts, while DSC results revealed alterations in thermal behavior, suggesting formation of new solid phases. X-ray diffraction patterns indicated improved crystallinity in all co-crystals, most notably with Saponin, which showed the highest intensity and sharpness of peaks. SEM analysis supported these findings by showing distinct morphological changes across formulations, with the Saponin co-crystal displaying a favourable composite structure. Overall, co-crystallization with selected coformers effectively enhanced the solubility, dissolution, and structural properties of Macitentan, with Saponin emerging as the most promising coformer for formulation development.

The study reveals that co-crystallization is an effective method for enhancing the solubility and dissolution rate of poorly water-soluble drugs like Macitentan, utilizing coformers such as Saponin, Quercetin, and Glycyrrhyzic acid. Saponin emerged as the most effective in improving solubility and drug properties. Given the challenges of low solubility in BCS Class II drugs, conventional methods often come with limitations regarding cost and safety. This study advocates for herbal ingredients as safer, cost-effective alternatives due to their favorable physicochemical properties that enhance drug dissolution. The findings support the use of these natural excipients, aligning with green chemistry principles and emphasizing the need for standardization and regulatory acceptance to ensure their effectiveness in pharmaceutical applications.

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