A study on herbal ingredients to improve solubility and dissolution rate of BCS Class-II drugs

Kshitija M. Tomar*, Hemant Sawarkar, Unmesh Joshi, Kailash Biyani

[1-4] **Anuradha College of Pharmacy, Chikhali, Dist. Buldana (M.S.) 443201**

Abstract

The oral route remains the most preferred method of drug administration due to patient compliance and ease of manufacturing. However, the efficacy of oral formulations is frequently hampered by the poor aqueous solubility of the Active Pharmaceutical Ingredient (API). According to the Biopharmaceutics Classification System (BCS), Class-II drugs exhibit low solubility but high permeability, making dissolution the rate-limiting step in their absorption. While synthetic excipients have traditionally been employed to address this, there is a paradigm shift towards "Green Pharmacy"—the use of herbal ingredients. This review explores the potential of natural polymers (gums, mucilages), bio-enhancers, and natural surfactants in enhancing the solubility and dissolution rates of BCS Class-II drugs. We critically examine the mechanisms of action, including wettability improvement, amorphous transformation, and inclusion complexation, and evaluate the safety and sustainability of these herbal alternatives.

1. Introduction

1.1 The Solubility Paradox in Modern Drug Discovery

Modern combinatorial chemistry and high-throughput screening have led to a surge in new chemical entities (NCEs) with potent therapeutic activities. However, it is estimated that nearly 40% of marketed drugs and up to 90% of drugs in the development pipeline are poorly water- soluble [1, 2, 3]. This presents a significant challenge for formulation scientists: how to deliver these potent molecules effectively into the systemic circulation.

1.2 BCS Class-II Drugs: The Target

The Biopharmaceutics Classification System (BCS), introduced by Amidon et al. in 1995, categorizes drugs into four classes based on aqueous solubility and intestinal permeability.

- **Class I:** High Solubility, High Permeability
- **Class II:** Low Solubility, High Permeability
- **Class III:** High Solubility, Low Permeability

- **Class IV:** Low Solubility, Low Permeability

For BCS Class-II drugs (e.g., Ibuprofen, Griseofulvin, Ketoprofen, Glimepiride), permeation across the biological membrane is efficient, but the drug fails to dissolve rapidly enough in the gastrointestinal fluids to facilitate this permeation. Consequently, the dissolution rate becomes the rate-limiting step for bioavailability [4].

1.3 The Shift to Herbal Excipients

Traditionally, solubility enhancement has relied on synthetic polymers (e.g., PVP, HPMC) and surfactants (e.g., Tween 80). While effective, synthetic excipients often carry disadvantages such as high cost, environmental concerns during synthesis, and potential incompatibility with certain APIs. Herbal ingredients offer a compelling alternative. Derived from renewable plant sources, they are generally biocompatible (GRAS status), biodegradable, and cost-effective [5].

2. Mechanisms of Solubility Enhancement by Herbal Ingredients

To understand how herbal ingredients improve BCS Class-II drugs, one must understand the physical chemistry behind the interactions.

2.1 Amorphous Solid Dispersion

One of the most effective strategies is disrupting the crystal lattice of the drug. Crystalline drugs have high lattice energy, requiring significant energy to dissolve. Natural polymers (like guar gum or chitosan) can stabilize the drug in an amorphous state (disordered structure). The amorphous form requires less energy to dissolve, resulting in a "spring and parachute" effect where solubility spikes (spring) and the polymer prevents re-crystallization (parachute) [6].

2.2 Wettability Improvement & Surfactancy

Many herbal ingredients, particularly those containing saponins (e.g., *Glycyrrhiza glabra*), act as natural surfactants. They reduce the interfacial tension between the hydrophobic drug particle and the aqueous GI fluid [7]. This reduction in contact angle allows water to penetrate the drug powder more easily, increasing the effective surface area available for dissolution as described by the Noyes-Whitney equation.

2.3 Viscosity and Micro-Environment Modulation

Hydrophilic gums (e.g., Acacia, Tragacanth) swell upon contact with water, forming a gelatinous layer around the drug particles. While high viscosity can sometimes retard release, optimized ratios create a hydrophilic micro-environment. This layer ensures that the drug is constantly wetted and prevents the aggregation of hydrophobic drug particles [5].

3. Key Herbal Ingredients for Solubility Enhancement

3.1 Natural Polymers: Gums and Mucilages

Polysaccharides obtained from plants are the workhorses of herbal solubility enhancement.

- **Guar Gum:** Derived from *Cyamopsis tetragonolobus*, this galactomannan significantly improves dissolution rates of NSAIDs. Studies on Ibuprofen solid dispersions utilizing guar gum demonstrated superior dissolution efficiency compared to pure drug, attributed to the gum's high swelling capacity and wetting ability [8, 9].

- **Chitosan:** A cationic polysaccharide derived from crustacean shells. It interacts with anionic drugs to form complexes and improves dissolution by enhancing wettability and temporarily opening tight junctions in the intestinal epithelium [10].

- **Ocimum basilicum (Basil) Mucilage:** Recent studies have highlighted basil seed mucilage as a superior solubilizer. Research on Aceclofenac (a BCS Class-II drug) showed that solid dispersions using basil mucilage exhibited up to a 6-fold increase in solubility compared to the pure drug, outperforming some synthetic polymers [11, 12].

- **Ziziphus spina-christi Gum:** A novel polymer extracted from the Sidr tree. It has been successfully used to enhance the solubility of Loratadine via solid dispersion. The modified gum formulation showed a 51-fold increase in solubility and a significant improvement in bioavailability in animal models [13, 14].

3.2 Herbal Bio-enhancers

- **Piperine:** The alkaloid responsible for the pungency of black pepper (*Piper nigrum*). It was the first scientifically validated bio-enhancer. Shoba et al. (1998) famously demonstrated that Piperine enhances the bioavailability of Curcumin by 2000% in humans by inhibiting glucuronidation and P-gp efflux pumps [15].

- **Glycyrrhizin:** Obtained from Licorice root. It possesses strong surfactant activity due to its amphiphilic nature, aiding in the solubilization of hydrophobic antibiotics [16].

4. Techniques Utilizing Herbal Ingredients

4.1 Solid Dispersions (SD)

This is the most common technique. The drug and the herbal polymer are combined to form a eutectic mixture or amorphous suspension using Solvent Evaporation or Fusion methods. The herbal polymer intersperses between drug molecules, preventing them from re-associating into a crystal lattice [16].

4.2 Inclusion Complexes

Cyclodextrins are cyclic oligosaccharides produced from starch (natural origin) via enzymatic conversion. They form a "host-guest" relationship where the hydrophobic drug sits inside the lipophilic cavity of the cyclodextrin, while the hydrophilic outer shell ensures water solubility [17].

4.3 Herbal-Based Nanotechnology

- **Nanosuspensions:** Stabilized using natural surfactants like Acacia or Lecithin. Reducing particle size to the nanometer range increases surface area exponentially.
- **Self-Emulsifying Drug Delivery Systems (SEDDS):** Formulations using natural oils (e.g., Peppermint oil) as the lipid phase. These oils solubilize lipophilic drugs and spontaneously form fine emulsions in the gut.

5. Case Studies: Evidence from Literature

Drug (BCS Class II)	Herbal Ingredient	Technique Used	Outcome	Reference
Aceclofenac	*Ocimum basilicum* mucilage	Solid Dispersion	6-fold increase in solubility; improved wetting.	[11, 12]
Curcumin	Piperine (*Piper nigrum*)	Physical Mixture	2000% increase in bioavailability via metabolic inhibition.	[15]
Loratadine	*Ziziphus* Gum	Solid Dispersion	51-fold improvement in solubility; 6-fold bioavailablity increase.	[13]
Ibuprofen	Guar Gum	Solid Dispersion	Enhanced dissolution efficiency (DE) at 60 minutes.	[8, 9]
Glimepiride	Modified Gum Karaya	Kneading Method	Modified gum showed lower viscosity and better drug release.	[18]

6. Challenges and Limitations

Despite the "Green" appeal, herbal ingredients face specific hurdles:

1. **Standardization:** Unlike synthetic polymers (e.g., HPMC K100M) which have precise molecular weights, natural gums vary batch-to-batch depending on harvest season and geography [15].
2. **Microbial Load:** Natural gums are susceptible to bacterial and fungal growth if not properly sterilized.
3. **Viscosity Issues:** Native gums often have very high viscosity, which can sometimes retard drug release. This necessitates *modification* (e.g., carboxymethylation) of the natural gum to optimize its properties

[18].

7. Future Perspectives and Conclusion

The pharmaceutical industry is increasingly embracing sustainability. The use of herbal ingredients to improve the solubility of BCS Class-II drugs is a scientifically viable approach. Future research is steering towards Modified Natural Polymers—chemically altering natural gums to retain their biodegradability while ensuring consistent viscosity and solubility profiles. Furthermore, the integration of herbal ingredients into Nano-formulations represents the next frontier. By combining the safety of herbs with the efficiency of nanotechnology, we can unlock the full therapeutic potential of poorly soluble drugs.

8. References

1. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm Res*. 1995;12(3):413-420.

2. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. *J Pharmacol Toxicol Methods*. 2000;44(1):235-249.

3. Kalepu S, Nekkanti V. Insoluble drug delivery strategies: review of recent advances and business prospects. *Acta Pharm Sin B*. 2015;5(5):442-453.

4. Khadka P, Ro J, Kim H, et al. Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability. *Asian J Pharm Sci*. 2014;9(6):304-316.

5. Patel RP, Patel MP. A review on natural gums and mucilages in drug delivery systems. *Int J Pharm Sci*. 2011;4(1):21-27.

6. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. *Drug Discov Today*. 2007;12(23-24):1068- 1075.

7. Singh B, et al. Psyllium mucilage as a potential natural superdisintegrant for fast dissolving tablets. *J Pharm Pharmacol*. 2012;64:123-129.

8. Jambukiya VV, Parmar RB, Dudhrejiya AV. Enhancement of Solubility and Dissolution Rate of Poorly Water Soluble Drug by Using Modified Guar Gum. *Asian J Res Pharm Sci*. 2013;3(1):25-30.

9. Sahoo S, et al. Dissolution and Solubility Enhancement of Ibuprofen Using Solid Dispersion. *Int J Pharma Sci*. 2020.

10. Sinha VR, Singla AK, Wadhawan S, et al. Chitosan microspheres as a potential carrier for drugs. *Int J Pharm*. 2004;274(1-2):1-33.

11. Malviya R. Formulation and Evaluation of Aceclofenac Solid Dispersion for Improving the Solubility and Dissolution Rate. *Int J Pharm Sci Inv*. 2017;6(10):34-40.

12. Kulkarni U, et al. Safety and Pharmaceutical Evaluation of a Novel Natural Polymer, Ocicum, as Solubility and Dissolution Enhancer in Solid Dispersion. *PMC*. 2022.

13. Alwossabi AM, et al. Enhanced Oral Bioavailability and Stability Studies of Loratadine Tablets Based on Solid Dispersion of Modified Ziziphus spina-christi Gum. *Recent Adv Drug Deliv Formul*. 2024;18(3).

14. Ibrahim SRM, et al. Solubility enhancement of some poorly soluble drugs by solid dispersion using Ziziphus spina-christi gum polymer. *PubMed Central*. 2022.

15. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Med*. 1998;64(4):353-356.

16. Atal CK, et al. Scientific evidence on the role of Ayurvedic herbals on bioavailability of drugs. *J Ethnopharmacol*. 1981;4(2):229-232.

17. Brewster ME, Loftsson T. Cyclodextrins as pharmaceutical solubilizers. *Adv Drug Deliv Rev*. 2007;59(7):645-666.

18. Murali M, et al. Natural polymers: Best carriers for improving bioavailability of poorly water soluble drugs in solid dispersions. *ResearchGate*. 2020.