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A REVIEW - COMPLEXATION STRATEGIES FOR IMPROVING SOLUBILITY AND BIOAVAILABILITY OF POORLY SOLUBLE DRUGS: A FOCUS ON BCS CLASS II & IV COMPOUNDS

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ABSTRACT

The improvement in solubility is a vital challenge in the pharmaceutical development of Biopharmaceutical Classification System (BCS) Class II & IV drugs, which are characterized by low solubility, high permeability and low solubility, low permeability independently. Insufficient absorption profiles, decreased drug availability in biological system, and formulation issues caused by poor solubility, which lengthens development timelines and raises expenses. Drugs that fall under BCS Class II, faces the problem of poor solubility but the permeation is high, have a restricted rate of dissolution, which causes steady absorption as well as reduced bioavailability. Low solubility and low permeability present even more challenges for class IV drugs which can result in unpredictable absorption, intra- and inter-subject variability, and notable dietary effects, all of which might impair oral delivery. This review paper explores the different ways of complexation employed to enhance the solubility of these chemical entities, aiming on methods like cyclodextrin complexation, solid dispersions, co-crystallization and kneading method. The mechanisms of complexation techniques and their useful applications in resolving the problem of solubility are highlighted in this review. It also emphasizes the significance of solubility enhancement strategies in enhancing the therapeutic efficacy of BCS Class II and IV drugs, boosting drug delivery, and upgrade patient compliance.

KEYWORDS: BCS, Cyclodextrin, Complexation, Solubility, Stability, Bioavailability.

INTRODUCTION

The Biopharmaceutical Classification System (BCS) individuate drugs on the basis of their solubility and permeability properties. There are four categories in which drugs are divided, class I to class IV. Class II drugs of BCS have high permeability but low aqueous solubility which results in reduced oral bioavailability because their absorption depends upon dissolution in the gastrointestinal tract, as well as class IV drugs also exhibit low solubility and low permeability which causing issues with oral bioavailability.[1,2] These drugs have an excellent absorption property, beside shows less disintegration which eventually reduce their bioavailability. In vivo drug disintegration is the rate restricting high level step for retention, besides in extremely high portion numbers. These drugs have shifted bioavailability and require further developed dissolvability or disintegration to increment bioavailability. These compounds are appropriate for outlining sustained and controlled release compositions. Class II drugs typically exhibit an in vitro-in vivo association. BCS acts as a regulatory tool. It is suitable for both preclinical and clinical testing.[3]

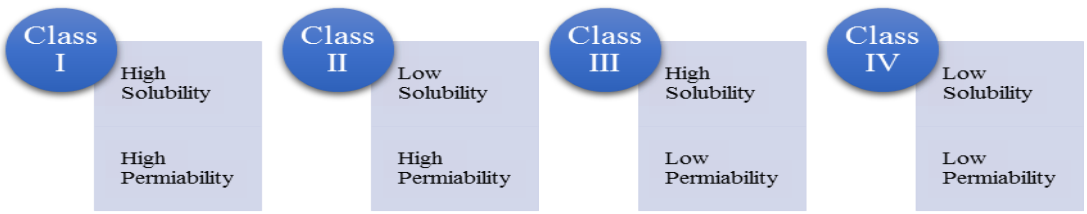

Figure 1: Biopharmaceutical Classification System.

➢ **Challenges Associated with BCS Class II & IV Drugs**

BCS Class II & IV drugs often face significant formulation challenges due to their poor solubility. This limitation can lead to inconsistent absorption profiles and reduced therapeutic effectiveness. Factors influencing solubility include:

- Molecule Size: More modest molecule sizes increase surface region and upgrade disintegration rates.
- Polymorphism: Different crystalline structures can show fluctuating solvency qualities.
- Ecological Circumstances: pH and ionic strength can altogether influence drug solubility.

BCS Class II & Class IV Drugs: These drugs show low solubility, high permeability & low solubility, low permeability respectively.[3]

- Low Bioavailability - Due to their low solubility, BCS class II drugs often have slower dissolution rates and limited bioavailability. The absorption process for Class II drugs relies predominantly on the rate at which they get dissolved in the gastrointestinal tract, making them dependent on the dissolution rate for entry into the bloodstream.
- Formulation Difficulties - The poor aqueous solubility of BCS Class II drugs results in poor oral bioavailability, which makes drug formulation development more difficult.[4]
- Poor Oral Delivery- BCS class IV drugs have problematic characteristics for effective oral delivery, such as low aqueous solubility, poor permeability, erratic and poor absorption, inter and intra subject variability and a significant positive food effect, resulting in low and variable bioavailability.[5]
- P-glycoprotein Substrates- Mostly class IV drugs are substrates for P-glycoprotein (low permeability) and CYP3A4 (extensive pre-systemic metabolism), which further increases the issue of poor therapeutic potential of these drugs.[6]

➢ **Complexation Techniques to enhancing the solubility of BCS Class II & IV drugs**

Complexation techniques have developed as effective methods for increasing the solubility of BCS Class II and IV drugs. These methods involve formation of complexes between the drug and a suitable excipient, which can improve its solubility and stability. Techniques for complexation are as follows:

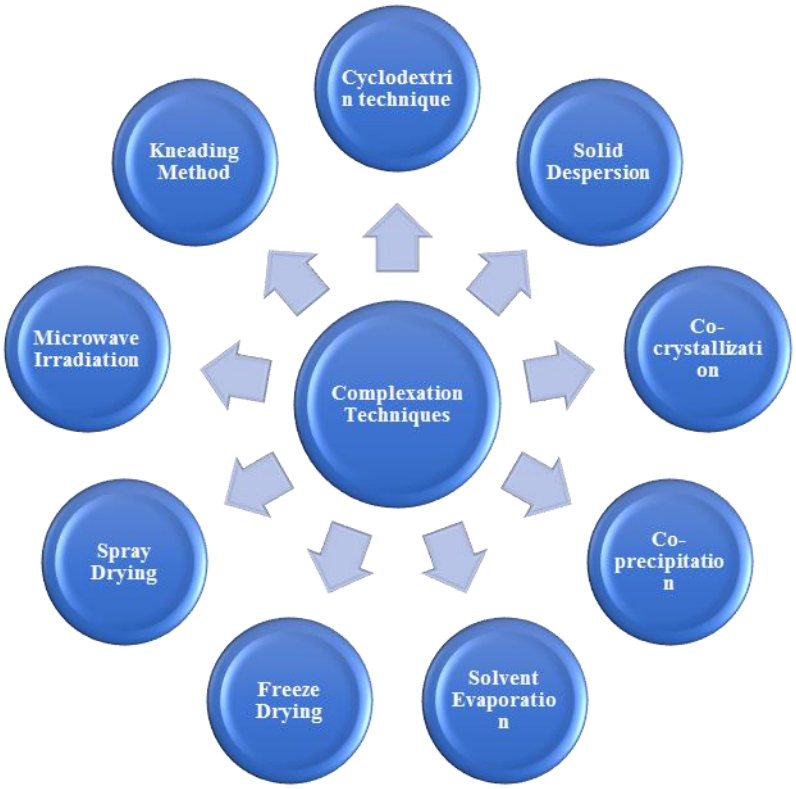

Fig. No. 2: Complexation Techniques to enhancing the solubility.

Cyclodextrin Complexation

Cyclodextrins are cyclic oligosaccharides that can form inclusion complexes with hydrophobic drug molecules. They are made up of at least six glucose units. The three main types are α-CD (six units), β-CD (seven units) and γ-CD (eight units). They have a toroidal (doughnut-shaped) structure with a hydrophilic exterior and a hydrophobic interior cavity. This allows them to form inclusion complexes with hydrophobic molecules, enhancing solubility and stability. This interaction enhances the solubility of poorly soluble drugs. Various studies have demonstrated the effectiveness of β-

cyclodextrin to improve the solubility of drugs.[7]

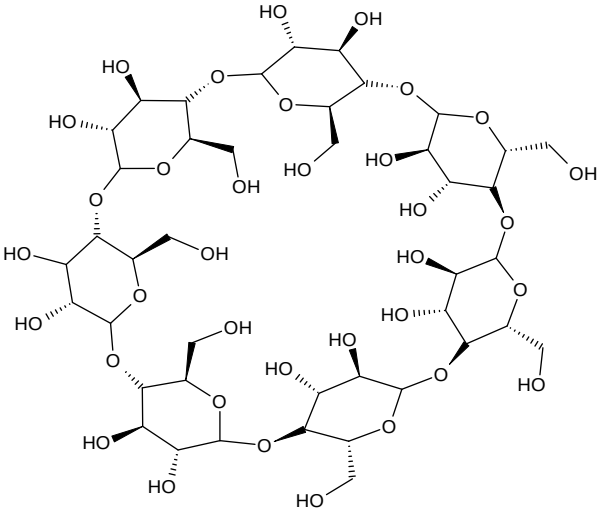

Fig. No 2. β-cyclodextrin.

Solid Dispersions

Solid dispersions involve dispersing a drug in a polymer matrix to enhance its dissolution rate. This technique can significantly increase the apparent solubility of BCS Class II & IV drugs by converting them into an amorphous form, which has higher solubility than crystalline forms. Fortunately, the most commonly used polymer matrix for solid dispersions, polyvinylpyrrolidone and hydroxypropyl methylcellulose, are known to prevent drug precipitation. The solid dispersion approach is considered a successful and commercially viable method as evidenced by various marketed solid dispersion formulations.[8,9]

Co-crystallization

Co-crystallization is another promising method where a drug is crystallized together with a co-former to create a new crystalline entity with improved solubility properties. This technique not only enhances solubility but can also modify the physicochemical properties of the drug, leading to improved bioavailability.[9]

Co-precipitation method

In this method, drug and cyclodextrin were dissolved at the desired molar ratio (1:1) in methanol: water. The drug solution was added to the cyclodextrin solution dropwise. This mixture with specified process parameters is subjected to magnetic agitation and kept away from light. The precipitate is separated by vacuum filtration and dried at room temperature to avoid water loss from the inclusion complex before being stored in sealed containers for later use.[9,10,11,12]

Solvent evaporation method

At a temperature of 25°C, the drug and solubilizing agents such as acetone were dissolved. Later, add the appropriate moles of β-cyclodextrin in hot distilled water dropwise and stir continuously for one hour. The generated complexes were filtered and vacuum-dried. The formed solid mass was then vacuum-sealed and kept in a desiccator to maintain its weight. The dried materials were removed, crushed and passed through sieve no.100 before being stored in an airtight container.[12,13,14,15]

Freeze drying technique

Lyophilization/freeze drying is a viable procedure for producing a porous, amorphous powder with a high degree of interaction between the drug and the CD. Lyophilization/freeze drying is an alternative to solvent evaporation and involves the molecular mixing of drugs and carrier in a common solvent. This procedure eliminates the solvent system from the solution by first freezing and then drying the solution containing the drugs and CD under low pressure. This process successfully converts thermolabile compounds into complex forms. The limitations of this technology are that it takes a long time to process and produces a poor flowing powder.[16]

Spray-drying method

Drug was dissolved in specific solution. The required stoichiometric amount of β-CD was dissolved in 300 ml of purified water. Solutions were mixed by sonicator for 20 min to produce a clear solution, which was then spray-dried. The conditions were: flow rate 800 ml/hour; inlet temperature 152°C; outlet temperature 85°C; air flow rate 400 NI/hour. This method is a promising technique for enhancing the solubility of BCS Class II and IV drugs. By converting drugs into amorphous forms and utilizing complexation strategies, this method can significantly improve bioavailability and therapeutic efficacy. Further research and optimization are necessary to address challenges related to thermal stability and scalability.[17,18,19]

Microwave Irradiation Method

This technique uses a microwave oven to irradiate the drug and complexing agent. In a round bottom flask, a defined proportion of water and organic solvent is used to dissolve the drug and CD in a specific molar ratio. Microwave the mixture for 1-2 minutes at 60°C. After the reaction is complete, an appropriate amount of solvent mixture is added to the above reaction mixture to eliminate any remaining uncomplexed free drug and CD. The precipitate is separated using whatman filter paper and dried in a vacuum oven at 40°C for 48 hours.[19,20]

Kneading method

This procedure involves impregnating CDs with a small amount of water or hydroalcoholic solution, which is then turned into a paste. The drug is then mixed into the aforesaid paste and kneaded for the prescribed period. The kneaded mixture is then dried and put through a sieve if necessary. In laboratory scale kneading can be achieved by using a mortar and pestle & in large scale the kneading can be done by utilizing the extruders and other machines. This is the most frequent and straightforward method for preparing inclusion complexes, with a very cheap manufacturing cost.

The kneading method is widely recognized for its effectiveness in enhancing drug solubility, particularly for poorly soluble drugs. Here are the main advantages of using this technique:

1. Improved Drug-Carrier Interaction
Kneading allows for intimate mixing of the drug with a hydrophilic carrier, which enhances their interaction. This close contact helps to create a more uniform distribution of the drug within the carrier matrix, leading to improved solubility and dissolution rates.

2. Versatility with different Carriers
Kneading can be effectively used with a variety of hydrophilic carriers, such as poloxamers and polyvinyl pyrrolidone (PVP). This versatility allows formulators to select appropriate carriers that can optimize drug solubility based on specific drug characteristics.[21]

3. Amorphization of Drug Crystals
The kneading process can transform crystalline drugs into amorphous forms. Amorphous materials are generally more soluble than crystalline materials because they do not require energy to break a crystal lattice during dissolution. This change considerably increases the surface area available for dissolution, therefore improving the solubility and bioavailability.[21,22]

4. Enhanced Wettability and Dissolution Rate
Kneading improves the wettability of drug particles, which is crucial for dissolution. Increased wettability allows solvents to penetrate drug particles more effectively, resulting in faster dissolution rates. Studies have shown that solid dispersions prepared through kneading exhibit superior dissolution profiles compared to those produced by other methods.[23]

5. Cost-Effectiveness and Simplicity
The kneading method is relatively simple and cost-effective compared to more complex techniques like spray drying or hot melt extrusion. It requires minimal equipment and can be performed with readily available materials, making it accessible for various pharmaceutical applications.[24]

6. Scalability
The kneading method can be easily scaled up for industrial production, making it suitable for commercial applications. Its straightforward nature allows for efficient production processes without significant changes in methodology.[25]

The kneading method's ability to enhance drug-carrier interactions, promote amorphization, improve wettability, along with its cost-effectiveness and versatility make it a preferred choice for enhancing the solubility of BCS Class II and IV drugs compared to other complexation methods.

➢ **Factors to be considered in Complexation**

1. Nature of the Drug and Complexing Agent

- Polarity and Size: The polarity and molecular size of both the drug and the complexing agent are crucial. A good match between the hydrophobicity/hydrophilicity of the drug and the complexing agent can lead to better solubility outcomes. For example, cyclodextrins, which are cyclic oligosaccharides, can form inclusion complexes with hydrophobic drugs, enhancing their solubility in aqueous environments.[26,27]
- Chemical Properties: The chemical structure and functional groups of both the drug and complexing agent can affect their interaction. Drugs that can ionize or form hydrogen bonds are often more amenable to complexation.[28]

2. Type of Complexation

- Inclusion Complexes: These involve a drug being encapsulated within a host molecule (e.g., cyclodextrins). This method has been shown to significantly improve solubility by allowing poorly soluble drugs to dissolve more readily in water.[25,27]
- Cocrystals: These are formed by combining a drug with an inactive pharmaceutical ingredient (conformer), which can enhance solubility without altering the drug's pharmacological properties.[27]
- Coordination Complexes: Metal ions interact with the medication in these complexes, potentially increasing solubility through a variety of ways, including changes to the drug's electrical characteristics.[28]

3. Physical Characteristics

- Particle Size: Reducing a drug's particle size can increase its surface area and wettability, leading to enhanced dissolution rates. This is particularly important for drugs that are poorly soluble in their crystalline forms.
- Amorphous vs. Crystalline State: Converting drugs from a crystalline state to an amorphous state can significantly enhance solubility due to higher energy levels in amorphous forms.[28]

4. Stability Considerations

- Thermodynamics of Complex Formation: Understanding the stability constants associated with complex formation is essential. A more stable complex typically indicates better solubility enhancement due to favorable thermodynamic interactions between the drug and complexing agent.

➢ **Purpose of Solubility and Dissolution Rate Enhancement**

The purpose of enhancing solubility and dissolution rates for BCS Class II and IV drugs is primarily to improve their bioavailability, which is crucial for effective therapeutic outcomes. As BCS (Biopharmaceutical Classification System) Class II and IV drugs are characterized by low solubility but high permeability and

low permeability respectively, meaning that their absorption in the gastrointestinal tract is limited by their solubility rather than their permeability.

Importance of Solubility and Dissolution Rate Enhancement

1. Bioavailability Improvement

Poorly soluble drugs often exhibit low bioavailability due to insufficient dissolution in gastrointestinal fluids. By enhancing solubility, the amount of drug available for absorption increases, leading to higher bioavailability and therapeutic efficacy.[29]

2. Overcoming Formulation Challenges

Drug formulation can be complicated by low solubility, which can result in longer development times and higher costs. Improving solubility facilitates more effective drug development procedures by reducing these difficulties.

3. Patient Compliance

Drugs with low solubility may require higher doses or frequent administration to achieve therapeutic levels, which can burden patients. Improving solubility allows for lower doses and potentially less frequent dosing, enhancing patient adherence to treatment regimens.[30]

Fig. No. 3. Analytical techniques to confirm drug complexation.

- **Analytical techniques to confirm drug complexation include**
- **Spectroscopic Techniques:** These are useful in characterizing drug-cyclodextrin inclusion complexes. Spectroscopic methods include NMR (Nuclear Magnetic Resonance) which can show the interaction between the drug and cyclodextrin.[31] Aromatic protons in the drug can show a significant up-field shift due to the presence of cyclodextrin, and the hydroxyl group of cyclodextrin also contributes to complex formation.
- **Thermal Analysis:** Differential Scanning Calorimetry (DSC) is used to study the thermal behavior of drug complexes. Cyclodextrins can cause new peaks to appear or cause shifting, broadening or diminishing of some peaks. In some instances when a drug is complexed with β-CD, the endothermic peak of the drug may vanish entirely in the inclusion complex.
- **Fourier Transform Infrared Spectroscopy (FTIR):** FTIR spectroscopy works by measuring the absorption of infrared radiation by a sample. Molecules absorb IR light at specific frequencies, which correspond to the vibrational energies of their bonds. The resulting spectrum, a plot of absorption versus frequency, acts as a unique fingerprint for the molecule. FTIR is used to confirm chemical interactions by analyzing functional groups before and after complexation & it can observe shifts in absorption bands that suggest interactions such as hydrogen bonding or van der Waals forces.
- **Powder X-Ray Diffraction (PXRD):** It operates on the principle of X-ray diffraction, where a beam of X-rays is directed at a powdered sample. The X-rays

interact with the orderly arrangement of atoms in the crystal lattice, leading to constructive interference at specific angles. PXRD is a valuable technique for quick recognition of new crystalline phases in the solid state, delivering evidence for the existence of crystalline forms of drugs and disclosing the probable organization of molecules.

- **Scanning Electron Microscopy (SEM):** SEM is used to observe the morphology of drug particles or cocrystals. By comparing SEM images of the drug before and after complexation, changes in particle size, shape and surface texture can be observed. A significant alteration in these characteristics often indicates successful complex formation.
- **Molecular Docking:** Docking approaches can examine the attachment behavior of a drug with cyclodextrin. Molecular docking serves as an invaluable tool in predicting and understanding the complexation behavior between drugs and cyclodextrins. By providing insights into binding affinities and interaction mechanisms, this approach aids in designing formulations that significantly enhance drug solubility and bioavailability. The integration of molecular docking with experimental validation further strengthens its applicability in pharmaceutical development.
- **Particle Size Analysis:** The particle size of drug complexes can be measured, with changes indicating complex formation. Particle size analysis plays a crucial role in confirming the formation of drug-cyclodextrin complexes that enhance solubility. Various analytical technique like Laser Diffraction, Dynamic Light Scattering, Microscopy Techniques, Sieve Analysis used to measure changes in particle size before and after complexation. Due to this, researchers can gain valuable insights into the efficiency and effectiveness of these formulations. The relationship between particle size reduction and improved solubility underscores the importance of optimizing this parameter in pharmaceutical development.[32]

➢ **Stability and Apparent Solubility**

Stability and apparent solubility are critical concepts in the pharmaceutical evaluation of drugs, particularly for those classified under the Biopharmaceutical Classification System (BCS) Class II and Class IV categories.

- **Stability**

Stability refers to the ability of a drug to maintain its physical and chemical properties over time. In the context of drug formulation, stability is essential to ensure that the drug remains effective and safe for throughout its shelf life. Stability can be influenced by various factors, including temperature, humidity, light exposure and the presence of other substances.

For drug complexes, stability is often quantified using a stability constant ($K_{m:n}$), which indicates the affinity between the drug and the complexing agent (e.g., cyclodextrins). A higher stability constant suggests a stronger interaction, which can enhance the drug's solubility and bioavailability.[33,34]

Factors Affecting Stability

1. Temperature: Higher temperatures can accelerate degradation or dissociation of the complex.
2. Humidity: Moisture can affect the physical state and interaction between the drug and cyclodextrin.
3. Light: Some drugs are photosensitive and light exposure can cause degradation, impacting the complex's integrity.
4. Drug-Cyclodextrin Ratio: The molar ratio influences complex formation and stability. An optimized ratio maximizes complexation and minimizes free drug or cyclodextrin.
5. Method of Preparation: The complexation method (e.g., kneading, co-precipitation, spray drying) can affect the solid-state properties and consequently the stability of the complex.

- **Apparent Solubility**

Apparent solubility is a measure of how much of a drug can dissolve in a given volume of solvent under specific conditions. It is influenced by factors such as pH, temperature and the presence of solubilizing agents. For poorly soluble drugs, enhancing apparent solubility is crucial for improving their absorption in the gastrointestinal tract.

The relationship between solubility and stability can be represented through phase-solubility diagrams, which help in understanding how different concentrations of complexing agents affect the solubility of drugs.[35]

Table 1: Methods of solubility and stability Parameters.

Parameter	Method	Information Gained
Stability	Accelerated Stability Studies	Predicted shelf life under stress conditions
	Real-Time Stability Studies	Actual stability under recommended storage conditions
Apparent Solubility	Phase Solubility Studies	Solubility of the drug in the presence of cyclodextrin, stability constant, stoichiometry
	UV-Vis Spectroscopy	Concentration of dissolved drug in complex
	HPLC	Accurate quantification of the drug concentration

Both stability and apparent solubility are vital for the formulation of BCS Class II and IV drugs. Effective complexation strategies can significantly enhance their bioavailability by improving their solubility and maintaining stability throughout their shelf life.

CONCLUSION

Enhancing the solubility of Biopharmaceutical Classification System (BCS) Class II and IV drugs remains a critical challenge in pharmaceutical development due to their inherent low solubility and, in the case of Class IV drugs, low permeability. This review has highlighted several complexation techniques, including cyclodextrin complexation, solid dispersions, co-crystallization, co-precipitation and the kneading method, as effective strategies to improve the solubility and, consequently, the bioavailability of these drugs. These methods facilitate enhanced dissolution rates and can lead to improved therapeutic efficacy. Factors such as the nature of the drug and complexing agent, the type of complexation, physical characteristics, and stability considerations all play a crucial role in the success of these techniques. While each approach offers unique advantages, the kneading method stands out for its simplicity, cost-effectiveness, and scalability. Ultimately, the application of these complexation techniques, tailored to the specific properties of the drug, holds significant promise for overcoming the limitations associated with BCS Class II and IV drugs, leading to better drug products and improved patient outcomes.

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