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Review Article

Cyclodextrin-Based Inclusion Complex as a Solubility Enhancement Technique: A Comprehensive Review

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ABSTRACT

Solubility enhancement is a crucial challenge in pharmaceutical formulation, especially for poorly water-soluble drugs that belong to BCS Class II and IV. Inclusion complexation has emerged as a promising strategy to overcome solubility and bioavailability limitations. Cyclodextrins, the most widely used host molecules, form non-covalent complexes with hydrophobic drugs, improving their aqueous solubility, chemical stability, and dissolution rate. This review highlights the fundamental principles of inclusion complexation, types of cyclodextrins, preparation methods, and characterization techniques. Recent advancements in modified cyclodextrins and novel excipient-based delivery systems are also discussed. Inclusion complexes continue to play a vital role in modern drug delivery due to their safety, versatility, and efficacy.

INTRODUCTION

Solubility is one of the most critical parameters influencing the rate and extent of drug absorption, and consequently, its therapeutic effectiveness. A significant proportion of newly discovered chemical entities (NCEs), particularly those classified under the Biopharmaceutics Classification System (BCS) Class II and Class IV, exhibit poor aqueous solubility [1, 2]. This inherent limitation not only affects their oral bioavailability but also poses substantial challenges in the design and development of effective dosage forms. Therefore, improving the solubility and dissolution behavior of such drugs has become a focal point in modern pharmaceutical research. Several strategies have been explored to enhance the solubility of poorly water-soluble drugs, including particle size reduction, solid dispersions, salt formation, nanosuspension technology, use of surfactants, and complexation techniques [5,6,]. Among these,

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inclusion complexation—particularly with cyclodextrins—has emerged as a versatile and widely accepted method due to its simplicity, efficacy, and regulatory acceptance [3,5]. Cyclodextrins are cyclic oligosaccharides composed of α-D-glucopyranose units connected via α-1,4 glycosidic bonds. Their unique structure, comprising a hydrophobic central cavity and a hydrophilic outer surface, allows them to form non-covalent host–guest inclusion complexes with a wide range of hydrophobic drug molecules. This molecular encapsulation alters the solubility profile of the guest molecule, enhances its chemical stability, and often masks undesirable organoleptic properties such as bitterness or odor [1,3]. This review aims to provide a comprehensive understanding of inclusion complexation as a solubility enhancement technique. It explores the fundamental principles of inclusion complex formation, the various types of cyclodextrins and their derivatives, methods of complex preparation, analytical characterization techniques, and practical applications in formulation development [13]. Furthermore, it highlights recent advancements, the role of novel excipients, and the potential of inclusion complexes in overcoming solubility barriers in pharmaceutical development [7].

1.1Overview of Solubility Enhancement Techniques

Physical Modification Techniques

Physical modification techniques are among the most commonly employed strategies for enhancing the solubility and dissolution rate of poorly water-soluble drugs. These methods primarily aim to increase the surface area of drug particles, improve wettability, and alter the solid-state characteristics of the drug to improve its solubility profile [5,6].

a. Particle Size Reduction (Micronization/Nanonization):

Reducing the particle size of a drug increases its surface area, leading to a faster dissolution rate as per the Noyes–Whitney equation. This technique is especially effective for drugs with poor aqueous solubility [5]. Commonly used methods include jet milling, ball milling, and high-pressure homogenization. While micronization reduces particles to the micrometer range, nanonization can bring them down to the nanometer scale, further improving dissolution and absorption [6].

b. Solid Dispersion:

Solid dispersion involves dispersing a poorly soluble drug into a hydrophilic carrier matrix such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), or hydroxypropyl methylcellulose (HPMC). This approach enhances solubility by improving drug wettability and often converting the drug from a crystalline to an amorphous state, which possesses higher free energy and solubility [5,6]. Techniques used for preparing solid dispersions include melting (fusion method), solvent evaporation, and spray drying.

c. Cryogenic Techniques:

Cryogenic techniques involve rapidly freezing a solution or suspension of the drug with a carrier, followed by lyophilization (freeze-drying). This process results in the formation of porous structures with a large surface area, which significantly enhances the solubility and dissolution rate of the drug [7]. Cryogenic methods are particularly useful for heat-sensitive drugs and can also help in preserving the amorphous nature of the formulation.

Overall, physical modification techniques are simple, scalable, and effective in improving the solubility and bioavailability of hydrophobic drug

molecules. However, factors such as stability, reproducibility, and scalability need to be carefully considered during formulation development [6].

2. Chemical Modification Techniques

Chemical modification techniques aim to enhance the solubility of poorly water-soluble drugs by altering their molecular interactions or forming new molecular entities without compromising their pharmacological activity [5].

a. Salt Formation:

Salt formation is one of the most established and widely used techniques for improving the solubility of ionizable drugs. By converting a drug into its salt form, its ionic nature is modified, leading to better aqueous solubility and faster dissolution [6]. However, a key limitation is that not all drugs possess ionizable functional groups, making them unsuitable for salt formation.

b. Co-crystallization:

Co-crystallization involves the formation of a crystalline complex between the active pharmaceutical ingredient (API) and a pharmaceutically acceptable co-former. These co-crystals are held together by non-covalent interactions such as hydrogen bonding, resulting in a new crystalline material with improved solubility and physical stability [5,14]. Unlike salt formation, co-crystallization does not require the drug to be ionizable, and it preserves the solid-state form of the drug.

c. Complexation:

Complexation is based on the formation of non-covalent molecular complexes between the drug and a complexing agent. One of the most effective and widely used complexing agents is cyclodextrin, which forms inclusion complexes by trapping the drug molecule within its hydrophobic cavity [1, 3]. This inclusion alters the drug's physicochemical properties, resulting in improved aqueous solubility, chemical stability, and taste masking [10]. Cyclodextrin-based inclusion complexes are generally safe, regulatory-approved, and compatible with various dosage forms [13].

3. Miscellaneous Approaches

Apart from physical and chemical modifications, several other innovative and supportive techniques are employed to enhance the solubility of poorly water-soluble drugs. These miscellaneous approaches are often used alone or in combination with other methods to achieve better drug solubilization, improved bioavailability, and formulation flexibility [7, 10].

a. Use of Surfactants:

Surfactants are amphiphilic compounds that reduce the surface tension between drug particles and the dissolution medium, thereby enhancing drug wettability and dispersion [6]. Common pharmaceutical surfactants include polysorbates (e.g., Tween 80), sodium lauryl sulphate (SLS), and Cremophor EL.

b. Use of Co-solvents:

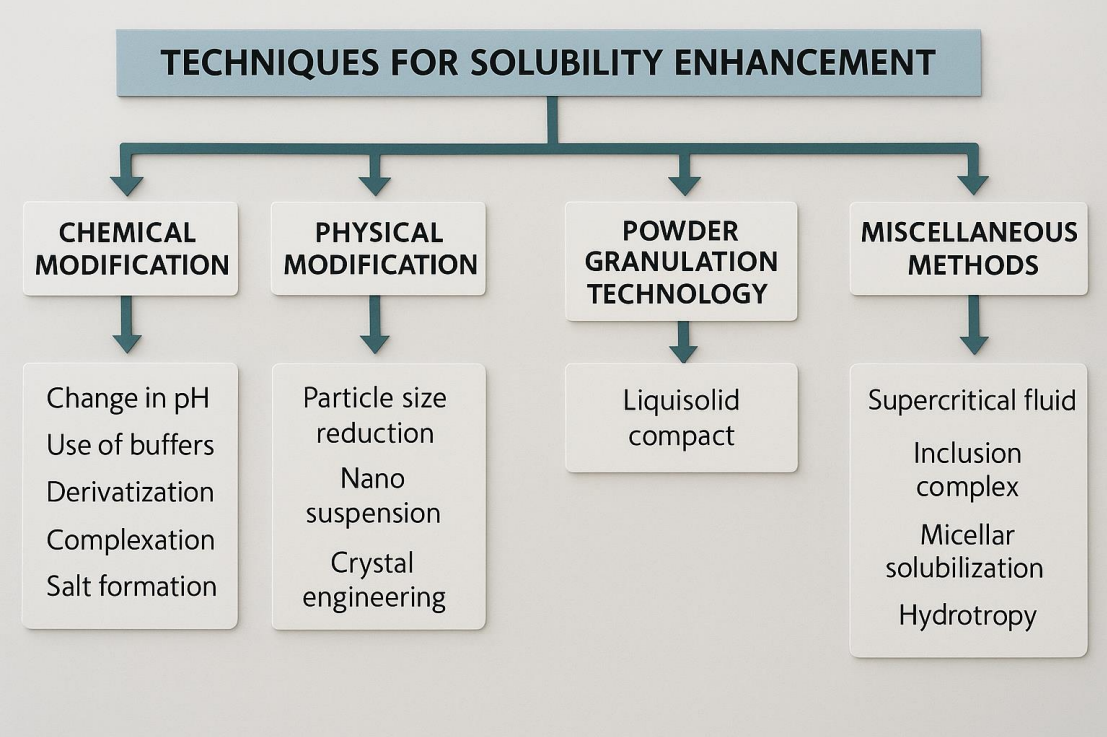
Co-solvent systems are effective in dissolving poorly soluble drugs by altering the polarity of the solvent environment [5]. Co-solvents such as ethanol, propylene glycol, and polyethylene glycol 400 (PEG 400) improve solubility by reducing interfacial tension and enhancing drug-solvent interaction.

c. Lipid-Based Formulations:

Lipid-based drug delivery systems, including self-emulsifying drug delivery systems (SEDDS), nano

emulsions, and liposomes, have shown great potential in enhancing the solubility and absorption of hydrophobic drugs [14, 19]. These systems promote lymphatic transport and bypass hepatic first-pass metabolism.

d. Supercritical Fluid Technology: This emerging technique utilizes supercritical carbon dioxide (CO_2) to produce nano- or microparticles with improved solubility and dissolution [19]. It allows precise control over particle size and is eco-friendly and residue-free, making it suitable for thermolabile substances. These approaches offer diverse, flexible, and efficient solutions for formulation challenges associated with poor solubility in drug development [10,13].



1.2 Importance of Solubility

Solubility is a fundamental property that plays a crucial role in the development and effectiveness of pharmaceutical drug products. It directly affects the absorption, distribution, metabolism, and excretion (ADME) of a drug, especially when administered through the oral route [1, 2]. For a drug to be therapeutically effective, it must first dissolve in the aqueous fluids of the gastrointestinal tract before it can be absorbed into systemic circulation. Hence, solubility is often the rate-limiting step in the absorption of poorly water-soluble drugs [3, 5]. A significant proportion of newly discovered drugs exhibit poor water solubility, which limits their oral bioavailability and therapeutic efficacy [13]. According to the Biopharmaceutics Classification System (BCS), many drugs belong to Class II and Class IV, where solubility is a major challenge [14]. These drugs, despite having good permeability, show low or inconsistent absorption due to inadequate dissolution in gastrointestinal fluids [10]. This results in higher doses being required to achieve the desired therapeutic effect, potentially leading to side effects, increased formulation costs, and poor patient compliance [6, 7]. Enhancing solubility can bring several formulation and therapeutic advantages, including improved bioavailability, reduced dose frequency,

rapid onset of action, and better patient adherence [6]. It also facilitates the development of various dosage forms such as tablets, capsules, suspensions, and injectables [14]. From a manufacturing perspective, improving solubility early in the drug development process can reduce formulation failures, accelerate clinical trials, and enhance the commercial success of a pharmaceutical product [12, 13]. Therefore, understanding and optimizing solubility is essential in modern drug development. Various techniques such as particle size reduction, solid dispersion, salt formation, complexation, and lipid-based formulations are routinely employed to overcome solubility-related challenges [5, 6, 10]. Among these, inclusion complexation with cyclodextrins has gained particular importance due to its efficiency, simplicity, and regulatory acceptance [1,3]. In conclusion, solubility is not merely a physical property but a key determinant of a drug's performance, making its enhancement a central objective in the formulation of poorly soluble drugs.

1.3 Need of Solubility

The solubility of a drug substance is a critical factor in determining its therapeutic effectiveness, particularly in orally administered formulations [2, 14]. For a drug to be absorbed through the gastrointestinal tract and reach systemic circulation, it must first dissolve in the surrounding biological fluids [3, 6]. Therefore, adequate solubility is essential to ensure that the drug becomes available at the site of absorption in sufficient concentrations [5]. In recent years, a growing number of newly developed drug candidates have exhibited poor aqueous solubility, limiting their bioavailability and clinical efficacy [13]. According to scientific reports, nearly 40–60% of new chemical entities (NCEs) fall under this category [7, 14]. These poorly soluble drugs often lead to inconsistent drug absorption, delayed onset of action, and the need for higher doses, which can increase the risk of toxicity and reduce patient compliance [6, 10]. The need to improve solubility arises from both therapeutic and pharmaceutical perspectives. From a therapeutic standpoint, solubility enhancement helps in achieving desired plasma drug concentrations more rapidly and consistently [5, 6]. From a formulation and manufacturing perspective, it enables the development of stable, effective, and patient-friendly dosage forms such as tablets, capsules, oral suspensions, and injectables [12, 14]. Moreover, regulatory bodies like the FDA and EMA stress the importance of solubility during the early stages of drug development, as it impacts formulation design, selection of excipients, process optimization, and overall product performance [13]. In light of these challenges, it becomes essential to adopt appropriate solubility enhancement strategies such as particle size reduction, salt formation, solid dispersion, lipid-based systems, and inclusion complexation to overcome formulation hurdles and ensure the success of pharmaceutical products [5, 6]

2.Inclusion Complexation: An Overview

Inclusion complexation is a widely studied and applied technique in pharmaceutical sciences for enhancing the solubility, stability, and bioavailability of poorly water-soluble drugs. It involves the formation of a non-covalent complex between two or more molecules, where one molecule (the host) forms a cavity into which the other molecule (the guest) can fit partially or fully. Among the various host molecules, cyclodextrins (CDs) are most commonly used in pharmaceutical inclusion complexes due to their unique molecular structure and biocompatibility. [3,4]

2.1 Concept of Inclusion Complex

An inclusion complex is a type of molecular complex formed when a guest molecule (such as a drug) is physically entrapped within the cavity of a host molecule without the formation of any covalent bonds. Cyclodextrins are cyclic oligosaccharides composed of glucose units arranged in a truncated cone shape, possessing a hydrophobic internal cavity and a hydrophilic outer surface. This unique arrangement allows them to accommodate lipophilic drug molecules inside their cavity, enhancing their aqueous solubility and masking undesirable properties like bitterness or odor. The driving forces behind inclusion complex formation include van der Waals forces, hydrogen bonding, hydrophobic interactions, and dipole–dipole interactions. The formation of an inclusion complex is typically reversible and does not chemically alter the drug molecule, making it a safe and effective method for improving drug delivery profiles. [8,9]

2.2 Mechanism of Action

The mechanism of inclusion complexation relies on the host–guest interaction between the drug and the cyclodextrin. When a poorly water-soluble drug is introduced to an aqueous solution containing cyclodextrin, the hydrophobic part of the drug molecule enters the central cavity of the cyclodextrin due to hydrophobic interactions, thereby forming a stable complex.

This inclusion into the cavity leads to:

- Improved aqueous solubility of the drug, as the external hydrophilic portion of the cyclodextrin allows the complex to dissolve in water.
- Enhanced chemical and physical stability, as the drug is shielded from environmental factors such as light, heat, and oxidation.
- Taste masking, by preventing direct interaction of bitter-tasting drugs with taste receptors.

Furthermore, the equilibrium between the free drug and the complex allows for controlled and sustained release, making inclusion complexes beneficial in both immediate and modified-release formulations. The success of inclusion complexation depends on the size compatibility between the host cavity and the guest molecule, as well as the thermodynamic stability of the complex. Modified cyclodextrins (e.g., hydroxypropyl-β-CD, sulfobutyl ether-β-CD) have been developed to improve solubility, safety, and complexation efficiency for various drug molecules. [10,11]

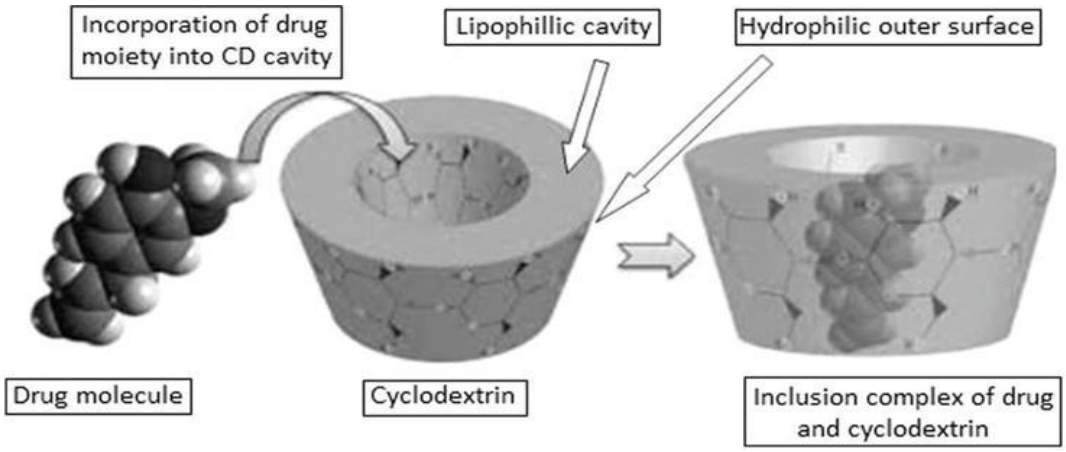


Fig. Mechanism of Action of inclusion complex

3.Methods of Preparation of Inclusion Complexes

Inclusion complexes are commonly prepared through a variety of techniques that facilitate non-covalent interactions between a guest molecule (usually a poorly soluble drug) and a host molecule (commonly cyclodextrin). The method chosen impacts the efficiency, yield, stability, and scalability of the final formulation. The following are the most prominent and effective methods: [11,12]

3.1 Kneading Method

The kneading method is one of the most conventional and straightforward techniques used for the preparation of inclusion complexes. In this method, a molar equivalent of cyclodextrin is mixed with a small amount of water or a hydroalcoholic solution to form a paste. The drug is then gradually incorporated into this paste, and the mixture is thoroughly kneaded using a mortar and pestle or mechanical kneader for about 30 to 60 minutes. Adequate consistency is maintained by periodically adding small amounts of solvent. Once kneading is complete, the paste is dried in a hot air oven or vacuum dryer at a temperature range of 40–50°C. The dried mass is pulverized and sieved to obtain a uniform powdered inclusion complex, which is then stored in a desiccator. This method enhances molecular contact between the host and guest molecules, thereby promoting effective complexation. However, it is generally limited to small-scale or laboratory applications due to its manual and time-consuming nature. [13,14]

3.2 Co-precipitation Method

The co-precipitation technique involves the separate dissolution of the drug and cyclodextrin in suitable solvents—typically, water for cyclodextrin and an organic solvent such as ethanol or methanol for the drug, especially if it is poorly water-soluble. The drug solution is slowly added to the cyclodextrin solution with continuous stirring to allow for molecular interaction and complex formation. [11,12] The inclusion complex is precipitated by either cooling the solution, evaporating the solvent, or adding a non-solvent like ethanol or acetone to reduce solubility. The precipitate is then filtered, washed with cold water or non-solvent to remove uncomplexed drug, and dried at 40–50°C. The final dried mass is ground and sieved to yield a fine inclusion complex powder. This method provides good inclusion efficiency and is particularly useful when the drug and cyclodextrin exhibit differing solubility profiles. However, solvent handling and complete removal are critical factors that need careful optimization.

3.3 Spray Drying Method

Spray drying is a modern and industrially scalable method for inclusion complex formation. It involves the preparation of a clear solution or suspension containing the drug and cyclodextrin in water, ethanol, or a mixture of both. The solution is filtered to eliminate any particulate matter and then introduced into a spray dryer equipped with a suitable atomizer. The atomized solution forms fine droplets that are instantly dried by a stream of hot air, typically at inlet temperatures of 100–150°C and outlet temperatures of 40–80°C. The resulting dry particles are collected in a cyclone separator and stored in air-tight containers or desiccators. This method produces uniform, amorphous particles with enhanced solubility and dissolution properties. However, it may not be suitable for thermolabile drugs due to the exposure to elevated temperatures during the drying process. [14,15]

3.4 Freeze Drying (Lyophilization)

Freeze drying is particularly suited for heat-sensitive or unstable drugs. In this method, an aqueous solution of the drug and cyclodextrin is prepared and filtered to remove insoluble impurities. The solution is then frozen rapidly at low temperatures ranging from −40°C to −80°C. Once frozen, the material is subjected to lyophilization under reduced pressure, where the ice sublimates directly into vapor without passing through the liquid phase. This results in a dry, porous matrix of the inclusion complex. The product is then ground into a fine powder and stored in moisture-proof containers. Freeze drying yields highly stable and porous inclusion complexes with superior dissolution rates. Nevertheless, the process is time-intensive and cost-prohibitive, which can limit its use in large-scale manufacturing. [15,16]

3.5 Other Emerging Methods

Recent advancements in pharmaceutical technology have led to the development of innovative and more efficient techniques for inclusion complexation:

- **Supercritical Fluid Method:** This eco-friendly approach uses supercritical CO_2 as a solvent or anti-solvent. The drug and cyclodextrin are dissolved in a suitable organic solvent and introduced into a high-pressure CO_2 chamber. Upon solvent removal under supercritical conditions, fine particles of the inclusion complex are formed and collected. This method produces high-purity complexes without residual solvents.

- **Microwave Irradiation:** This technique uses microwave energy to accelerate the interaction between the drug and cyclodextrin. A physical mixture is moistened with minimal solvent and exposed to controlled microwave heating, resulting in a rapid and efficient formation of inclusion complexes.

- **Ultrasonication (Sono chemical Method):** In this method, ultrasonic waves are used to enhance the mixing and interaction of the drug and cyclodextrin dissolved in a solvent. The process typically lasts 15–60 minutes, after which the solvent is removed by evaporation or freeze drying.

- **Hot Melt Extrusion:** This solvent-free technique involves physical blending of the drug and cyclodextrin followed by processing through a heated extruder. The mixture is exposed to high temperature and shear, producing a homogenous inclusion complex in the form of extrudates, which are then cooled, milled, and sieved.

These emerging methods offer improved reproducibility, efficiency, and scalability, making them increasingly relevant for both research and commercial pharmaceutical development. [26,25]

4.Characterization Techniques for Inclusion Complexes

To confirm the formation of inclusion complexes and understand the physicochemical modifications involved, various analytical techniques are employed. These characterization methods provide insights into molecular interactions, crystallinity changes, thermal behavior, and surface morphology. The following are key techniques used to evaluate inclusion complexes: [10,11]

Fourier Transform Infrared Spectroscopy (FTIR):

FTIR is a widely used tool to detect interactions between the drug and cyclodextrin at the molecular level. Inclusion complexation often

leads to changes in the vibrational frequencies of functional groups, which can be observed as shifts, reductions, or disappearance of characteristic peaks in the infrared spectra. Comparing the FTIR spectra of the pure drug, cyclodextrin, their physical mixture, and the inclusion complex can reveal evidence of hydrogen bonding or encapsulation, confirming the formation of the complex.

Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA): DSC provides information about the thermal transitions of substances, such as melting, crystallization, or glass transition temperatures. In the case of inclusion complexes, the melting peak of the drug may disappear or shift, indicating reduced crystallinity or amorphous transformation due to complexation. TGA complements DSC by measuring the weight loss of the sample as a function of temperature, offering data on moisture content, thermal stability, and degradation patterns. Together, DSC and TGA help assess the physical state and thermal behavior of the complex.

X-ray Diffraction (XRD): XRD is an essential technique to evaluate the crystalline nature of substances. Pure drugs usually exhibit sharp, well-defined peaks in the diffractogram due to their crystalline structure. Upon inclusion with cyclodextrins, these peaks may reduce in intensity or disappear, suggesting a loss of crystallinity or conversion to an amorphous state. This change in diffraction pattern serves as clear evidence of inclusion complex formation and distinguishes it from mere physical mixtures.

Scanning Electron Microscopy (SEM): SEM is used to study the surface morphology and structural features of the inclusion complex. It provides high-resolution images that reveal changes in particle size, shape, and texture. The inclusion complex typically shows a more irregular or amorphous surface compared to the distinct crystalline structure of the pure drug. Morphological differences between the raw materials and the final complex further confirm the successful formation of inclusion complexes. In conclusion, a combination of these techniques—FTIR, DSC/TGA, XRD, and SEM—offers comprehensive evidence of inclusion complexation. They validate the physical and chemical transformations that enhance the solubility, stability, and bioavailability of poorly water-soluble drugs.

5.Applications of Inclusion Complexes in Drug Delivery

Inclusion complexes have emerged as a powerful approach in pharmaceutical sciences to overcome various challenges associated with drug formulation and delivery. By encapsulating drug molecules within the cavity of cyclodextrins or other host molecules, inclusion complexes significantly enhance the physicochemical properties of the active pharmaceutical ingredient (API), particularly solubility, stability, and bioavailability. Their applications span across multiple drug delivery systems, as detailed below**:** [22,23]

1 Solubility and Dissolution Enhancement

One of the most prominent applications of inclusion complexes is in enhancing the aqueous solubility and dissolution rate of poorly water-soluble drugs. Cyclodextrins form water-soluble inclusion complexes that can convert crystalline drugs into amorphous forms, improving their bioavailability. This has been widely applied in the formulation of antifungal, antiviral, and anticancer drugs with low intrinsic solubility.[23,24]

2 Stability Improvement

Inclusion complexes protect labile drugs from degradation caused by environmental factors such as heat, light, humidity, and oxidation. Encapsulation within a cyclodextrin cavity can shield sensitive functional groups, thereby prolong the shelf life of the drug and enhance its chemical and thermal stability.

3 Taste and Odor Masking

Unpleasant taste and odor are major barriers in pediatric and geriatric formulations. Inclusion complexes are effective in masking the bitter taste and offensive odor of certain drugs by preventing their interaction with taste buds and olfactory receptors, thereby improving patient compliance.

4 Controlled and Sustained Release

Modified cyclodextrin-based complexes can be used to achieve controlled or sustained drug release. The complexation affects the drug's release profile by modulating its solubility and diffusion, making it suitable for extended-release formulations and targeted drug delivery.

5 Enhancement of Permeability and Absorption

Inclusion complexes, especially with modified cyclodextrins, can improve the permeability of drugs across biological membranes. This is particularly beneficial in enhancing the oral bioavailability of Biopharmaceutical Classification System (BCS) Class II and IV drugs.

6 Parenteral and Ocular Delivery

Water-insoluble drugs often face formulation challenges for injectable and ophthalmic delivery. Inclusion complexes enhance the solubility and stability of these drugs in aqueous vehicles, enabling their use in sterile dosage forms without the need for toxic organic solvents.

7 Targeted and Site-Specific Delivery

Functionalized cyclodextrins can be conjugated with ligands or polymers for targeted drug delivery to specific tissues or cells, such as tumors or the brain. This allows for enhanced therapeutic efficacy with reduced systemic side effects.

6. Role of Novel Excipients in Inclusion Complexation

Novel excipients play a crucial role in enhancing the effectiveness of inclusion complexation techniques, especially for drugs with poor solubility and stability. Unlike traditional excipients that serve basic functions (e.g., fillers, binders, or disintegrants), novel excipients are specifically engineered or modified to perform specialized tasks, such as improving solubility, bioavailability, and targeted delivery. [18,16] In the context of inclusion complexes, novel excipients such as modified cyclodextrins (e.g., hydroxypropyl-β-cyclodextrin, sulfobutyl ether-β-cyclodextrin) and polymeric carriers (e.g., Soluplus, poloxamers, and PEG-based systems) significantly enhance drug–host interactions. These excipients increase the aqueous solubility of poorly water-soluble drugs, provide better complexation efficiency, and improve the pharmacokinetic profile. Furthermore, novel excipients can impart additional functionalities like mucoadhesion, thermosensitivity, and pH-responsiveness to the formulation, thereby expanding the therapeutic application of inclusion complexes.[21,22]

7. **Advantages and Limitations of Inclusion Complexation**

ADVANTAGES:

- **Enhanced Solubility and Dissolution Rate:** Particularly for BCS Class II and IV drugs.
- **Improved Stability:** Protection against degradation by light, heat, and oxidation.
- **Taste and Odor Masking:** Ideal for pediatric and geriatric use.
- **Reduction in Irritation and Toxicity:** By minimizing direct contact of the drug with mucosal tissues.
- **Versatility in Dosage Forms:** Applicable to oral, parenteral, topical, and ocular routes.[20]

Limitation

- **Limited Loading Capacity:** Only a portion of the drug can be encapsulated.
- **Cost:** Modified cyclodextrins and advanced excipients can be expensive.
- **Complex Manufacturing Processes:** Some preparation methods require strict conditions and special equipment.
- **Stability of the Complex:** May be affected by moisture or temperature, requiring careful packaging and storage. [27,28]

8. Future Perspectives

The future of inclusion complexation, especially using novel excipients, appears promising. Advances in material science and nanotechnology are expected to yield intelligent excipients that offer stimuli-responsive release, enhanced targeting, and biodegradability. Further research into the development of hybrid systems that combine cyclodextrins with nanoparticles, micelles, or dendrimers could unlock new therapeutic strategies. In addition, the integration of green technologies like supercritical fluid processing and solvent-free methods will likely enhance the scalability and environmental sustainability of inclusion complex preparation. Regulatory acceptance and safety profiling of novel excipients will also be key to their widespread adoption.

9.CONCLUSION

Inclusion complexation has proven to be a highly effective and versatile technique for enhancing the solubility, stability, and bioavailability of poorly water-soluble drugs. The use of novel excipients, particularly modified cyclodextrins and smart polymeric carriers, has further amplified the potential of this approach by offering improved complexation efficiency and broader formulation flexibility. Despite some limitations, inclusion complexes hold significant promise in modern drug delivery systems. With continued advancements in excipient design, preparation methods, and regulatory frameworks, inclusion complexation is poised to remain a cornerstone strategy in pharmaceutical formulation for years to come.

REFERENCES

1. Loftsson T, Brewster ME. Pharmaceutical applications of cyclodextrins: Basic science and product development. J Pharm Pharmacol. 2010;62(11):1607–21. https://doi.org/10.1111/j.2042-7158.2010.01139.x
2. Szejtli J. Introduction and general overview of cyclodextrin chemistry. Chem Rev. 1998;98(5):1743–53. https://doi.org/10.1021/cr970022c
3. Khar RK. Cyclodextrins in drug delivery: An updated review. AAPS Pharm SciTech. 2005;6(2):E329–57. https://doi.org/10.1208/pt060243

4. Patel RP, Patel MM, Patel NM, Patel JK. Inclusion complexes of ketoconazole for improved solubility. Int J Pharm Sci Res. 2020;11(6):2882–90.
5. Sharma M, Sharma R, Sharma S. Cyclodextrin based drug delivery systems: A review. Pharmaceutics. 2021;13(4):452. https://doi.org/10.3390/pharmaceutics13040452
6. Kumar A, Verma A, Panwar A, Kumar A, Bansal M, Kumar P. Solubility enhancement of ibuprofen using HPβCD: A study on complexation and formulation. Asian J Pharm Sci. 2019;14(2):215–25. https://doi.org/10.1016/j.ajps.2018.02.002
7. Cheirsilp B, Rakmai J. Inclusion complex formation of cyclodextrin with its guest and their applications. Biotechnol Bioresour Util. 2016;4(1):12–24.
8. Rismawanti R, Astuti I, Hadi S, Yuliani SH. Evaluation of cyclodextrin inclusion complex to optimize aqueous solubility: A review. J Funct Genomics. 2023;10(3):321–31.
9. Rajewski RA, Stella VJ. Pharmaceutical applications of cyclodextrins. 2. In vivo drug delivery. J Pharm Sci. 1996;85(11):1142–69. https://doi.org/10.1021/js960189s
10. Brewster ME, Loftsson T. Cyclodextrins as pharmaceutical solubilizers. Adv Drug Deliv Rev. 2007;59(7):645–66. https://doi.org/10.1016/j.addr.2007.05.012
11. Stella VJ, He Q. Cyclodextrins. Toxicol Pathol. 2008;36(1):30–42. https://doi.org/10.1177/0192623307310945
12. Jambhekar SS, Breen P. Cyclodextrins in pharmaceutical formulations I: Structure and physicochemical properties, formation of complexes, and types of complex. Drug Discov Today. 2016;21(2):356–62. https://doi.org/10.1016/j.drudis.2015.11.017
13. Duchêne D, Bochot A. Thirty years with cyclodextrins. Int J Pharm. 2016;514(1):58–72. https://doi.org/10.1016/j.ijpharm.2016.07.024
14. Jansook P, Ogawa N, Loftsson T. Cyclodextrins: Structure, physicochemical properties and pharmaceutical applications. Int J Pharm. 2018;535(1–2):272–84. https://doi.org/10.1016/j.ijpharm.2017.11.018
15. Chowdary KPR, Srinivas L. Cyclodextrins as drug carrier systems. Indian J Pharm Sci. 2006;68(3):384–92. https://doi.org/10.4103/0250-474X.26660
16. Loftsson T, Duchêne D. Cyclodextrins and their pharmaceutical applications. Int J Pharm. 2007;329(1–2):1–11.
17. Brewster ME, Loftsson T. Cyclodextrins as pharmaceutical solubilizers. Adv Drug Deliv Rev. 2007;59(7):645–66. doi: 10.1016/j.addr.2007.05.012.
18. Wang Y, et al. Cyclodextrins and derivatives in drug delivery: new developments, relevant clinical trials, and advanced products. Carbohydr Polym. 2024[Epub ahead of print]. sciencedirect.com+15en.wikipedia.org+15researchgate.net+15
19. Trojanowicz M, et al. Cyclodextrin–hydrogel hybrids in advanced drug delivery. Gels. 2023;11(3):177. mdpi.com
20. Bernkop Schnürch A, et al. Thiolated cyclodextrins: Nano sized drug carriers. Coord Chem Rev. 2020; Epub ahead of print]. en.wikipedia.org
21. Chen H, et al. Cyclodextrins as drug delivery carriers in chemotherapy: CD based polymers and nanoparticles. Front Cell Dev Biol. 2022; 10:984311.
22. Specogna E, Li KW, Djabourov M, Carn F, Bouchemal K. Dehydration, dissolution and melting of cyclodextrin crystals. arXiv. 2018. arxiv.org+1arxiv.org+1
23. Khuntawee W, Karttunen M, Wong ekkabut J. Molecular dynamics study of β cyclodextrin derivatives in solvents. arXiv. 2017.

arxiv.org+15arxiv.org+15en.wikipedia.org+15

24. Carn F, Nowak S, Chaab I, Salmeron RD, Djabourov M. Alpha cyclodextrin–polysaccharide microplatelets. arXiv. 2018. en.wikipedia.org+11arxiv.org+11arxiv.org+11
25. Davis ME, et al. CRLX101: cyclodextrin polymer nanoparticle conjugate for cancer therapy. Invest New Drugs. 2010;28(1):69–75. en.wikipedia.org+1frontiersin.org+1
26. Trotta F, Zanetti M, Cavalli R. Cyclodextrin based nanosponges for drug delivery. Beilstein J Org Chem. 2012; 8:2091–98. en.wikipedia.org
27. KDreview. Cyclodextrin complexes: perspective from drug delivery and toxicity. Drug Dev Res. 2017;78(6):402–15. onlinelibrary.wiley.com
28. Sprockel O, et al. Characterization and dissolution behaviour of ketoconazole/β cyclodextrin complexes. Int J Pharm. 1996;140(2):161–68. researchgate.net+3sciencedirect.com+3researchgate.net+3
29. Xu J, et al. Inclusion complexes of ketoconazole with β cyclodextrin: physicochemical and dissolution studies. Pharmazie. 1995;50(5):347–50. researchgate.net+1ouci.dntb.gov.ua+1
30. Su P C, et al. Cyclodextrin encapsulation of essential oils and volatile drugs: a review. Food Funct. 2019;10(10):6524–36.

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