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Improving Ofloxacin's Solubility and Bioavailability by Cyclodextrin Complexation: An Extensive Analysis

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Futuristic Publications

Abstract

One of the biggest obstacles to efficient oral drug administration is still poor aqueous solubility, especially for BCS Class II compounds like ofloxacin, where absorption is limited by dissolution rather than membrane penetration. Cyclodextrins (CDs), which are cyclic oligosaccharides with a hydrophilic exterior and a hydrophobic cavity, are frequently employed to improve formulation flexibility, stability, and apparent aqueous solubility by forming inclusion complexes with lipophilic medications. Ofloxacin–CD systems (including native ß-CD and substituted derivatives like methyl-ß-CD and hydroxypropyl-ß-CD) are summarized in this review along with the physicochemical and spectroscopic characterization (phase-solubility, FTIR, DSC, XRD, NMR), effects on in-vitro dissolution and stability, and methods of complex preparation (kneading, co-precipitation, solvent evaporation, freeze-drying, and phase-solubility). According to representative research, ß-cyclodextrin can boost the solubility of ofloxacin by multiple times, and derivative CDs typically result in higher complexation efficiency and solubility enhancement than native CDs. According to more comprehensive analyses of antibiotic–CD complexes, CD inclusion usually results in better solubility, pharmacokinetic exposure, and therapeutic efficacy for antibiotics that are poorly soluble. Limitations (drug loading, cost, and safety at high CD concentrations), formulation implications, and future directions such as CD-polymer hybrids and nanostructured CD assemblies for optimal delivery are also covered in the review. All things considered, cyclodextrin complexation shows promise as a workable and expandable method to lessen the solubility constraints of ofloxacin and enhance its biopharmaceutical efficacy [1].

Keywords: Ofloxacin; Cyclodextrins; Inclusion complex; Solubility enhancement; Bioavailability; ß-Cyclodextrin; Hydroxypropyl-ß-cyclodextrin; Dissolution rate; Photostability; Drug delivery systems.

INTRODUCTION:

Ofloxacin is a fluoroquinolone antibiotic that works against a wide range of bacteria. It is often used to treat bacterial infections because it penetrates well, kills germs, and has good pharmacokinetics [2]. Ofloxacin (OFX) has a high membrane permeability, but it does not dissolve well in

water, especially at physiological pH levels [3]. This slows down its dissolving rate and makes it less available in the body when taken by mouth. This makes it hard to make drugs that have stable therapeutic levels, work quickly, and have a low dose variability [4].

Physicochemical Properties & Solubility Challenges:

The molecular structure of ofloxacin has functional groups that can give up or take on ions, which means that its solubility is very sensitive on ph. It can be more soluble in strongly acidic or basic conditions because its charged parts can gain or lose protons. However, at neutral pH, where it resides in zwitterionic or less ionized forms, its solubility drops sharply [5].

Ofloxacin has low inherent solubility in water. One study found that it was "sparingly soluble" in pure water (pH neutral) and that it became more soluble but remained limited in acidic or alkaline pH [6].

As a feature of BCS Class II medicines (high permeability, low solubility), ofloxacin's low solubility results in sluggish dissolution in the gastrointestinal tract, making the rate of dissolution the rate-limiting step for absorption.

Chemical structure and general properties:

The chemical formula of ofloxacin is $C_{18}H_{20}FN_3O_4$, and its molecular weight is approximately 361.37 g/mol. It is a fluoroquinolone antibiotic [7].

Its functional groups include a basic piperazine moiety, a carboxylic acid, a ketone, and fluorine substitution on the quinolone ring. It has pH-dependent ionization states because of these ionizable groups [8].

Depending on the pH of the solution, ofloxacin can exist in cationic, neutral (zwitterionic), or anionic forms according to its pKa values (for the acidic and basic functional groups). This has a major impact on its solubility profile [9].

Solubility in water and at different pH;

The solubility of ofloxacin in water is low to moderate. It has a lowest solubility around neutral pH (zwitterionic form) due to decreased ionization, and is more soluble in acidic (when the basic groups are protonated) or very alkaline (when the acidic groups deprotonate) environments [10].

Temperature increases solubility in experimental data. For instance, solubility rises with increasing temperature in the water solubility research from 293.15 K to 323.15 K [10].

According to one study, ofloxacin is nearly insoluble in water (~0.11 mg/mL) at neutral pH, although this rises dramatically at favourable pH or with the introduction of solubilizers [11].

Effect of ionization / speciation (pH dependence):

The ionization state of the molecule has a major impact on its solubility. Solubility is higher in cationic form (low pH), decreases as it moves through neutral/zwitterionic near physiological pH, and then increases once more in high pH (anionic form) [9].

One study, for instance, shown that the cationic and anionic forms of ofloxacin are significantly more soluble than the zwitterionic form [9].

Thermodynamics and solubility in different solvents:

Ofloxacin's solubility has been assessed in a variety of organic solvents and mixtures, including dichloromethane, chloroform, and carbon tetrachloride, in addition to water. Solubility in nonpolar solvents is frequently significantly higher [12].

For dissolve in water as opposed to nonpolar solvents, thermodynamic parameters (Gibbs free energy, enthalpy, and entropy) have been computed; dissolution in water frequently necessitates overcoming larger thermodynamic barriers [13].

Challenges in formulation because of solubility behaviour:

The zwitterionic form predominates at physiological pH (~7.0–7.4), resulting in low solubility that restricts the rate of dissolution in gastrointestinal fluids. For oral preparations, this delays absorption. (Because only drugs that are dissolved can get through membranes.) [9].

Temperature dependence: solubility may be understated if dissolution/dissolution testing is carried out at room temperature as opposed to body temperature. Formulations

must consider the solubility behaviour at body temperature (37°C).

Interaction with other components:

Ofloxacin's solubility and bioavailability may be impacted by metallic cations (found in antacids or dietary minerals) that combine to create complexes or salts. According to one study, several cations, including calcium, magnesium, iron, ferric, and aluminium, improve the water solubility of ofloxacin. This is most likely due to the production of soluble carboxylate salts or complexes [14].

In solid dispersions, solubilizers, co-solvents, or carriers (such as urea or mannitol) can greatly increase solubility by decreasing crystallinity or interacting through hydrogen bonding, etc [15].

Impact on Bioavailability & Therapeutic Performance:

One important pharmacokinetic metric that measures the amount and speed at which the active pharmaceutical ingredient (API) enters the bloodstream is bioavailability. It has a direct impact on a drug's safety profile, dosage schedule, and therapeutic efficacy. Higher dosages or other methods of administration may be necessary for medications with limited bioavailability to produce the intended therapeutic effect, which could raise the risk of adverse effects and patient non-compliance.

Factors Affecting Bioavailability:

Physicochemical Properties of the Drug:

Drugs with poor aqueous solubility or low permeability often exhibit low bioavailability. For instance, BCS Class II drugs, which have high permeability but low solubility, are particularly challenging. Enhancing their solubility can significantly improve their bioavailability [16].

Formulation Factors:

The design of the drug formulation, including particle size, polymorphism, and the presence of excipients, can impact the dissolution rate and, consequently, the bioavailability. Techniques like solid dispersion, complexation, and the use of surfactants are commonly employed to enhance solubility [17].

Strategies for Solubility Enhancement:

Several methods have been investigated for ofloxacin to get around these problems, including:

Solid dispersions:

Increasing surface area and decreasing crystallinity through the use of polymers or carriers (such as urea or mannitol) to improve dissolving. For instance, ofloxacin's dissolution rate was greatly increased by solid dispersions of the drug with urea-mannitol [15].

pH modulation and use of solubilizers:

Adjusting pH, using cosolvents or surfactants to improve solubility. One report showed that mixed solubilizer blends improved ofloxacin solubility in aqueous media to >4 mg/mL, compared to its very low solubility in plain water [11].

Cyclodextrin Complexation as a Promising Approach:

Cyclodextrins (CDs) are cyclic oligosaccharides that can form inclusion complexes with the right guest molecules. They have a hydrophilic outer surface and a hydrophobic inner cavity. These complexes of hosts and guests can:

1. By encasing hydrophobic or partially hydrophobic drug moieties in the hydrophobic cavity, you can increase their apparent aqueous solubility.
2. Boost the rates of disintegration.
3. Boost stability (defence against hydrolysis or photodegradation).
4. In some formulations, it may enhance flavour and lessen discomfort.

Aim & Scope of This Review:

This review seeks to address the limitations of ofloxacin's solubility as well as the encouraging findings of cyclodextrin complexation research.

1. Describe in detail the physicochemical limitations of ofloxacin that affect its bioavailability.
2. Compile and evaluate the various cyclodextrin types (native and modified derivatives), complexation techniques, and molar ratios.
3. Compile information from the literature on enhancements in pharmacokinetic parameters, stability (chemical and

photostability), solubility, and dissolution rate.

4. Discuss the use of cyclodextrin complexation for ofloxacin or similar antibiotics, including practical formulation issues, potential drawbacks (drug loading, cost, toxicity), and emerging trends (hybrid systems, nanocarriers).

Cyclodextrins: Structure and Properties:

Fundamental Structure:

The cyclic oligosaccharides known as cyclodextrins are made up of glucose units connected by α-1,4-glycosidic linkages. They are perfect for encasing hydrophobic molecules because of their shape, which produces a truncated cone with a hydrophilic outside surface and a hydrophobic core chamber.

A. α-CD: Composed of six glucose units

1. Basic Structure:

The cyclic oligosaccharide α-cyclodextrin is made up of six α-D-glucopyranose units joined by α-1,4 glycosidic linkages to create a ring, or "hexasaccharide."[18].

Conformation:

The ring has a rather stiff, albeit slightly flexible, shape because each glucose unit is in the ^4C₁ (chair) conformation [19].

Overall geometry:

With a narrower aperture at one rim and a larger opening at the other, the molecule resembles a truncated cone (or toroidal) structure [19].

Hydroxyl orientation:

Because each glucose unit has hydroxyl groups pointing outward, the outside surface of α-CD is hydrophilic. On C6, the primary hydroxyls face the smaller rim, whereas on C2 and C3, the secondary hydroxyls face the wider rim [20].

Methine/methylene carbons from the glucose units and glycosidic oxygen atoms line the interior cavity, which is comparatively hydrophobic (nonpolar). Encapsulation (inclusion) of nonpolar or moderately polar guest molecules is made possible by its hydrophobic interior [20].

2. Dimensions & Physical Properties

Cavity size and dimensions: α-CD's cavity diameter and depth are less than those of ß-CD and γ-CD, the smallest of the "native" cyclodextrins, which restricts the size of guest molecules it can hold [21].

Flexibility and rigidity: The ring has some conformational flexibility (such as in glycosidic bond torsions), which can somewhat alter the cavity size to aid guest binding, even if it is generally rigid in terms of individual glucose units [20].

Because of its hydrophilic surface, α-cyclodextrin is soluble in water, but it is insoluble or only weakly soluble in a variety of organic solvents [20].

Non-reducing sugar: α-CD is regarded as a nonreducing cyclic oligosaccharide since the ring closes (no free reducing end) [21].

3. Functional and Practical Aspects:

Guest binding/inclusion: Because the cavity of α-CD is rather small, it is selective for smaller guest molecules that can enter it, such as small organic compounds or hydrophobic moieties. Bigger molecules might only partially embed or not fit at all [20].

Selectivity and specificity: α-CD frequently shows higher specificity (i.e., more discriminating binding) for specific tiny hydrophobic or linear guest molecules than ß- or γ-CD due to its smaller cavity [20].

B. β-CD: Composed of seven glucose units

1. Basic Structure:

The cyclic oligosaccharide ß-Cyclodextrin is made up of seven α-D-glucopyranose units connected by α-1,4 glycosidic linkages.

Ring shape: A truncated cone or toroidal structure is formed by the seven glucose units. Because of the hydroxyl groups on the glucose units, the outside of this torus is hydrophilic, while the core is more hydrophobic [23].

Hydroxyl orientations: Secondary hydroxyl groups (on C2 and C3) are found on the larger rim, while primary hydroxyl groups (on C6 of each glucose) protrude on the narrower rim. These hydroxyl groups offer locations for modification and hydrogen bonding [23].

2. Physical & Chemical Properties:

a. Cavity dimensions and size:

In terms of guest size compatibility, ß-CD is in the middle, with an internal cavity diameter that is larger than α-CD but smaller than γ-CD [24].

A review table states that the cavity diameter of ß-CD is roughly 6.0–6.4 Å, the outside diameter is approximately 15.4 Å, and the height is approximately 7.8 Å [24].

Since the cavity polarity is frequently thought to be comparable to that of ethanol, hydrophobic interactions with guest molecules are supported [25].

b. Solubility:

The water solubility of native ß-CD is comparatively lower than that of α- or γ-CD. For instance, the solubility at 25 °C can be around 1.8 g/100 mL (i.e., 1.8% w/v), whereas the solubilities of α- and γ-CD are higher [26].

Derivatives (such as hydroxypropyl-ß-CD, methyl-ß-CD, and sulfobutylether-ß-CD) are used in many pharmaceutical applications to increase aqueous solubility and usefulness due to its restricted solubility [26].

c. Self-association and aggregation:

Above specific concentrations (the critical aggregation concentration), ß-CDs may self-aggregate in solution. Diffusion, complexation efficiency, and binding stoichiometry may all be impacted by this aggregation [25].

Compared to native ß-CD, modified ß-CDs (such as methyl-ß-CD and hydroxypropyl-ß-CD) have a lesser propensity to self-aggregate, which may improve binding efficiency for specific guest molecules [26].

d. Interactions with substances that are guests:

Van der Waals (hydrophobic) interactions are the main factors that drive the creation of ß-CD inclusion complexes; dipole interactions and weak hydrogen bonds from substituents or polar groups are frequently added as well [27].

Another thermodynamic driving force is the discharge of energetically unfavourable water molecules (also known as "high energy water") from the ß-CD cavity upon guest entry. Because there are fewer hydrogen bonds and less stabilization of the water molecules inside the hollow, their displacement is advantageous [27].

Size, polarity, and charge all affect how guest molecules are oriented inside ß-CD; depending on steric and electrostatic limitations, a portion of charged guests may protrude outside the rims [27].

e. Water content and hydration

Although reported hydration values vary, ß-CD can exist in hydrated forms in solid form, usually having approximately 10–12 water molecules per ß-CD unit. These water molecules interact with hydroxyl groups or occupy the cavity [25].

Initially, the cavity in solution contains water molecules; these so-called "high-energy water" molecules are displaced into the bulk solvent during the complexation process, which helps to produce advantageous entropy changes [26].

Benefits and Drawbacks of Using Pharmaceuticals

Benefits:

1. Due of its accessibility and affordability, ß-CD is frequently used in both formulation research and industry.
2. Many small to moderately sized drug molecules can fit within its cavity size, allowing for inclusion complexes that can enhance solubility, stability, and bioavailability.
3. Delivering inclusion complexes in aqueous media is facilitated by the outside hydrophilic surface's continued good water compatibility [27].

Restrictions:

1. The restricted water solubility of native ß-CD may limit its efficacy in specific formulations.
2. Aggregation may inhibit complex diffusion or decrease effective binding at higher doses.
3. Despite increasing solubility, substituents in derivatives can alter stability, selectivity, and binding behaviour when compared to the native form. The intricacy needs to be carefully described [27].

C. γ-CD: Composed of eight glucose units.

1 .Basic Structure:

The cyclic oligosaccharide γ-Cyclodextrin is composed of eight α-D-glucopyranose units connected by α-1,4 glycosidic linkages.

Like other cyclodextrins, it takes the form of a truncated cone, or toroid, with the orientations of its hydroxyl groups defining its narrower and wider ends.

Encapsulating hydrophobic guest molecules in aqueous conditions is made possible by the interior cavity's relative hydrophobicity and the external surface's hydrophilia (caused by the number of hydroxyl groups) [20].

2. Physical & Chemical Properties:

a. Cavity dimensions & size:

The cavity of γ-CD is larger than that of α-CD and ß-CD due to its eight glucose units, which makes it better suited to hold larger guest molecules.

The cavity diameter of γ-CD is roughly 7.5–8.3 Å, its height is approximately 7.8 Å, and its total molecular weight is approximately 1297 Da, according to comparison data (tabulated in reviews).

For the γ-CD, the outer diameter is greater, approximately 17.5 Å (as shown in the same table) [24].

b. Aggregation and solubility:

In comparison to ß-CD, γ-CD is comparatively more soluble in water, and in some cases, it is frequently more soluble than α-CD. (According to tabular statistics, γ-CD solubility is approximately 25.6 g/100 mL at 25 °C, while ß-CD is around 1.8 g/100 mL and α-CD is approximately 12.8 g/100 mL.).

According to one publication, γ-CD has a CAC of around 4.2% (w/v) in pure aqueous solution, but this lowers to about 2.5% (w/v) when guest molecules like carbamazepine are present [25].

c. Water and hydration in the cavities:

The cavity and interface regions of γ-CD are occupied by water molecules (hydrate water) in the solid/hydrate form. Guest molecules may displace these "high-energy" water molecules during complexation, resulting in advantageous entropy changes.

The creation of inclusion complexes is mostly driven by the idea of water displacement from the CD cavity; the "release" of poorly hydrogen-bonded water, or strained water, is thermodynamically advantageous when a guest molecule takes its place [24].

d. Chemical bonds and interactions:

Van der Waals forces, hydrophobic contacts, and occasionally dipole interactions maintain inclusion complexes formed by guest molecules that fit the cavity quite well. Usually, nonpolar or weakly polar visitors adhere better because the cavity is hydrophobic.

Compared to α or ß forms, the flexibility of γ-CD and its internal cavity environment allow for partial insertion or the accommodation of larger visitors [24].

Uses and Benefits

1. γ-CD is especially helpful when the guest molecule is too large to fit inside α- or ß-CD cavities due to its larger cavity.
2. It is used in food, cosmetics, medicines (drug delivery), and environmental systems where encapsulation is required for bigger guest molecules (such vitamins and aromatic chemicals).
3. Compared to low-solubility CDs, its comparatively increased aqueous solubility facilitates the formulation of inclusion complexes in aqueous systems [25].

Structural and Physical Characteristics comparison:

Property	**α-Cyclodextrin**	**β-Cyclodextrin**	**γ-Cyclodextrin**
Number of glucose units	6	7	8
Cavity diameter (Å)	4.7–5.3	6.0–6.5	7.5–7.8
Outer diameter (Å)	14.6	15.4	17.3
Height (Å)	7.9	7.9	7.9
Molecular weight (Da)	972	1135	1297
Water solubility (g/100 mL at 25°C)	14.5	1.8	25.6

Derivatives

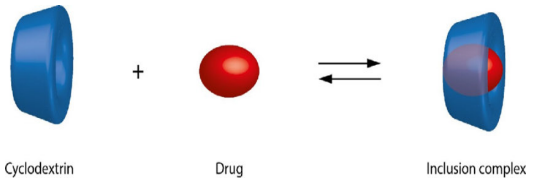
1. Numerous compounds have been created to enhance the solubility and functioning of CDs, including:
2. Hydroxypropyl-ß-cyclodextrin, or HP-ß-CD, adds hydroxypropyl groups to improve its solubility in water.
3. M-ß-CD (Methyl-ß-cyclodextrin): Methylation increases membrane permeability and lipophilicity.
4. Sulfobutyl ether groups increase solubility and decrease toxicity in SBE-ß-CD (sulfobutylether-ß-cyclodextrin).

Mechanism of Inclusion Complex Formation by Cyclodextrins:

Cyclodextrins (α-, ß-, and γ-CDs) are cyclic oligosaccharides that have an interior cavity that is hydrophobic and an exterior surface that is hydrophilic. Because of their special structure, they can create inclusion complexes with guest molecules that are hydrophobic or poorly soluble in water without creating covalent bonds.

Step-by-Step Mechanism:

1. Initial Interaction:
   Water molecules envelop CDs in aqueous solution. The "high-energy" water molecules in the inner cavity are comparatively unstable and have weak hydrogen bonds. Van der Waals interactions and hydrophobic effects facilitate a hydrophobic guest molecule's admission into the CD cavity as it approaches [24].
2. Guest Molecule Entry:
   The hydrophobic effect reduces the amount of water that nonpolar areas are exposed to by allowing the hydrophobic part of the guest molecule to enter the cavity.
   The complex's thermodynamic stability is enhanced by the displacement of high-energy water molecules from the cavity into the bulk solution, which raises entropy [19].
3. Stabilization of Complex:
   The inclusion complex is stabilized by non-covalent forces such hydrogen bonds, dipole–dipole interactions, and van der Waals interactions.
   The complex stays soluble in aqueous conditions thanks to interactions between the external hydroxyl groups of CD and water molecules [25].
4. Dynamic Equilibrium:
   Free CD and free guest molecules are in dynamic equilibrium with the inclusion complex.
   The size, shape, polarity, and kind of CD cavity of the visitor all affect the equilibrium. For instance:
   a. α-CD has a smaller cavity and is appropriate for tiny molecules.
   b. The most popular intermediate cavity for drug administration is ß-CD.
   c. γ-CD has a bigger cavity that can hold heavier molecules [20].



Rationale for Using Cyclodextrin with Ofloxacin:

Ofloxacin: Poor Solubility and Aqueous Instability

A common broad-spectrum fluoroquinolone antibiotic for bacterial infections is ofloxacin (OFX). A significant drawback for oral and parenteral preparations of OFX is its poor water solubility, even with its good pharmacokinetics and strong membrane permeability [28].

Poor Solubility in Water

Solubility based on pH: At physiological pH (~7.4), ofloxacin is zwitterionic, which decreases its water solubility. Because the carboxyl group is protonated, its solubility is higher in acidic environments (pH 1-3), but it drastically drops close to neutral pH [29].

Low rate of dissolution: Oral bioavailability and therapeutic efficacy are impacted by limited solubility, which causes sluggish dissolution in the digestive tract [29].

Formulation difficulties: To reach therapeutic plasma concentrations, poorly soluble medications such as OFX need larger dosages or specific formulations (such as solid dispersions or cyclodextrin complexes) [28].

Unpredictability in Watery Media

Susceptibility to hydrolysis: OFX degrades hydrolytically in aqueous situations, especially when the pH is extremely high or low.

Photodegradation: Because OFX is light-sensitive, degradation products may occur, which may lessen the effectiveness of the medication.

Effects of temperature: High temperatures hasten photolytic and hydrolytic deterioration, further jeopardizing stability in solution [29].

Implications:

Decreased bioavailability: Instability and poor solubility impair the effectiveness of treatment by reducing systemic absorption.

Strategies to improve solubility are required: To get over these obstacles,

strategies including cyclodextrin inclusion complexes, solid dispersions, nanoparticles, and pH-adjusted formulations are frequently used [30].

Enhancing Drug Solubility, Dissolution, and Stability via Cyclodextrin Complexation:

Cyclodextrins (CDs) are cyclic oligosaccharides with an interior cavity that is hydrophobic and an exterior surface that is hydrophilic. They can create non-covalent inclusion complexes with hydrophobic medications thanks to their special architecture, which enhances their physicochemical and biologic qualities [18].

1. Enhanced Solubility;

The CD cavity encapsulates hydrophobic guest molecules like ofloxacin.

The medicine is successfully dissolved in water via the interaction of the hydrophilic exterior with the aqueous environment (Poulson et al., 2022). Because they are more soluble in water than native ß-CD, cyclodextrin derivatives such as hydroxypropyl-ß-CD (HP-ß-CD) are frequently employed to further improve solubility.

2. Improved dissolution rate:

The drug's wettability and dispersibility in aqueous solutions are enhanced by the inclusion complex.

Because the medication is already partially "solubilized" inside the CD cavity, the energy barrier for dissolution is lowered, enabling a higher rate of disintegration and faster release.

For medications that are poorly soluble in water, such as ofloxacin, where dissolution is the rate-limiting stage in absorption, this is very helpful.

3. Improved Stability:

The medicine is shielded from environmental stressors such hydrolysis, oxidation, and photodegradation by encapsulation inside the CD cavity.

Chemical stability is increased because the guest molecule is protected from direct interaction with water or reactive species.

Research indicates that OFX-CD complexes do not degrade and maintain their therapeutic effectiveness whether exposed to light or different pH levels.

Extra Benefits

1. CDs are appealing for oral formulations because they can lessen dosage variability, enhance absorption, and cover the harsh taste.
2. Because inclusion complex formation is non-covalent and reversible, the drug's pharmacological efficacy is maintained while its formulation qualities are improved [31].

Protection of Ofloxacin from Photodegradation and Hydrolysis via Cyclodextrin Complexation;

Protection Mechanisms

Protecting Against Photodegradation, The hydrophobic aromatic rings of OFX are encapsulated within the hydrophobic cavity of cyclodextrins like ß-CD and hydroxypropyl-ß-CD (HP-ß-CD).

By limiting the drug's exposure to light, this encapsulation lowers the rate of photodegradation.

According to studies, OFX-CD complexes maintain a higher drug concentration and potency when exposed to light, demonstrating better photostability than the free drug.

Hydrolytic Degradation Prevention

By restricting OFX's interaction with water molecules, the inclusion complexation with CDs lowers the rate of hydrolytic breakdown.

Given that OFX is susceptible to hydrolytic breakage of its quinolone ring in aqueous formulations, this protection is very advantageous.

According to stability tests, OFX-CD complexes exhibit improved hydrolysis resistance, maintaining the drug's integrity over time.

Implications for Pharmaceuticals

Enhanced Stability: OFX's chemical stability is greatly increased by CD complexation, which makes it more appropriate for use in a range of pharmaceutical dosage forms.

Increased Shelf-Life: Because of lower rates of degradation, formulations incorporating OFX-CD complexes have longer shelf lives.

Optimized Therapeutic Efficacy: CD complexation guarantees steady therapeutic results by preserving OFX stability [12].

Improved taste masking and patient compliance:

It is commonly known that cyclodextrins (CDs) might improve patient compliance, especially in the elderly and paediatric populations, by masking the disagreeable tastes of bitter active pharmaceutical ingredients (APIs). By creating inclusion complexes between the CD and the API, the drug's bitter ingredients are successfully encapsulated within the hydrophobic cavity of the CD, producing this taste-masking effect.

Mechanisms via Which Cyclodextrins Mask Taste

Inclusion Complex Formation: Hydrophobic medication molecules can be encapsulated in CDs' hydrophobic chamber, minimizing their direct interaction with the tongue's taste receptors.

Decreased Drug Release: The encapsulated medication releases more slowly, which can both disguise the taste and extend its duration of action.

Better Palatability: Formulations that use CDs frequently have a smoother mouthfeel and less bitterness, which increases patient acceptance.

Effect on Patient Adherence

CDs are essential for increasing patient adherence to recommended treatments because they make drugs more palatable. This is especially crucial when treating long-term illnesses and for people who might have trouble swallowing pills or capsules [31, 32, 33, 34].

1. Kneading Method (KM):

Principle: Formation of inclusion complexes by triturating drug + CD with minimal solvent.

Procedure:

1. Accurately weigh **Ofloxacin** and **β-Cyclodextrin / HP-β-Cyclodextrin** in a **1:1 or 1:2 molar ratio**.
2. Transfer the mixture to a mortar.
3. Add small amount of **50% ethanol–water** solution dropwise to make a thick paste.
4. Continue kneading for **45–60 minutes**.
5. Dry the paste at **40–50°C**.
6. Pulverize and sieve (60–80 mesh).
7. Store in air-tight container.

Advantages:

- Simple
- Suitable for heat-sensitive drugs
- Good complexation efficiency [35]

2. Co-precipitation Method (CP):

Principle: Complex formation by dissolving CD in water and drug in ethanol.

Procedure:

1. Dissolve **β-CD / HP-β-CD** in distilled water.
2. Dissolve **Ofloxacin** in ethanol.
3. Add drug solution into CD solution with continuous stirring.
4. Maintain temperature at **45–50°C** for 1 hour.
5. Cool and allow the precipitate to form.
6. Filter and dry the solid complex.

Application:

- High yield inclusion complexes
- Better for industrial scale [36]

3. Solvent Evaporation Method (SE)

Principle: Evaporation of solvent after dissolving drug + CD in compatible media.

Procedure:

1. Dissolve **Ofloxacin** in ethanol or methanol.
2. Dissolve CDs in warm water.
3. Mix solutions under magnetic stirring for **2–3 hours**.
4. Evaporate solvent using:
   - Rotary evaporator, *or*
   - Water-bath at **50°C**
5. Dry and pulverize.

Advantage:

- Greater solubility enhancement
- Uniform complex formation [37]

4. Freeze-Drying (Lyophilization) Method (FD)

Principle: Freezing followed by sublimation of water to yield amorphous complexes.

Procedure:

1. Dissolve **Ofloxacin + CD** in distilled water/ ethanol mixture.
2. Stir until a clear solution appears.
3. Freeze at **–20 to –80°C** overnight.
4. Lyophilize for **24–48 hours**.
5. Store in desiccator.

Benefits:

- Highest solubility
- Amorphous, highly porous complex
- Ideal for poorly soluble drugs. [38]

5. Phase-Solubility Method (Al- Type Diagram)

Principle: Determination of complex stoichiometry and stability constant.

Procedure:

1. Prepare CD solutions in increasing concentrations.
2. Add excess Ofloxacin.
3. Shake for **48 hours** at 25°C.
4. Filter and analyse supernatant using UV.
5. Plot **solubility vs CD concentration**.

EVALUATION OF OFLOXACIN-CYCLODEXTRIN COMPLEXES:

Below are the standard pharmaceutical evaluation parameters with purposes, descriptions, and references.

1. Phase Solubility Study:

- Determines **drug solubility enhancement**
- Follows Higuchi–Connors model
- Gives **stability constant (Ks)** and **complexation efficiency (CE)**

2. Fourier Transform Infrared Spectroscopy (FTIR)

- Detects chemical interactions
- Shifts in peaks confirm inclusion complex formation

3. Differential Scanning Calorimetry (DSC)

- Shows disappearance of drug melting peak
- Confirms amorphous complexation

4. Powder X-Ray Diffraction (PXRD)

- Loss of crystallinity
- Formation of amorphous inclusion complex

5. Scanning Electron Microscopy (SEM)

- Surface morphology characterization.
- Distinct change from crystalline → amorphous indicates complex formation.

6. In-Vitro Dissolution Study:

- Measures percentage drug release.
- Inclusion complexes show **faster dissolution** than pure Ofloxacin.

7. Stability Study (ICH Guideline)

Conditions:

- 40°C ± 2°C / 75% RH ± 5%
- Evaluate drug degradation, moisture content, solubility, dissolution.

8. Photostability Study:

- CD complexes protect Ofloxacin from light.

9. Hydrolytic Stability Testing:

- Inclusion complex reduces hydrolytic degradation.

10. Taste Masking Evaluation:

- CDs reduce bitterness due to inclusion.

11. Drug Content/ Assay:

- Determine OFX content using UV at 287 nm.

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