REVIEW ARTICLE

Auxiliary Substances for Enhancement of Complexation Efficiency and Dissolution Rate of Drug-Cyclodextrin Complexes

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ABSTRACT

Background: Enzymatic starch breakdown yields 1, 4-linked D-glucopyranoside subunits, which are the building blocks of the cyclodextrin (CD) family of macromolecules. β-Cyclodetrins (β-CDs) have the capability to improve the solubility of partially soluble drugs, as well as their permeability across biological membranes and stability. However, factors like limited solubility, high cost of derivatives and their toxicity at high concentrations has directed the researchers toward multicomponent inclusion complexes (MCIC).

Introduction: Incorporating auxiliary substances (AS) leads to MCIC formation during complexation. The auxiliary agent interacts at the molecular level with the CDs, enhances the complexation competence of β-CD or its derivatives, and minimizes the amount required for solubilization of poorly soluble drugs. They also enhance stability of drug-CD complex. Due to these advantages, the popularity of MCIC has increased amongst formulation scientists.

Conclusion: This review describes various AS that could be used to prepare MCIC to expand solubility and other properties of drugs and minimize cost of related formulation.

Keywords: Cyclodextrin, Solubility, Multicomponent inclusion complex, Bioavailability, Auxiliary substances.

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INTRODUCTION

Enzymatic starch breakdown produces cyclic oligosaccharides known as cyclodextrins (CDs). It is composed of α-(1,4)-glycosidic connections joining D-glucopyranosyl units together. CDs can change a physicochemical property of poorly soluble drug molecules by encapsulating them into their inner cavity, indicating improved dissolution rate, absorption, oral bioavailability, and reduction in dosage and cost.[1] The D-glucopyranose units that make up the natural CDs, αCD, βCD, and γCD, are 6, 7, and 8 units, respectively. The cavity's dimensions within the CD molecule are determined by quantity of D-glucopyranose units present. The free hydroxyls outside of CDs provide a higher hydrophilic character than hydrogen atoms inside the cavity and oxygen atom's in glycosidic linkages, enabling the dissolution of poorly soluble compounds in aqueous conditions. Furthermore, compounds with restricted solubility can form inclusion complexes within the interior region of CDs.[2-4] Since an inclusion complex is formed when host (CD) and guest (drug) molecules contact, structural complementarity among the interacting compounds is essential.

About 30 different medicinal products are available worldwide, including drug-CD inclusion complexes. The majority of CDs' use in the pharmaceutical sector has been as complexing agents, with the goal of increasing the bioavailability, stability, and water solubility of medicines that are otherwise poorly soluble. CDs are useful for converting liquid medications into amorphous or microcrystalline powder, reducing gastrointestinal drug irritation, and preventing drug-excipient interactions. Table 1 summarises a few CD-based marketed formulations[5].

The β-CD is seen as a probable option for improving the bioavailability of poorly soluble medications because of its reduced price and a cavity size that can accommodate a large number of these compounds. Regardless, γ-CD has limited applications because it dissolves poorly in water. However, despite their high solubility, β-CD compounds are expensive and poisonous beyond a certain concentration. To overcome this problem, MCIC is being prepared, which involves the addition of an AS during the formation of the drug-CD inclusion complex. This leads to an enhancement of the complexation efficiency of CDs and the complex's stability,

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thus minimizing the amount of CD required for solubilization and stabilization of poorly soluble drug.[6,7]

An MCIC or ternary inclusion complex is a drug-CD complex associated with an auxiliary molecule. To improve the therapeutic applicability of many drugs, MCIC development with CDs and a third AS has grown in popularity.[7] This allows for the use of much lower CD concentrations, which optimizes toxicity, volume of formulation in the final product and cost. Drug transport and physicochemical characteristics may be improved or altered when these AS interact with CDs.[8] The drug's pharmacokinetic profile may change due to this interaction, which may alter drug solubility *in-vitro* and *in-vivo*. It is also feasible to lessen the medications' toxicological characteristics and other undesirable behaviors by picking an AS with care to add to the MCIC. In light of the many possible uses and benefits of AS in improving solubility and dissolving, this article will discuss the most important MCICs made with AS and how these AS work. The particular instances from the literature that have been summarized are mainly based on *in-vitro* and *in-vivo* approaches.[9-12]

Categories of Auxiliary Agents

The various categories of auxiliary agents that have been reported for enhancing complexation efficiency and the solubilizing effect of CDs are presented in Table 2**.** As most of the auxiliary agents given in Table 2 show similar action on drug-CD complexation, studies involving selective and commonly used AS have been discussed further.[13-44]

Hydroxy Acid

Citric and tartaric acids are the most widely used organic hydroxy acids frequently employed as pH adjusters to enhance solubility or stability of drugs complex with CDs. The hydrogen carbonate salts in many effervescent formulations are converted to carbon dioxide gas by the presence of hydroxy acids, primarily citric or tartaric acid. Numerous studies have been conducted on multicomponent systems of drug/CD/hydroxy acid. The third component, a hydroxy acid, was discovered to significantly enhance the drug and CD solubility.[45] Miconazole, hydroxy-propyl-β-CD (HPβCD), and maleic acid were able to create a stable inclusion complex. This miconazole malate salt is produced by a process that improves the drug's oral bioavailability, dissolution, and solubility.[46] Indomethacin was complexed with β-CD to produce the sodium salt of indomethacin, which has a 15-fold improvement in solubility over indomethacin. This combination also results in a superior *in-vitro* release in GI media (pH 1.4).[47] A ternary complex formed, including vinpocetine, tartaric acid, and β-CD. Two ways tartaric acid enhanced these medications' solubilization and complexation were by developing hydrogen bonds with CDs and their several hydroxyl groups and by drug ionization. A synergistic effect of tartaric acid and CD improved solubility of vinpocetine. This complex helped to achieve a great extent of solubilization of vinpocetine.[48] Increasing the concentration of citric acid can improve solubility of β-CD. This can be achieved by modifying system of intramolecular and intermolecular hydrogen bonds. Mechanism changed way CDs' hydroxyl groups bonded to or interacted with surrounding water molecules.[49,50] Ternary complex system was formed with carvedilol, hydroxy-propyl-β-CD, and tartaric acid. Adding hydroxy acids like tartaric acid in the system enhanced solubility and the complexation efficiency of CDs. The addition of tartaric acid in the aqueous media caused the drug's ionization, resulting in the enhancement of carvedilol's solubility.[51] The ternary complex comprising Iloperidone and HPβCD was formed when tartaric acid interacted with HPβCD by hydrogen bonding, salt production, and electrostatic interactions. It facilitated the hydrophobic interaction between the drug and HPβCD. Since Iloperidone is a basic drug, tartaric acid's higher acidity and the less viscous character of its solution are also responsible for improved complexation efficiency, stability constant, and solubility. The ability of the clarithromycin-CD-citric acid MCIC, to enhance the rate of drug solubility in basic solutions at pH 6.8. The MCIC shows improvement in the bioavailability of clarithromycin due to the formation of a complex with CD and citric acid which help to dissolve more drug in the intestine and make it available for absorption in the duodenum.[52] Additionally, the efficacy of HPβCD's multicomponent complexation by the addition of hydroxy acids greatly increased the solubility of cinnarizine. The cinnarizine solubility increased by 1223 times in water due to the formation of a ternary complex (drug-CD-hydroxy acid) developed using tartaric acid.[53] The solubility of the weakly basic medication dapoxetine hydrochloride is pH-dependent, which means that it may not dissolve as well in physiologically neutral fluids, as stated by Aldawsari *et al*., tartaric acid and HPβCD act as solubilizing agents. The solubility of tartaric acid was shown to be enhanced due to its pH-changing capabilities, which had a greater impact on the microenvironment's pH surrounding the drug particles.[54] Chantasart and Rakkaew explored several methods for producing haloperidol-lactic acid ternary complexes on dry CDs. Compared to ternary complexes produced by solvent evaporation and physical mixing, those produced by freeze-drying had a greater inclusion yield. We looked into the 1H NMR data and found that haloperidol interacted with the carboxyl and hydroxyl groups of CD and lactic acid through hydrogen bonds and van der Waals interactions inside and outside the hollow.[55] Table 3 describes the various drug/CD/hydroxy acid ternary complexes that enhanced the solubilizing efficiency of CD.

Amino Acids

Amino acids are often utilized in pharmaceutical applications due to their physicochemical characteristics. Amino acids are generally considered harmless, and they can interact with CDs and medications in a number of ways, including hydrogen bonding, electrostatic interactions, and salt formation. To enhance undesirable pharmacological characteristics of drug, there is considerable interest in using amino acids in the synthesis of MCIC. Amino acids like glutamic acid, lysine, arginine, cysteine, proline, and aspartic acid have been utilized

Table 1: Marketed formulations containing CD

S. No	*CD+ Drug*	*Trade name*	*Dosage form*	*Company country*
1	Piroxicam+ Bcd	Brexin, FlogeneCicladon	Tablet Suppository Liquid	Chiesi, Italy several European countries Ache, Brasil
2	Nitroglycerin+β-CD	Nitropen	Sublingual tablet	Nihon Kayaku, Japan
3	Itraconazole+HPβCD	Sporanox	Oral and i.v. Solutions	Janssen, Belgium and USA
4	Alprostadil+Acd	Rigidur	i.v. solution	Ferring, Denmark
5	Mitomycin+HPβCD	MitoExtra Mitozytrex	i.v. infusion	Novartis, Switzerland
6	Cisapride + HPβCD	Propulsid	Suppository	Janssen, Belgium
7	Voriconazole+ SBEβCD	Vfend	I.V. solution	Pfizer, USA

Table 2: Auxiliary Substances to improve complexation competence and solubilizing effects of CDs

S. No	*Category*	*Example of auxiliary substances*
1.	Hydroxy acids	Ascorbic acid, citric acid, tartaric acids, lactic acid, succinic acid.
2.	Amino acids	Arginine, L-threonine, glycine, glutamic acid, L-lysine, valine, isoleucine and aspartic acid.
3.	Hydrophilic polymer	Hydroxypropyl methylcellulose 4000 (HPMC), polyvinyl pyrrolidone (PVP K-90), sodium carboxy methyl cellulose(CMC), trimethyl chitosan (TMC), Plasdone S-630.
4.	Polyglycolized glycerides	Gelucire (44/14 or 50/13).
5.	Sugar alcohol	Mannitol.
6.	Surfactant	Poloxamer-407 (PLX), Poloxamer-188
7.	Co-solvent	1-methyl-2-pyrrolidone, triethanolamine (TEA), monoethanolamine (MEA), diethanolamine (DEA), ethanol, propylene glycol (PG)
8.	Metal ions	Mg ions (MgCl2·6H2O)
9.	Hydrotropes and miscellaneous	Sodium acetate, sodium salicylate, benzalkonium chloride, urea, nicotinamide. Phospholipids, soybean lecithin, meglumine (N-acetyl glucamine), soluplus, hyaluronic acid (HA)

Table 3: Different drug/CD/hydroxy acid ternary complexes for enhancing the solubilizing efficiency of CDs.

Sr. No.	*Drug*	*CDs*	*Hydroxy acid/AS*	*Mechanism*
1.	Ziprasidone	β-CD	Citric acid	The interaction of surrounding water molecules is affected by hydroxy acid.[56]
2.	Carvedilol,	β-CD	Citric acid	Formation of carvedilol citrate salt and hydrogen bonding interaction with β-CD.[57]
3.	Clarithromycin	β-CD	Citric acid	Because the complex forms in an acidic environment, clarithromycin dissolves at higher pH (5−6).[58]
4.	Rofecoxib	β-CD	Citric acid/Ascorbic acid	β-CD makes the drug molecules more soluble by forming an acidic environment surrounding them.[59]
5.	Vinpocetine	β-CD	Tartaric acid	Using hydroxy acid to alter the hydrogen bond network of nearby water molecules.[60]
6.	Haloperidol	β-CD	Lactic acid/ Succinic acid	Haloperidol interacts with unionized lactic acid species via hydrogen bonding.[61]

in the production of MCIC. However, arginine has been shown to be the most effective in this regard. For instance, amino acids (AAs) have demonstrated their value by boosting antibacterial action and lowering drug toxicity. Table 4 shows some of the drug/CD/AA ternary systems and mechanisms by which AAs enhance the complexation efficiency of CDs. It investigated how the addition of third components, such as β-CDs and benzoic acid (BA), affected AAs' structural and energetic properties. The phase-solubility investigation confirmed the respective binding affinities of BA-β-CD-AA ternary complex. Hydrogen bonding with a hydroxyl group on the broad rim of β-CD was shown by molecular docking of ternary complex, including arginine. The molecular modeling technique helped to study the structural-affinity relationships and screening of β-CDs inclusion complex. HPβCD and AAs improved the solubility of carbamazepine. AAs and non-ionizable drug molecules engaged in electrostatic interactions. Additional hydrophobic drug molecules could dissolve into these solvent holes because

AAs create ion pairs with non-ionizable drug molecules by disrupting the ordered structures of water molecules. The hydrotropic nature of AAs caused this. The nateglinide (NAT) with HPβCD and L-arginine (ARG) complex proved the drug's change from crystalline to amorphous forms. According to molecular modeling studies, the development of a hydrogen bond and the van der Wall's interaction between NAT and ARG with HPβCD, as well as this interaction with ARG, appear to be key factors in the complex's increased stability and solubility. Consequently, this combination demonstrated improved drug solubility and dissolution rate. ARG forms a ternary complex with naproxen, and HPβCD, and exhibits greater solubility and synergistic effects. The interaction between the basic AA, the CD (by hydrogen bonding), and the medicine (via electrostatic interactions and salt production) forms a ternary complex responsible for this effect.[62] Repaglinide (RPG), HP-β-CD, and ARG formed a supramolecular ternary complex that included a hydrophobic section and a hydrophilic polar head, which led to RPG's amphiphilic structure formation. By acting as a surfactant and reducing the water's surface tension, the hydrophilic portion of an amphiphilic structure can enhance the drug's solubility and wettability.[63] Various additives, including polyvinylpyrrolidone K-30, poloxamer-188, lactose, sodium lauryl sulfate, and ARG with HPβCD, were tested to find the optimal addition for creating a ternary complex of glyburide. One medication that is used to treat low blood sugar, gliburide, does not dissolve well in water. Compared to other binary and ternary complexes, the solubility of the ternary complex Glyb-HPβCD-ARG was improved.[64] The formation of cefixime-CD-arginine ternary complexes may increase the drug's solubility and dissolution, according to Jadhav *et al*. When ARG is present, both βCD and HPβCD can enhance complexation efficiency and the stability constant. Compared to binary complexes generated using the spray drying method, the ternary complex containing HPβCD had the best results regarding drug solubility rates.[65] The MCIC formation with CD and ARG was shown by Dan Cordoba *et al*. to be a suitable method for enhancing rifampicin's solubility and dissolution profile as well as its antibiofilm activity against bacterial strains. The authors discovered through theoretical research that ARG can form hydrogen bond interactions with CD and drug, increasing the stability of the MCIC.[66]

Hydrophilic Polymer

There is evidence that hydrophilic polymers can act on the drug-CD complexes to form aggregates or co-complexes with greater stability constant values than drug-CD binary complex. They aid in stability by preventing complicated aggregations of different molecules in pharmaceutical systems. Altering the hydration characteristics of CD molecules is another way they can reduce complicated solubility and boost mobility.[73]Many different hydrophilic polymers, including hyaluronic acid, polyethylene glycol, chitosan, and polyvinylpyrrolidone (PVP), can be used to create an AS. An experimental ternary complex was formed by mixing the HPMC, praziquantel (PRZ), and β-CD. Hydrophilic polymer cyclodextrin (HPMC) altered the bond energy, hydrophobic drug-cyclodextrin contact energy, and Vander waals interaction energy upon heating in this complex. Its solubility, stability constant, and ability to compound with CD were all improved by the HPMC.[74] A ternary complex was formed by combining fenofibrate, β-CD, and several hydrophilic polymers. The drug and CD complex was complexed more efficiently with the addition of a little amount of the hydrophilic polymer PVP K-30, which enhanced the stability constant of the complex and drug's solubility. The enhanced complexability of CDs was due to a combination of factors, including hydrophobic connections, hydrogen bonds, van der Waals dispersion forces, and encouragement of the release of high-energy water molecules from their cavities. The Fenofibrate drug solubility rate was improved in the ternary complex, including fenofibrate, β-CD, and PVP K-30.[75]A ternary complex is formed by gemfibrozil (GFZ), κ-CD, and Plasdone S-630. Thanks to the hydrophilic polymer/auxiliary compounds Plasdone S-630, this complex demonstrates an improvement in complexation efficiency and apparent stability constant. The hydrophilic polymer attaches to the drug through a combination of electrostatic interactions, hydrogen bridges, Vander waals forces, and ion-to-dipole and dipole-to-dipole connections. The drug's size has decreased due to the ternary complex forming a new solid phase, although some of its components are still amorphous. This was verified by SEM, XRD, FTIR, and DSC investigations. Gemfibrozil, the medicine, is now more soluble and easier to dissolve. The other ternary complexes prepared using water-soluble polymers as AS are given in Table 5.

Polyglycolized Glycerides

There is a lot of interest these days in using lipid-based amphiphilic carriers that can dissolve things. It is possible to make a ternary complex with sulfobutyl ether beta-cyclodextrins (SBE-β-CD), loratadine, and gelucire (50/13) that works better at complexation and dissolving than a binary complex. As the drug's size decreased, it changed into an amorphous form. Rate of dissolution also increased because the higher stability constant values for the ternary complex and the formation of a hydrogen bond between loratadine and CDs made the complex more stable.

Sugar Alcohol

Sugars are rarely used as a carrier in solid dispersion because they don't dissolve well in maximum organic solvents, have a high freezing point, are hygroscopic, and are crystallized. Mannitol, dextrose, sorbitol, galactose, and xylitol are sugar alcohols that are often used to make medicines more soluble.[86] Adding citric acid, mannitol, β-CD, and the aceclofenac complex made aceclofenac more soluble by making it easier for the drug to get stuck in the β-CD structure and by making the complex more water-soluble. The taste-masking properties of CD make it better at dissolving, which makes aceclofenac easier to dissolve and faster to dissolve.[87] It was easier for miconazole to dissolve when it was mixed with lactose, β-CD, and PEG 6000. This is because the drug's surface was changed from crystalline to amorphous, which made it easier for miconazole to dissolve.[88] This compound made it easier for

Table 4: Different drug/CD/amino acid multicomponent systems for enhancing solubilizing efficiency of CDs

S.No	*Drug*	*CDs*	*Amino acid/ AS*	*Mechanism*
1.	Meloxicam	HPβCD	ARG	HPβCD and ARG engage in hydrogen bonding, while drug and ARG interact over electrostatic interactions and salt production.[67]
2.	Chloramphenicol		β-CD	Glycine	Glycine forms hydrogen bonding connections with β-CD and electrostatic contacts with the drug.[68]
3.	Cefixime		β-CD, HPβCD	ARG	Electrostatic interaction take place between ARG and drug and CDs via hydrogen bonding.[69]
4.	Cefuroxime		β-CD	ARG	ARG simultaneously interacts with β-CD and Cefuroxime.[70]
5.	Lornoxicam		β-CD	ARG	Intermolecular hydrogen bonding with β-CD and electrostatic interaction with drug.[71]
6.	Bicalutamide		HPβCD	ARG	Electrostatic interaction and saltformation take place by ARG and drug and HPβCD through hydrogen bonding.[72]

Table 5: Different drug/CD/hydrophilic polymer multicomponent systems for enhancing solubilizing efficiency of CDs

S. No.	*Drug*	*CD*	*Hydrophilic Polymer/AS*	*Mechanism*
1.	Norfloxacin	β-CD	HPMC	hydroxyl group of β-CD and hydroxypropyl methyl group of HPMC interact.[76]
2.	Alprazolam	HPβCD	HPMC	Water-soluble aggregates of several drug-CD complexes can be formed by self-association of drug-CD complexes.[77]
3.	Zaleplon	CD and RAMEB	HPMC	Decrease in relative drug crystallinity.[78]
4.	Piroxicam	HPβCD	PVP K-15 and L-lysine	The inclusion of the hydrophilic PVP K-15 polymer prevents drug from recrystallizing, whereas lysine concurrently forms salts with both the drug and the CD through electrostatic contact and hydrogen bonding.[79]
5.	Progesterone	β-CD	PEG 6000,	Enhanced wettability, smaller drug particles, and less crystallinity.[80]
6.	Silymarin	β-CD	PEG 6000	Polymers enhance CDs' solubilizing effect by raising the complex's apparent stability constant (Kc).[81]
7.	Cefuroxime axetil	HPβCD	PEG 4000	The creation of a stable inclusion complex between Cefuroxime and HPβCD, together with decrease in particle size, wetting property, and hydrophilicity of HPβCD, all contributed to the solubility improvement in ternary micro-complexes.[82]
8.	Cefpodoxi meproxetil	HPβCD	Sodium carboxy methyl cellulose	When these polymers are used, the complexation rate and stability go up constantly.[83]
9.	Modafinil	HPβCD	Trimethyl chitosan	HPβCD and Trimethyl chitosan interact due to physical cross-linking and hydrogen bonding.[22]
10.	Oxaprozin	RAMEB	Trimethyl chitosan	Formation of interactions between Chitosan and CD.[84]
11.	Vinpocetine	SBE-β-CD	PVP and HPMC	From the MCIC, we can see that the complex is becoming less crystallized and more diffuse.[85]

DOM to dissolve and dissolve faster because the drug became less crystallized and had a larger surface area. This was shown by XRD and SEM analysis, and it also formed a non-covalent bond between the mannitol and the other parts. It was also seen that a hydrophilic environment formed and drug ionization happened, which helped make DOM more soluble and speed up the rate at which it broke down.

Surfactants

Poly(oxyethylene) and poly(oxypropylene) copolymer is a non-ionic polymer known as poloxamer. Previous studies have demonstrated that the poloxamer with CD causes the formation of colloidal particle systems and drug nanocarriers. Drug solubility and chemical stability can both be increased by incorporating the drug into poloxamer micelles. Connected to the lipophilic portion are two hydrophilic regions. Its surfactant characteristics make it a go-to for making medications that otherwise wouldn't dissolve more easily. Cell accumulation, which affects efflux pumps and biodistribution, can also be controlled.[89] Poloxamer 188, β-CD, and diflunisal formed a ternary complex (Diclofenac/ βCD/PXM-188), improving

Table 6: Different drug/CD/surfactant multicomponent systems for enhancing solubilizing efficiency of CDs

S.No.	*Drug*	*CDs*	*Surfactant/AS*	*Mechanism*
1.	Valsartan	β-CD	Poloxamer 407	Because poloxamer 188 acts as a surfactant.[92]
2.	Atenolol	β-CD	Poloxamer 188	1) The drug's and aqueous medium's surface tension is reduced by poloxamer and 2) A decrease in the crystallinity and also the formation of hydrogen bond shoe the high degree of interaction between atenolol and CD.[93]
3.	Rilpivirine	β-CD	Tocopherol polyethylene glycol succinate	Tocopherol polyethylene glycol succinate can reduce solid-liquid interfacial tension and increase the drug's wettability.[94]
4.	Flurbiprofen	β-CD	Tween 80	Interaction occurs at the solid interfaces of surfactant and drug interaction occurs with single surfactant molecules.[95]

Table 7: Different drug/CD/co-solvent multicomponent systems for enhancing solubilizing efficiency of CDs

Sr.No.	*Drug*	*CDs*	*Co-solvent/AS*	*Mechanism*
1.	Methotrexate	β-CD	TEA	expressivelyrises methotrexate affinity for β-CD compared.[97]
2.	Diclofenac	M-β-CD	MEA	Diclofenac MCIC leads to amorphization of the sample which indicates complexation of salt into cavity of M-β-CD.[98]
3.	Oleanolic acid and ursolic acid	HPβCD	Ethanol	Growing complexation effectiveness of oleanolic acid and ursolic acid.
4.	Atenolol, diazepam, lamotrigine.	β-CD	Propylene glycol + water	Increasing the complexation.
5.	Fluasterone	HPβCD	Ethanol	Deviations in solvophobic characteristics on medium.[99,100]

Table 8: Different multicomponent systems of some drugs and CDs with hydrotropes and miscellaneous substances

Sr.No.	*Drug*	*CDs*	*AS*	*Mechanism*
1.	Hydrocortisone	β-CD	Sodium acetate	Solubility of β-CDs and inclusion complex improved. Hydrocortisone/β-CD micro-aggregates formed in the aqueous solutions get solubilize due to the acetate ions.
2	Curcumin	HPβCD	Phospholipids	Complexes gives smaller particle size which helps reduce surface tension of phospholipids-HP-β-CD complexes and increase flexibility due to the presence of phospholipids
3.	Dihydroartemisinin	HPβCD	Lecithin	Lecithin interacted with dihydroartemisinin by hydrophobic interactions and with HP-β-CD *via* hydrogen bonding
4.	Meglumine	HPβCD	Meglumine	Meglumine (DRF-4367) enhances complexation efficiency and solubilization due to the hydrogen bond formation with the host molecule.
5.	Itraconazole	HPβCD	Soluplus	Increasing the complexation of the complex.
6.	Tocopherol	β-CD	Hyaluronic acid	Drug amorphization.

Diflunisal's solubility, stability, and release. This can be done by increasing the poloxamer 188 polymer's ability to solubilize and complex CD more effectively. Additionally, drug's crystallinity was reduced, and its amorphization, or rise in surface area, contributed to the improvement of drug's solubility and dissolution.[90] Furosemide (FSM), β-CD, and sodium lauryl sulfate (SLS) came together to make tertiary inclusion complexes. The solubility and dissolution of FSM were improved when β-CD was added in the presence of SLS due to the greater apparent stability constant and complexation efficiency.[31] Ameeduzzafar Zafar *et al*. created the ternary inclusion complex of genistein-HPβCD-poloxamer 188 to enhance the solubility and cytotoxicity of cancer cells. The study concluded that genistein has substantial promise for the treatment of cancer since a notable improvement in dissolution was shown with the introduction of genistein in the ternary complex.[91] Table 6 shows other studies involving use of various surfactants as AS to enhance the solubilizing efficiency of CDs.

Co-solvent

Various co-solvents like ethanol, triethanolamine (TEA), monoethanolamine (MEA), and propylene glycol are successfully used along with CD to form ternary complex. Ternary inclusion complex of sulfisoxazole, HPβCD, and TEA was developed successfully. TEA improved sulfisoxazole's solubility through a mechanism involving the complexation of the drug's hydrophobic portion into HPβCD, interaction of countering with a hydrogen-bond system of CD, or by

ionization of drug molecule through pH changes.[96] Ternary complex of methotrexate, β-CD, and TEA was formulated and it was found that TEA expressively increases methotrexate affinity for β-CD with increased solubility. Some other ternary systems prepared using co-solvents and AS are given in Table 7.

Metal Ions

The liquid formulation of T-3912, a new non-fluorinated topical quinolone, was created by Tetsumi Yamakawa *et al*. by combining magnesium ions and HPβCD, which had a synergistic solubilizing effect. It was thought that using Mg_2 + ions and HPβCD together had a synergistic effect. It has also been noted that the dissolving rate of norfloxacin, which was shown to be lower in a solution containing Al or Mg ions, was improved by β-CD. The solubility of norfloxacin was found to be enhanced due to the hydrogen bonding interaction involved in the complex which may reduce the availability of chelation sites for Mg^{2+} and Al^{3+}.[101] In a comprehensive literature review, Yang Xu *et al*. examined the creation and potential applications of CD-based metal-organic frameworks. In this research, the authors detailed the process of creating CD-based metal-organic frameworks by combining cyclodextrins like α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin with metal ions like calcium, potassium, titanium, silver, iron, and yttrium through meticulously planned metal-ligand coordination interactions. It has been observed that among the cyclodextrin varieties, γ-cyclodextrin was the most appropriate for creating metal-organic frameworks with biocompatible and non-toxic features. The research group also discussed different CD-metal ion complex uses in the pharmaceutical and food industries.[102]

Hydrotropes and Miscellaneous Substances

A substance is known as a hydrotrope if it solubilizes hydrophobic substances in aqueous solutions by a process other than micellar solubilization. A hydrophobic component is usually too little to induce spontaneous self-aggregation, but hydrotropes often contain both a hydrophilic and a hydrophobic component. Some hydrotropes that are used to increase the solubility of inclusion complexes and CD include urea, sodium benzoate, sodium acetate, and potassium acetate.[103, 104] Besides, some other substances like phospholipids, meglumine, lecithin, hyaluronic acid etc. have also shown efficiency to enhance the complexation efficiency of CDs. Table 8 shows some hydrotropes and miscellaneous substances used for the preparation of multicomponent systems, along with their mechanism of action. Physically cross-linked hydrogels made of poly (ethylene glycol)-cholesterol and cyclodextrin polymer were developed by Shaaban K. Osman *et al*. to be carriers for macromolecules and small drug molecules. These findings support the hypothesis that the p-CD/PEG-chol hydrogel may serve as a flexible drug delivery technology for compounds exhibiting diverse properties and molecular weights.[105] The topical drug delivery method known as ketorolac tromethamine was created by Ahmed A. H. Abdellatif *et al*., employing CD/Adamantane-grafted PEG. The strong binding constants with a 1:1 stoichiometric ratio showed that the cyclodextrin and adamantane moieties formed an inclusion complex. The outcomes also demonstrated its sustained, quantitative release via a semi-permeable barrier (over 24 h) and its effective integration into the revised system.[106]

CONCLUSION

One attractive option for carriers in the pharmaceutical business is CDs, which are naturally occurring cyclic oligosaccharides. CDs have the ability to influence various pharmacological properties by forming drug-CD complexes. In the past few decades, multicomponent systems have opened up new possibilities for CDs to regulate pharmacological qualities like stability and biological activity and improve drug solubility, dissolving, and bioavailability. A third AS improved the complexation efficiency of CDs, stability constant, and solubility of medicines that are weakly water-soluble, as demonstrated by the production of MCIC. Various AS, including hydroxy acids, amino acids, hydrophilic polymers, surfactants, sugar alcohols, polyglycolic glycerides, co-solvents, metal ions, and hydrotropes, have demonstrated their efficient role in modulating the solubilizing property of CD and improvising the solubility, bioavailability and pharmacological activity of drugs. However, more advanced research needs to be done to establish the clinical efficacy of the complexes.

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