Cyclodextrin Multicomponent Complexes: Pharmaceutical Applications

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Cyclodextrins (CD) are a family of macromolecules obtained by enzymatic degradation of starch. Their structure resembles a truncated cone, with a somewhat lipophilic central cavity and an external hydrophilic surface. Due to these characteristics the pharmaceutical applications are mostly related to the ability of CDs to form inclusion complexes, formed by interactions between guest (drug) and host (CD) molecules, and they have the ability to modulate several properties positively affecting the performances and therapeutic profiles of drugs.

Besides, a drug–CD complex with the addition of an auxiliary substance, that are called multicomponent or ternary complex, can have a synergic effect, allowing the use of low concentrations of the host compounds, thereby optimizing the cost, toxicity and formulation volume in the final product. Also, these additives such as amino acids, organic acids and bases, and water-soluble polymers interacting with CDs can modulate in vitro and in vivo drug dissolution, thereby modifying the drug's pharmacokinetic profile.

Keywords: auxiliary agents ; complexation efficiency amino acids ; organic acids ; organic bases ; water-soluble polymers

1. Amino Acids as Auxiliary Agents

Amino acids (AAs) present a series of adequate properties for pharmaceutical applications, so they are generally regarded as safe and have great potential for interacting with CDs and drugs via hydrogen bonding with CDs and via electrostatic interactions and salt formation with drugs. Several examples of multicomponent complexes of CD can be found in the literature in which AAs have been used as auxiliary agents not only to improve the solubility and dissolution rates of poorly soluble drugs, but also to allow the modulation of other drug properties. For example, AAs have shown their usefulness by increasing antimicrobial activity and reducing the toxicity of drugs. Among the AAs that have been used to prepare multicomponent complexes, it is possible to mention glycine, cysteine, proline, arginine, lysine, aspartic acid and glutamic acid, being arginine one of the AAs that has produced the best results in the formation of multicomponent complexes. Table 1 shows some reports on ternary complexes of CDs with arginine, incorporating the improvements in the pharmaceutical properties achieved.

Table 1. Summary of some reports on ternary complexes of CDs with arginine, including the improvements in pharmaceutical properties.

Ternary System	Solubility	Dissolution	Reference
naproxen-HPβCD-arginine	**synergistic action between HPβCD and arginine with 13-fold solubility increment**	**superior performance of coevaporate complex with 15 times increase in DE**	[1][2]
lornoxicam-βCD-arginine	**freeze-dried complex showed the higher solubility saturation in different buffer media**	**freeze-dried complexes exhibits >95% dissolution after 20 min**	[3]
etodolac-HPβCD-arginine	**Spray-dried and coevaporate ternary complex showed an increment of 163- and 100-fold, respectively, in water with respect to saturation solubility of pure drug**	**Spray-dried and coevaporate ternary complex exhibits an increase in percent drug release of 19- and 20-fold, respectively, with respect to pure etodolac.**	[4]

glyburide-HPβCD-arginine	ternary complex showed higher solubility in both aqueous media and buffer pH 7.5	ternary complex exhibits significant improvement in the dissolution profile compared with the pure drug in unbuffered aqueous media	[5]
cefixime-βCD-arginine cefixime-HPβCD-arginine	ternary complex showed better drug solubility	ternary complex with HPβCD exhibit better performance (DE2 = 25) compared with the drug alone (DE2 = 0.75)	[6]
rifampicin-βCD- arginine	ternary complex showed an increase in the drug solubility	ternary complex showed an increase in the dissolved percentage of the drug (53% versus 25% for drug alone)	[7]

2. Organic Acids as Auxiliary Agents

Multicomponent complexes with CDs and different acids have been studied to improve the properties by orders of magnitude of basic drugs in relation to classic drug–CD binary complexes. The auxiliary acid substances, together with the CDs, improve the physicochemical, chemical and transport properties of drugs, and therefore provide advantages in terms of bioavailability and pharmaceutical use. The mechanism of action of weak acids allows stabilizing a ternary complex through a combination of interactions (hydrogen bonding, salt formation and electrostatic interactions) depending on the nature and structural characteristics of the molecules. Among the hydroxy acids, the citric, gluconic, tartaric, lactic and malic acids are reported to be promising ternary candidates due to their potential ability to interact with CD molecules by forming hydrogen bonds with their numerous hydroxyl groups, and in Table 2 are shown some results obtained with ternary complexes of CDs and citric acid (CA).

Ternary System	Solubility	Dissolution	Other Properties	Reference
Econazole nitrate-SBEβCD-CA	synergistic action between SBEβCD and CA with 21.2 fold solubility increment	superior performance of co-ground system concentration increased to 479.07 ± 11.3 mg/mL after 45 min	higher antimycotic activity with respect to that of pure Econazole	[8][9]
Carvedilol-βCD-CA	spray-dried complex exhibits the higher solubility saturation in different buffer media	spray-dried complex exhibits significant improvement in the dissolution profile compared with the pure carvedilol	spray-dried complex is stable in exposition to 40 °C at 75% relative humidity	[10]
Clarithromycin-βCD-CA		freeze-dried complex exhibits rapid and enhanced dissolution rate in basic media	freeze-dried complex exhibits slightly improved absorption in beagle dogs	[11]
Ketoconazole-βCD-CA		spray-dried complex reach a dissolution percentage close to 100%		[12]

3. Organic Bases as Auxiliary Agents

Organic bases, whose structural diversity predetermines their magnitudes of effect upon drug–CD solution interactions, are being employed as tertiary components in ternary complexes, and they are used mainly when the drugs are acids. In these systems, the prominent role of electrostatic forces in the general interaction should be considered. Although the CD complexes obtained from non-ionized drugs have greater stability compared with their anionic analogues, the total solubility achieved and other properties of the drug such as chemical stability and bioavailability usually improve. Ternary systems with ethanolamines (monoethanolamine, diethanolamine and triethanolamine) improved the physicochemical properties of drugs, such as solubility and permeability through the cornea and duodenal epithelium, as well as increased therapeutic performance and decreased drug toxicity, as reported for acetazolamide [13][14].

Water-soluble polymers are known to interact with the outer surfaces of CD and drug–CD complexes, forming aggregates or co-complexes that show values of stability constants constant higher than those of binary drug–CD systems. They can also increase the solubility of complexes and decrease CD mobility by changing the hydration properties of CD molecules. Polymers such as Polyvinylpyrrolidone, Chitosan, Hydroxypropylmethylcellulose, Hyaluronic Acid, Polyethylene Glycol, Poloxamer, demonstrated enhancement of solubilization and permeation through biological membranes by means of the formation of multicomponent complexes with CDs. Also, it was evaluated the anti-tumor effects *in vitro* and *in vivo* of a multicomponent system of β-lapachone, MβCD, and poloxamer and it was demonstrated a significantly decreased in the tumor volume while increasing apoptosis and DNA damage without evident toxicity to the liver or kidneys [15][16] .

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