

## Review Article

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# Cyclodextrins-block copolymer drug delivery systems: From design and development to preclinical studies

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**Abstract:** Cyclodextrin (CD)-block copolymer hybrid systems have recently received great attention from the pharmaceutical and materials research community because this combination can result in new biomaterials and supramolecular structures, which possess the physicochemical and thermotropic properties of both classes of materials. Different structures of CD-block copolymer systems have been described (*i.e.*, micelles, vehicles, core-shell structures, nanospheres, and membranes) and they can encapsulate active pharmaceutical ingredients or other bioactive compounds. The aim of this review is to summarize several examples, the properties, the morphological and physicochemical characteristics, the added value, the techniques used for their preparation and characterization, as well as the limitations of CD-block copolymer systems. Taking into consideration the wide variety of block copolymers and CD materials and the expected beneficial characteristics/behavior following their complexation, we could suggest them as new-generation formulations in the upcoming years.

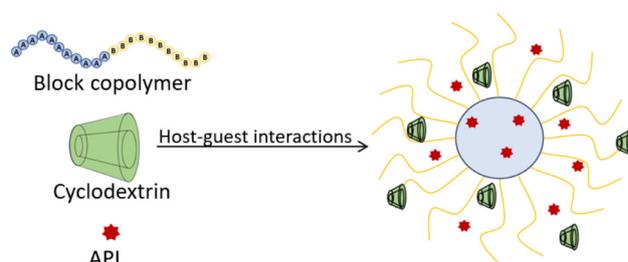
**Keywords:** biodegradable block copolymers, cyclodextrins, drug delivery systems, hybrid nanosystems

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Graphical abstract

## Abbreviations

APIs	active pharmaceutical ingredients
BM	benzimidazole
CDs	cyclodextrins
CMC	critical micelle concentration
DOX	doxorubicin
DM- $\beta$ -CD	heptakis-(2,6- <i>O</i> -dimethyl)- $\beta$ -CD
EMA	European medical agency
EPR	enhanced permeability and retention effect
FA-PEL-CD	folate-poly(ethylene glycol)-poly(D,L-lactide)- $\beta$ -CD
HP- $\beta$ -CD	hydroxypropyl- $\beta$ -CD
HP- $\gamma$ -CD	hydroxypropyl- $\gamma$ -CD
mPEG- <i>b</i> -PLA	methoxy poly(ethylene glycol)- <i>b</i> -poly(lactide)
MNPs	magnetic nanoparticles
M- $\beta$ -CD	methyl- $\beta$ -CD
NPs	nanoparticles
NSs	nanospheres
LCST	critical solution temperature
PAA	poly(acrylic acid)
PBLA	poly( <i>b</i> -benzyl-L-aspartate)
PCL	poly( $\epsilon$ -caprolactone)
PDI	polydispersity index
PDMAEMA	poly(2-(dimethylamino) ethyl methacrylate)
PEG	polyethylene glycol
PEO	poly(ethylene oxide)
PHB	poly[( <i>R</i> )-3-hydroxybutyrate]
PLGA	poly(lactic- <i>co</i> -glycolic acid)

PPEGGA	poly(polyethylene glycol methyl ether acrylate)
PPO	poly(propylene oxide)
PS- <i>b</i> -P4VP	polystyrene- <i>block</i> -poly(4-vinylpyridine)
PST	poly(styrene)
PVA	polyvinyl acetate
PVCL	polyvinyl caprolactam
SBE- $\beta$ -CD	sulfobutylether $\beta$ -CD sodium salt
SMGels	supramolecular hydrogels
tNEA	<i>trans</i> - <i>N</i> -(2-ethoxy-1,3-dioxan-5-yl) acrylamide
US-FDA	U.S. Food and Drug Administration

## 1 Introduction

Cyclodextrins (CDs) are a group of cyclic oligosaccharides and they possess molecular structures with a configuration of a truncated cone [1], consisting of a hydrophobic interior environment and hydrophilic exterior surfaces. This configuration permits them to accommodate diverse molecules into their cavities. Therefore, they can form inclusion (host-guest) complexes with noncovalent interactions, without complex chemical reactions, encapsulating poorly water-soluble compounds to improve their solubility in water and their stability, as well as to diminish the side reactions of drugs to a certain extent [2]. A large gamut of interactions between guests and host molecules contribute to the formation of complexes, like hydrophobic interactions, hydrogen bonds, van der Waals forces, and size effects [3,4].

Concerning the other substances of hybrid systems, polymers have many potentials as excipients for the pharmaceutical industry. A significant application of polymer nanoparticulate platforms is the design of innovative delivery systems for the transport of Active Pharmaceutical Ingredients (APIs) and nucleic acids. However, some factors compromise the use of polymers and they must be considered for the application of polymers in clinical practice, including the possible toxicity due to the use of cationic polymers, physicochemical instability of drug-containing systems which show changes in the size distribution and nanoparticle size of polymer-based formulations, system stability problems in the human body, reduced ability for the transfection of cell-target, and high expenses for scale up production of the final formulation [5]. The selection of the most appropriate polymer for creating a novel drug delivery platform is associated with the way of administration, the physicochemical profile of the incorporated drug, the properties of polymers utilized, the interactions between the different materials of the composed platforms, as well as several other factors [6].

Research over the past years led to the identification of amphiphilic block copolymers as potent therapeutic moieties for curing challenging human diseases, that tend to self-assemble in aqueous media leading to a plethora of nano-assemblies [7]. Thus, they can encapsulate hydrophobic compounds such as drugs or other bioactive molecules into their cavity. The aim of this review is to investigate the potential of CD-block copolymer hybrid systems. To the best of the authors' knowledge, this is the first report in the literature where these drug delivery platforms and applications are addressed.

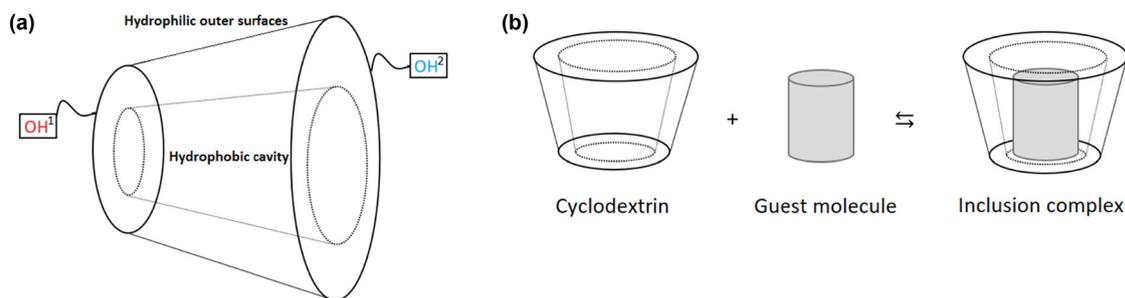
## 2 Methodology of literature review

A comprehensive search and review of literature concerning CD-block copolymer systems were conducted across multiple platforms, including PubMed, Medline, Scopus, and Web of Science, as well as through the consideration of abstract presentations at international conferences. The publications from 2006 to 2024 served as a comprehensive guide for the systematic investigation of CD-block copolymer systems. The search was based on the following terms: polymer-based nanocarriers, block copolymer, CD, drug delivery carriers, and hybrid systems. The authors performed the literature search excluding the studies with full text unavailable and publication language other than English.

## 3 Cyclodextrins systems

### 3.1 CDs

CDs, also called cycloamyloses, cyclomaltoses, or Schardinger dextrins [8], due to their backbone consisting of sugars, are a group of cyclic oligosaccharides composed of six ( $\alpha$ -CD), seven ( $\beta$ -CD), or eight ( $\gamma$ -CD) D(+)-glucopyranose units, linked by  $\alpha$ -1,4 glycosidic [9], shaping supramolecular structures with a toroidal configuration [1]. Due to the formation of sugars, the secondary 2- and 3-hydroxy groups are extended from the broader edge, whereas the primary 6-hydroxy groups are located at the narrower edge [10]. CDs contain hydrophobic central inner cavities, surrounded by hydrophilic outer surfaces (Figure 1a) [11]. Their shape permits them to accommodate diverse molecules. Therefore, they can create inclusion (host-guest) complexes through noncovalent interactions, without complex chemical reactions, enabling the encapsulation of hydrophobic compounds (Figure 1b). This



**Figure 1:** (a) Structure of CDs.  $\text{OH}^1$ : primary 6-hydroxy groups;  $\text{OH}^2$ : secondary 2-, 3-hydroxy groups and (b) schematic configuration of inclusion complex formation (1:1) between CD and a guest compound.

encapsulation serves the purpose of enhancing water solubility and stability of the compounds, as well as decreasing the side reactions of drugs to a certain extent [2].

CDs are natural products, which are formed by the enzymatic degradation of starch, catalyzed by CD glucanotransferases from various bacteria like *Bacillus* strains. Larger CDs, containing 9 ( $\delta$ -CD), 10 ( $\epsilon$ -CD), 11 ( $\zeta$ -CD), 12 ( $\eta$ -CD), and 13 ( $\theta$ -CD) glucopyranose units have been reported, but they do not have applications in the pharmaceutical industry [3]. A wide variety of interactions contributes to the formation of guest-host complexes, such as hydrogen bonds, hydrophobic interactions, van der Waals forces, and size effects [3,4].

The most commonly abundant CD in medicinal and pharmaceutical industries is  $\beta$ -CD [12]. The beneficial size of its cavity permits the accommodation of many bioactive compounds with a molecular weight of 200–800 g/mol, whereas the easy production process, availability in pure form, low cost, efficient formation of inclusion complexes, ability to enhance the bioavailability of drugs, and ameliorated toxicological profile [3,13,23] are some of the advantages that make  $\beta$ -CD the most frequently used CD in pharmaceutical applications.

### 3.2 CD derivatives

Despite the inherent hydrophilicity of natural CDs, their solubility in water remains inadequate, particularly in the case of  $\beta$ -CD. This deficiency can be attributed to the extremely strong intermolecular hydrogen bonding of CD in the crystalline state [10]. To overcome this obstacle, scientists have designed and developed various hydrophilic, lipophilic, and ionic derivatives of CDs which show superior inclusion capacity, specific water solubility, improved complexation efficacy, greater physicochemical properties, and lower toxicity in comparison with the natural ones [3]. The enhancement of natural CDs' solubility could be achieved by

the substitution of hydroxy groups using a wide variety of reagents, even lipophilic entities like those found in randomly methylated  $\beta$ -CD (M- $\beta$ -CD) [14]. The improved water solubility is attributed to the random substitution process, which transforms the crystalline solids of natural CDs into physically stable, amorphous mixtures of isomers [14].

The number of CD derivatives is approximately more than 11,000. According to a search in SciFinder<sup>®</sup>, there are at least 2,000 different substituted derivatives for  $\alpha$ -CD, more than 8,000 for  $\beta$ -CD and almost 1,000 for  $\gamma$ -CD [15]. For instance, the replacement of natural  $\beta$ -CD and  $\gamma$ -CD by propylene oxide leads to the formation of hydroxypropylated CD derivatives [16]. Hydroxypropyl- $\beta$ -CD (HP- $\beta$ -CD), heptakis-(2,6-*O*-dimethyl)  $\beta$ -CD, hydroxypropyl- $\gamma$ -CD (HP- $\gamma$ -CD), randomly M- $\beta$ -CD, sulfobutylether  $\beta$ -CD sodium salt (SBE- $\beta$ -CD), and the branched CDs such as glucosyl- $\beta$ -CD, are some synthesized derivatives of high pharmaceutical interest [17].

### 3.3 Applications of CDs in the pharmaceutical industry

CDs are useful as one of the most common drug carriers [15]. In the pharmaceutical industry, the most widely highlighted application is the use of CDs for the formulation of hydrophobic drugs with insufficient bioavailability [11], increasing their poor aqueous solubility and physicochemical stability [18]. Their cavity is a substrate, which interacts with non-covalent bonds with drug molecules. As CDs act like molecular encapsulants, they modify dramatically the chemical, physical, and biological properties of the encapsulated organic molecules [19]. Also, CDs can be modified to CDs with specific features, such as hydrophobically-modified CDs to decrease the aqueous solubility of hydrophilic compounds, as well as peracylated CDs, characterized by high solubility in organic solvents, such as ethanol and acetone, and low solubility in water, that are

used to reduce the water-solubility, prolong the elimination half-life, and permit favorable release properties through the formation of water-insoluble drug/CD complexes [18].

They can also act as flavor masking agents of unsavory drugs and reduce nasal mucosa damage, as well as irritation of the eye, skin, and gastrointestinal tract, because of the embedment of the drug molecules in CD cavity, making them useful tools for ameliorating drug delivery through the nasal, ocular, and pulmonary routes of administration [3,16]. Indeed, the progressive release of the drug from the complex with a slow rate permits the maintenance of free drug's concentration below the levels that could be vexatious for the mucosa [20]. Furthermore, CDs can also prevent the interactions between drugs, or between drugs and excipients, and prevent the conversion of liquid compounds into amorphous or microcrystalline powder [21]. Another noteworthy application of CD complexes is their ability to separate enantiomers of drugs, obtaining the enantiomer with the most favorable properties [22]. Last but not least, CDs play a crucial role in facilitating the dissolution and delivery of hydrophobic drugs across lipophilic biological membrane barriers [23]. The chemical structure, hydrophilicity, and high molecular weight of CDs give them the ability to act as alternative penetration enhancers by concentrating the drug on the surface of the cell membrane without disturbing the integrity of the biological membrane [23,24].

### 3.4 Methods of creating drug-CD inclusion complexes

Solid drug-CD complexes can be performed using the following main techniques: 1. physical mixing; 2. kneading; 3. freeze-drying; 4. co-evaporation [13], as well as other methods and techniques such as co-precipitation, heating, damp mixing, extrusion, dry mixing, paste complexation, and slurry complexation [25]. Regarding the main techniques used, at physical mixing, the drug and CD are homogeneously blended by using a mortar and pestle. The interactions developed between the API and CD molecules due to the mechanical stirring facilitate the formation of the inclusion complex. The kneading method represents a modification of the physical mixing approach wherein a minor quantity of co-solvent is introduced into the drug-CD blend during the kneading process to augment the formation of the complex. This leads to the creation of a uniform paste, which is subsequently dried to yield a finely powdered product. Within the freeze-drying technique, the

drug and CD are dissolved in a solvent. Following this, the solution undergoes freezing, and in the presence of a vacuum, the solvent is effectively removed, resulting in the formation of the inclusion complex. In the co-evaporation technique, the drug is dissolved within an appropriate solvent, followed by the addition of a CD solution. This combined liquid mixture is subsequently exposed to an evaporation process, leading to the formation of the inclusion complex through precipitation. The used method determines the physicochemical characteristics of the complexes [25].

### 3.5 Medicinal products with CDs

A large gamut of pharmaceutical products containing CDs are currently undergoing clinical trials or have already been introduced to the global market [26]. These medicines are given using different ways of administration, like oral, nasal, pulmonary, rectal, dermal, ocular, and parenteral routes (Figure 2) [27]. According to the European Medicines Agency (EMA), some examples of the use of CDs in medicinal products on the European market include  $\beta$ -CD in brivaracetam film-coated tablets [28] and in glucagon nasal powder [29]. HP- $\beta$ -CD has been used in the authorized Jcovden vaccine against Adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein [30], in cladribine tablets [31], in hard capsules of fingolimod [32] and Larotrectinib [33] and in film-coated capsules of letermovir [34]. SBE- $\beta$ -CD has also been utilized in many marketed medicinal products in Europe. For example, it is contained in aripiprazole tablets [35], in carfilzomib powder for solution for infusion [36], in the veterinary tablets of citrate monohydrate [37], in concentrate for solution for infusion products of posaconazole [38], remdesivir [39], and voriconazole [40], as well as in film-coated voriconazole tablets [41]. Table 1 presents the authorized medical products in the European market that contain CDs (API, type of CD, trade name, pharmaceutical form, manufacturing company, EMA product number, and date of marketing authorization).

### 3.6 Safety of the use of CD based drug delivery systems in clinical applications

Safety is a factor of paramount importance and should be taken into consideration for the incorporation of CDs in pharmaceutical formulations. The route of administration

is the most crucial parameter which affects the toxicity or safety of these products.

First, the administration of CDs products by the oral route does not cause any irradiated effects because these substances are not absorbable due to their high hydrophilicity and their large configuration [27]. According to EMA, high doses of CD products administered orally could lead to gastrointestinal disorders in animals [27,42]. Nevertheless, it is noticed that pure compounds can be used as food additives as they are considered safe [42].

Concerning dermal products, natural CDs present a safety profile at low concentrations (up to 0.1%), whereas some CD derivatives (e.g., HP- $\beta$ -CD) are used as excipients in cosmetics due to good skin tolerability [42,43].

Furthermore, it has been reported that suppositories including a high quantity of  $\beta$ -CD (230 mg) and 12% HP- $\beta$ -CD do not induce damage in the rectal epithelium of humans and rabbits, respectively. Nevertheless,  $\alpha$ -CD affects the rectal mucosa in the opposite way [42,43].

Regarding the nasal and pulmonary CDs administered, EMA [42] and Asai *et al.* [44] have demonstrated that amount of CD solutions lower than 10% do not cause degradation of the nasal mucosal tissue.

As CDs are capable of acting as alternative penetration enhancers, they can be incorporated into ocular products to improve drug penetration into the eye. Concentrations of  $\alpha$ -CD and randomly M- $\beta$ -CD up to 4 and 5%, respectively, can cause epithelial toxicity in the cornea of rabbits. On the other hand, concentrations of 10% SBE- $\beta$ -CD and 12.5% HP- $\beta$ -CD are well tolerable by the corneal surface of rabbit eyes [42,43].

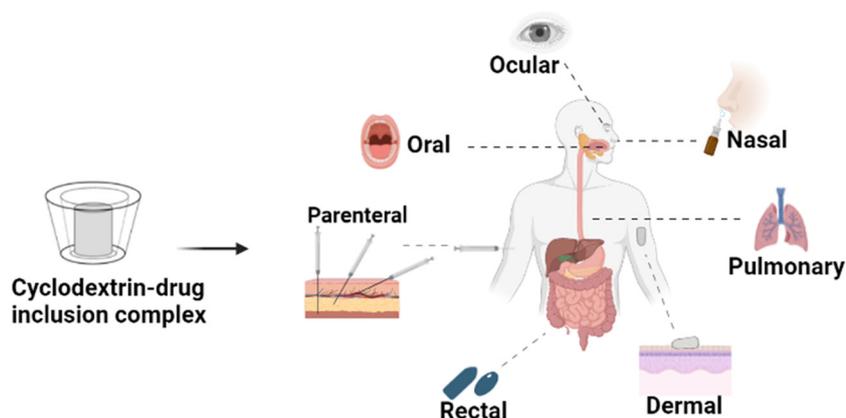
Most intravenously administered CDs are excreted through urine rapidly. EMA and US Food and Drug Administration (USFDA) do not permit the use of medicinal products of  $\alpha$ -CD,  $\beta$ -CD, and randomly M- $\beta$ -CD given intravenously because even in

relatively low doses they are considered nephrotoxic. On the contrary, two modified derivatives of  $\beta$ -CD, HP- $\beta$ -CD, and SBE- $\beta$ -CD are used as excipients in parenteral products as they are considered safe even in relatively high doses. According to EMA, the evaluation of two approved products revealed the safety of these derivatives at the dose of 250 mg/kg/day over a period of 3 weeks and 6 months for HP- $\beta$ -CD and SBE- $\beta$ -CD, respectively [27]. Several studies have indicated the severe hemolytic effect that the administration of CDs can cause which is correlated with their capability to solubilize the lipids of cellular membranes, like cholesterol [43]. Leroy-Lechat and co-workers listed the CDs in accordance with their augmented *in vitro* hemolytic activity. More specifically, they reported that  $\beta$ -CD influenced the erythrocytes collected from human and P388 murine leukemic cells with the most negative effect, followed in order by  $\alpha$ -CD, HP- $\beta$ -CD,  $\gamma$ -CD, HP- $\gamma$ -CD, and HP- $\alpha$ -CD [45].

## 4 Polymers: Copolymers-block copolymers

Polymers are high molecular weight substances made up of recurring units known as monomers, which link together in elongated chains. Polymers can be composed of identical monomers, forming homopolymers, or a combination of various monomers, known as copolymers. Several different types of copolymers can arise from the diverse orientations and structures of monomers along the polymer chain [5,46]. The four principal copolymer structures are illustrated in Figure 3, and they can assume the subsequent configurations:

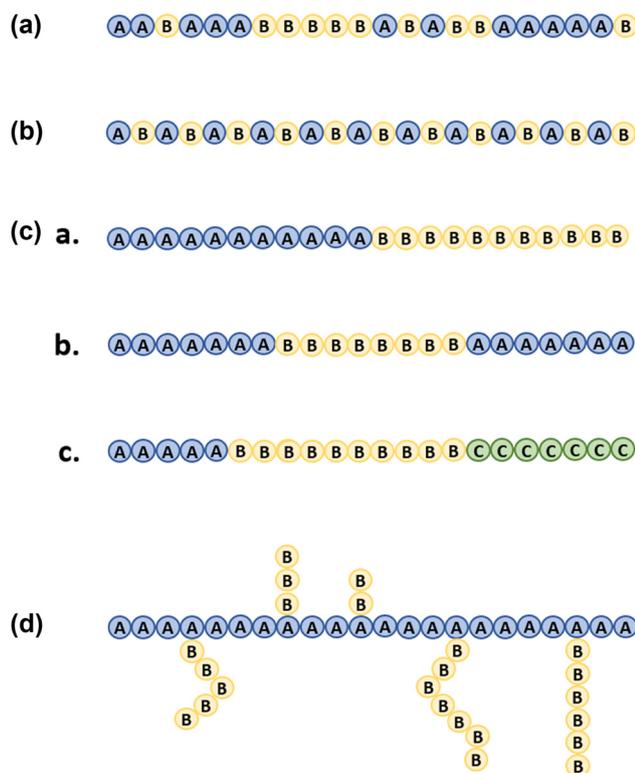
1. Random copolymers: In which the different monomer units are organized in a random sequence along the linear polymer chain.



**Figure 2:** Routes of administration of cyclodextrin-drug inclusion complexes based on EMA [27].

**Table 1:** Authorized medical products in the European market that contain CDs

API	CD	Trade name	Pharmaceutical form	Company	EMA product number	Date of marketing authorization	Ref.
Adenovirus type 26 encoding the SARS-CoV-2 spike glycoprotein	HP-	Jcovden (previously COVID-19 Vaccine Janssen)	Suspension for injection	Janssen-Cilag International NV	EMEA/H/C/005737	11/03/2021	[30]
	β-CD	ABILIFY	Tablets	Otsuka Pharmaceutical Netherlands B.V.	EMEA/H/C/000471	04/06/2004	[35]
Aripiprazole	β-CD	Briviact (in Italy: Nubriveo)	Film-coated tablets	UCB Pharma SA	EMEA/H/C/003898	13/01/2016	[28]
Brivacetam	β-CD	Kyprolis	Powder for solution for infusion	Amgen Europe	EMEA/H/C/003790	19/11/2015	[36]
Carfilzomib	β-CD	Cerenia	Tablets (veterinary)	Zoetis Belgium SA	EMEA/V/C/000106	28/09/2006	[37]
Citrate monohydrate	β-CD	Mavenclad	Tablets	Merck Europe B.V.	EMEA/H/C/004230	22/08/2017	[31]
Cladribine	HP-	Gilenya	Hard capsules	Merck Europe B.V.	EMEA/H/C/004230	22/08/2017	[32]
Fingolimod	β-CD	Baqsimi	Nasal powder in single-dose container	Eli Lilly Nederland B.V.	EMEA/H/C/003848	16/12/2019	[29]
Glucagon	β-CD	Vitrakvi	Hard capsules	Bayer AG	EMEA/H/C/004919	19/09/2019	[33]
Larotrectinib sulfate	HP-	Preymis	Film-coated tablets	Merck Sharp & Dohme B.V.	EMEA/H/C/004536	08/01/2018	[34]
Letemovir	β-CD	Noxafil	Concentrate for solution for infusion	Merck Sharp and Dohme B.V.	EMEA/H/C/000610	25/10/2005	[38]
Posaconazole	β-CD	Veklury	Powder for concentrate for solution for infusion	Gilead Sciences Ireland UC	EMEA/H/C/005622	03/07/2020	[39]
Remdesivir	β-CD	VFEND	Film-coated tablets	Pfizer Europe MA EEIG	EMEA/H/C/000387	19/03/2002	[41]
Voriconazole	β-CD	Voriconazole Hikma	Powder for solution for infusion	Hikma Farmaceutica (Portugal) S.A.	EMEA/H/C/003737	27/05/2015	[40]



**Figure 3:** The diverse categories of copolymers: (a) Random copolymer; (b) alternating copolymer; (c) block ((a) diblock, (b) triblock, and (c) multiblock copolymer) and (d) Graft copolymer.

2. Alternating copolymers: In which the different monomer units are arranged in a repeating pattern of the different monomers along the linear polymer chain.
3. Block copolymers: These are composed of separate monomer blocks which are linked in a linear chain. Depending on the number of blocks they contain they can be categorized as:
  - Diblock copolymers: Contain two different blocks (AB)
  - Triblock copolymers: Contain three different blocks (ABA or BAB)
  - Multiblock copolymers: Contain more than three different blocks (ABC, ABCDAC)
4. Graft copolymers: Involve a main monomer that constitutes the central chain, accompanied by a different monomer that is attached as side chains along the central chain.

Polymers-based nanotheranostic platforms have attracted the interest of polymer scientists for many decades [47,48]. It is a fast-growing field that provides significant therapeutic solutions for many diseases [48,49]. The capability of different architectures of copolymers to self-assemble in various nanostructures and morphologies makes them potential multifunctional candidates as drug, gene, and

bio-imaging carriers [50–52]. The self-assembly of them in aqueous solutions can provide interesting structures, including, uni- and multi-molecular micelles, vesicles, polymersomes, and nanogels. These structures have the capacity to encapsulate hydrophobic molecules such as drugs or other bioactive compounds within their hydrophobic domains [53–55].

The ability of block copolymers to self-assemble in aqueous media has gained considerable attention [56]. This phenomenon can yield ordered nanostructures in a wide range of morphologies such as spheres, cylinders, vesicles, micelles, and many other complex assemblies. The properties of these polymeric aggregates provide potential applications in many fields. Drug encapsulation and delivery are facilitated by the amphiphilicity of block copolymers in solution [57].

## 4.1 Methods of creating polymer-based drug delivery systems

The incompatibility between their different components results in their self-assembly into polymeric micelles or polymeric aggregates [58]. The encapsulation of hydrophobic drugs in the micellar hydrophobic core enhances its solubility in water [59]. Many drug encapsulation protocols have been created for the delivery of hydrophobic drugs. Among these, two main methods have been established to create drug-polymer systems: the thin film hydration protocol and the dialysis method. These techniques represent the principal approaches for encapsulating drugs within the polymeric core [58,60].

## 4.2 Studies on polymer-based drug delivery systems

Qiao *et al.* [61] reported an interesting thermo-sensitive diblock copolymer system as a co-loaded carrier. The block copolymer was prepared by atom transfer radical polymerization of *trans-N*-(2-ethoxy-1,3-dioxan-5-yl) acrylamide (tNEA) and poly(ethylene oxide)<sub>45</sub> (PEO)<sub>45</sub> as a macroinitiator. PEO<sub>45</sub>-b-PtNEA<sub>*n*</sub>, (*n* = 22, 44, 63, 91, and 172) at low temperatures was soluble in water, while at above 37°C, this polymeric system formed aggregates with different morphologies by changing the chain length of PtNEA each time. Specifically, the formation of spherical aggregates gradually changed into polymersomes with rod-like structure at the

intermediate PtNEA length. Both NPs formed were stable at physiological conditions and were able to be co-loaded efficiently by the hydrophobic drug doxorubicin (DOX), and water-soluble fluorescein isothiocyanate-lysozyme. The drug release profiles revealed that at acidic environment, a greater drug release takes place than at physiological conditions. Furthermore, DOX-loaded carriers demonstrated an excellent cytotoxicity against HepG2 cells. These novel co-loaded spherical and rod-like NPs could be a promising candidate for diseases such as cancer [61].

Liu and co-workers [62] developed a novel pH-sensitive poly( $\epsilon$ -caprolactone-*b*-2-(*N,N*-dimethylamino)ethyl methacrylate) amphiphilic dendritic star-block copolymer system by ring-opening polymerization and atom transfer radical polymerization. The study of these copolymers in aqueous media revealed their self-organization into unimolecular or multimolecular micelles with sizes around 28 and 190 nm, respectively. Dynamic light scattering technique exhibits bimodal size distribution. Camptothecin was used as a model drug for its encapsulation in the hydrophobic environment of the micelles. The drug release profiles showed different release rates by altering the buffer conditions. Specifically, under acidic conditions, the drug was released more quickly and to a greater extent than under physiological conditions. Also, the cytotoxicity studies corroborated the low level of cytotoxicity of these micelles. Confocal laser scanning microscopy was able to determine the penetration of the drug-loaded NPs into the cell membrane and those being internalized into cytoplasm and cell nucleus of HeLa cells. These pH-responsive micelles could be promising candidates as drug delivery carriers [62].

Another interesting work for the treatment of cancer was reported by Yang's team [63]. An amphiphilic star-shaped polycarbonate/polyethylene glycol (PEG) copolymer system was constructed by ring-opening polymerization, forming micelles which easily converted to vesicles in aqueous media for the effective delivery of the anticancer drug, DOX. DOX encapsulation was achieved by the dialysis method and DOX-loaded vesicles exhibited high drug loading capacity (22.5% in weight) for DOX. Subsequently, DOX-loaded vesicles were inserted into 4T1 tumor-bearing mice and presented an increased accumulation in tumor tissues due to the improved permeation and retention effect. An important observation was that the DOX-loaded vesicles showed a higher tumor growth inhibition than free DOX without side effects. All these features, give the possibility to utilize these vesicles as potential candidates for cancer treatment [63].

Mandal *et al.* [64] fabricated a series of dual stimuli responsive spherical nanogels with different sets of star block copolymers based on pentaerythritol-poly( $\epsilon$ -caprolactone)-*b*-poly(acrylic acid) by using ring-opening and

atom transfer radical polymerization. These dually responsive (pH and magneto) nanogels have been synthesized in order to incorporate the magnetic NPs (MNPs)  $\text{Fe}_3\text{O}_4$  via hydrogen bonding interactions of amine groups of MNPs and that of carboxylic groups of the poly(acrylic acid) (PAA) components of the copolymers. Dynamic light scattering method determined the hydrodynamic radius of these nanogels in the range of 65–616 nm. These nanogels were used for the encapsulation of an anticancer and hydrophobic drug, DOX. The drug release profiles revealed that a greater amount (73%) of encapsulated DOX was released at the physiological pH of the cancer cells, while it increased to 76% when an external magnetic field was applied. The MNPs/DOX-loaded nanogels presented selectively great cell uptake when the magnetic field was applied which enhanced its magnetic targeting ability. *In vitro* cytotoxicity studies exhibited high toxicity of DOX-loaded nanogels against the C6 glioma cell lines [64].

Wang's group [65] reported a brush-shaped poly[styrene-*b*-poly(polyethylene glycol methyl ether acrylate)] (PST-*b*-PPEGA) block copolymer and poly(PEGA) homopolymer containing a  $-\text{C}_{12}\text{H}_{25}$  end group constructed by reversible addition fragmentation chain transfer polymerization. Polystyrene was the hydrophobic component of the formed micelles and polyPEG was the hydrophilic corona. These micelles were designed for the encapsulation of ruthenium(II) complex anticancer drug in aqueous media. Cytotoxicity investigations of these loaded micelles enhanced the drug's toxicity to human liver cancer cells (SK-HEP-1) by 3-fold under dark and 12-fold under light. Furthermore, both blank and drug-loaded polymeric micelles presented no toxicity to the normal cells, indicating their important role in the treatment of cancer [65].

Bai *et al.* [66] synthesized two pH-responsive drug delivery systems containing fluorescent properties by atom transfer radical polymerization. They developed poly(ethylene glycol)-*b*-poly(2-(diisopropylamino) ethyl methacrylate-*co*-dithiomaleimide) and poly(ethylene glycol)-*b*-poly(2-(dibutylamino) ethyl methacrylate-*co*-dithiomaleimide) amphiphilic block copolymers. The copolymerization of dithiomaleimide monomer within pH-responsive polymers led to an enhanced efficacy for cell imaging and an improved drug release profile. These polymeric systems formed micelles in aqueous solutions which were used as drug vehicles for the encapsulation of the anticancer drug, DOX. Both systems showed a greater DOX release profile in acidic environments than at physiological conditions. Also, the poly(ethylene glycol)-*b*-poly(2-(diisopropylamino) ethyl methacrylate-*co*-dithiomaleimide) exhibits a better antitumor effect than the polymer with poly(2-(dibutylamino) ethyl methacrylate) responsive component. Both systems, revealed significant biocompatibilities, as almost 85% of cells survive

in the presence of these fluorescent micelles at a concentration of up to 200  $\mu\text{g}/\text{mL}$  [66].

Recently Mandal and co-workers [67] reported the same nanogel system as mentioned above but in its more advanced form. The current responsive system has an extra stimulus for more efficiency and targeted drug delivery. Specifically, they synthesized an amphiphilic pentaerythritol-poly(*ε*-caprolactone)-*b*-poly(acrylic acid) triple-responsive (pH, magneto, redox) block copolymer which formed nanogel. The PAA monomer is assumed to participate in the reaction with 2-hydroxyethyl disulfide generating redox and pH sensitive nanogel. The spherical nanogels were able to form nanosized particles (120 nm) and encapsulate DOX. Drug release studies revealed their responsive character, under the participation of all three stimuli. Especially, at physiological conditions, the nanogel showed low percentage of drug release, while, at acidic conditions the release of DOX improved significantly. Furthermore, the DOX release was significantly reinforced to 65% in 1 h at acidic conditions in the presence of 10 mM glutathione and external magnetic field [67].

### 4.3 Safety of polymer-based drug delivery systems

As mentioned above, safety and biocompatibility are crucial parameters, which should be taken into account for the involvement of block copolymers in pharmaceutical formulations. The design of block copolymers aims to adjust the *in vivo* pharmacokinetics, stability, and distribution profiles of drug-loaded block copolymers. Several systems based on block copolymers are currently undergoing clinical studies. However, an important challenge in the research and development of these materials is to specify the physicochemical characteristics that influence the properties of the drug cargo *in vivo*.

Poloxamers also known as “Pluronics” are amphiphilic triblock copolymers consisting of a central hydrophobic chain of poly(propylene oxide) (PPO) and hydrophilic chains of PEO [68]. These block copolymers are the most studied materials used to form drug-loaded polymeric systems for drug delivery, as they are commercially available and biocompatible with low toxicity [69,70]. However, there are some limitations related to the inability of these polymers to encapsulate large amounts of hydrophobic drugs, as well as their high critical micelle concentrations (CMC), which lead to the low stability of micelles and their increased dissociation when diluted in the blood stream during intravenous injection [71].

One way to improve the stability of formed micelles is to mix poloxamers with a more hydrophobic copolymer which can significantly improve their stability and thus the bioavailability of encapsulated drugs. A characteristic example was reported by Mu *et al.* [72]. Specifically, they mixed poloxamer copolymers L61, L62, and P85 each with methoxy poly(ethylene glycol)-*b*-poly(lactide) (mPEG-*b*-PLA) that presented lower CMC at different ratios. The acquired data revealed sizes at nanoscale for all mixed systems in a range from 19.6 to 28.5 nm, in contrast to pure poloxamers forming large particles of approximately 1,000 nm. The anticancer drug docetaxel was entrapped in these mixed NPs and both *in vitro* and *in vivo* results revealed superior effectiveness and bioavailability compared to the commercial formulation, Taxotere.

Another interesting work to enhance the CMC, *in vivo* bioavailability, and drug loading capacity was reported by Lo and co-workers [73]. They tried to control the low critical solution temperature (LCST) of mixed micelles. Methoxy poly(ethylene glycol)-*block*-poly(*N-n*-propylacrylamide-*co*-vinylimidazole) is a temperature-responsive copolymer and it presents LCST around 31°C. Above LCST, this copolymer forms micelles. Below LCST, the polymeric micelles dissociated as poly(*N-n*-propylacrylamide-*co*-vinylimidazole) and becomes hydrophilic. Thus, there is a chance of premature release of the drug when the drug is encapsulated in the copolymer and its storage is at a temperature below LCST. By mixing the copolymer with mPEG-*b*-PLA of low CMC, the mobility of the temperature-responsive copolymer was limited due to the interactions with PLA block, thus lowering the LCST. Therefore, stable mixed micelles were able to form at room temperature and in dilute solutions.

Popovici *et al.* [74] reported the fabrication of polymeric micelles for the encapsulation and delivery of 1-(5'-nitrobenzimidazole-2'-yl-sulphonyl-acetyl)-4-aryl-thiosemicarbazide to address bacterial oral diseases. Notably, they created poloxamer 407/API micellar systems characterized by a particle size of approximately 20 nm and physical stability at the refrigerator temperature without significant modifications of zeta-potential value. These systems demonstrated a remarkable encapsulation efficiency of 85% at a polymer/API ratio of 10/1, exhibiting both hemocompatibility and cytocompatibility. Significantly, the drug-loaded poloxamer micelles demonstrated enhanced antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli*, highlighting the potential of these nanoscale formulations to overcome the challenges posed by multidrug-resistant bacterial infections [74].

## 5 CD-block copolymer drug delivery systems

### 5.1 Exploring the synergistic potential of hybrid CD-block copolymer systems

From the technological point of view, polymers and, consequently, CDs-block copolymer NPs offer design versatility [75]. First, there are different types (compositions and architectures) of polymers and CDs and consequently, different types of NPs can be prepared (*i.e.*, micelles, polymerosomes, hydrogels, polymeric NPs, hybrid particles, *etc.*).

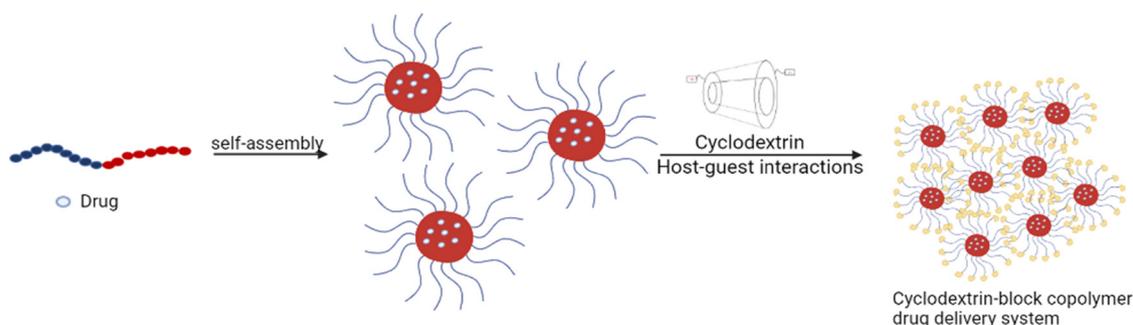
This review article recapitulates the potential applications of CD-block copolymer mixed systems in different drug delivery platforms. In this part, we present and analyze different examples from the recent literature. Figure 4 illustrates the combination of block copolymers with CDs for the formation of a drug delivery system.

First, DOX has gained great interest as the drug model in many studies. Poudel *et al.* [76] fabricated a hydrogel exploiting the interactions developed between the  $\alpha$ -CD and the amphiphilic PEG-*b*-PLA block copolymer micelles as a potent injectable DOX carrier for tumor treatment. More specifically, PEG-*b*-PLA micelles were created through hydrophobic interactions in an aqueous environment, followed by the formation of polypseudorotaxane microcrystals *via* host-guest interactions between  $\alpha$ -CD and PEG chains. The prepared micelles presented spherical structure with their hydrodynamic diameter ranging from 40–80 nm. Results obtained by rheological studies indicated that the higher concentration of  $\alpha$ -CD led to faster gel formation and improved viscosity. Moreover, altering the proportion of  $\alpha$ -CD in the hydrogel formulation resulted in controllable and sustained drug release. The shear-thinning and self-healing behaviors of the composed hydrogel and the long-term superior inhibition efficacy against cancer cells *in vitro* were also demonstrated. Therefore, the great biocompatibility

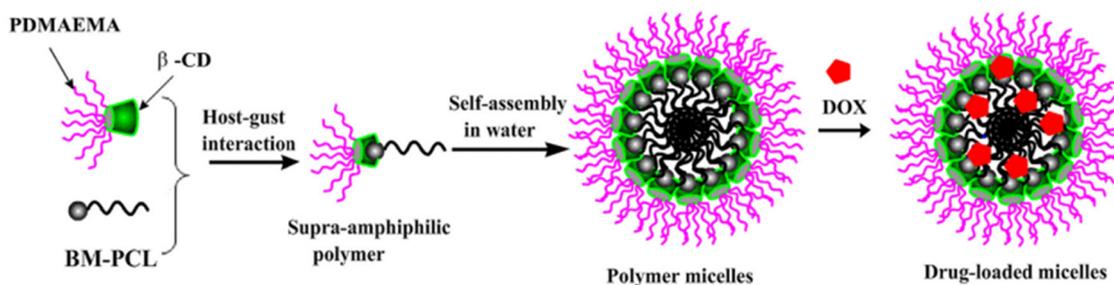
and excellent rheological properties of hydrogel based on PEG-*b*-PLA block copolymer micelles and  $\alpha$ -CD created a better profile of the formulation for application in cancer therapy [76].

A new generation of non-viral gene carrier, the amphiphilic star-like polymer was proposed by Cheng *et al.* to facilitate immunotherapy [77]. The core of the system was comprised of a biocompatible  $\beta$ -CD core, and hydrophobic poly( $\epsilon$ -caprolactone) (PCL) segments and the extending hydrophilic cationic poly(2-(dimethylamino) ethyl methacrylate) (PDMAEMA) arms were the main components of the shell. The prepared spherical NPs could condense plasmid DNA, forming stable polymeric micelles with particle size around 220 nm, narrow size distribution, positive zeta potential values, and the absence of obvious agglomeration phenomena. Owing to the micelle formation by PCL segments, it was proven to have enhanced stability after complexation with genes, lower toxicity, and greater condensation ability of plasmid DNA than the system without PCL chains. Using the most widely utilized nonviral gene transfection reagent lipofectamine as a reference, they showed superior transfection efficiency of more than 10.8%. Finally, the capability of the system to deliver genes and hydrophobic drugs, such as dexamethasone into macrophages was proven, and consequently reduce inflammatory reactions, making it a high-promising system for immune cell therapy [77].

Zhou's team [78] prepared supramolecular micelles combining PDMAEMA based on  $\beta$ -CD ( $\beta$ -CD-(PDMAEMA)<sub>7</sub>) and benzimidazole (BM) modified PCL through the host-guest recognition between  $\beta$ -CD and BM (Figure 5). The hydrophobic complex of  $\beta$ -CD and the modified drug resided preferably in the core, while the pH-sensitive PDMAEMA acted as the shell, forming micelles with regular spherical configuration. The entrapment efficiency of drug molecules like DOX was proven since drug-loading content and entrapment efficiency values ranged up to 40 and 86%, respectively. Owing to the presence of pH-sensitive PDMAEMA, supramolecular micelles exhibited pH-sensitivity, leading



**Figure 4:** Illustration of a drug delivery system formed after the combination of CDs with block copolymers.



**Figure 5:** Formation of supramolecular micelles from  $\beta$ -CD-(PDMAEMA)<sub>7</sub> star polymer. Adopted from Zhou *et al.* [78].

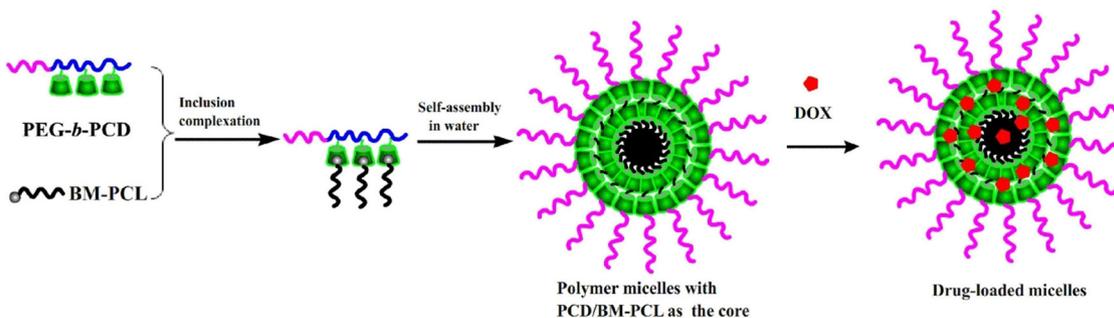
to different results under neutral and acidic conditions as the drug release could be accelerated with the decrease in pH and simultaneously with the increase in temperature. Thus, the above properties, in combination with the excellent anticancer activity, offer great prospects to supramolecular micelles as nanocarriers of anticancer drugs [78].

A similar study was conducted by Cui and co-workers [79], who developed supramolecular assemblies through inclusion complexation between  $\beta$ -CD and BM after the combination of chitosan-graft- $\beta$ -CD with BM end functionalized PEG-*b*-PCL block copolymer. PCL segments and  $\beta$ -CD cavity functioned as the hydrophobic membrane of the complex vehicles, while the corona consisted of hydrophilic PEG chains and chitosan. The complex vehicle size was around 100 nm and they could efficiently host both hydrophilic DOX and hydrophobic curcumin. The drug loading content was up to 38.4 and 20.2% for DOX and curcumin, respectively. As it was mentioned in the previous study [78], due to the sensitivity of host-guest interactions between  $\beta$ -CD and BM, the release of both drugs from supramolecular micelles could be controlled by altering the surrounding temperature and pH conditions. More specifically, at neutral pH conditions, BM has a hydrophobic character and could be incorporated into CD cavity. In contrast, acidic pH leads to the protonation of BM and therefore to the dissociation of the complex. Consistent with the results taken

by cytotoxicity assays showed that the prepared drug-loaded vesicles retained higher inhibition of proliferation efficiency than free drugs. As a result, these dual drug carriers could have good prospects as intelligent tools for anticancer drug delivery [79].

A novel vector based on folate-conjugated amphiphilic copolymer folate-poly(ethylene glycol)-poly(D,L-lactide)- $\beta$ -CD (FA-PEL-CD) was synthesized by Zhang *et al.* [80]. Results demonstrated the ability of PEL-CD and FA-PEL-CD to form stable micelles at low concentrations, due to their low colloidal micelles concentrations. The particle size of polymeric systems was around 100–150 nm, whereas that of DOX-loaded micelles ranged from 100 to 200 nm, presenting smooth exterior part and low size distribution. Treatment with FA-PEL-CD/DOX micelles induced significantly superior tumor growth inhibition (86%) compared to treatment with the same dose of micelles without the conjunction of folate (73%). Thus, this innovative micellar drug delivery system is suggested to be a potential nanocarrier for targeted DOX delivery, with high accumulation of the drug in tumor sites, ameliorated anticancer activity and alleviated toxic side effects in healthy tissues [80].

Gao *et al.* [81] prepared stimuli-responsive complex micelles with core-shell morphology driven by host-guest interactions between  $\beta$ -CD containing block copolymer PEG-*b*-PCD and BM modified PCL (Figure 6). Complex



**Figure 6:** Formation of complex micelles for drug loading. Adopted from Gao *et al.* [81].

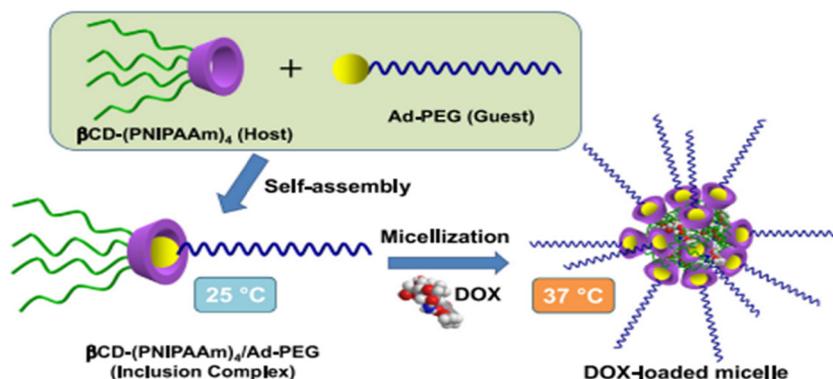
micelles presented as regular spheres with narrow size distribution and their diameter was around 255 nm. DOX was used as a model drug and the study demonstrated the high encapsulation efficiency of micelles for DOX, which was up to 74.77%. *In vitro* drug release studies revealed a significantly faster release of DOX under mildly acidic environments or high temperatures compared to neutral environments and lower temperatures. These polymeric micelles represent a potential new smart drug carrier for long-term controlled release of drugs as guest molecules [81].

Another promising candidate for the cure of cancer is a micellar drug delivery system developed by Song *et al.* [82]. They formed non-covalently connected micelles consisting of a hydrophobic, poly(*N*-isopropylacrylamide) core and hydrophilic PEG corona, whereas a well-defined  $\beta$ -CD-based poly(*N*-isopropylacrylamide) star host polymer with a degree of polymerization of 21 per arm and adamantyl-containing PEG guest polymer was synthesized (Figure 7). Subsequently, the host polymer and the guest polymer formed a pseudo-block copolymer *via* inclusion complexation between  $\beta$ -CD core of the host polymer and adamantyl-moiety of the guest polymer. Poly(*N*-isopropylacrylamide) is a widely used thermoresponsive polymer which is soluble in water below its LCST (32°C) and it experiences a reversible, abrupt coil-to-globule phase transition above its LCST [83,84]. The thermoresponsive properties of the micellar drug delivery system were identified. More specifically, the pseudo-block copolymer was hydrophilic and soluble in aqueous media at room temperature (below the LCST), while the hydrophobic character of the poly(*N*-isopropylacrylamide) host polymer was prevailing at body temperature, leading to micelles formation. At the same conditions and at the concentration of 0.2 mg/mL, there were micelles formed with particle size around

282 nm, which was a suitable size for drug carriers. Afterwards, Song *et al.* loaded DOX into the interior of the micelles, and they achieved a loading efficiency of 17%. *In vitro* cell cytotoxicity studies demonstrated good biocompatibility, enhanced antitumor activity and ability to circumvent the multidrug resistance in cancer cells. All these properties permitted this thermoresponsive platform to deliver successfully and to achieve desired therapeutic effects of the incorporated guest-molecule [82].

To combine both drug release advantages of physical cross-linked injectable hydrogels and NPs, Zhu *et al.* [85] presented a new type of self-assembled supramolecular hydrogels composed of cisplatin-coordinated polymeric micelles poly(ethylene glycol)-*b*-poly(acrylic acid) (PEG-*b*-PAA) and  $\alpha$ -CD which is a promising injectable system for sustained delivery of cisplatin in cancer therapy. The creation of a network construction was accomplished due to the cooperative interactions between platinum(II) atoms and PAA blocks, as well as the complexation of PEG chains with  $\alpha$ -CDs. These composite hydrogelated micelles provide indispensable cross-links, the micellar cores, as an integral part of the network structure in comparison with other hydrogel/micelle and hydrogel/microsphere systems. The research of Zhu *et al.* indicated that the gelation properties could be tuned by altering concentrations of the polymers and cisplatin, as well as by adding PEG homopolymers or poloxamer copolymers. Finally, the thixotropic behavior, reversibility, and relatively high cytotoxicity to human bladder carcinoma EJ cells of cisplatin-coordinated PEG-*b*-PAA/ $\alpha$ -CD supramolecular hydrogels offer them great potential for applications in sustained delivery of cisplatin by injection [85].

Xu *et al.* [86] presented unimolecular micelles of star-like amphiphilic polymers consisting of a  $\beta$ -CD core, from which 21 hydrophobic PLA arms and hydrophilic PEG arms



**Figure 7:** Illustration of the formation of  $\beta$ -CD-(poly(*N*-isopropylacrylamide))<sub>4</sub>/adamantyl-containing PEG supramolecular pseudo-block copolymer *via* host-guest interactions, followed by the thermoresponsive micellization while encapsulating drug molecules into the core, forming drug-loaded micelles for drug delivery and overcoming drug resistance. Adopted from Song *et al.* [82].

were grafted sequentially. This cooperation effect of complexation resulted in the formation of robust, monodisperse unimolecular micelles that were uniform and stable in aqueous solution. The composed biocompatible micelles showed little cytotoxicity against HeLa and HEK 293T cells accompanied by their efficient ability to encapsulate hydrophobic anticancer agents, such as DOX, in the hydrophobic domain of PLA and to demonstrate pH-controlled release behavior. Thus, the unimolecular micelles formed by this star-like  $\beta$ -CD-PLA-PEG constitute a new promising drug delivery system for a wide variety of bioactive agents [86].

Vega *et al.* [87] examined the influence of HP- $\beta$ -CD as a cryoprotectant to poly(lactic-co-glycolic acid) (PLGA)-PEG diblock copolymer nanospheres (NSs) incorporating flurbiprofen and they evaluated the effect of freeze-drying and  $\gamma$ -irradiation sterilization on the properties of NSs. It was demonstrated that HP- $\beta$ -CD offered efficient cryoprotection to maintain the NSs unaffected and  $\gamma$ -irradiation was an appropriate way that permitted the sterilization of the formulations for ophthalmic administration preventing the development of contaminants. All formulations prepared were characterized by suitable particle size (less than 250 nm) with a narrow particle size distribution for ocular administration. *In vitro* drug release studies showed that the presence of HP- $\beta$ -CD led to the reduction in the burst effect, providing an enhanced sustained release of the drug, whereas a significant reduction in the flurbiprofen transcorneal permeation of NSs containing HP- $\beta$ -CD was observed in the *in vitro* results. Finally, Vega *et al.* suggested that NSs penetrated corneal epithelium through a transcellular pathway. They showed that  $\gamma$ -irradiated NSs stored as freeze-dried powders maintained their initial characteristics and were stable for 3 months of storage in the aqueous form at 4°C [87].

Highly auspicious nanovehicles for targeted anticancer therapy were the innovative amphiphilic star-shaped reductive stimulus-responsive nanocarriers which were composed of M- $\beta$ -CD conjugated with mPEG-*b*-PCL and hydrosulfonyls

through disulfide links (Figure 8) [88]. The hydrophobic cores of assemblies were mainly composed of methyl groups and PCL, while the extending PEG chains were the main component of the shell. The resultant NSs had core-shell structure and micellar properties and their particle size ranged from 50 to 70 nm, permitting the entrapment of hydrophobic drugs like DOX in the inner cavity. Therefore, Li *et al.* developed amphiphilic drug delivery platforms which displayed excellent drug loading capacity, targeted uptake in cancer cells, good biocompatibility *in vivo*, controlled drug release under reductive conditions, superior anticancer performance, high tumor clearance with minimal toxicity to normal cells, making them promising candidates which should be further evaluated in clinical practice [88].

Çirpanli *et al.* designed, developed, and compared thoroughly polymeric and amphiphilic CD NPs for the incorporation and delivery of the hydrophobic drug camptothecin, using amphiphilic  $\beta$ -CDs (6-*O*-Capro- $\beta$ -CD,  $\beta$ -CDC6, HP- $\beta$ -CD), PLGA, or PCL. Particle size was less than 275 nm and polydispersity index (PDI) less than 0.2, whereas drug-loading values of amphiphilic CD NPs were higher than those of PLGA and PCL polymeric NPs. Furthermore, a superior controlled release profile was observed with a duration of 12 days for amphiphilic CD NPs in comparison with the duration of 2 days for polymeric NPs. Finally, CD NPs showed higher anticancer efficacy than PLGA or PCL NPs loaded with camptothecin. These NPs were characterized by their small size, stability, effectiveness, safety, syringeability, and membrane filterability, representing a new generation carrier system for the effective delivery of hydrophobic APIs with a similar hydrophobic profile to camptothecin [89].

Aiming to improve the encapsulation efficiency of relatively hydrophilic sepiapterin drug within the lipophilic cavity of methoxy-PEG-PCL NPs, Kuplennik and Sosnik used 2,3,6-triacetyl- $\beta$ -CD for the complexation and augmentation of hydrophobicity of sepiapterin [18]. They used two different methods for the achievement of nanoencapsulation: drying with copolymer and preparation of a



**Figure 8:** Detailed synthetic routes of a series of CD-block copolymers complex. Adopted from Li *et al.* [88].

sepiapterin/2,3,6-triacetyl- $\beta$ -CD complex by the spray-drying technique. By means of the nano-precipitation method between the sepiapterin/2,3,6-triacetyl- $\beta$ -CD spray-dried complex and methoxy-PEG-PCL solution at the appropriate molar ratio, they obtained NPs with a particle size of 74–75 nm and SD = 21–22 nm. The encapsulation efficiency (85%) and drug loading (2.6%) values were significantly higher than those of the pristine API (14 and 0.6%, respectively), whereas sepiapterin release from NPs exhibited a relatively low burst effect of 20%. Overall, the obtained results pave the way for the use of this innovative strategy for nanoencapsulation of hydrophilic drugs, such as sepiapterin [18].

Li *et al.* [90] created NPs complexes by combining PLGA polymer with 2-HP- $\beta$ -CD to accomplish the therapeutic efficacy and improve the bioavailability and ocular delivery of triamcinolone acetonide, which is a highly lipophilic drug. The composed systems had spherical and uniform dispersion of NPs. Their average particle size was less than 200 nm, proving their ability to carry drugs around the cornea and deliver them to the posterior segment of the eye, whereas  $\zeta$ -potential measurements demonstrated negative values. The cumulative permeation amount, loading capacity, and entrapment efficiency values were significantly higher than that of the PLGA NPs, proving that the presence of CD enhanced the entrapment efficiency due to the increase in drug's solubility and system's stability [90].

Supramolecular hydrogels (SMGels) are multifunctional systems, formed by CDs and polymers achieving the establishment of a three dimensional solid-like network through intermolecular non-covalent bonds that are capable to absorb large amounts of water [9]. Due to their advantageous biocompatibility and their capacity to absorb large amounts of water, they have been widely investigated for biomedical applications and particularly for the controlled and sustained release of the encapsulated bioactive compounds [91].

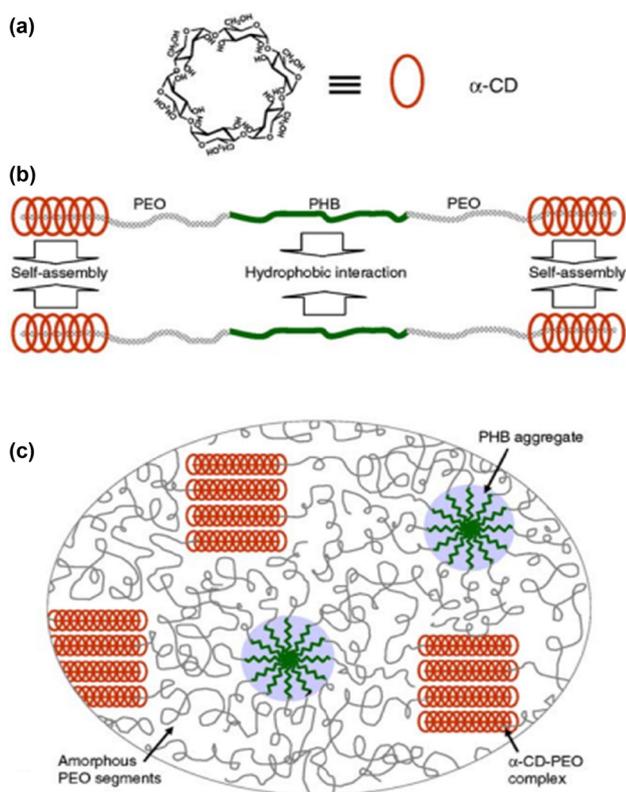
SMGel formed by triblock PCL-PEG-PCL copolymer and  $\gamma$ -CD was investigated for injectable delivery of insulin by Khodaverdi *et al.* [9]. The formulation of a hydrogel loaded with insulin was prepared by mixing an aqueous solution of copolymer and drug with an aqueous  $\gamma$ -CD solution in less than a minute. The result was the formation of a hydrogel with a three-dimensional porous foam-like structure, thixotropic behavior, good water-swelling ability in distilled water, and excellent syringeability. *In vitro* release studies demonstrated that insulin-loaded SMGel has a continuous release profile of above 80% of the drug over a 20 days period, whereas insulin maintained its native state after formulating and releasing from the SMGel. In other words, the prepared, biocompatible, biodegradable

formulation could be a novel carrier for injectable sustained release of insulin [9].

In the same manner, the same research group developed self-assembled SMGels through inclusion complexation of PCL-PEG-PCL micelles and  $\gamma$ -CD for the controlled release of dexamethasone [92]. Many formulations with different ratios of components were tested. Among them, only the aqueous solution containing 10 and 20% (w/v), and the one containing 2.5 and 25% (w/v) of copolymer and  $\gamma$ -CD, respectively, formed hydrogels at 25°C. They used the first one which was formed successfully in just 4 s. The SMGel showed a porous, foam-like structure and good water-swelling ability because its weight increased 1.5 times after 15 min. It also demonstrated shear-thinning and thixotropic behavior, making it capable to absorb large amounts of water, resulting in the increase in the system's biocompatibility. Results of *in vitro* release studies indicated the slow-release rate of dexamethasone from the SMGel, with a slight burst release. The greater the amount of dexamethasone was, the significantly higher the rate of release, whereas SMGel degradation occurred after more than 3 weeks. The aforementioned results suggested the potential use of the prepared hydrogel as a sustained-release system for dexamethasone [92].

A new supramolecular hydrogel self-assembled between  $\alpha$ -CD and a biodegradable poly(ethylene oxide)-poly[(R)-3-hydroxybutyrate]-poly(ethylene oxide) (PEO-PHB-PEO) triblock copolymer was developed by Li *et al.* (Figure 9) [93]. The interactions that took place between copolymer segments with  $\alpha$ -CD led to the formation of a self-assembled SMGel that produced a strong macromolecular network. The composition, molecular weight, and chemical structure of the copolymers could be modified to ameliorate the hydrogel properties. The *in vitro* release kinetics studies indicated the potential of hydrogels for long-term sustained controlled release of drugs, whereas rheological experiments demonstrated that it was thixotropic and reversible, holding great potential as injectable drug delivery systems of macromolecular drugs [93].

The potential of the innovative CD-functionalized asymmetric block copolymer films was demonstrated by the work of Huang and co-workers [94]. They combined the amphiphilic polystyrene-*block*-poly(4-vinylpyridine) (PS-*b*-P4VP) block copolymer with  $\beta$ -CD, to construct highly adsorptive, asymmetric membranes, that were characterized by a thin layer of highly ordered and uniform cylindrical nano-channels on top of a non-ordered macroporous sponge-like layer. The membranes showed excellent biocompatibility and outstanding adhesion capability to various kinds of substrates, which was of paramount importance for application in medical devices, whereas the cytotoxicity assay results confirmed



**Figure 9:** (a) The structure of  $\alpha$ -CD, (b) the schematic illustrations of the proposed structures of  $\alpha$ -CD/PEO-PHB-PEO inclusion complex, and (c)  $\alpha$ -CD/PEO-PHB-PEO supramolecular hydrogel. Adopted from Li *et al.* [93].

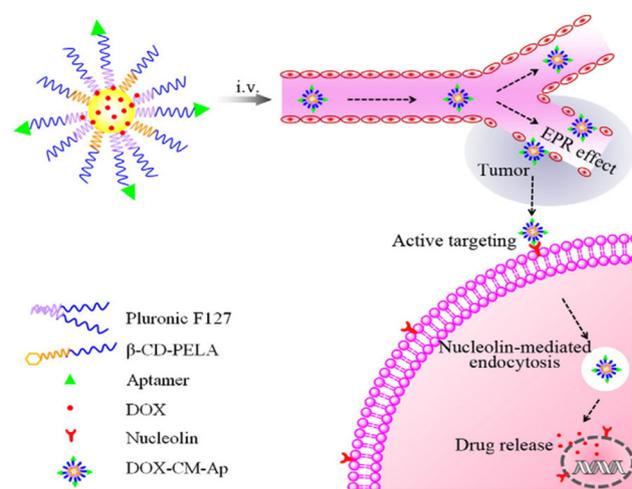
their biocompatibility and safe application, showing minimal cytotoxicity. The relatively thick (about 50  $\mu\text{m}$ ) macroporous sponge-like sublayer acted as a reservoir for the drug molecules. Moreover, the supramolecular interaction of CD and the spongy highly porous sublayer of the membranes provide them a large space to load in a high extent the model drug, triclosan. Drug release lasted for more than 2 weeks without an initial burst effect, showing a pH-responsive release behavior and a significant antibacterial effect against *Escherichia coli* due to the triclosan release. As such, from all we mentioned, it is obvious that the isoporous block copolymer membranes could serve as a novel high-capacity reservoir for drug delivery [94].

Another new generation nanocarrier for the delivery of lipophilic drugs was developed by Zhang *et al.* [95]. They synthesized double hydrophilic copolymers (PEG-*b*-PCDs) consisting of one PEG block and a block containing  $\beta$ -CD units, which in the presence of the hydrophobic poly(*b*-benzyl L-aspartate) (PBLA) formed complex assemblies with a core-shell structure due to host-guest interactions between  $\beta$ -CD and hydrophobic benzyl group. The hydrophobic core composed of PBLA homopolymer was surrounded by hydrophilic PEG chains at the outer surface

of the corona. It was found that the increase in PBLA's molecular weight resulted in a decrease in particle size of the assemblies. Finally, they proved that the prepared assemblies maintain their stability during long-term storage and their reconstitution ability after freeze-drying [95].

As mentioned before, poloxamers are amphiphilic triblock copolymers that have received approval for pharmaceutical application by the US-FDA [96]. These polymers have gained high scientific interest due to their high degree of biocompatibility and their self-assembly behavior, forming several structures, from micelles to polymersomes and polymeric particles, which are ideal for drug delivery purposes. They are commonly utilized to increase the solubilization of some hydrophobic drugs [96] and can also be modified for bioconjugation purposes [97]. In the existing literature, numerous studies explore the synergy effect of poloxamers and CDs to formulate hybrid drug delivery systems.

An attractive drug delivery vehicle for targeted delivery of DOX to human breast tumors was developed by the combination of poloxamer 407 with surface modification of aptamer AS1411 and  $\beta$ -CD linked PEG-*b*-PLA (Figure 10) [97]. This novel binary system loaded with DOX exhibited enhanced antitumor activity and decreased induction of cardiotoxicity in comparison to the non-AS1411-modified system. Also, it showed a long-circulation profile *in vivo* with a longer half-life, larger AUC, and slower clearance when compared to free DOX, permitting it to accumulate more efficiently within the tumor tissues *via* the enhanced permeability and retention (EPR) effect and through the selective binding to receptors on MCF-7 cells. Results indicated a dependence of *in vitro* drug release on pH conditions, as the



**Figure 10:** Schematic diagram of the multifunctional composite micelles modified by aptamer AS1411 and the mechanism of interaction between nucleolin receptors and aptamer AS1411 ligands. Adopted from Li *et al.* [97].

amount of released DOX from micelles and pH values were inversely related. Overall, this multifunctional composite micelle modified with aptamer AS1411 is suitable for DOX loading with efficient capacity, enhanced micelle stability, precise and effective tumor targeting, greater cellular uptake, prolonged circulation time in blood, better accumulation in tumor, increased anticancer activity, and alleviated side effects compared to free DOX [97].

In another report, Jansook *et al.* formulated CD-poloxamer P407 micelles as self-assembled nanocarriers for dexamethasone and amphotericin B [98]. The formation of inclusion complex occurred by entering the PPO part into the  $\gamma$ -CD cavity. The presence of a more hydrophilic  $\gamma$ -CD derivative, HP- $\gamma$ -CD, resulted in the improvement of drug solubility, reduction in the crystallinity of CD-poloxamer aggregates, and avoidance of hemolytic effect, making the ternary system appropriate for ophthalmic drug delivery. In their study, they tested two different model drugs: dexamethasone, a small hydrophobic drug molecule, and amphotericin B, a large amphiphilic drug. Results indicated that dexamethasone and other similar molecules in combination with the ternary system might form large complex aggregates with improved water solubility, in contrast to drugs like amphotericin B, which did not hold great potential for delivery with these nanocarriers due to low drug aqueous solubility occurring by the competitive effect. Also, they observed that the surface tension of the formulations and poloxamer P407 concentration were inversely related, whereas higher P407 amounts in the formulations led to the higher formation of complex aggregates with a slower drug release rate. Consequently, adjusting the molar ratios and concentrations of the used components could lead to a desirable ocular drug formulation development [98].

Mixed micelles of Soluplus, that is polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol (PVCL-PVA-PEG) graft copolymer with amphiphilic characteristics, and poloxamer P103 and their combination with  $\alpha$ -CD could lead to the formation of polypseudorotaxanes [99]. The aforementioned hybrid system was developed as a suitable platform to regulate drug release and improve the ocular permeability of poorly soluble drugs, like natamycin. Zeta potential showed slight negative values, whereas the particle size of mixed micelles (150–110 nm) was significantly higher than poloxamer P103 micelles (16–20 nm) and Soluplus micelles (90–103 nm), indicating that the large PPO segment of poloxamer P103 inserted into the Soluplus cores. Mixed micelles increased natamycin solubility up to 2.77-fold. Overall, the results of this study indicated that mixed micelles and their related polypseudorotaxanes can be used for the controlled release of drugs with relatively low water aqueous solubility, permitting middle diffusion of

drug, cornea, and sclera accumulation, and sclera permeability coefficients, without damaging effects on biocompatibility [99].

Ni *et al.* [100] developed a novel SMGel based on self-assembly between poloxamer triblock copolymers and  $\alpha$ -CD. They concluded that the gelation was induced by the complex formation between the PEO segments of the PEO-PPO-PEO triblock copolymer and  $\alpha$ -CD, and the further self-assembly of the partially formed inclusion complexes. The gelation process could be aided by the addition of  $\alpha$ -CD, reducing the concentration of the copolymer needed. The hydrogels were found to be thixotropic and reversible and can be applied as a promising injectable drug delivery system [100].

Zafar *et al.* [101] used HP- $\beta$ -CD and poloxamer 188 to incorporate genistein into binary (genistein:HP- $\beta$ -CD, 1:1) and ternary (genistein:HP- $\beta$ -CD:poloxamer188, 1:1:0.5) inclusion complexes. The obtained results of the study revealed a remarkably greater release profile of genistein from inclusion complexes. Furthermore, the existence of poloxamer 188 in the ternary complex permitted them to exhibit a significant enhancement in dissolution rate in comparison to the binary complexes. There was also observed an increase in activity and a significantly higher concentration-dependent cytotoxicity to cancer cells in ternary genistein-inclusion complex than in pure API, whereas the crystal structure of genistein converted to an amorphous structure with a rough and irregular shape in genistein ternary systems. Consequently, the ternary system could be a promising way for ameliorating the solubility profile of genistein, making it a promising candidate for the cure of breast cancer [101].

Nogueiras-Nieto *et al.* [102] showed that the incorporation of poloxamer 407 into the drug-CD complexes aqueous solutions involved competition with studied drugs, triamcinolone acetonide and ciclopirox olamine, for the cavity of the CD molecule. They used two hydrophilic derivatives of  $\beta$ -CD, HP- $\beta$ -CD, and partially M- $\beta$ -CD. This competitive mechanism of action led to the displacement of the drug from the CD cavity and the formation of soluble polypseudorotaxanes that stack forming nanorods, which had a crucial impact on the release of the drugs studied. Therefore, noteworthy changes in the release rate and the solubility properties of the systems have taken place, depending on the stability of the drug-CD inclusion complex and on CD concentration in the bulk solution. Thus, the formation of polypseudorotaxanes can be employed to modulate drug-controlled release from thermosensitive hydrogels [102].

Simões *et al.* [103] formulated a syringeable gel formulation for sustained delivery of vancomycin, taking advantage of the capability of poloxamer 407 to form

supramolecular gels with  $\alpha$ -CD. The results of the study showed that the augmentation of  $\alpha$ -CD concentration led to faster gel formation. Other crucial parameters that affect remarkably not only the gel rate formation but also the physical stability of the prepared systems were the molar ratio of the components and the storage temperature. Indeed, the gels composed of a low proportion of  $\alpha$ -CD showed phase separation at 4 or 37°C, whereas the systems containing 6.5% copolymer and at least 5%  $\alpha$ -CD at 20°C appeared to have the most physical stability. Also, they reported that the proportion of 6.5–13% triblock copolymer and 5–7%  $\alpha$ -CD appeared to be the most adequate for the preparation of injectable drug depots for the local treatment of infections against *Staphylococcus aureus*. From all taken results, they suggested that the most promising formulation was that which contained 13% poloxamer 407 and 5%  $\alpha$ -CD, since it was characterized by high viscoelastic behavior, stability at least for 1 month, rapid gel formation, easy syringeability, and controlled drug release for several days [103].

The combination of poloxamer 407 with M- $\beta$ -CD or HP- $\beta$ -CD as components of drug delivery systems for possible brain targeting after nasal administration of ropinirole has also been reported in our recent article [104]. The findings of our study demonstrated the existence of a range of interactions between the compounds, likely due to the creation of an inclusion complex. The NPs presented spherical shape and were stable during the 1 month stability assessment. *In vitro* cytotoxicity evaluation on HEK293 cell lines revealed that the prepared systems were biocompatible at low concentrations. *In vitro* diffusion experiments revealed that more than 90% of the loading dose was released up to 4 h, and *ex vivo* permeation experiments through rabbit nasal mucosa showed enhanced permeability of RH up to 50% compared to the API solution. Thus, these NPs have potential for efficient drug delivery, specifically for nose-to-brain delivery of the antiparkinsonian drug, ropinirole [104].

Lin *et al.* [105] formulated a thermoresponsive gel containing the triblock copolymers poloxamer 407 and poloxamer 188, as well as PEG 6000 and HP- $\beta$ -CD for the intranasal administration of rhynchophylline for managing Parkinson's disease. The use of polymers prompts the transformation of gel from the solution state to the semi-solid state after intranasal administration. The pharmacokinetic analysis revealed that the system's components could serve as permeation enhancers of rhynchophylline through nasal mucosa. Indeed, *in vivo* studies in mice revealed that this nasally administered formulation enhanced the bioavailability and brain targeting of rhynchophylline, improved the damaged dopaminergic neurons caused by Parkinson's

disease and offered neuroprotection and recovery of motor behavior [105].

## 5.2 Drug molecules encapsulation in CD-block copolymer delivery systems

The combination of block copolymers with CDs can result in new biomaterials and supramolecular structures, which possess the physicochemical and thermotropic properties of both classes of materials. A significant application of their combination is the design of innovative delivery systems for the transport of genes and APIs. In the literature, there is available a large gamut of APIs that can be encapsulated into these systems, such as amphotericin B, camptothecin, ciclopirox olamine, cisplatin, curcumin, dexamethasone, doxorubicin, insulin, flurbiprofen, genistein, natamycin, rhynchophylline, ropinirole, sepiapterin, triamcinolone acetonide, triclosan, and vancomycin. Table 2 presents some examples of CD-block copolymer formulations from the literature, showcasing their added value alongside the corresponding encapsulated molecules and the related diseases they are used for.

## 5.3 Preparation techniques and physicochemical characterization of CD-block copolymer based drug delivery systems

As it has been described in the literature, a wide spectrum of techniques has been conducted for the preparation and characterization of CD-block copolymer-based drug delivery systems. More specifically, these techniques include the co-lyophilization method, co-solvent evaporation method, nanoprecipitation method, ring-opening polymerization technique with microwave irradiation, oil/water method, cold method, dropwise mixing, and magnetic stirring. Regarding the characterization of the CD-block copolymer based drug delivery systems, differential scanning calorimetry has been used for the evaluation of the physicochemical state and thermal transitions of the pristine compounds, their combination, and the whole system, as well as the interactions between them. Furthermore, dynamic light scattering, electrophoretic light scattering, static light scattering, scanning electron microscope analysis, transmission electron microscopy, high-performance liquid chromatography, proton nuclear magnetic resonance and carbon-13 nuclear magnetic resonance, Fourier

**Table 2:** CD-block copolymer formulations, their added value, and corresponding encapsulated molecules and associated diseases

Formulation	Block copolymer	CD	APIs	Disease	Added value	Ref.
Micelles	PEG- <i>b</i> -PLA	$\alpha$ -CD	Doxorubicin	Cervical cancer	<ul style="list-style-type: none"> <li>- Sustained and controlled release rate of DOX from SMGel</li> <li>- Enhanced and prolonged inhibition efficacy against tumor cells <i>in vitro</i> compared to the free DOX</li> <li>- Biocompatibility</li> <li>- Superior rheological characteristics</li> </ul>	[76]
NPs/micelles	PCL- <i>b</i> -PDMAEMA	$\beta$ -CD	<ul style="list-style-type: none"> <li>- Dexamethasone</li> <li>- Genes</li> </ul>	—	<ul style="list-style-type: none"> <li>- Superior transfection efficiency compared to the most popular nonviral gene transfection reagent</li> </ul>	[77]
Micelles	<ul style="list-style-type: none"> <li>- PDMAEMA</li> <li>- PCL</li> </ul>		Doxorubicin	Cancer	<ul style="list-style-type: none"> <li>- High value of (%) encapsulation efficiency</li> <li>- pH responsiveness</li> <li>- Improved anticancer activity compared to free DOX</li> </ul>	[78]
Supramolecular assemblies	PEG-PCL	$\beta$ -CD	<ul style="list-style-type: none"> <li>- Doxorubicin</li> <li>- Curcumin</li> </ul>	Cancer	<ul style="list-style-type: none"> <li>- pH-responsive properties</li> <li>- Temperature-responsive properties</li> <li>- Controlled release rate of DOX and curcumin</li> </ul>	[79]
Micelles	PEG-PLA	$\beta$ -CD	Doxorubicin	Cancer	<ul style="list-style-type: none"> <li>- Biocompatibility</li> <li>- Improved antitumor activity compared to free DOX</li> </ul>	[80]
Micelles	PEG-PCL	$\beta$ -CD	Doxorubicin	Cancer	<ul style="list-style-type: none"> <li>- Decreased cardiotoxicity compared to free DOX</li> </ul>	[81]
Micelles	<ul style="list-style-type: none"> <li>- Poly(<i>N</i>-isopropylacrylamide)</li> <li>- PEG</li> </ul>	$\beta$ -CD	Doxorubicin	Cancer	<ul style="list-style-type: none"> <li>- High values of (%) encapsulation efficiency and drug loading</li> <li>- Thermoresponsive properties</li> </ul>	[82]
Hydrogelated micelles	PEG- <i>b</i> -PAA	$\alpha$ -CD	Cisplatin	Cancer	<ul style="list-style-type: none"> <li>- Biocompatibility of blank micelles</li> <li>- Improved antitumor efficacy compared to free DOX</li> </ul>	[85]
Micelles	PLA-PEG	$\beta$ -CD	Doxorubicin	Cancer	<ul style="list-style-type: none"> <li>- Sustained and controlled release rate of cisplatin</li> </ul>	[86]
Nanospheres	PLGA-PEG	HP- $\beta$ -CD	Flurbiprofen	Inflammatory diseases concerning ocular structures	<ul style="list-style-type: none"> <li>- pH-responsive sustainable drug release</li> <li>- Biocompatibility</li> <li>- Stable for 3 months at 4°C</li> </ul>	[87]
Nanospheres	PEG-PCL	M- $\beta$ -CD	Doxorubicin	Cancer	<ul style="list-style-type: none"> <li>- High DOX loading capacity</li> <li>- Biocompatibility</li> <li>- Targeted uptake in cancer cells</li> <li>- Controlled release rate of DOX</li> <li>- Reduced toxic effects in normal cells compared to free DOX</li> </ul>	[88]

(Continued)

Table 2: Continued

Formulation	Block copolymer	CD	APIs	Disease	Added value	Ref.
NPs	- PLGA - PCL	- 6-O-Caproyl- $\beta$ -CD - $\beta$ -CDC6 - HP- $\beta$ -CD	Camptothecin	Cancer	- Enhanced anticancer activity - Controlled release rate of camptothecin from NPs - Syringeability	[89]
NPs	Methoxy-PEG-PCL	2,3,6-triacetyl- $\beta$ -CD	Sepiapterin	Tetrahydrobiopterin deficiency	- Sustained and controlled release rate of Sepiapterin	[18]
NPs	PLGA	HP- $\beta$ -CD	Triamcinolone acetonide	Inflammatory diseases	- Improved bioavailability compared to the free triamcinolone acetonide	[90]
SMGel/Vehicles	PCL-PEG-PCL	$\gamma$ -CD	Insulin	Diabetes mellitus	- Greater release profile compared to pure insulin - Excellent syringeability of SMGel - Sustained and controlled release rate of insulin from SMGel with an initial burst effect (significant advantage compared to similar drug delivery systems)	[9]
SMGel/micelles	PCL-PEG-PCL	$\gamma$ -CD	Dexamethasone	Inflammation in response to infectious, immunological, mechanical, and chemical stimuli	- Thixotropic behavior - Excellent syringeability of SMGel - Sustained and controlled release rate of dexamethasone from SMGel - Biocompatibility	[92]
SMGel/micelles	PEO-PHB-PEO	$\alpha$ -CD	Macromolecular drugs	—	- Long-term sustained and controlled release of macromolecular drugs	[93]
Films/membranes	PS- <i>b</i> -P4VP	$\beta$ -CD	Triclosan	Antibacterial	- High values of (%) encapsulation efficiency and drug loading - Biocompatibility - Long-term extended drug release behavior of triclosan	[94]
Core-shell structure	- PEG - PBLA	$\beta$ -CD	Doxorubicin	Cancer	- pH-responsive properties - Excellent adhesion properties on various substrates - Controlled release rate of DOX - Enhanced antitumor activity compared to free DOX	[95]
Micelles		$\beta$ -CD	Doxorubicin	Breast cancer	- Alleviated systemic toxicity compared to free DOX	[97]

(Continued)

Table 2: Continued

Formulation	Block copolymer	CD	APIs	Disease	Added value	Ref.
	- Poloxamer 407 (PEO-PPO-PEO) - PEG- <i>b</i> -PLA				- High values of (%) encapsulation efficiency and drug loading - Improved antitumor activity/efficacy compared to free DOX - Prolonged circulation time in blood compared to free DOX - Enhanced accumulation in tumor compared to free DOX - Decreased cardiotoxicity compared to free DOX	
Micelles	Poloxamer 407 (PEO-PPO-PEO)	- $\gamma$ -CD - HP- $\gamma$ -CD	- Dexamethasone - Amphotericin B	Eye inflammation	- Improved aqueous solubility compared to the pure DEX	[98]
Micelles	- Poloxamer 103 (PEO-PPO-PEO) - Soluplus (PVCL-PVA-PEG)	$\alpha$ -CD	Natamycin	Fungal keratitis	- Improved aqueous solubility compared to the pure natamycin - Prolonged permanence due to the temperature-responsive properties	[99]
SMGel	Poloxamer (PEO-PPO-PEO)	$\alpha$ -CD	Injectable drug	—	- Thixotropic and reversible SMGel	[100]
Inclusion complexes	Poloxamer 188 (PEO-PPO-PEO)	HP- $\beta$ -CD	Genistein	Breast cancer	- Improved aqueous solubility compared to the pure genistein - Enhanced cytotoxicity to cancer cells compared to free genistein	[101]
Polypseudotaxanes	Poloxamer 407 (PEO-PPO-PEO)	- M- $\beta$ -CD - HP- $\beta$ -CD	- Triamcinolone acetamide - Ciclopirox olamine	- Inflammation - Fungal and dermatological infections	- Thermoresponsive properties - Controlled release rate of triamcinolone acetamide and ciclopirox olamine	[102]
SMGel	Poloxamer 407 (PEO-PPO-PEO)	$\alpha$ -CD	Vancomycin	Activity against <i>Staphylococcus aureus</i>	- Easy syringeability of SMGel - High viscoelastic behavior of SMGel - Sustained and controlled release rate of Vancomycin from SMGel	[103]
NPs	Poloxamer 407 (PEO-PPO-PEO)	- HP- $\beta$ -CD - M- $\beta$ -CD	Ropinirole	Parkinson's disease	- Biocompatibility - Stable for 2 months at 20°C - Thixotropic behavior - Temperature-responsive properties	[104]
					- Physical stability of NPs - No cytotoxicity in low concentration in HEK 293 cell lines - High value of (%) encapsulation efficiency - Greater release profile compared to pure ropinirole solution	

(Continued)

Table 2: Continued

Formulation	Block copolymer	CD	APIs	Disease	Added value	Ref.
SMGel/micelles	- Poloxamer 407 - Poloxamer 188 (PEO- PPO-PEO) - PEG	HP- $\beta$ -CD	Rhynchophylline	Parkinson's disease	- Enhanced permeation profile of ropinirole through rabbit nasal mucosa compared to free ropinirole solution - Thermoresponsive properties - Biocompatibility - Sustained release rate of rhynchophylline - Enhanced permeation profile through nasal mucosa compared to free rhynchophylline - Improved bioavailability and brain targeting compared to free rhynchophylline	[105]

transform infrared-attenuated total reflection, UV-vis and fluorescence spectroscopy, and X-ray powder diffraction have been used to extract information on structural, morphological, and physicochemical properties of the aforementioned systems.

#### 5.4 Challenges in developing and scaling up CD-block copolymer hybrid systems at the industrial level

We have described several examples of hybrid systems containing CDs and block copolymers that have appeared in the literature. The findings of these studies were very optimistic, indicating the added value and promising prospects for fabricating CD-block copolymer-based platforms in the field of drug delivery applications. However, to the best of our knowledge, there is no CD-block copolymer product that has been approved by the EMA or the USFDA, nor has it been investigated in clinical trials, and for this purpose, this review could be a roadmap for the further development of these hybrid platforms, summarizing their properties, added value, and limitations in clinical translation.

Some important issues prevent their investigation in clinical trials and further scale-up at the industrial level. First of all, the development of polymer therapeutics faces a challenge in synthesizing new polymers with minimal nanotoxicity and low immunogenicity [75,106].

Moreover, an extensive physicochemical and morphological characterization is crucial for the development of all nanomedicine products. According to EMA [107], the identification of critical quality attributes of block copolymer micelle products is essential for ensuring Pharmaceutical Quality. For block copolymer micelle products, these attributes include their mean particle size, size distribution, morphology, zeta potential value, CMC, critical association concentration, drug loading, surface properties, chemical structure, *in vitro* stability and *in vitro* degradation of the block copolymer micelle in plasma and/or relevant media, *in vitro* release of the API from the block copolymer micelle product in plasma and/or relevant media, as well as the properties related to the manufacturing process (validated process for reconstitution and for ensuring sterility) and properties related to the *in vivo* behavior (osmolarity, fraction of active substance that is surface-associated, release rate and place of active substance release, degradation rate and place of degradation). Consequently, the elevated cost of the techniques employed for this purpose, in comparison to those used for other pharmaceutical

formulations, poses a significant obstacle for pharmaceutical companies [75,106,108].

The CD-block copolymer is a hybrid drug delivery system that behaves as a new material. For this reason, the degree of complexity of this new hybrid material is higher than that of each material separately. The techniques used during the pre-formulation, formulation, stability, and scale-up studies are separate, with limited access for the industrial units in some cases. The last increase is also the cost of the clinical translation of these hybrid platforms; even their added value is very important for the efficacy of the medicine.

Pharmaceutical industries also necessitate scientists, including chemists and formulation scientists, with training and significant experience in the synthesis and characterization of materials and the further design and development of CD-block copolymer formulations. Simultaneously, academics should collaborate with them to facilitate knowledge transfer from academic institutions to pharmaceutical companies [75,109].

Finally, the regulatory landscape is not very clear containing grey areas for the nanoformulations, and this is an additional obstacle to the preparation and scale-up of CD-block copolymer hybrid nanosystems. To overcome all these limitations, the scientific community should consider them as opportunities for research and collaboration.

## 6 Conclusion

This article presents a comprehensive review of CD-block copolymer systems. Important information about the components of these hybrid formulations, as well as several examples from the relevant literature on these mixed systems are analyzed in this review article. The combination of CDs with block copolymers into hybrid formulations can result in new biomaterials and supramolecular structures, which encompass the physicochemical and thermotropic properties of both classes of materials. Despite the fact that there is no CD-block copolymer product that has been authorized yet, the added value of these systems is well established in the literature. Finally, considering the diversity of block copolymers and CD materials, and the potential benefits of their mixing/complexation, we could suggest them as promising candidates for new-generation formulations in the upcoming future.

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