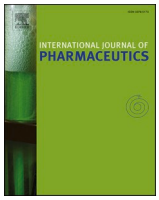
International Journal of Pharmaceutics 654 (2024) 123976

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm



Multifunctionality of cyclodextrin-based polymeric nanoparticulate delivery systems for chemotherapeutics, combination therapy, and theranostics

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ARTICLE INFO

Keywords:
Cyclodextrin
Inclusion complex
Polymeric nanoparticles
Anticancer
Drug Delivery
Pharmaceuticals

ABSTRACT

As cancer being the most difficult disease to treat, different kinds of medications and therapeutic approaches have been prominently developed by scientists. For certain families of drugs, such as immuno-therapeutics or antibody-drug conjugates, efficient delivery systems are required during administration to protect the drugs from chemical degradation or biological inactivation. Delivery systems with the ability to carry different therapeutics or diagnostic agents or both, hold promising potential to tackle the abnormalities behind cancer. In this context, this review provides updated insights on how cyclodextrin-based polymeric nanosystems have become an effective treatment approach against cancer. Cyclodextrins (CDs) are natural oligosaccharides that are famously exploited in pharmaceutical research due to their exceptional quality of entrapping water-insoluble molecules inside their hydrophobic core and providing enhanced solubility with the help of their hydrophilic exterior. Combining the properties of CDs with polymeric nanoparticles (PNPs) brings out excellent versatile and tunable profiles, thanks to the submicron-sized PNPs. By introducing the significance of CD as a delivery system, a collective discussion on different binding approaches and release mechanisms of CD-drug complexation, followed by their characterization studies has been done in this review. Further, in light of recent studies, the article majorly focuses on conveying how promoting CD to a polymeric and nanoscale elevates the multifunctional advantages against cancer that can be successfully applied in combination therapy and theranostics. Moreover, CD-based delivery systems including CALAA-01, CRLX101, and CRLX301, have demonstrated improved tumor targeting, reduced side effects, and prolonged drug release in preclinical studies and clinical trials.

1. Introduction

Clinically practiced conventional cancer treatments, such as chemotherapy, surgery, radiation, and immunotherapy, come with their own shortcomings like increased toxicity, resistance of cancer cells to therapies, non-specificity towards cancer cells, severe side effects, poor water solubility, and reduced therapeutic indices (Cho et al., 2008; Soni and Yadav, 2015; Jabir et al., 2018; Ansari, Nov. 2022). In reflection of these facts, along with nearly one in six deaths in 2020, cancer remains one of the leading causes of death worldwide and a significant barrier to cumulative life expectancy (Ferlay et al.,0000; Bray et al., 2021). The increasing difficulties in cancer treatment, causing severe side effects like hair loss, consistent vomiting, organ loss, psychological problems, etc., trigger uneasiness in patients making the conventional therapies ineffective in absolute treatment (Yu et al., Apr. 2022; Mun et al., 2018; Liu et al., 2021). In modern times, as part of developing anticancer medications in the biopharmaceutical world, drugs like immune checkpoint blockers, antibody-drug conjugates, further anticancer immuno-therapeutics, and genetic drugs have become more and more prominent in the latest therapeutic strategies (Chen, 2022; Dugger et al.,

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https://doi.org/10.1016/j.ijpharm.2024.123976
Received 3 November 2023; Received in revised form 26 February 2024; Accepted 4 March 2024
Available online 6 March 2024

Feb. 2018). This family of drugs requires delivery systems for their efficacious administration to prevent chemical degradation and biological inactivation *in vivo*. Moreover, such delivery systems mark their relevance in modulating tumor microenvironment and improving patient adherence to anticancer treatments (Chen, 2022; Le et al., Feb. 2022).

In this scenario, the research in nanomedicine has progressed extensively, ever since the first cancer nanomedicine was clinically approved by the US Food and Drug Administration (FDA) in 1995 (Salvioni et al., 2019). To overcome the inadequacies of conventional cancer treatments, nanotechnology-based potential delivery systems have been engineered using various nanoparticulate formulations such as liposomes, dendrimers, polymeric nanoparticles, micelles, metallic nanoparticles, and more, due to their promising approach of improved diagnostic sensitivity and therapeutic effectiveness (Gandhi and Shende, 2021) (Alhaj-Suliman et al., Oct. 2022). Delivery systems with the ability of multiple therapeutic administrations at the same time or combination therapy appear to be promising with their numerous advantages, including maximized therapeutic indices. Remaining within the threshold dose-limiting toxicity, efficient medicinal effects can be achieved with combination treatment, as it permits the usage of lower individual doses (Haley et al., 2020). The fabrication of more sensitive nanovehicles has been a contribution to various diagnostic tools for delivering contrast agents to cancerous sites, providing an early diagnosis. Although existing techniques such as magnetic resonance imaging (MRI), computed tomography, endoscopy, and other imaging techniques can assist in cancer detection, early diagnosis will be challenging because of their difficulty in discriminating cancer cells from healthy ones (Ansari, Nov. 2022). Eventually, this can buy time for cancer cells to attain potential for propagation and metastasis before diagnosis (Ansari, Nov. 2022; Zhang, 2019). Diagnosis and treatment of cancer can be challenging due to the difficulty in locating the hidden tumor in the body. Performing diagnosis followed by therapy without much delay could be more efficient in treating tumors. Theranostics is a combined term coined for therapy and diagnostics that defines an emerging field of medicine where drugs and techniques are uniquely combined to simultaneously or sequentially diagnose and treat cancer (Xie et al., Oct. 2011; Huang et al., Nov. 2013). Nanotheranostics, where both the imaging and curing potentials are incorporated on a single nanovehicle, is becoming a revolutionary approach for consistent tracking of drug delivery, image-guided therapy, and therapy response study (Lu, 2016). Lately, researchers have been actively tailing innovative ways to implement effective and economical combination therapy and nanotheranostic tools.

Cyclodextrin (CD) is an attractive supramolecular sugar polymer with a central hydrophobic cavity and an external hydrophilic peripheral. The hydrophobic cavity in the center possesses glucose units networked in a way that forms a hollow conical structure (Poulson, 2021). Poorly water-soluble molecules with suitable size can be entrapped into this cavity through the hydrophobic host–guest interaction between the guest molecules and the hydrophobic host cavity. This leads to the formation of an inclusion complex which is the major attraction and practicality of CD in drug delivery applications as it provides stability and sustained release of the guest drug and protects it from external influence and degradation (Szejtli, 1982; Sandilya et al., Oct. 2020). The outer hydrophilic region possesses highly polar hydroxyl groups that can interact with water, solving the poor solubility problem of the encapsulated hydrophobic guest molecule. This unique structure and behavior of CD bring wide attention to be experimented with for combination therapy and theranostics applications in the pharmaceutical field (Szejtli, 1998).

Particles engineered between the range of 20–500 nm are generally used as drug carriers since the renal clearance level is known to be about 5 nm (Hoshyar et al., 2016; Peng et al., 2020; Petros and Desimone, 2010). Their small particle size could be taken advantage of in a customized way to infiltrate tumor cell membranes for a target-oriented delivery (Cao and Bae, 2012; Li et al., Feb. 2017). Based on the composition, polymeric nanoparticles (PNPs) possess biocompatibility, biodegradability, and hydrophilicity or hydrophobicity. Their versatility aids the entrapment or conjugation of the desired anticancer drug, either inside or on the surface of the PNPs, via physical (hydrophobic or hydrophilic) or chemical interactions (Li et al., Feb. 2017; Masood, 2016). Loaded PNPs are active means for targeted delivery systems for steady release to specific targets. Customizable and versatile properties of PNP systems can boost the therapeutic performance, avoidance of rapid renal clearance, and multi-functionalities to attain higher sensitivity and specificity towards malignant cells and their microenvironment (Loo et al.,May, 2022).

With combined structural-supramolecular qualities of CD and versatile qualities of PNPs, the CD-functionalized polymeric nanosystem emerges as a promising potential delivery system to overcome conventional therapy limitations. Starting with a brief introduction to the characteristic relevance of CD for drug delivery application, this review gives a collective overview of the approaches of CD-drug interaction and their characterization studies. Further, the article distinctively focuses on how CD-PNP association positively influences the merits of combination therapy and theranostics in cancer treatment, which will provide effective ways towards improved and less harmful cancer therapy. Relevant clinical trials on CD-based delivery systems which have shown promise in inhibiting tumor growth and reducing tumor size in various types of cancer, were also briefly discussed.

2. Cyclodextrin for drug delivery

Many conventional drugs, which theoretically and experimentally proved their better anticancer potential, would hardly be clinically effective due to their lack of stability, biocompatibility, and water solubility (Wang, 2016). Although many tumor-targeting therapeutics, like antibody-drug conjugates, are available to overcome the aforementioned shortcomings (Puthenveetil et al., 2016; Levengood, 2017), their complex chemical construction can alter their stereo-structure which affects the pharmacokinetic and pharmacodynamic properties of the drugs making it hard to administer them (Kumar, 2021; Santos, 2017). This is where the necessity to fabricate a safe and potential drug delivery system emerges, as it can effectively reduce the side effects of the drug (Zhang et al., 2019). Various studies have established CD, which is a supramolecular host molecule, as a promising pharmaceutical excipient due to its many practical advantages of better water solubility, non-toxicity, easy modification, and prominent biological compatibility (Ghitman and Voicu, Jun. 2023; Kumari and Badwaik, Jan. 2019).

2.1. Cyclodextrin: structure and properties

CDs are natural, cyclic, non-reducing oligosaccharides composed of a series of α-1,4-glycosidic bonded α-D-glucopyranose subunits. With six, seven, and eight D-glucose units, native CDs can be classified as α, β, and γ-CD, respectively (Fig. 1a) (Szejtli, 1998). Geometrically, CDs with a homogeneous crystalline structure, exhibit a toroidal cone shape (Fig. 1b) with a hydrophobic interior cavity lined with carbons and ethereal oxygens of the glucose residues surrounded by a significant number of hydrophilic hydroxyl groups which make these sugar polymers stable in water and some organic solvents (Szejtli, 1998; Loftsson and Brewster, 2011; Loftsson et al., 2007; Zhang and Ma, 2013; Davis and Brewster, 2004). More detailed information about the structure and conformation of CD can be referred to the reviews (Szejtli, 1998; Tafazzoli and Ghiasi, 2009; Sandilya et al., 2020).

CDs are an excellent candidate widely used in pharmaceutical research for their ability to improve the aqueous solubility of hydrophobic molecules. To be noticed, CDs are highly soluble in water however, their non-hygroscopic nature, their water solubility can be slowed down when the CD is in the native conformation and due to the intramolecular hydrogen bonding between C2– and C3– hydroxyl groups.

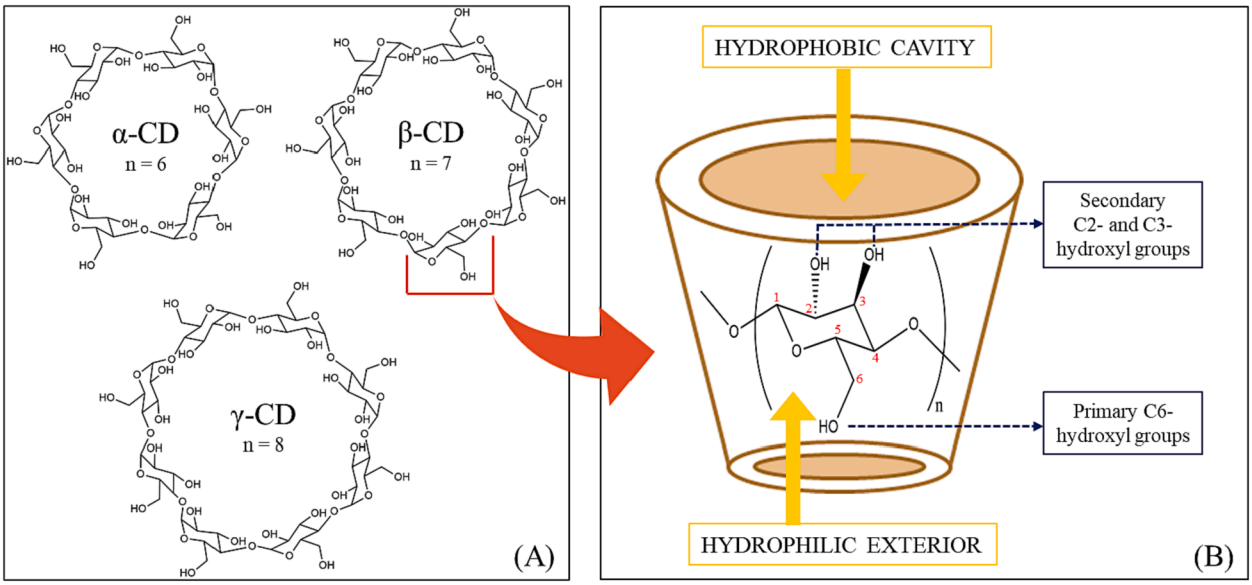

Fig. 1. (a) Chemical structures of native CDs classified as alpha, beta, and gamma, where 'n' is the number of glucose units; (b) illustration of toroidal cone shape of CD revealing the secondary and primary hydroxyl groups.

This is why, the derivatization of CDs has gotten more attention, as the solubility could be enhanced by tailoring their strongly bonded hydroxyl groups (Fredy, Mar. 2017; Lai, 2019). Indeed, modified CDs, due to their amorphous nature, are more highly soluble than native CDs (Shelley and Babu, Jul. 2018; Jug, Jan. 2020). Various derivatives of CD have been formulated to reduce the drawbacks of native CDs. CD possesses primary C6- hydroxyl groups and secondary C2– and C3-hydroxyl groups (Fig. 1b). The primary OH group is freely movable and accessible for chemical modifications, while the secondary OH-groups are inaccessible for modifications because of their rigidity on CD caused by their intramolecular bonding attraction with adjacent glucopyranose units. However, they could be disturbed under strong and particular reaction conditions (Poulson, 2021). The balance and chemical variance between these hydroxyl groups matches with multiple modification kinds (Table 1). Thus, CD rings can undergo chemical modifications by bonding either with substituents or other CD rings, leading to the development of a wide variety of nano-forms with endlessly advancing derivatizations and applications (Jiménez Blanco et al., 2017; Haimhoffer, et al., 2019). Even though modified CD has reduced limitations than natural ones, a higher degree of modification may lead to high steric hindrance, which may impose a negative effect on the ability of complex formation of CD (Stella and He, 2008; Rasheed, 2008). *Liu et al.* and *Khan et al.* talk more deeply about different types and methods of CD functionalization from a structural and conformational point of view (Liu et al., 2020; Khan et al., 1998).

The amphiphilic nature of innate CDs can be justified by their structure. On account of their torus structure and supramolecular chemistry, the clathrate-forming ability of CDs generates stable inclusion complexes through non-covalent interactions (Negi and Singh, 2013; Roy et al., 2016; Saha et al., 2016; Roy et al., 2016; Roy et al., 2016; Datta et al., 2016; Arima et al., 2015). As mentioned by Wei (Wei, 2015), dipolar interaction, van der Waals force, electrostatic and hydrogen bonding attractions play the main weak intermolecular forces between the host and guest. These weak bonding of inclusion complexation permits the temporary entrapment of the drug, reducing the drawbacks caused by the drug (Arima et al., 2015). Moreover, the inclusion complex can help CD protect the entrapped molecules from non-specific interactions and stabilize them for delivery (Mellet et al., 2011). In a recent study, the inclusion complexes of an anticancer hydrophobic drug 5-fluorouracil (5-FU) with β-CD in 1:1 and 1:2 stoichiometries were explored with the aid of molecular mechanics and molecular dynamics. Both stoichiometric inclusion complexes were found with similar interaction energy and stability. The 1:1 stoichiometric inclusion complex had its fluorine atom aligned towards either the primary or secondary edge of CD, while the second fluorine atom of 1:2 stoichiometry was partially exposed from the secondary edge, aligned either almost perpendicular or parallel to the former fluorine atom. This revealed the higher mobility and faster release rate of the partially exposed 1:2 stoichiometric drug, compared to the other one. Moreover, the solubility of the drug seems to be improved after its complexation with CD via van der Waals interactions (Raffaini et al., 2022). Overall, the ability to form inclusion complexes that could efficiently retain and advance the biological activity and physicochemical features of the entrapped therapeutic molecules is one of the principal reasons for the extensive usage of CD (Aytac, et al., 2016; Pinho et al., 2014).

2.2. *Types of Cyclodextrin and their safety implications*

Practical and clinical concern over human safety increases the attraction towards CDs as they have been approved as a Generally Recognized As Safe (GRAS) component by the FDA as food additives (szentecyclolabhu, 0000) and European Medicines Agency (EMA) for its use in pharmaceutical formulations (E. Medicines Agency, "Background review for cyclodextrins used as excipients,", 2014; Păduraru et al., 2022; Braga, 2019; Wüpper et al., 2021). Despite being biocompatible, their toxicity depends on choosing the right type of CD and path of administration. Usually, the α-CD is used in the parenteral path, while β-CD and γ-CD are not advised for direct parenteral administration. The reason for this is that despite high water solubility, as mentioned before, their water solubility can be slowed down due to their non-hygroscopic nature. With this fact, β-CD can lead to microcrystalline accumulation in the kidney and its nephrotoxicity and can cause aggregate formation in aqueous solution by γ-CD. As introduced before, more hydrophilic derivatives of β-CD and γ-CD can overcome these problems (Stella and He, 2008; Rasheed, 2008; Munro et al., 2004). Oral administration of any type of CDs is practically considered safe as they are barely absorbed from the GI tract due to their bulky and hydrophilic features. However, a higher dose of CDs (>1000 mg/kg/day) could be harmful as they are observed as reversible diarrhea and irreversible kidney dysfunction (Stella and He, 2008; Luke et al., 2010). More specifically, the γ-CD is instantly digested, while α-CD and β-CD are barely digested in the small

Table 1
Summarization of different modification approaches for the hydroxyl groups of CD.

OH–group positions	Features	Modification conditions	Ref
C2	• OH-group attached to the second carbon atoms of each glucose unit • Points towards the wide rim of CD cone • Most acidic and least nucleophilic • Low reactivity • High steric hindrance	• Using a strong base (deprotonation) and a non-complexing electrophile. This may result in the modification of both C2 and C6 positions. • Initial protection of the C6 position and reacting under basic conditions with any electrophile leads to selective modification of the C2 position. • C2 activation by using a metal catalyst, followed by a reaction with an electrophile. • Reaction using a weak base and any electrophile, with selective protection and deprotection of other OH groups.	(Liu et al., 2020; Poulson, et al., 2021; Yousaf et al., 2023; Przybyla et al., 2020; Rezanka, 2018)
C3	• OH-group attached to the third carbon atom of each glucose unit • Points towards the narrow rim of CD cone • Least accessible • Least reactivity • Low nucleophilicity • High steric hindrance		
C6	• OH-group attached to the sixth carbon atom of each glucose unit • Most accessible • Most reactive • High nucleophilicity • Low steric hindrance	• Normal and straightforward reactivity under a mild base and a non-complexing electrophile. • The choice of electrophile depends on the type of desired products. For example, an ether derivative of CD can be obtained by using an alkyl halide as an electrophile. Whereas an ester derivative of CD can be obtained by using an acid anhydride or a carboxylic acid as an electrophile. • In some cases, protection of the C2 position is required while using any base and any electrophile.	
A mixture of all three	_	• Reaction by complex formation using a complexing electrophile. • By using a reagent that can react with all OH groups indiscriminately.	

intestine (Parmar et al., 2018).

2.3. Cyclodextrin: approaches for CD-drug complexation

Inclusion complexation is a unique characteristic of CD. The ability of complex formation, in chemical terms, is a function of certain parameters such as steric and thermodynamics, whereas the stability of the complex primarily depends on the properties of guest molecules (drug). High hydrophobic guest increases the complex stability. However, it can be altered depending on the number of guest substituents being filled up in the CD core (Parmar et al., 2018). Generally, complex formation is mainly governed by the non-covalent or covalent interaction of CD with the guest.

2.3.1. Non-covalent binding

The supramolecular chemistry allows the CD to be an original molecular receptacle because of having a suitable-sized lipophilic cavity leaving the rest of its structure hydrophilic. This structural quality of CD was found compatible to load hydrophobic anti-cancer drugs via inclusion complexation (Fig. 2a), as it will improve the aqueous solubility and biocompatibility of the drug.

The driving force of host–guest inclusion formation is the escape of enthalpy-rich water molecules from the lipophilic cavity due to the pressure from the lipophilic guest. Although no chemical bonds are created or destroyed in the process, the guest substituents are partially or completely accommodated and protected from external influences such as water, oxygen, heat, and radiation, thus the guests are blocked from any degradation (Shelley and Babu, Jul. 2018; Parmar et al., 2018). The non-covalent process takes place in either liquid phase, solid phase, or heterogeneous conditions, considering specific parameters (de Melo, 2016; Couto et al., 2019). In the solid phase, host and guest are heated under comparative humidity conditions of 60–75 % and at a specific temperature and time for complex formation. Here neither co-solvent is added, nor any mechanical stirring is required (Ullah et al., 2014; Thamizharasan and Saravanan, 2017). When the inclusion formation is carried out in the liquid phase, studies have shown that the rate of reaction gets faster in liquid phase conditions than in the solid phase (Cramer et al., 1967; Manor and Saenger, 1974; Fourmentin et al., 2013; Rezaei et al., 2019; Tian et al., 2020). This is mostly because of the influence of exterior OH-groups of CD that could be advantageous for the hydrophobic guest molecules with poor aqueous solubility (A. v. Simakin, V. v. Voronov, N. A. Kirichenko, and G. A. Shafeev, , 2004). Heterogeneous conditions for inclusion involve combining two different phases. Here the solution of guest molecule well dissolved in a suitable solvent is added to the aqueous solution of CD, or even the direct addition of guest to aqueous CD solution with forceful stirring at room temperature giving a stable product (Abou El-Nour et al., 2010; Evert,

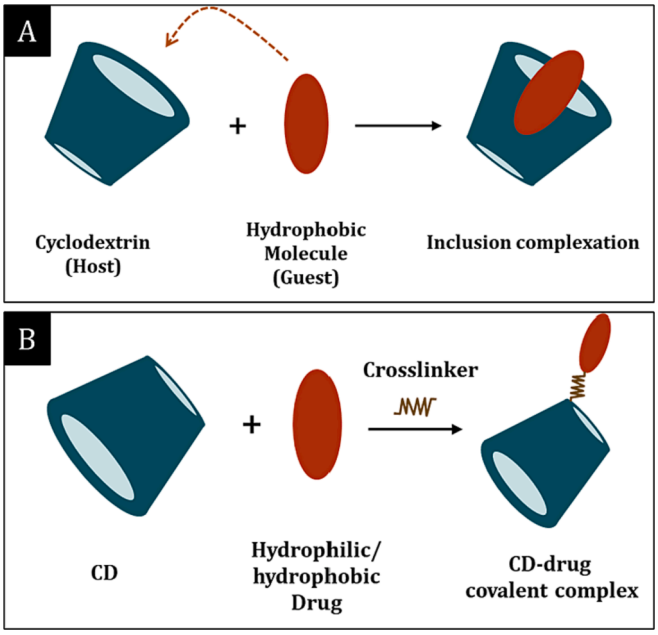

Fig. 2. A standard illustration of: (a) inclusion complex formation via non-covalent host–guest hydrophobic interaction; (b) covalently bound CD-drug complex.

2012; Shen et al., 2020; Song, 2020).

The encounterable challenges with the noncovalent binding approach are that the vulnerability of the native CD cavity towards the size of the guest molecule leads to a small amount of drug encapsulation, resulting in a reasonable increase in the administration dose (Tian et al., 2020). Also, despite good stability towards heat and light, the inclusion complex was found weakly stable in the acidic and basic environment (Monti and Sortino, 2002; Mura et al., 2003). Therefore, the application of polymerization in CD inclusion formulation has gained wide attraction as it created more stable and efficient CD polymers (Tian et al., 2020). Furthermore, the polymerization of CD has been deeply discussed in Paragraph 3.

2.3.2. Covalent binding

This approach occurs by connecting the host and guest molecules via chemical bonds, usually as ester or amide bonds, using a crosslinking agent (Fig. 2b) (Yano et al., 2002). The higher reactivity and easy accessibility of primary hydroxyl groups of CDs, which are present on their exterior sides, allow them to undergo feasible modification to form corresponding derivatives that can react towards anticancer molecules. On the other hand, secondary hydroxyl groups are less reactive than primary hydroxyl groups (Tian et al., 2020; Liu et al., 2020) therefore, initial protection of primary OH-groups is necessary before the modification of the secondary ones. Overall, the necessity of complex reaction conditions, including the addition of the protecting and deprotecting processes, makes the derivatization of secondary hydroxyl groups relatively complicated (Řezanka, 2019; Khan et al., 1998). Thus, playing around with these hydroxyl groups was potentially explored to generate various CD conjugates, especially CD-drug covalent association (Table 1).

2.4. Mechanism of drug release from CD complexes

The majority of anticancer drugs are hydrophobic in nature, raising concerns regarding solubility and therapeutic efficiency. Thus, an efficient release profile for the antitumor drugs is undoubtedly relevant in tumor therapy. Introducing CD to carry water-insoluble medications can rapidly solve the solubility impediment and improve drug stability for better treatment. Furthermore, with CD as a carrier, the drugs are protected from degradation and limited from adverse bio-distribution, providing a stable drug release. The antitumor drug release profile from a CD-based carrier depends on whether the interaction mode of the drug with the CD is non-covalent or covalent. Considering the merits and demerits of each interaction, a suitable approach can be utilized during system formulation. During oral administration, once the drug-carrying complex reaches the gastrointestinal tract, the non-covalent bonds between the CD cavity and the drug are broken by the influence of the external acid-base environment, releasing the drug. Carrier complexes with weak acidic groups are more soluble in neutral or high pH regions as the acidic groups undergo ionization. Because of the hydrophobic CD cavity and depending on the prolonged survival of CD in an external environment without getting damaged, durable drug release can be attained during the complexation between the drug and CD (Anirudhan et al., 2015; Jin et al., 2010; Wielińska et al., 2019). However, the release of guest molecules from an inclusion profile is based on a time-dependent release mechanism, for instance, dissociation by dilution, which is primarily forced by the binding affinity with the supramolecular matrix. In covalent-bound drug release, the chemical bond between the drug and CD restricts the drug from premature release by initial burst and maintains the wholeness of the drug from metabolization before release. Retaining the structural coherence, the covalently-loaded biopolymer carrier reaches the colon to end up facing the enzymes triggering the drug release via enzymatic degradation of the covalent carrier (Tian et al., 2020). But, of course, the system durability and release behavior could extremely differ with different types of covalent bonds. It was observed from some studies that the drugs linked with both ester and amide bonds steadily advanced to the colon. But, when the ester-linked drugs got released successfully, an instantaneous and effective drug release was found difficult from amide linkage (Lu, Oct. 2010; Onodera et al., 0000). *Bai et al.* formulated an α-CD-polyrotaxanes based polymeric prodrug unimolecular micelles in which a hydrophobic anticancer camptothecin (CPT) was covalently linked via disulfide bond in polymeric form. *In vitro* studies showed that more than 85 % of CPT was released by redox-stimulated disulfide bond breakage. However, compared to the free drug with no delivery system, an immediate antitumor activity from the disulfide-bound CPT system was not observed because of the delayed and ineffectual release of the cross-linked drug (Bai, Aug. 2018). When the covalently bound CD-drug reaches the colon, polysaccharide degrading enzymes (such as pectinase, amylase, and xylanase) initiate hydrolysis to convert CD-drug covalent complex to smaller sugar molecules paving the way for drug release via enzymatic action (Tian et al., 2020; Patel et al., 2016; Kirk et al., 2002).

Besides dissociation due to dilution, drug release could also happen due to the competition of other molecules with the drug for the CD cavity causing drug displacement (Nogueiras-Nieto et al., 2012), drug absorption by tissues and plasma when the drug is inaccessible to the complex or CD (Rajewski and Stella, 1996), and elimination of CD (Dietzel et al., 1990; Stella et al., 1999). It is to be noted that when the means for dilution is limited, especially for the topical route of administration, drug uptake can be hindered by the presence of CDs. This circumstance suggests the avoidance of high concentrations of CD for better drug release (Jansook et al., 2018). More about the drug release mechanism from CD complex can be studied from *B. Tian et al.* and *V.J. Stella et al.* reviews (Tian et al., 2020; Stella et al., 1999).

3. Introducing polymerization to cyclodextrin

Polymerization is basically the process of combining small molecules using chemical interactions to produce large networked molecules with unique properties (Polymerization, 0000). The process itself is very versatile and tailorable to bring out new compounds with desirable features for different applications. Introducing the polymer science to CD unleashes distinctive generations of CD polymers by taking advantage of the abundant presence of reactive exterior hydroxyl groups. Polymer production involves different polymerization methods, including free radical polymerization (FRP), atom transfer radical polymerization (ATRP), reversible addition-fragmentation transfer (RAFT), ring-opening polymerization (ROP), condensation reaction and click reaction, etc. (Tian et al., 2020; Zhang and Ma, 2013). The important elements involved in CD polymerization are the cross-linking agent, reacting substituents, and reaction time (Szejtli, 1982; Krause and Mamba, 2010; Rossi, Oct. 2014). Some crosslinkers include citric acid (Garcia-Fernandez, Sep. 2016; Gidwani and Vyas, Feb. 2014), epichlorohydrin (Gidwani and Vyas, Feb. 2014), isocyanate (Thatiparti and Von Recum, Jan. 2010; Rodriguez-Tenreiro et al., Jan. 2006), ethylene glycol digycetal ether (Rodriguez-Tenreiro et al., Jan. 2006), and polycarboxylic acid (Euvrard, Aug. 2016).

Although CDs alone possess the potential to improve the properties of the loaded drug, as discussed before, their weak steadiness in acidic/basic conditions, low loading ability, and release behavioral demerits are some major challenges to overcome in order to be an efficient practical antitumor delivery system. Grafting CD onto polymer chains, such as chitosan (Li and Liu, Dec. 2018; Yuan, Mar. 2013), hyaluronic acid (Ji et al., Oct. 2017), etc., using a crosslinker (Fig. 3b) or conjugating CDs with other PNPs or the polymer chains brings out the major possibilities of external/internal stimuli-responsive behavior, controlled release profile, surface modifications with target moieties, and a tailorable system (Shelley and Babu, Jul. 2018). The conjugated polymers come in different forms as CD-capped polymers (CD linked to an end of another polymer chain), CD-terminated polymers (two CDs linked to the two ends of another polymer chain), or CD-pendent/ CD-suspended

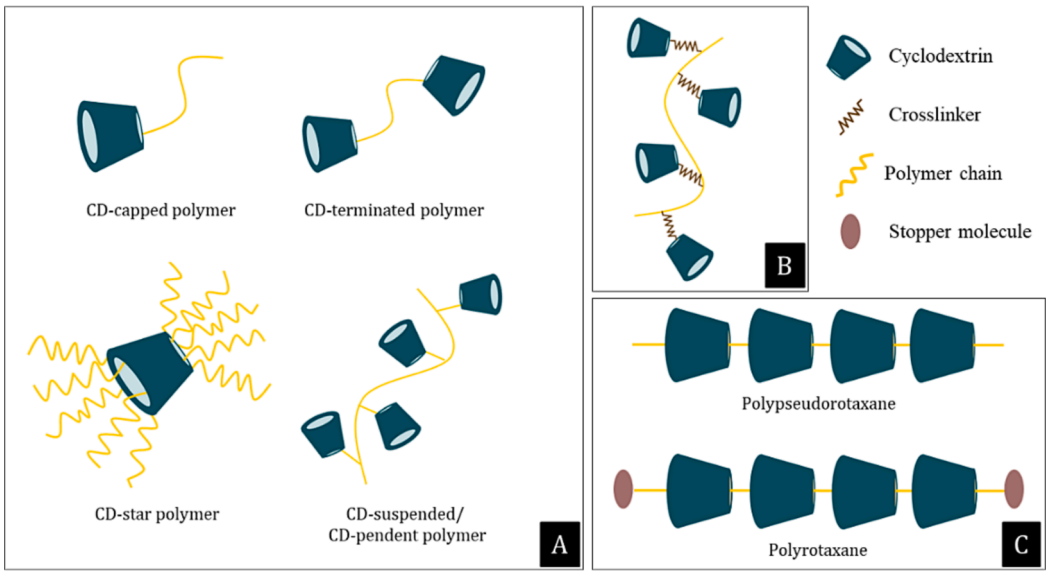

Fig. 3. (a) Conjugated CD polymers where CD is linked to other polymer chains in different forms; (b) Grafted CD polymer where CD is linked to other polymer chains via a crosslinker; (c) Polypseudorotaxane and polyrotaxane of CD.

polymers (several CD moieties connected to multiple side chains of another polymer) (Fig. 3a) (Yao et al., Jun. 2019; Tian and Liu, Jun. 2020). There are also star polymers with CD at the core where the centered CD molecule is circularly connected by linear polymer chains utilizing the exterior hydroxyl groups of CD. *Song et al.* synthesized a thermosensitive nanocarrier composed of a 4-armed β-CD-based poly(*N*-isopropylacrylamide) (β-CD-(PNIPAAm)$_4$) star polymer with a polymerization degree of 32 % per arm, which means 32 units of NIPAAm polymerized on each arm. Formation of supramolecular inclusion complex with the anticancer paclitaxel (PTX) occurred via host–guest hydrophobic interaction at room temperature. At room temperature, the hydrophilic PNIPAAm arms seemed to improve the aqueous solubility of the encapsulated PTX. With increase in temperature, the hydrophilic PNIPAAm chains were found to become hydrophobic leading to aggregation in aqueous solution. This phase transition of PNIPAAm chains led to thermosensitive formation of nanoparticles causing efficient drug release, and cellular uptake of CD-drug complex, and also can hinder the multi-drug resistance of tumor cells (Song et al., Dec. 2016).

A reversible assembly of supramolecular CD molecules being mechanically interlocked along a single polymer chain, like a bunch of rings connected along a thread, is called polypseudorotaxane. When the two ends of this polymer chain are coupled with bulky stopper groups, the dismantling or disassociation of the CD rings from the thread is restricted, and this irreversible assembling is called polyrotaxane (Fig. 3c) (Haimhoffer, et al., 2019). Although there are no covalent bonds between the CD rings, they are found firmly remained on their polymer axle. While CD molecules can freely move along the polymer chain in polypseudorotaxane, CDs are imprisoned in polyrotaxane until they are triggered to release (Haley et al., 2020). α-CD/poly(ethylene glycol) (α-CD/PEG) based polyrotaxane nanoparticles were formulated using self-assembly method by *Zhang et al.* and group. The polyrotaxane was generated by capping the two ends of PEG chain with cinnamate groups followed by the self-assembly of α-CDs over the PEG chain. The anticancer drug methotrexate (MTX) was found loaded on the surface of polyrotaxane nanoparticles via Van der Waals and hydrogen bond interactions, which led to rapid drug release of about 98 % within the first four hours, providing potential anticancer treatment (Zhang et al., 2014).

CD nanosponges (CDNS) are nanosized porous particles of 3-dimensional highly-networked CD polymers (Haimhoffer, et al., 2019; Utzeri et al., Mar. 2022). A glutathione-stimulated β-CD nanosponges (GSH-CDNS), synthesized in presence of β-CD, 2-hydroxyethyl disulfide, and pyromellitic dianhydride as crosslinker (Fig. 4a), was found to be releasing drugs in response to high GSH amount due to the cleavage of disulfide bonds, and pH. Loaded with the anticancer drug doxorubicin (DOX), an improved anticancer effect was observed *in vitro*. Uptake studies with HepG2 cells revealed a higher DOX level in DOX-GSH-NS treated cells, demonstrating a speedy and efficient intracellular accumulation of the nanosponges (Fig. 4b). *Ex vivo* analysis of hepatotoxicity of DOX-GSH-NS and free DOX using rat precision-cut liver slices (PCLS) showed comparable results. Furthermore, the uptake of DOX and DOX-GSH-NS was analyzed in PCLS using confocal fluorescence microscopy, and a higher accumulation of DOX was observed after DOX-GSH-NS treatment compared to free DOX (Fig. 4c), consistent with observations in HepG2 cells. No accumulation in the liver evidenced the safety profile of the system and justice to overcoming drug resistance by the target cells was noted due to their escaping ability from the efflux drug pump (de Graaf et al., 2020). More detailed information and discussions about the concept of CD-based polymerization can be read from the mentioned reviews (Yao et al., Jun. 2019; Tian and Liu, Jun. 2020; Van De Manakker et al., Dec. 2009). Different strategies as described here are approached for the formulation of efficient CD-based PNPs to act as a suitable drug delivery system against cancer.

4. Cyclodextrin-based polymeric nanoparticles

Using biodegradable polymers for drug delivery applications has become quite important due to their ability to break down inside the body, aiding their elimination. Besides biodegradability, the demanding properties for the PNPs to be drug carriers are tunability and biocompatibility. In possession of such properties, widely used polymers for drug delivery application may involve hyaluronic acid, chitosan, dextran, alginate, poly (glycolic acid), poly (lactic acid), poly (lactic-co-glycolide), and more (Zielí Nska et al., 0000; Lombardo et al., 2019). PNPs are highly versatile, and over their potential passive uptake, they can be targeted directly to cancer cells by performing nanoparticle-surface modifications using several kinds of ligands to the receptors over-expressed on the cancer cells (Parhi et al., 2012). PNPs own up to a characteristic degradation curve which helps them to influence the drug release rate (Sun et al., 2014; Begines, 2020). The alterable properties of PNP systems can boost the therapeutic effects, avoid rapid renal clearance, and add multi-functionalities to attain higher sensitivity and

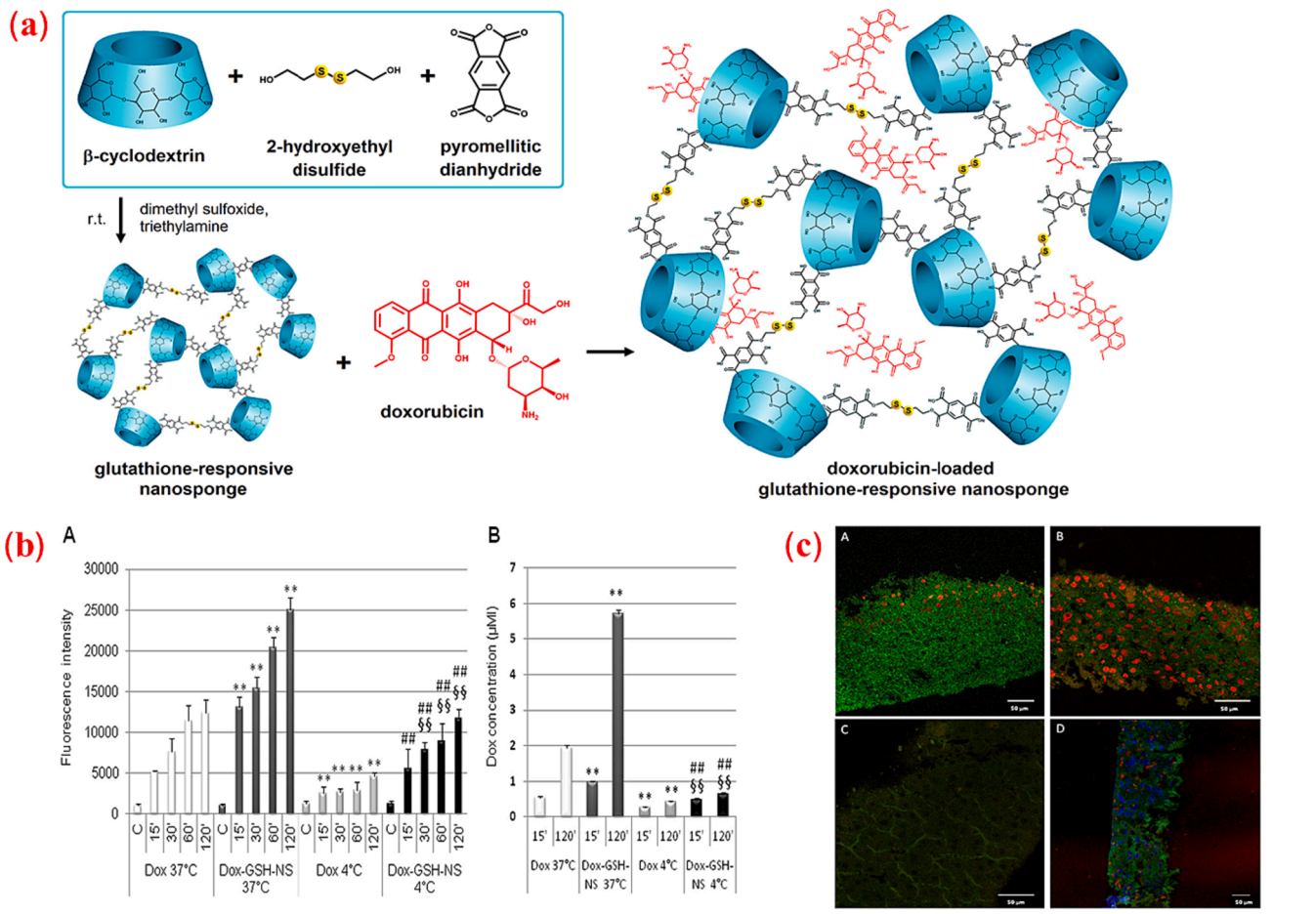

Fig. 4. (a) Illustration showing the one-step synthesis of GSH responsive CDNS, followed by the loading of DOX; (b) *in vitro* uptake analysis of red fluorescent intensity of DOX using cytofluorimeter and HPLC in DOX and DOX-GSH-NS 10 μM treated HepG2 cells at 37 °C and 4 °C and gathered at the indicated times (min); (c) Confocal fluorescence microscopy images of PCLS after 3 h incubation with 10 μM Dox, 10 μM Dox-GSH-NS, and untreated. Figures reprinted with permission from M. Daga et al. (2020). (de Graaf et al., 2020). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

specificity towards malignant cells and their microenvironment (Loo et al.,May, 2022). As discussed before, CDs have unique practical qualities that are highly contributive to drug delivery systems. Conjugating PNPs and CDs obviously could result in an efficient delivery system. In many studies, CD-based PNP systems were formulated to be contributed as stimuli-responsive delivery systems. When CD works to improve the behavioral efficiency of the cargo, the presence of PNP can be taken advantage of to tune the system to produce responsive or smart delivery systems that would be sensitive to changes in endogenous stimuli such as pH, enzymatic conditions, temperature, or exogenous stimuli such as magnetic field, light, and ultrasound. This quick responsiveness can be actively exploited in drug delivery applications as the drug release can be accelerated by external stimuli (Mura et al., 2013; Torchilin, 2000). The release of the anti-cancer drug DOX was investigated using magnetic iron oxide nanoparticles grafted hyaluronic acid/CD nanosystem at pH 7.4 and 5.6 (Khodayari et al., Feb. 2023). After 48 h, the pH dependency of the system was observed with a higher rate of DOX release of 92.43 % at pH 5.6 than the 77.05 % release at physiological pH (7.4). It is stated that the hydrophobic interaction between the drug and the β-CD of the system weakens at acidic pH increasing the drug release rate (Broxterman and Georgopapadakou, 2005).

The CD-based polymeric nanoparticulate system will be able to successfully allow the PNPs for a targeted and specific delivery of less soluble anticancer drugs by entrapping it within the CD-hydrophobic core. Although it is not an accurate portrayal, Fig. 5 might aid in

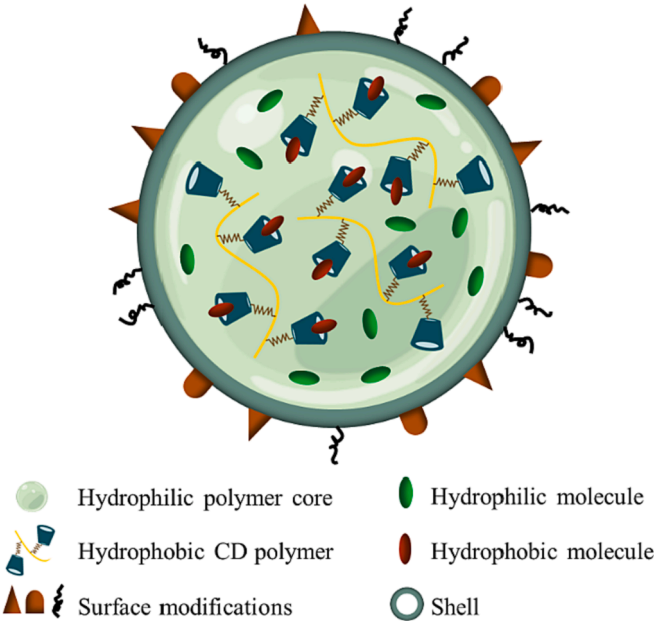

Fig. 5. A generalized representation of CD-based polymeric nanoparticulate drug carrier system.

getting a generalized understanding of the CD-based polymeric nanosystem. Besides, the limitations caused by either noncovalent or covalent complexes such as instability towards acid-base conditions, or vulnerability towards reaction conditions during formulation could be mitigated by CD-polymer conjugation as it showed better loading efficiency and stability (Rohner et al., 2019; Singh, 2017).

In a study of the solubilization and dissolution profile of a poorly soluble anticancer drug, pomalidomide (POM) after being complexed with sulfobutylether-βCD (SBEβCD), it was shown that the inclusion complexation led to a significant improvement in the solubility of the drug and a faster dissolution with an immediate drug release (Szabó, 2021). Moreover, the cytotoxicity study using the LP-1 human myeloma cell line revealed that the antiproliferative activity of the POM has not been affected by the involvement of supramolecular interaction. More grasp of the influence of complex formation was studied using the poorly soluble and unstable anticancer drug temozolomide (TMZ) with severe side effects. The study was done by complexing the drug with three different CDs (β-CD, 2-hydroxy-propyl-β-CD, 2-hydroxy-propyl-γ-CD). Although the drug did not show a notable preference for any of the CDs, it was observed that as the amount of CD increases, the solubility of the drug also increases. About 25 % of solubility in water was increased by the influence of complexation, thereby increasing the drug bioavailability (Gürten et al., 2018).

As previously discussed, the fact that the CD cavity is susceptible to the molecule size can negatively affect the loading amount of the molecule. This is where a favorable role of polymerization was expected. β-CD-PEG-guanosine (β-CD-PEG-G) molecules which can self-assemble into negatively charged spherical aggregates (β-CD-PEG-G aggregates) were formulated as an excipient for drug delivery system and were encapsulated with DOX. The aggregates were found stable in aqueous solution and showed approximately 79 ± 6.3 % encapsulation efficiency and a high loading ratio of DOX. Cell and animal experiments revealed better biocompatibility, extremely reduced toxicity, and antitumor effect. The final β-CD-PEG-G-DOX nanosystem was found to effectively induce apoptosis of cancer cells to exert antitumor influence and possibly delay tumor growth. In this study, a sustained release in response to pH was exhibited by the system (Li, 2020). It was stated before in this review that the release of covalently bound drugs from CD can be difficult at certain times depending on the bond type interfering with immediate and stable release. Whereas drug release from an inclusion complex can come with an anticipation of an initial burst. However, with the aid of polymerization, the release profile of CD-based carriers was found to be controlled in a sustainable way. Moreover, fabricating the system to a nanoscale dimension seems to further enhance the release profile. A supramolecular micelle based on host–guest interaction between β-CD and adamantine (AD) from β-CD-grafted star poly(N-vinylpyrrolidone) (β-CD-$(PNVP)_4$) and adamantine-ended linear-poly(lactic-co-glycolide) (AD-PLGA) was developed as a promising anticancer delivery system. A successful encapsulation efficiency of about 63 % and loading capacity of 7.82 % were obtained with the anticancer drug DOX. The release studies were done in response to pH 6.4 and 7.4. A controlled release behavior was seen in both cases. However, in pH 6.4, an 80 % release in 24 h followed by an immediate and steady release was observed, while in pH 7.4, a 60 % release in 24 h and a total of 67 % release in 48 h were observed. The improved aqueous solubility of DOX due to its protonation of primary amines and the hydrogen bond disturbance between AD and β-CD was stated to be the reason behind the swift and stable release. Different mathematical models of release studies pointed out that the release caused due to the disintegration of polymers. The sustained release in acidic pH presumably gave higher cytotoxicity against C6 cancer cell lines. β-CD-$(PNVP)_4$-AD-PLGA and β-CD-$(PNVP)_4$-AD-PLGA/DOX were proved hemocompatible and safe for intravenous administration by hemolysis and coagulation experiments (Ramesh et al., 2021).

With the association of PNPs, explorable possibilities towards an efficient system increased. The major drawback faced with chemotherapeutic drugs was severe side effects due to damage in normal tissues. From this perception, developing a system that can deliver the therapeutic agent specifically to the diseased cells becomes highly relevant in order to avoid damaging normal cells. Building a smart system with the ability to unload the drug at the right time and location in response to some trigger is thought-provoking when it comes to targeted delivery. Degradable nanosponges based on β-CD-modified hypercrosslinked polymer were built to have glutathione (GSH)/pH dual- bioresponsiveness. This system showed improved antitumor performance by efficiently delivering DOX into cancer cells and responding to cytoplasmic GSH as well as endosomal pH to enhance sustained intracellular DOX release. The disulfide bonds, and carboxyl and amino groups were taken advantage of as GSH and pH were the triggering factors to mimic the cancer microenvironments. About 70 % drug release was obtained with acidic influence and cytosolic reduction. Although a drug leakage of about 11 % was seen at the physiological pH 7.4, it should be noted that such low leakage can be significantly practical due to the low side effects on the normal cells. Low degradability and good drug-loading efficiency were exhibited by the smart nanosponges (Dai, 2021).

Nanohydrogels can be described as swollen nanosized particles (nanoparticles) that are constructed by chemically or physically crosslinked polymer networks with high swelling capacity by holding water (Bayat and Nasri, Jan. 2019; Szekely and Didaskalou, Jan. 2016). They have gained noticeable popularity in the field of pharmaceutical and biomedical due to their interesting properties, such as excellent biocompatibility, minimal invasiveness, shrinking-swelling behavior, prolonged release profile, etc. (Szekely and Didaskalou, Jan. 2016; Paul et al., Jan. 2017; Kasa et al., 2019; Pathak et al., 2019). β-CD-based magnetic pH-responsive nanohydrogel was developed as a "smart" drug delivery system. Acetylated β-CD was grafted with poly(2-ethyl-2-oxazoline) (PEtOx) via cationic ring-opening polymerization and then crosslinked with cystamine and amine-ended Fe_3O_4 nanoparticles simultaneously producing the reduction- and pH-responsive magnetic drug delivery system. Good loading capabilities and encapsulation efficiencies were observed by loading the doxorubicin hydrochloride (DOX.HCl) drug into the magnetic nanoparticles-hydrogel system via hydrogen bonding. The porous morphology and the hydrophilic interaction of DOX with CD exterior and PEtOx feasibly contributed to the physical loading of the drug. The hypothesis of possible combination therapy is promising when considering the presence of CD hydrophobic cavity. Thanks to the crosslinking breakage of cystamine under reduction and the quick swelling nature of PEtOx in acidic pH, a drug release of 89.2 % was observed under pH 5.3 and GSH 10 mM. The MTT assay against MCF7 cells showed a good cytocompatibility of the nanohydrogel and eventually revealed excellent antitumor behavior under chemo/hypothermia therapy compared to chemotherapy alone. With applicable magnetic features, about 74 % high loading value, and slow but stimuli-triggered release behavior, the developed β-CD-g-(PEtOx)7/Fe3O4-DOX system was proved as a potential and "smart" drug delivery system for treatment as well as diagnosis of cancer (Soleimani et al., 2021).

How generating a system in nanoscale dimension can positively influence the drug encapsulation and release behavior was evidenced in one study where β-CD-dextran conjugated hybrid polymer was coated on magnetic nickel ferrite nanoparticles making the nanoparticle size around 6 nm. CPT, an anticancer drug was loaded for about 88 % and underwent sustained release over a duration of 500 min. The drug-loaded system showed high cytotoxicity against HeLa, A549, and MDA-MB-231 cancer cell lines. The study stated an upgraded survival of the entrapped CPT against cancer cells, proving the viability and support of the carrier system for the drug. Interesting enough to observe that the strategy of drug loading on the surface of the carrier via host–guest interaction is a possible efficient approach for targeting cancer (Ramasamy and Enoch, 2020).

5. Cyclodextrin in combination therapy

Although most of the single drug carrier nanosystems possess good loading efficiency and targeted delivery with the aid of biocompatible chemical modifications, the fact that the cancer cells gradually gain defense mechanisms against therapy by the overexpression of efflux pump, increase in drug metabolism, expressing different therapeutic targets and improved self-repair ability often contributes to drug resistance in single-agent therapy (Gottesman, 2002; Hu et al., 2010). This necessitates the development of multi-drug or combination therapy, which will provide the synergistic influence of multiple drugs. In contrast to single-agent therapy, combination therapy has the ability to amplify the drug effect without crossing toxicity levels and control various signaling pathways in cancer cells (Broxterman and Georgopapadakou, 2005). Typical fluctuating behavior of therapeutics, in terms of pharmacodynamics and pharmacokinetics (Kang and Lee, 2009; DiPiro et al., 2006), consequently makes them lose target specificity. The development of an optimized multi-drug carrier system contributes to target-focused effective cargo delivery systems. Simultaneous caging of multiple drugs into biocompatible polymeric nanosystems is usually accomplished via chemical conjugation (Cao and Bae, 2012). Due to their multi-functionalities, CDs would be more advantageous in combination treatment systems. CDs can function as a crosslinker and a host to encapsulate molecules. When the cavity of CDs can carry different types of drugs by forming inclusion complexes, their hydroxyl groups can be modified to link an additional cargo. From this perception, along with the versatile influence of PNPs, it is fairly justifiable to consider the CD-based polymeric nanosystem as an efficient multi-drug system (Haley et al., 2020). Some studies of CD-based polymeric nanoparticulate systems formulated for combination therapy can be viewed below in Table 2.

Anirudhan et al. (Anirudhan et al., 2017) constructed a nanoparticle-based polymer patches as a transdermal drug delivery system (TDDS) by coupling alginate-coated aminated dextran and chitosan-coated aminated β-CD nanoparticles via electrostatic forces by inducing opposite surface charges. Then, 5-FU and curcumin (CUR) were simultaneously encapsulated into the hydrophilic core of dextran and the hydrophobic core of β-CD nanoparticles respectively. The drugs were chosen to be released with varying kinetics as a function of eluting solvents, that is the drugs could be released along with the solvents through skin penetration. The selective affinity of the developed nanoparticulate delivery systems towards solvents was studied and confirmed by *in vitro* analysis. Some previous studies show that the penetration profile of drugs through moist skin is easier for which the patches can be taken advantage of and that the penetration intensity and skin irritation are not directly related (Cilurzo, et al., 2014; Kanikkannan and Singh, 2002). Sustained release was tested for 5-FU and CUR in both ethanol (EtOH) and 1-butanol (BuOH) using Franz diffusion cell on rat skin. Although 5-FU and CUR were more soluble respectively in EtOH and BuOH, nonetheless a small amount of the less soluble drug for each solvent was observed, unlocking combinatorial therapy. Results showed that solvents could not only elute the drugs in a sustained manner but also act as penetration enhancers. Generally, even with simultaneous dual drug administration, effective combinatorial treatment could be difficult due to physiological barriers (Neervannan, 2006). But in this case, possible shortcomings of combination treatment could be mitigated by the application of nanoparticle-assisted TDDS, where the entrapped drug would be released by eluting solvent via skin (Rastogi and Yadav, 2012). Moreover, the nanoparticles seem to improve the solubility and bioavailability of the drug. This study helped bring economical TDDS which can possibly lessen the influence of side effects and be considered as a promising approach for skin cancer treatment.

Besides the synergistic advantages, carrying cocktails of drugs raises the questions regarding different stabilities and solubilities of the drugs which could possibly affect the releasing and loading abilities. Recently, a biocompatible system of β-CD-based glycodendrimer immobilized on zinc oxide coated magnetic nanoparticles was designed and synthesized for delivering multiple anti-cancer drugs against breast cancer cells, such as DOX and MTX. Loading studies confirmed the high loading efficiencies of 96.08 % and 68.03 % for DOX and MTX, respectively. The *in vitro* release studies were done at different pHs of 5.0, 6.8, and 7.4 at 37 °C, proving the controlled, pH-sensitive, and tumor-specific release

Table 2
Some CD based PNP systems for combination therapy.

System	Anti-cancer cargo	System/cargo interactions involved	Cancer cells/ Type of cancer	Note	Ref
Alginate-coated aminated dextran coupled with chitosan-coated folate decorated aminated β-CD nanoparticles	5-flurouracil + curcumin	Electrostatic force + hydrophilic interaction + host–guest hydrophobic interaction	HCT 116 cell lines (colon cancer)	Solvent selective transdermal dual drug delivery system with sustained release behavior over proper tuning of copolymer composition	(Anirudhan et al., 2017)
β-CD-based glycodendrimer immobilized on magnetic ZnO-coated nanocomposite (Fe_3O_4@ZnO@CAMAD-β-CD)	Doxorubicin + methotrexate	Electrostatic interaction + π-π interaction + hydrogen bonding + host–guest hydrophobic interaction	MDA-MB-231 cell lines (breast cancer)	Biocompatible and targeted dual drug delivery, controlled and pH-stimulated release behavior, high loading efficiency and antioxidant activity, highly stable system	(Karimi and Namazi, Aug. 2022)
Folate-appended-polyethylenimine-β-CD (roFPC)	Doxorubicin + human telomerase reverse transcriptase-small interfering RNA	Host-guest hydrophobic interaction + electrostatic interaction	MDA-MB-231, MCF-7 cells (breast cancer)	Controlled and pH-responsive intracellular drug release, redox-stimulated degradation, efficient gene transfection, simultaneous high cancer cell apoptosis and improved drug efficiency	(Mousazadeh et al., 2022)
CD nanosponge based hydrogel (CDNS)	Curcumin + resveratrol	Host-guest hydrophobic interaction	MCF-7 cells (breast cancer)	Transdermal co-delivery, enhanced permeation of drugs, high cytotoxicity against cancer cells	(Pushpalatha et al., 2019)
Polyprodrug nanoreactor based on β-CD	Camptothecin + doxorubicin	Crosslinked via disulfide bond + hydrophobic-hydrophobic interaction	HeLa cells and MCF-7 cells (cervical and breast cancer)	Dual responsive (pH and reduction) system, controlled release of CPT and DOX in reductive and low pH, better blood compatibility	(Gao, 2019)
β-CD based nanogels linked with CQDs and D-galactose (D-Gal) moieties (CQDs/β-CD/ NIPAM@AA-Gal)	Methotrexate + doxorubicin	Hydrogen bond formation + charge interaction + inclusion complexation	HepG2 cells (liver cancer)	Dual responsive (pH and temperature) and photoluminescent system, good biocompatibility, sustained release behavior, bioimaging potential	(Pooresmaeil et al., 2022)
Injectable nanocarrier with carbon nanotubes (CNTs) rationally embedded on β-CD	Curcumin + Doxorubicin Hydrochloride	Hydrophobic interaction + Hydrophilic interaction + π-π stacking interactions within CNTs	MCF-7 cell + HeLa cell (breast and cervical cancer	pH and thermo responsive polymer, anti-angiogenic potential, improved multi-drug resistance reversal, enhanced drug release	(Das, 2020)

behavior. A higher release profile of 95.89 % for DOX and 70.35 % for MTX was observed at acidic pH 5, while the release percents reduced to 29.35 % and 17.15 % at pH 7.4. The presence of β-CD seems to enhance the pH-sensitive controlled release of the hydrophobic drug DOX, while the increase in hydrophilicity of both drugs at acidic conditions also leads to their increased release rate. The flow cytometry analysis revealed a higher apoptotic effect because of the synergistic influence of the system than the free drugs. The cell apoptosis results proved the potential of the system as an efficient intracellular multi-delivery system (Karimi and Namazi, Aug. 2022).

The conventional fluctuating behavior of a single therapeutic is a challenge and when it is multiple therapeutic molecules, it demands the necessity to develop an optimized stimuli-sensitive cocktail-drug carrier system to improve the target specificity. Supramolecular nanoparticles composed of folate-appended polyethylenimine-β-CD (roFPC) are formulated as targeted combined-delivery system to carry human telomerase reverse transcriptase-small interfering RNA (hTERT siRNA) and DOX for cancer treatment. Adamantane-modified DOX was loaded into the system via host–guest chemistry, followed by the electrostatic self-assembly of hTERT siRNA with the system. Controlled and pH-dependent intracellular DOX release and simultaneous gene transfection were successfully observed by the influence of the supramolecular structures of roFPC. The polymeric part of roFPC which holds the gene undergoes redox-stimulated degradation via thiol-disulfide exchange reaction, thus imposing reduced toxicity by hindering the polymer accumulation. The system shows reliable biocompatibility, water solubility, and high hemocompatibility (Mousazadeh et al., 2022).

CD nanosponges (CDNSs), composed of well-arranged structure of branched CD polymer, are considered potential nanocarriers against cancer. CDNSs were built using pyromellitic dianhydride as crosslinker and loaded with the anticancer drugs, CUR and resveratrol (RES) via host–guest hydrophobic interaction. Comparative studies were done after incorporating carbomer-based transdermal hydrogel with drug-loaded CDNSs and plain drugs without CDNSs. The system with drug-loaded CDNSs showed higher *in vitro* drug release than that with just plain drugs. The combined performance of CUR-CDNS and RES-CDNS evidenced enhanced synergistic cytotoxicity against MCF-7 cells. Photo-stabilization of CUR and RES were achieved when loaded with nanosponges. From the *ex vivo* skin permeation study, the drugs seemed to have enhanced permeation when released with nanosponges (Pushpalatha et al., 2019).

Settling on the possibility of improved loading efficiency and sustained release, a dual-responsive β-CD-based polyprodrug nanoreactor (CCDO) were formulated with a hydrophobic part of CPT prodrug and poly[2-(diisopropylamino)ethyl methacrylate], and a hydrophilic chain of poly-(ethylene glycol) methyl ether methacrylate. Stable unimolecular micelles were formed by the system that could get internalized by cancer cells. Moreover, the anticancer drug DOX was incorporated into CCDO via hydrophobic interaction in order to efficiently increase the therapeutic effect. Controlled release of CPT and DOX by CCDO/DOX system in reductive environment and acidic pH was observed through *in vitro* studies. The CCDO/DOX micelles showed proportional time-dependent and enhanced cytotoxicity against HeLa and MCF-7 cell lines than CCDO system. *In vivo* studies evidenced the good hemocompatibility of the micelles (Gao, 2019).

β-CD based nanogels linked with photoluminescent carbon quantum dots (CQDs) and D-galactose (D-Gal) moieties (CQDs/β-CD/NIPAM@AA-Gal) proved its efficiency and intelligence as a targeted co-delivery system via dual stimuli responsive release of the anticancer drugs MTX and DOX. The drug loading is based on the hydrogen bond formations and inclusion complexation of the drugs with β-CD. Moreover, the π–π interaction between the drugs and the networked CQDs, hydrogen bonding and electrostatic interactions between the nanogel system and the polar groups of the drugs lets both the drugs to load inside the nanogels. Weakening of the π–π bonding leading to the network collapse in the nanogel causes the drug release at high temperature. Alongside non-function of hydrogen bonding and increased hydrophilicity of the drugs enhances the release rate at lower pH. *In vitro* studies demonstrated the sustained release behavior of the drugs. The dual-responsive system showed good biocompatibility, biodegradability, colloidal stability, and efficient loading and release profile against liver hepatocellular cancer (Pooresmaeil et al., 2022).

Fighting against typical challenges like non-specific drug delivery and multidrug resistance could get easier with a combined attack of cocktail chemotherapy or multidrug therapy, photothermal therapy, and anti-angiogenesis. An injectable nanocarrier was developed by functionalizing carbon nanotubes (CNTs) with modified CD polymer, loaded with CUR and DOX. HCl, has successfully demonstrated high drug entrapment efficiency and sustained pH and thermal responsive *in vitro* drug release over 30 h. The simultaneous loading of both drugs revealed a synergistic therapeutic effect forcing antitumor activities (Fig. 6a-b). Furthermore, the system demonstrated high near-infrared (NIR) triggered photothermal efficiency, leading to more than 80 % cell mortality due to NIR light-assisted drug release. When the *ex-ovo* anti-angiogenesis was done by treating chick embryos with the dual drug-loaded nano system, a down regulation of the growth factor genes FGF2 and VEGF was happening which encouraged tumor regression (Fig. 6 c). High expectations of efficient treatment with low drug dosage can be hoped with the combinatorial therapy of cocktail chemo-photothermal (Das, 2020).

In a typical polymeric system for combination therapy, the drug molecule is normally covalently conjugated with the polymeric carrier through a biodegradable linker (Greco and Vicent, 2009). Introducing a polymeric nanosystem for multi-drug delivery comes with practically and clinically relevant benefits, such as a considerable decrease in toxicity (Vasey, et al., 1999), solubility increase of the cargo (Meerum Terwogt, et al., 2001), provocative influence in immunostimulatory effects (Říhová, 2003; Sirova, et al., 2007), and ability to overcome multiple drug resistance (Minko et al., 1998). Along with the aid of nanoparticles, the polymer system affects enhanced permeation and retention effect (EPR) as a rationale for passive tumor targeting (Yuan, Mar. 2013). While the combination therapy comes with numerous advantages, it poses relevant challenges, such as realizing suitable drug combination in suitable ratio regarding the delivery system and the tumor cells, drug release mechanism, loading potentiality, clinical development, and correlative anticancer behavior of both *in vitro* and *in vivo* studies. Furthermore, due to the complexity of polymer-drug conjugates, a complete physicochemical characterization would be difficult (Garcia-Fernandez, Sep. 2016). These problems could be logically overcome by using practically and physiochemically appropriate polymers like CD and nanoparticles. Thereby it is justified to say that the CD/PNP-based drug delivery systems can be considered promising in combination cancer treatment as they can regulate the progressive spatial circulation of the drug and possess colocalization as well as sequential/ratio metric dosage of multiple drugs (Poulson, 2021).

6. Cyclodextrin in theranostics

The idea of simultaneous identification and treatment of disease using a single system is undoubtedly convincing and exciting. A theranostic system, which is like a customizable personalized approach, possesses a diagnostic agent that acts as an imaging probe to track down the cancer cells and a therapeutic agent with anticancer behavior against the diagnosed cells (Quadros et al., 2021). By establishing therapeutic as well as diagnostic agents in a single-excipient system, theranostic materials smoothen the progress of disease identification, its treatment, and instant treatment checking. Such materials are deeply studied for theranostic cancer applications (Jo et al., 2016). Target specificity, better therapeutic behavior, reduced tumor propagation, reduced side effects, and reduced damage to healthy cells are some straightforward advantages of applying theranostics. It paves the way for better compatibility of the drug with the biological environment

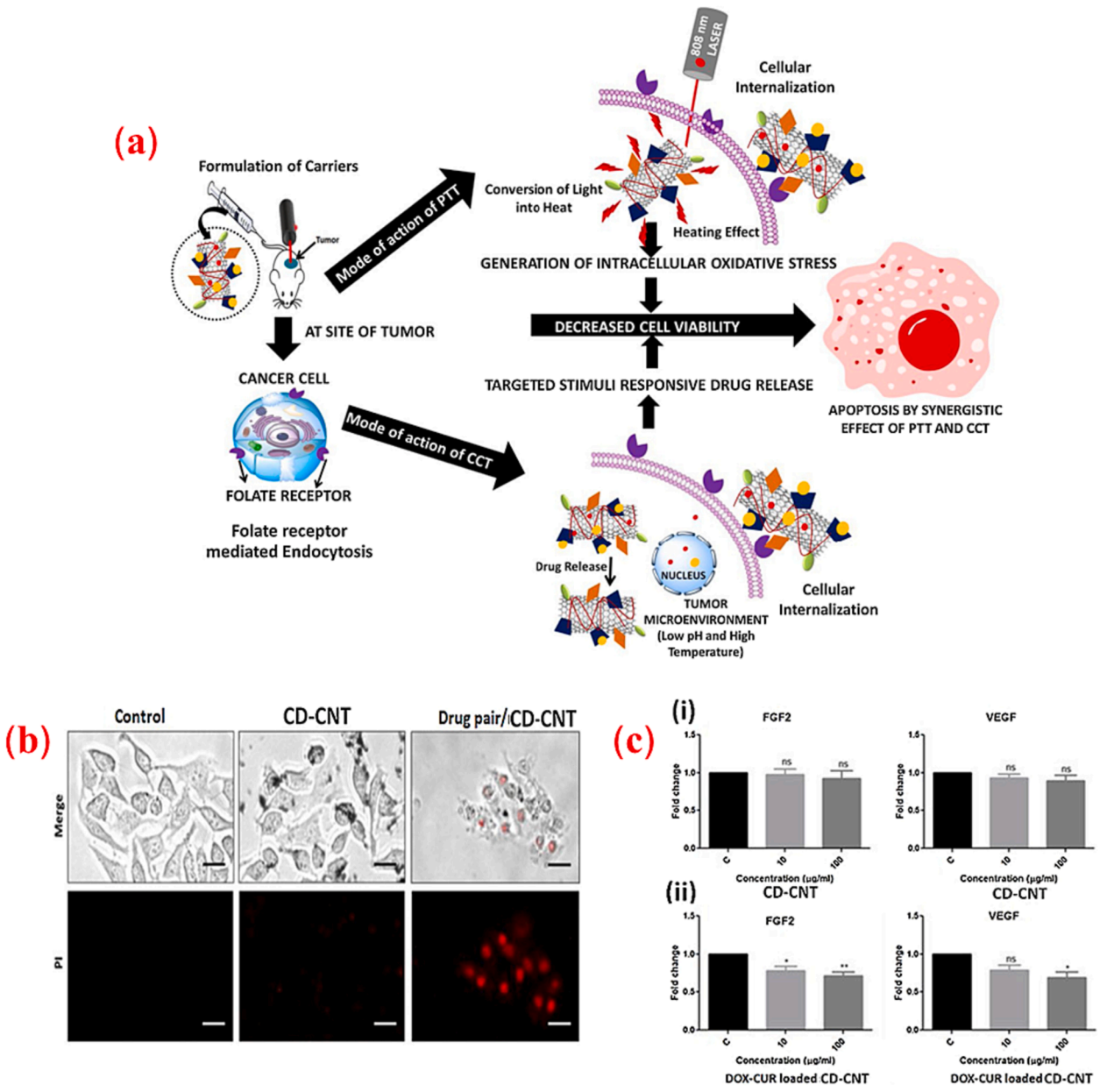

Fig. 6. (a) Mode of anti-tumor activity via synergistic therapy of cocktail chemotherapy and photothermal therapy; (b) Drug loaded CD-CNTs caused high apoptosis as observed through propidium iodide staining of Hela cells, indicating increased uptake of drugs and higher cell mortality; (c) mRNA levels of angiogenic FGF2 and VEGF genes in the chick embryos after treatment. Graph reveals the comparative fold change in FGF2 and VEGF expression of control with nanocarrier and drug loaded nanocarrier. Figures reprinted with permission from M. Das13 et al. (2020). (Das, 2020).

(Shende and Trivedi, 2021).

Due to the outstanding flexible structural conformation for chemical modification, the CD has been widely studied and considered an appropriate tool for theranostic applications. Being a crosslinker for different polymers, a core element in the formation of vastly branched star polymer, and a porter for various inorganic nanomaterials, CD promotes theranostic suitability (Mousazadeh et al., 2021). Along with the role of PNPs, CD-based theranostic systems could be considered clinically assuring. Some examples of CD-based polymeric nanoparticulate systems for theranostic purposes can be viewed in Table 3.

The basis of the evolution towards theranostics was the perception of modulating multifunctional materials to have more than one application in a single system. In light of this view, numerous pieces of research were done to engineer an ideal theranostic system in numerous different ways. Combination therapy and theranostics can be viewed in an overlapped manner. Instead of multiple drugs alone, imaging agents can also be incorporated in a combination delivery system, simply to put theranostic combination therapy. *Heo et al.* (Heo, et al., 2012) developed gold nanoparticles based theranostic agent surface-functionalized with PEG as a solvated shell, biotin as cancer targeting ligand, rhodamine B linked β-CD as a drug carrier, and PTX as an anticancer drug (Fig. 7a). Effective release of PTX from the β-CD cavity was triggered by the intracellular GSH level of 10 mM. The intracellular uptake studies of the nanoparticle system using confocal laser scanning microscopy (CLSM) and flow cytometry were done and found the higher affinity of the system to HeLa, MG63, and A549 cancer cell lines than to NIH3T3 fibroblast normal cells (Fig. 7b). *In vitro* studies showed that the loaded PEG, biotin, and rhodamine B linked β-CD surface-functionalized AuNP-5 system exhibits a higher mortality rate of HeLa cell and below one fold cytotoxicity in NIH3T3 fibroblast, proving itself as a useful carrier for targeted drug delivery against cancer cells without harming normal cells (Fig. 7c).

Table 3
Some CD-based PNP systems for theranostic applications.

System	Therapeutic agent	Diagnostic agent	Cancer cells/Type of cancer	Imaging/diagnosis techniques	Ref
Gold nanoparticle (AuNP) surface-functionalized with PEG, biotin, paclitaxel (PTX) and rhodamine B linked β-CD (AuNP-5′)	Paclitaxel	Gold nanoparticles + Rhodamine B	HeLa, A549, and MG63 (cervical, lung, and bone cancer)	Confocal laser scanning microscopy, fluorescence-activated cell-sorting, and cell viability analyses	(Heo, et al., 2012)
β-CD-{poly(lactide)-poly(2-(dimethylamino) ethyl methacrylate)-poly[oligo(2-ethyl-2-oxazoline) methacrylate]}$_{21}$ unimolecular micelles	Doxorubicin	Gold nanoparticles	HepG2 cells (liver cancer)	Computed tomography (CT) imaging	(Lin, 2017)
Fe_3O_4 nanoparticles coated with gadolinium ions decorated-poly CD	Curcumin	Iron-oxide nanoparticles	4 T1 cells (breast cancer)	Magnetic resonance imaging	(Mansouri, 2021)
Superparamagnetic iron oxide nanoparticles based β-CD with polyethylene glycol	Paclitaxel	RGD-conjugated poly (ethylene glycol)	HeLa cells (cervical cancer)	Flow cytometry and confocal laser scanning microscopy	(Nguyen et al., 2016)
β-CD conjugated silica core–shell nanoparticles	*trans*-retinoic acid	Iron-oxide nanoparticles	HeLa cells and MCF-7 cells (cervical and breast cancer)	Confocal laser scanning microscopy	(Badruddoza, et al., 2013)
Nanocarriers based on β-CD modified with Maleic anhydride and NIPAM	Curcumin + doxorubicin. Hydrochloride	Iron-oxide nanoparticles	HeLa (cervical cancer)	Fluorescent imaging	(Das et al., 2019)
Folic acid coated magnetic β-CD nanosponge	Curcumin	Iron-oxide nanoparticles	M109 cells (lung cancer)	Magnetic resonance imaging	(Gholibegloo, 2019)

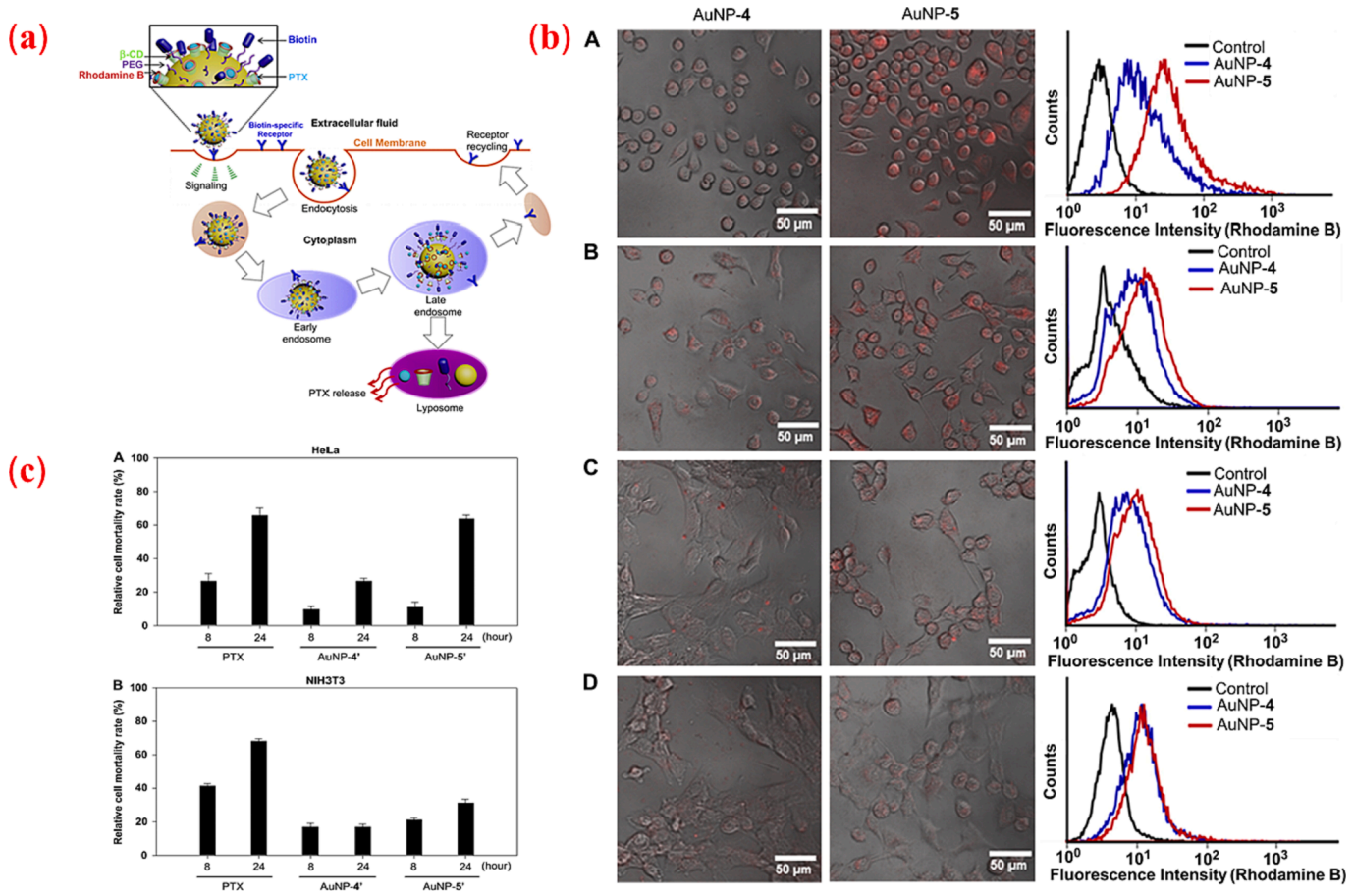

Fig. 7. (a) Schematic representation of targeted PTX delivery mechanism of PEG, biotin and rhodamine B linked β-CD surface-functionalized AuNP-5 as theranostic agent; (b) Intracellular uptakes of rhodamine B linked β-CD surface-functionalized AuNP-4 and PEG, biotin and rhodamine B linked β-CD surface-functionalized AuNP-5 on HeLa, A549, MG63 and NIH3T3 cells, measured by CLSM and flow cytometry analysis using fluorescence-activated cell sorting analysis;(c) Graph showing mortality rate of HeLa cancer cell and NIH3T3 fibroblast involved with PTX, AuNPs-4 and AuNPs-5. Figures reprinted with permission from D. N. Heo et al. (2012). (Heo, et al., 2012).

A pH responsive β-CD-based unimolecular micelles, 21-arm star-like polymer β-CD-{poly(lactide)-poly(2-(dimethylamino) ethyl methacrylate)-poly[oligo(2-ethyl-2-oxazoline) methacrylate]}$_{21}$ (β-CD-(PLA-PDMAEMA-PEtOxMA)$_{21}$) gathered synergistic loading of gold nanoparticles (GNPs) as imaging agent and hydrophobic DOX as anti-cancer drug, which showed qualities of homogeneous sizes, enhanced

colloidal stability, entrapment efficiency, and *in vitro* pH stimulated drug release. *In vitro* and *in vivo* studies showed high computed tomography and anticancer efficacy under acidic tumor conditions. Dissipative particle dynamic simulation was done to get a deeper knowledge about the micelles formation, microstructures, and distribution of DOX and GNPs on the micelle system (Lin, 2017).

Poly CD-based nanoplatform was formulated for the chelation of gadolinium^{3+} ions and delivery of CUR, an anticancer hydrophobic drug. The system was conjugated on iron oxide nanoparticles. The release profile of CUR was pH-triggered. The gadolinium-loaded system showed no relevant toxicity against normal breast cell lines (MCF 10A) or cancer (4 T1) cell lines, whereas the system with both gadolinium and CUR showed higher toxicity towards 4 T1 than to MCF 10A cells. *In vivo,* studies exhibited the significant ability of the nanoplatform to shrink the tumor without affecting both normal tissues and body weight. *In vivo* MRI studies proved the enhanced diagnostic potentiality of the system (Mansouri, 2021).

Superparamagnetic iron oxide (SPIO) nanoparticles are popular in theranostic field due to their high biocompatibility and significant imaging-ability. β-CD, which can host polyethylene glycol (PEG) and PTX via high-affinity association, is covalently immobilized on SPIO nanoparticles. SPIO nanoparticles that can self-assemble into magnetic nanoclusters could change or control their cluster size by altering the SPIO/PEG ratio. With an increased cluster size and deep iron oxide core led to highly improved magnetic resonance contrast. When the CD-PEG complex was associated with tumor-targeting arginine–glycine–aspartic acid (RGD) peptide, an enhanced uptake of the magnetic nanoclusters to tumor cells was recorded by CLSM and flow cytometry. The loaded PTX drug was released via forced displacement by competing with small molecules (Nguyen et al., 2016).

Furthermore, another group linked magnetic iron oxide particles as core within fluorescent silica shell that can host fluorescent dye (FITC) and cancer-targeting folic acid (FA) ligand and surface conjugated with β-CD that can carry hydrophobic model drug all-*trans*-retinoic acid (RA). The CD involvement performs a controlled and sustained release of the drug over time. The successful incorporation of FITC and FA ligand triggered the nanosystem with good fluorescent features to locate the particles and guided the internalization of the loaded system into the targeted tumor, respectively (Badruddoza, et al., 2013). *Das et al.* performed an interesting approach of combining multi-functionalities via chemical conjugation. β-CD-based nanocarrier was formulated with maleic anhydride and pol (N-isopropylacrylamide) (NIPAM) modifications. Multi-drug delivery of CUR and DOX.HCl was performed with pH and thermo-responsive release profile. Loading and releasing of hydrophobic as well as the hydrophilic drug were successfully done, thanks to the presence of β-CD. Improved internalization after the targeted delivery by folate conjugation was able to be understood by fluorescence imaging due to the conjugation with iron oxide nanoparticles which act as imaging agents. The synergistic amalgamation of multiple functions such as specific targeting towards tumor cells, dual responsiveness for release behavior, combination drug delivery, and fluorescent imaging into a single nanoconjugate system, was an ideal approach for a smart theranostic cancer system (Das et al., 2019). Here, the CD was being used for inclusion complexation with the drug and to create a polymeric crosslinked network with the aid of its various hydroxyl groups to trap the drug molecule. Furthermore, it underwent covalent conjugation with magnetic nanoparticles, as this can enhance diagnostic and therapeutic performance.

So far, most diagnosis-related research associates their systems with magnetic nanoparticles because of their constructive way of tracking and clear-cut imaging ability with diagnostic techniques like MRI. CDNSs were synthesized via polymerization using epiclon B-4400 (EPI) as crosslinker, due to their cheap availability, biocompatibility, and short time of polymerization with β-CD. The nanosponges were loaded with CUR into the hydrophobic CD cavity and surface modified onto the magnetic iron oxide nanoparticle. When the drug-loaded CDNSs are attached to the surface of the magnetic nanoparticulate system, the possibility of high antitumor expression of the drug considerably increases. Then, the targeting ligand, FA, was decorated on the system increasing their targeting ability. The release profile of CUR was found pH sensitive from *in vitro* results. Cytotoxicity study revealed that the CUR-free empty system shows poor toxicity against both tumor (M109) and normal (MCF 10A) cells, whereas the CUR-loaded system showed higher cytotoxicity against diseased M109 cells than the normal cells. The hemolysis study showed lesser hemolytic activity of the system, revealing its hemocompatible nature. The MRI diagnosis efficiency and tumor targeting ability were assessed in the presence of both tumor and normal cells. Significant targeted antitumor activity of the nanocarrier system was observed because of increased tumor-cellular uptake of the nanocarrier via receptor-mediated endocytosis due to the high expression of FA with the surfaced folate receptors on M109 cells. This also contributed to enhanced T_2 magnetic resonance signals, implying its applicability as a negative contrast agent. The prominent magnetic behavior contributed by the iron oxide nanoparticles, highly selective targeting ability due to the FA ligand, and antitumor activity by the sustained release of CUR from β-CD cavity made the system considerably sensitive and selective to be an effective anti-tumor theranostic system (Gholibegloo, 2019).

The introduction of theranostic systems is undoubtedly anticipated to be highly promising for the early diagnosis of the disease in its premature state, followed by quick treatment. In account of previous discussions, the nanoscale theranostics can be considered more beneficial as they can easily absorbed, leading to a reduced dosage necessity. However, it should be noted that the theranostic nanosystems that function based on the properties of tumor regions can be vulnerable to tumor heterogeneity (Parchur, 2019). Intratumor heterogeneity is said to be the dominant lead to medication resistance and treatment failure (Ramón y Cajal, 2020), which can be hard to observe earlier. That being the case, more studies of the physicochemical characteristics of the developing theranostic systems have to be done deeply on the subject of heterogeneity. Furthermore, more *in vivo* studies are crucial to evaluate the compatibility of the nanosystem with respect to human biology (Singh et al., 2020).

7. Clinical trials and prospectives

Due to its complexity, cancer is driving continuous expansion and advancement in cancer research on a daily basis. This led to the emerging of various delivery platforms, including exosomes, nanoparticles, polymeric nanosystems, liposomes, etc., for chemotherapeutic drugs. Owing to the combined interdependent benefits, polymeric nanoplatforms exhibit potential in the realms of cancer therapy and theranostics. Because of the active aid in improving solubility, stability, bioavailability, and targeting of anticancer drugs, there have been several studies on the *in vivo* efficacy of CD and CD-based delivery systems for various types of cancer, such as breast, colon, lung, ovarian, and prostate cancer (Santos, 2021; Woods-Burnham et al., 2021). However, the concern over safety and effectiveness of their usage in humans brings out the practical relevance of the clinical trials. Many CD-based nanoformulations were clinically studied to improve the cancer treatment. For example, CALAA-01 is a targeted polymer-based nanoparticle based on CD and PEG, decorated with human transferrin, and contains anti-R2 siRNA. It is designed to inhibit the protein RRM2 which is a cancer therapeutic target and to specifically target the cancer cells that overexpress the transferrin receptor (View and Pharmaceuticals, 2009). CD act as an integral to this formulation, facilitating targeted delivery of siRNA and enhancing its therapeutic potential in cancer treatment. A phase Ib clinical trial involving 24 patients with varying cancer exhibited the potential of CALAA-01 to inhibit tumor growth and/or reduce tumor size in adults with solid tumors refractory to standard-of-care therapies (Zuckerman, et al., 2014). Additionally, tumor biopsies from metastatic melanoma patients demonstrated that nanoparticles

were only found in the tumor cells and not in the adjacent normal epidermis (Cuciniello et al., 2021). Other experimental approach to chemotherapy that is under investigation in human trials are CRLX101 and CRLX301, which are nanoparticle-drug conjugates of CD-based polymer (CDP) and an anti-cancer molecule, camptothecin and docetaxel respectively. They are preferentially designed to accumulate in tumor tissues, and have showed promising outcomes of improved tumor targeting, reduced toxic side effects, and prolonged drug release in preclinical studies (Serrano-Martínez et al., 2023; Piha-Paul, et al., 2021). CD in these formulations plays vital role in the encapsulation of hydrophobic drugs improving their solubility and stability for better delivery and distribution in the body. As the bonds between CD and the drugs can be designed to be sensitive to specific physiological conditions, such as acidic pH or enzymatic activity found in tumor microenvironments, CD serve as a trigger for controlled drug release enhancing therapeutic efficacy while minimizing off-target effects. Various research groups completed clinical trials on CRLX101 which demonstrated its toxicity behavior against different cancers including non-small cell lung cancer and stomach/gastroesophageal/ esophageal adenocarcinoma (Sa et al., 2023). The latest researches are more focused on exploring combination treatments due to the potential advantages against cancer. A recent sequential phase II study by *Krasner et al.* and group involving the combination of CRLX-101 with bevacizumab, a monoclonal antibody medication, for the treatment of recurrent ovarian cancer revealed improvement in progression-free survival and overall response rate leading to the approval of bevacizumab as a new standard of care in the US. The combination aims to enhance the efficacy of treatment by leveraging the anti-angiogenic effects of bevacizumab and the targeted drug delivery of CRLX-101 (Krasner, 2021). Another phase Ib/II trial of the combination of CRLX101 with neoadjuvant capecitabine (an anticancer drug) and radiotherapy in locally advanced rectal cancer showed promising results in terms of toxicity and pathologic complete response, and the weekly maximum tolerated dose of CRLX101 was determined to be 15 mg/m^2 (Sanoff, 2019). The merits of CRLX301 of having a well-tolerated profile, anticancer activity, and differentiated pharmacokinetic behavior suggest its potential to be a better agent in combination with other chemotherapeutic compounds for the better treatment of the patients (Markman, et al., 2016).

Regarding CD-based polymeric nanosystems, many human trials are still ongoing and being initiated to produce advanced results in the field of combination therapy for cancer. Majority ongoing studies, as mentioned previously, involves the combinations of multiple antitumor medications or together with immuno-therapeutics. Even with the so far significant experimentations, the safety and efficiency of the existing CD-based systems have not yet been completely established. The results of these clinical trials are promising, but more research is required to determine the full potential of these delivery systems in cancer chemotherapy. Unfortunately, no clinical trials have been performed so far to understand the performance of CD-based PNP systems in the application of theranostics. The presence of CD opens the possibility to have both hydrophobic and hydrophilic moieties which eventually opens the door to explore not only combination treatment, but also theranostics. Although the studies are being done more deeply involving the animal models, clinical trials are highly relevant to grasp more information for the better treatment and safety of the humans.

8. Conclusion

With the data brought together in this review, the rationality and relevance of the symbiotic relationship between CDs and PNPs have been exhibited and discussed. The flexibility of CD-PNP system to bring customized needs by playing around with different modifications as well as tuning the degree of modification invokes the interest to investigate their application in combination therapy and theranostics against cancer. Recent studies have exposed the effective role of CD-PNP association with excellent results of synergistic anti-tumor activities with highly reduced side effects, enhanced targeted delivery, synergistic cytotoxicity, controlled-release, and faster treatment approach. The advantageous chemical composition of CD, the versatility of PNPs, nanoscale dimensions, and stimuli-responsiveness are the key factors to be noted in this review on the subject of CD-PNP interaction as an efficient multifunctional delivery system against cancer. Although promising, the safety and effectiveness of CD-based delivery systems in humans are still being investigated, and more research, especially in clinical trials, is needed to fully understand their potential in cancer chemotherapy and theranostics.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Lakshmi Sathi Devi: Conceptualization, Writing – original draft, Writing – review & editing. **Cristina Casadidio:** Writing – review & editing, Conceptualization. **Maria Rosa Gigliobianco:** Writing – review & editing, Conceptualization. **Piera Di Martino:** Conceptualization, Writing – review & editing. **Roberta Censi:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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