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Controlled drug delivery mediated by cyclodextrin-based supramolecular self-assembled carriers: From design to clinical performances

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ABSTRACT

The need for solutions in the pharmaceutical field that respond to the new needs regarding the minimum impact of the active pharmaceutical substances on the body has led to an explosion of research on smart systems for controlled drug delivery. Supramolecular chemistry has provided in recent years powerful tools in the field of synthesis of these forms for controlled release, cyclodextrins offering the possibility for synthesis of complex supramolecular architectures that meet these requirements. But cyclodextrins can be used only with a carrier in order to benefit by their excellent properties and this review presents the latest achievements in the field of nanoparticles-based supramolecular architectures, taken into account the main methods of synthesis and the stimuli that control the release (light-responsive, pH-responsive, redox-responsive, and multi-responsive). The review also presents applications of these systems for cooperative co-delivery systems, non-viral vectors for gene delivery and theranostics and also the present status regarding commercial systems based on cyclodextrins and their characteristics.

1. Introduction

Owing to the steady scientific progress, the area of biomedicine is shifting from conventional treatment focused only on the disease toward personalized, noninvasive biomedicine that blur the limits between the organic chemistry and molecular biology, considerably improving the quality life of patients (Ghitman et al., 2020; Kumar et al., 2021). This paradigm shift fosters new advances in the field of therapeutics and diagnostics, *e.g.*, the design of drug delivery approaches with predictable, reversible and highly tunable features toward improving their specificity and bioavailability, in accordance with the therapeutic purpose (Biru et al., 2022; Kojima et al., 2015; Mura & Couvreur, 2012). This has led to an increased interest in developing new drug delivery strategies which can be designed and tailored to facilitate tuning of therapeutic dosage, drug selection/combination, or drug availability at the point-of-care, improving the patient compliance (Webber & Langer, 2017). Specifically, in the context of "precision medicine" (Webber & Langer, 2017), the formulated drug delivery carriers should guarantee the optimal therapeutic efficacy by preserving and delivering the necessary amount of the encapsulated therapeutic agent (*e.g.*, proteins, oligonucleotides, various types of drugs or imaging molecules) to the targeted site/cells, in a predetermined period of time, efficiently and precisely with reduced off-site exposure/toxicity, releasing it in a controlled and sustained manner, in accordance with the purpose, its pharmacological properties and patient-specific therapeutic function (Biru et al., 2022; Ghitman et al., 2020; Kojima et al., 2015; Mura & Couvreur, 2012; Salústio et al., 2011; Webber & Langer, 2017).

In the frame of the current challenges, the rational design of drug delivery strategies leveraging supramolecular chemistry or 'chemistry beyond the molecule' (Webber & Langer, 2017) represents a thriving strategy in constructing supramolecular self-assembly nanoscale carriers with more sophisticated architectures and functions (Harada et al., 2009; Yoon & Jang, 2010). Inspired by the transient nature, one of the essential characteristics of supramolecular chemistry is the multifarious design possibilities in constructing the supramolecular architectures, which represents a valuable benefit in the field of new drug delivery approaches (Jin et al., 2019; Webber & Langer, 2017). Besides, the activity of some biological species (*e.g.*, nucleic acids, proteins, membrane receptors) is driven by supramolecular interactions and can be modulated according to the biological conditions (van Dun et al., 2017).

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Considering that a supramolecular system is defined as an organization of two or more molecular entities self-assembled through non-covalent interactions (Lehn, 1995), which typically exist owing to a delicate balance of these intermolecular interactions (*e.g.*, hydrogen bonding, metal coordination, hydrophobic attractions, van der Waals forces, p–p, and electrostatic interactions) beside modularity, similar to biological supramolecular specimens these systems are characterized by reversibility, topology, dynamicity and multivalency (Chang et al., 2019; Jin et al., 2019; Ma & Zhao, 2015; Webber & Langer, 2017). All these features make the supramolecular systems indispensable candidates in construction of nanoscale functional drug delivery architectures with controlled encapsulation and release of therapeutic molecules, as well as predictable, reversible, and highly tunable features toward improving bioavailability and therapeutic efficiency in a particular clinical problem (Chang et al., 2019; Harada et al., 2009; Jin et al., 2019; Lehn, 1995; Ma & Zhao, 2015; Salústio et al., 2011; van Dun et al., 2017; Webber & Langer, 2017; Yoon & Jang, 2010). Supplementary, the modularity of supramolecular interactions provides the opportunity to combine multiple therapeutics along with targeting and/or imaging agents into one delivery platform, improving the precision of both academic and practical therapy. Among the complexity of chemical species that, supramolecular chemistry offered (*e.g.*, peptides (Chang et al., 2019), macrocycles (cucurbit[n]uril (Liu et al., 2017), calix[n]arenes (Naseer et al., 2017)) or other macromolecular compounds (*e.g.*, dendrimers, hyperbranched or star polymers) (Qin et al., 2020), cyclodextrins-based supramolecular systems are undoubtedly the most used and described systems to modify the features of therapeutics, registering one of the most important contribution in the development of controlled release systems. These macrocycles, owing to their bio-adaptability, multi-functional characteristics, ability to form highly organized drug delivery systems and inexpensive synthesis methods (Van De Manakker et al., 2009) along with the ability to alleviate the side effects of therapeutic molecules, regardless of the administration route, through the formation of inclusion complexes, are ubiquitous in drug delivery field (Biru et al., 2022; Haimhoffer et al., 2019; Tiwari et al., 2010; Webber & Langer, 2017). Materials science and chemistry has provided in the last 50 years a lot of solutions in the field of life sciences from hemodialysis (Radu & Voicu, 2022; Voicu et al., 2012), tissue engineering (Oprea & Voicu, 2020a,b), osseointegration (Corobea et al., 2015; Pandele et al., 2020) or removal of different interest species (Muhulet et al., 2020; Serbanescu et al., 2021; Serbanescu, Pandele, Miculescu, & Voicu, 2020). Cyclodextrins (CDs) are cyclic, non-reducing oligosaccharides commonly composed of five or more α-D-glucopyranoside units in a ring linked by α-1,4-glycosidic bonds units (Davis & Brewster, 2004), which are obtained from the enzymatic degradation of starch, one of the most important and highly profuse polysaccharides in nature (Crini, 2014). As seminatural compounds of macrocyclic cavitands family characterized by a truncated cone structure (Hu, Tang, & Chu, 2014), these consist of a hydrophilic outer shell and a dimensionally stable relative hydrophobic cavity which can accommodate a variety of guest molecules with diverse binding affinities (Antoniuk & Amiel, 2016; Hu et al., 2014). This type of encapsulation is known as "host−guest" supramolecular interaction and can modify and/or improve the physical, chemical, and/or biological characteristics of the guest molecule, bringing high versatility to self-assembly carriers (Crini, 2014; Davis & Brewster, 2004; Hu et al., 2014; Van De Manakker et al., 2009). Although this class of substances was discovered at the end of XIX century, when Antoine Villiers (Villiers, 1891) has noted that under the action of *Bacillus amylobacter* the potato starch turns into dextrins (the term was used since 1921 to describe the degradation products of starch (Maquenne, 1906)), at present the CDs family comprises literally thousands of various CDs with different ring size and activity that are not yet fully exploited. Therefore, the CDs nomenclature system derives from the number of glucose residues in their structure, while the frequently used CDs in pharmaceutical or biopharmaceutical practice are α, β and γ-CD (refers to 6, 7, respectively 8 glucose units) (Crini, 2014; Gómez-Graña et al., 2021; Li & Loh, 2008; Loftsson and Brewster, 2010) (Fig. 1).

According to Market Reports World, the global CD market was valued at 18.77 million USD in 2020 and will grow with a CAGR of 3.37% from 2020 to 2027 (Global cyclodextrin market research report, 2021). Beside this robust commercial impact, the clinical contribution of CDs in the advancement of biopharmaceutical and pharmaceutical fields is reflected in the increasing number of products or formulations containing various CDs (especially β-CD and its derivative) which are under clinical trials or are accessible on the pharmaceutical market (over 40 products), being approved by FDA (Table 1).

Currently, the potency of CDs in designing non-invasive drug delivery devices or the therapeutic activity of CDs *per se* in antiviral therapy have been explored in both academic and clinical research (Braga et al., 2021), while owing to their amenability and versatility in former-guest interactions, these molecules have become valuable compounds in the construction of materials with applications in various fields (*e.g.*, sensors (Serban et al., 2011) and biosensors (Ioniţă et al., 2017; Muhulet et al., 2018), different types of membranes (Ke et al., 2020; Liu et al., 2022), supramolecular encryption (Hou et al., 2015), self-repairing polymers (Tian et al., 2020c), etc.,). Among uses as host-guest cavities, cyclodextrins has been proved their efficiency as antibacterial agents for textile natural fibers (Ibrahim & Eid, 2016). Especially for cellulose fibers (Ibrahim et al., 2011; Ibrahim et al., 2018) and wool (Ibrahim et al., 2013; Ibrahim & El-Zairy, 2009), these molecules present the advantage to easily be immobilized due to the chemical structure and free hydroxyl groups at the surface of textiles, this fact assuring a homogenously functionalization and increased antibacterial activity. Although a large number of review papers have been published in recent years in the field of CDs- based systems for drug delivery, describing the synthesis/formulation conditions that could generate supramolecular architectures as optimal smart drug delivery systems (Fang et al., 2022; Tian, Liu, & Liu, 2021), or being focused on their applications (Tian et al., 2020a), this review presents an overview of the use of cyclodextrins in the synthesis of nanoparticles-based supramolecular architectures for smart controlled drug delivery, both from the perspective of the main methods used for synthesis and formulation, as well as from the perspective of the stimuli that can be used for controlled release (light-responsive, pH-responsive, redox-responsive, and multi-responsive). The applications of these systems for cooperative co-delivery systems, non-viral vectors for gene delivery and theranostics are also presented and discussed. Present status regarding commercial systems based on cyclodextrins and their characteristics are shown and discussed with up-to-date examples of commercial products available on the market. The main challenges that the field raises and what problems need to be solved to increase the share of these systems in commercial products are discussed at the end of the review.

2. Building CDs-based supramolecular nano-assemblies: Host CD cavity and guest partners

Generally, the CDS-based supramolecular nanoparticles used in biomedical field as controlled drug delivery systems are designed through one of two basic mechanisms: (1) non-covalent interactions - the physical interaction and assembling of molecules in an ordered structure or in a pathway-dependent non-equilibrium state, naturally originated from hydrogen bonding or π-π coordination of small building blocks; (2) covalent interactions - the cross-linking/grafting of oligomeric structures through complimentary dimerization of terminal functionalities or pendant supramolecular affinity groups (Tian et al., 2020b).

2.1. The non-covalent formulation

implies the hydrophobic characteristics of CDs cavity (Hu et al., 2014) that promotes the accommodation of various small hydrophobic

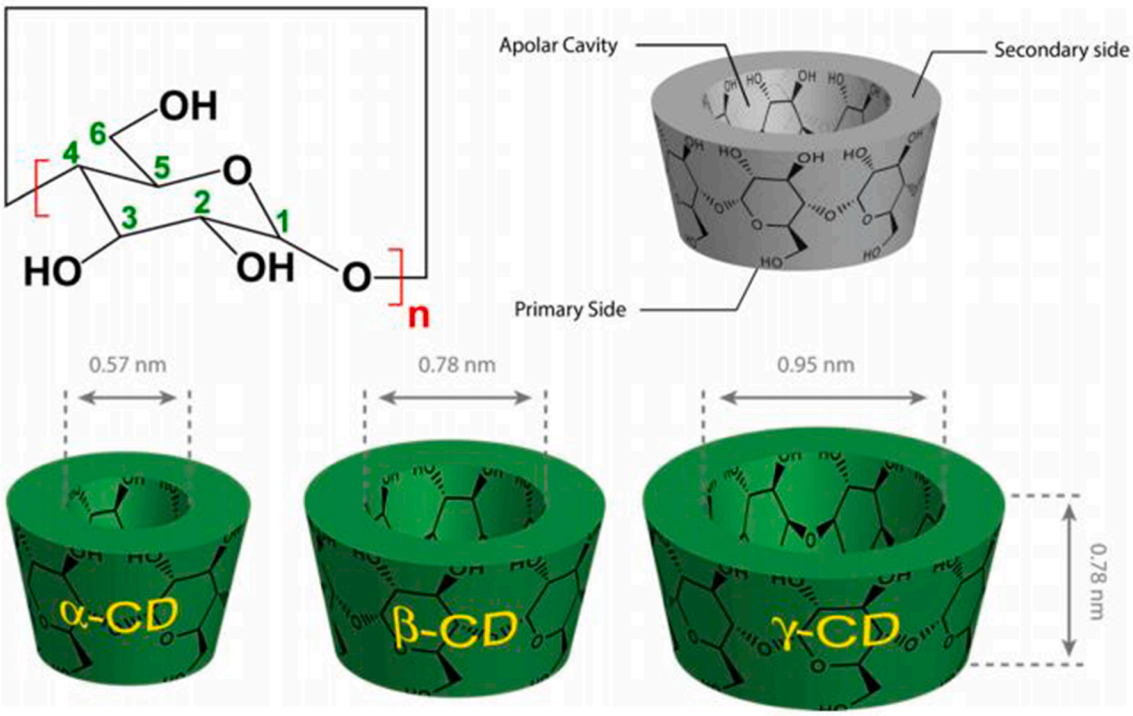

Fig 1. Representative structure of the commonly used CDs in academic and clinical practice. Top: Functional structural scheme of α-CD (n = 6), β-CD (n = 7), and γ-CD (n = 8). Bottom: Geometric dimensions of cyclodextrins. Reproduced with permission from (Crini, 2014).

Table 1
Current clinical status of CDs-containing therapeutics.

Name	*Therapeutic system*	*Investigated application*	*Company*	*Clinical status*	*Ref*
CRLX101	CD-based nanoparticle Champhotericin conjugate	Ovarian, renal cell, small cell lung, Or rectal cancers	Cerulean Pharma Inc.	Phase III completed	(Anselmo & Mitragotri, 2019)
Geodon® IM	Captisol®-enabled Ziprasidone mesylate	Antipsychotic schizophrenia, bipolar disorder	Pfizer Inc.	Approved 2002	(Sheehan, 2003)
Vfend® IV	Captisol®-enabled Voriconazole	Extended-spectrum antifungal medicine	Pfizer Inc.	Approved 2004	(Stella & Rajewski, 2020)
Cerenia®	Captisol®-enabled Maropitant citrate	NK1 receptor antagonist, antiemetic for animals	Pfizer Inc.	Approved 2007	(Stella & Rajewski, 2020)
Abilify®	Captisol®-enabled Aripiprazole	Manic or mixed episodes associated with Bipolar I Disorder	Bristol-Myers Squibb	Approved 2008	(Stella & Rajewski, 2020)
Kyprolis®	Captisol®-enabled Carfilzomib	Multiple myeloma	Onyx Pharmaceuticals Inc.	Approved 2012	(Kyprolis, 2021)
Nexterone®	Captisol®-enabled Amiodarone hydrochloride	Atrial fibrillations	Prism Pharmaceuticals	Approved 2008	(Stella & Rajewski, 2020)
Evomela™	Captisol®-enabled melphalan HCl	Multiple myeloma	Spectrum Pharmaceuticals, Inc.	Approved 2016	(Stella & Rajewski, 2020)
Noxafil®	Captisol®-enabled Posaconazole	Fungal Infection Prophylaxis	Merck & Co., Inc.	Approved 2014	(Noxafil, 2021)
Baxdela®	Captisol®-enabled Delafloxacin	Acute bacterial skin and skin structure infections	Melinta Therapeutics	Approved 2017	(Stella & Rajewski, 2020)
Carnexiv®	Captisol®-enabled Carbamazepine	Intravenous replacement therapy for oral carbamazepine formulations	Lundbeck LLC	Approved 2016	(Biosimilar, 2016)
Zulresso®	Captisol®-enabled Brexanolone	Moderate to severe postpartum depression	Sage Therapeutics, Inc	Approved 2019	(Powell, Garland, Preston, & Piszczatoski, 2020)
Veklury™	Captisol®-enabled Remdesivir	Coronavirus disease 2019, caused by severe acute respiratory syndrome SARS-CoV-2 infection	Gilead Sciences	Approved 2020	(Lamb, 2020)

* Captisol® is a patent-protected, chemically modified cyclodextrin with a structure designed to optimize the solubility, stability, bioavailability and dosing of active pharmaceutical ingredients, manufactured by CyDex Pharmaceuticals, Inc. part of Ligand Pharmaceuticals (Captisol, 2021; Stella & Rajewski, 2020).

molecules or small portion of polymeric structure by noncovalent interactions, while the exterior hydroxyl groups are not only responsible for aqueous solubility but also can interact with the hydrophilic functionalities forming water-soluble complex (Wankar et al., 2020).

Considering that the ability of CDs to generate the inclusion complexes is a function of steric and thermodynamic factors, the complexation process is driven by the Van der Waal forces, hydrophobic, and hydrogen bond interactions (Mohandoss et al., 2019; Wankar et al., 2020) that are accompanied by the subtraction of water molecules from the hydrophobic cavity and are directly impacted by the intrinsic characteristics of guest molecules (*e.g.*, chemical structure, acidity and functionalities) (Gidwani & Vyas, 2015). At the same time, the *in vitro* or *in vivo* release of therapeutics is usually triggered by the special biological environments, *i.e.*, pH conditions that can lead to the dissolution

of these bonds. Bai et al (Y. Bai et al., 2020) have managed to construct multiple hierarchical shape-regulated nanostructures based on β-CD trimer and unmodified curcumin (Cur). The morphology of supramolecular carriers could be easily tuned by adjusting the ratio of β-CD trimer to Cur due to the regulation of host-guest interactions and host-guest inclusion interactions leading to the spherical complex micelles, spindle-like complex micelles or multi-compartment vesicles. The authors have noted a pH dependent drug release kinetics and a shape-regulated biological performance, registering the highest cellular toxicity, uptake behaviors and apoptosis rates on PC3 and MCF-7 for spindle-like micelles unlike complex micelles that showed the poorest activity.

2.2. The covalent formulation

involves the synthesis of complexes with the formation of esthetic or amide bonds (Yano et al., 2002), between hydroxyl groups from CDs and functionalities of therapeutic active molecules. The advantage of the presence of CDs is given especially by an easier absorption of drugs in the gastrointestinal trajectory (Loftsson et al., 1994). According to the complexity of the constructed carriers and targeted application, the supramolecular systems may be engineered as single stimulus responsive (*e.g.*, temperature, magnetic, optical, enzymatic) or many stimuli responsive (combinations of at least two of those listed above) (Tian et al., 2021).

The construction of temperature-responsive carriers considers the synthesis of supramolecular architectures stable at normal body temperature (37 °C), but which disintegrate at temperatures specific to certain tumor sites, for example – 40–41 °C. One of the main advantages of these carriers is given by the fact that based on the conformation of a polymer depending on the temperature of the environment in which it is found, such systems can be easily simulated by computational chemistry, the success rate at their design being very high (Sirousazar, 2019).

Magnetic-responsive nanoparticles have usually typically applicability both in diagnosis (imaging) and controlled release, since can be easily manipulated to targeted site under the action of an external magnetic field. Such systems are based on magnetic nanoparticles (Fe) or on molecules containing superparamagnetic metals (Fe_3O_4). For instance, Nguyen et al (Nguyen et al., 2016) have approached a new method to construct multifunctional nanoclusters by hosting tumor-targeting moiety (c(RGDfC)-conjugated PEG) and paclitaxel (PTX) within the cavity of β-CD that was chemically coupled with iron oxide (SPIO) nanoparticles. The formulated 90 and 270 nm in diameter magnetic nanoclusters showed a high versatility in modulation of cluster size that can be easily controlled by manipulating the SPIO/PEG ratio in the assemblies, as well as drug loading and cellular uptake, to assure the optimal therapeutic outcomes in image-guided cancer chemotherapy.

Optically stimulated supramolecular formulations must contain in their composition molecules with a high degree of conjugation, which under the action of a UV-type radiation change their conformation and trigger the release of loaded therapeutic molecules. Azo benzenol or its derivatives have proven to be very effective binding molecules of CDs for the synthesis of such systems. Tetra-O-methoxy substituted azobenzene was used as a linker to bind functionalized mesoporous silica with aminated β-CD in the presence of p-coumaric acid, capable to release the loaded therapeutic under irradiation at a wavelength of 520 nm (Wang et al., 2015).

The efficiency of enzymatic triggered carriers is driven by the fact that in many tumor tissues there is an increase in the concentration of certain enzymes, such as phospholipases. It has been proven that butyrylcholinesterase is capable to easily hydrolyze the etheric bonds of supramolecular architectures consisting of β-CD and chloramphenicol and release the loaded cargo in a proportion of 50% in the first half hour and the entire amount after one hour (Guan et al., 2019).

Multi-responsive supramolecular carriers represent formulations capable to respond of at least two different stimuli, distinguishing both dual-response and triple-response systems. Zhou and collaborators (Zhou et al., 2018b) have reported the construction of thermo-/pH dual-sensitive supramolecular micelles with 50–100 nm in size based on star polymer β-CD-poly(N-isopropylacrylamide) (β-CD-PNIPAM) and benzimidazole terminated poly(ε-caprolactone) (BM-PCL) as intelligent carriers with enhanced anticancer activity *in vitro,* capable to efficiently load and then release the encapsulated DOX under acidic environment (~5.2) and body temperature (37 °C), at the same time suppressing the release of cargo at neutral pH owing to their stability (Fig. 2, A).

In an attempt to strength the stimuli-responsive specificity and active targeting of smart nanocarriers in chemotherapy, dual responsive pH- and esterase enzyme supramolecular self-assemblies based on host moiety β-CD-modified hyaluronic acid (HA-CD) and Curcumin-Oxoplatin guest conjugates (Cur-Pt) using Cur not only as chemo therapeutic but also as guest molecule in the inclusion interaction with β-CD, have been also constructed (Bai et al., 2020). The synthesis protocol was based on sonochemical method, putting in deionized water all the components, the mixture was subjected to ultrasonation for 10 minutes, following by mechanical agitation overnight, in the dark. The critical concentration of aggregation for defining the synthesis parameters was determined by fluorescent spectroscopy. The results of *in vitro* drug release experiments, performed under different conditions, highlighted the pH- and esterase-responsiveness release behaviors (the amount of released drug was improved to 83 % Cur and 85 % Oxo-Pt under esterase and acidic medium), while the basic cell experiments proved their active targeting ability and effective cellular toxicity against on A549 cells and PC3 with high expression of CD44 receptor, avoiding the cytotoxic effect on normal LO-2 cells (Fig. 2, B).

The combination of click chemistry with atom transfer radical polymerization opened new ways in the synthesis of smart supramolecular drug delivery systems with multi-stimuli responsiveness. Using this approach triple stimuli-triggered supramolecular micelles have been designed and explored as intelligent and smart nanocarriers in drug delivery field (Lu et al., 2017). The design is based on the inclusion complexation of host β-CD-poly[(2-(2-methoxyethoxy) ethyl methacrylate)-co-oligo(ethylene glycol)methacrylate] [β-CD-P(MEO_2-MA-co-OEGMA)], prepared by click chemistry and atom transfer radical polymerization, and guest polymer poly(ε-caprolactone)-SS-poly (ethylene glycol) with Azo group at one end (Azo-PCL-SS-PEG), synthesized by the combination of ring-opening polymerization and esterification reaction. Having as main property amphiphilicity, the supramolecular structures easily formed the spherical micelles and could respond to three stimuli – UV radiation, temperature and redox stimulus (Fig. 2, C). The authors have proven that the conformation and morphology of the supramolecular mycelium could be adjusted by UV irradiation (self-assembly and reversible super-molecular disassembly of the mycelium), temperature (at temperatures higher than a critical value, the mycelium became smaller and aggregated with each other) and redox potential (spherical micelles changed to irregular and became smaller).

3. CDs-based supramolecular nanoparticles for drug delivery

It is well-documented that bioavailability represents one of the key parameters that determine the pharmacodynamics, respectively the therapeutic efficiency of encapsulated agents, regardless of the administration route, *i.e.*, orally, intravenously or transdermal (Liu et al., 2021). Considering that many therapeutic agents are characterized by a low stability in biological environments (poor hydrophilicity, premature metabolization), various types of drug delivery systems have been engineering, aiming to protect the cargoes, improve their solubility/stability, and tune the pharmacokinetic and pharmacodynamic properties, modulating and controlling the drug release kinetics depending on the route of administration (Ghitman et al., 2018a, b; Wang et al., 2016). Besides, the characteristic multifarious design, versatility in functionalization and biophysical properties (*e.g.*, size,

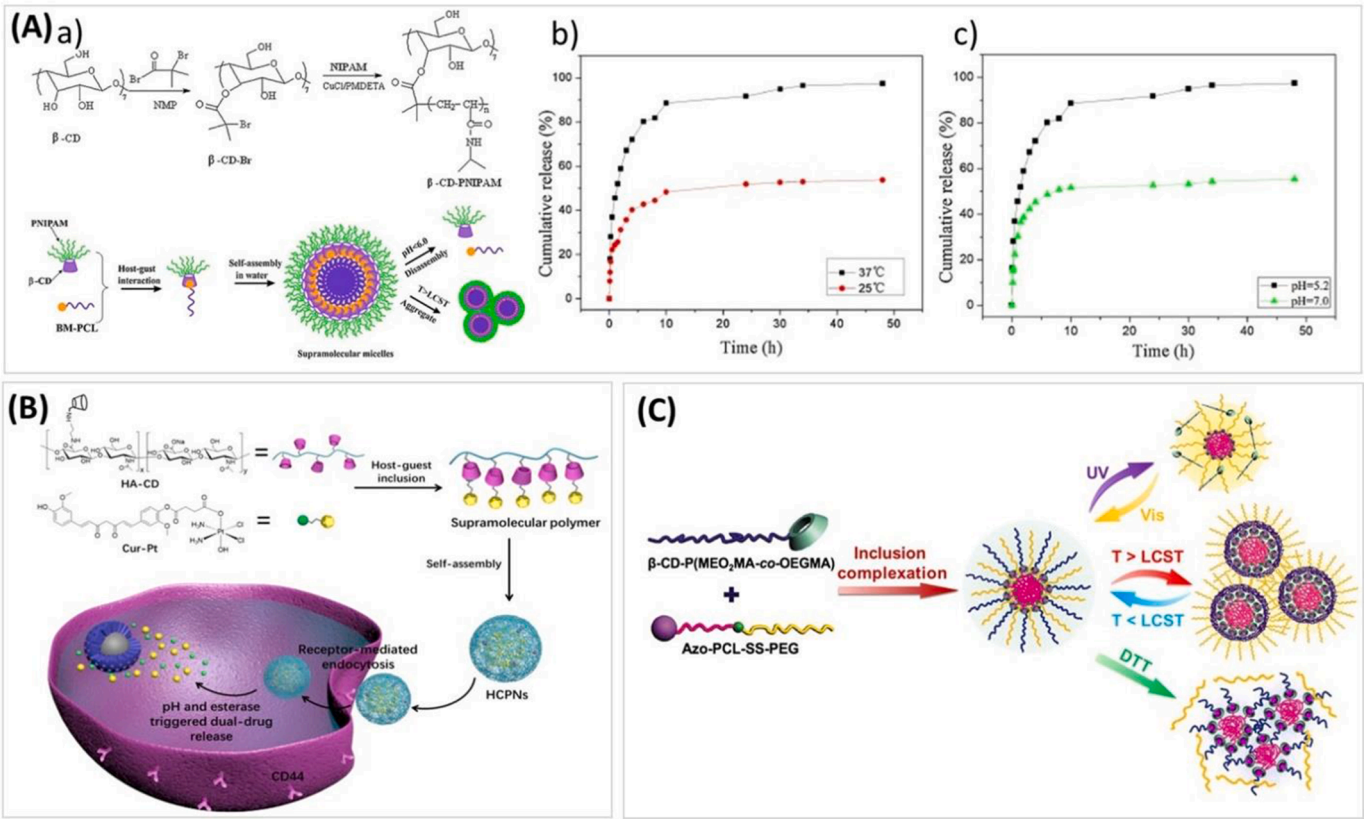

Fig 2. Representative building strategies: (A) – a) Schematic formation of temperature/pH dual-sensitive supramolecular micelles from β-CD-PNIPAM star polymer; Release of DOX from supramolecular micelles at different b) - temperature, and c) – pH (Reproduced with permission from (Hou et al., 2015); (B) – Construction of pH- and esterase- dual-responsive supramolecular self-assemblies HCPNs and their drug release behaviors (Reproduced with permission from (Bai et al., 2020b)); (C) - The formation, self-assembly, and triple stimuli-responses of the supramolecular polymer (Reproduced with permission from (Lu et al., 2017)).

charge, surface hydrophilicity and the nature and density of the ligands on their surface) the targeting ability and responsive release behavior are primordial features that can ensure and maintain the constant therapeutic concentration, maximizing the safety, bioavailability and efficiency of therapeutic agents *in vitro* and *in vivo* (Bonnet et al., 2015; Li et al., 2019; Wang et al., 2016). In this approach, the merits of self-assembly carriers based on CDs derivatives are noteworthy, primarily owing to their variable and controlled chemical structure as well as outstanding biocompatibility (Liu et al., 2021; Webber & Langer, 2017). The versatility in modulating and controlling the release behavior of therapeutic agents is generally driven by the amenability of CDs-based supramolecular architecture to accommodate various bioactive compounds either through host-guest/physical interactions (*e.g.*, electrostatic, ionic, radical or hydrophobic interactions) as well as through covalent attachment/entrapment of therapeutic molecules.

Besides, the supramolecular architectures afford the potential to control and tune the release profile of the passive loaded therapeutic agents *via* diffusion and/or convection-mediated mechanisms, which are corelated with the compatibility/affinity of "guest – host" system as well as intrinsic porosity of the entire biological network (Huang & Brazel, 2001). In this context, the passive encapsulation of therapeutic agents into CDs-based supramolecular architectures *via* host-guest interactions, leading the well-known CDs-drug complexes (or inclusion complexes) can afford a noteworthy contribution in facilitating the loading efficiency and tailoring the release profile of a wide variety of hydrophobic bioactive compounds (*e.g.*, small molecule pharmaceutics, proteins, etc.) by modifying the physicochemical and biological properties of the guest molecule as well as changing the pharmacodynamic potential and bioavailability of the entire system by reducing the premature decomposition of the therapeutic agent within biological environment (Gidwani & Vyas, 2015). Generally, the release of entrapped therapeutic molecules from the CDs cavity of inclusion complexes is described by a time dependent release mechanism (*e.g.*, dissociation upon dilution and competitive displacement of drug from the cavity by release medium constituents) and is mainly driven by the binding affinity of guest moieties to supramolecular matrix (Hirayama et al., 1995). Beside the association process, the dissociation/dissolution of guest–CD complexes followed by their subsequent dilution in aqueous environment, the process involved in the guest release from CD complexes, represent another key-parameter in the design of an optimal self-assembly drug delivery architecture.

3.1. *Classical way. Common/standard CDs-based supramolecular nanoparticles mediated drug delivery*

It is well-known that a potent drug delivery system should encapsulate the therapeutic agents, and release them in a controllable and sustained manner, ensuring a high therapeutic efficiency at the point-of-care with minimal site effects, decreasing the medication time and improving thus the patient compliance (Sun et al., 2016; Webber & Langer, 2017). In this respect, β-CD and its amphiphilic CDs derivatives can accommodate different small organic molecules by hydrophobic interactions forming inclusion complexes with improved solubility and stability of therapeutics (Mejia-Ariza et al., 2017). Considering that specific hydrophobic therapeutic agents are preferred in the β-CD, for instance, anticancer drugs (*e.g.*, doxorubicin, camptothecin, paclitaxel) or anti-inflammatory drugs (*e.g.*, indomethacin, dexamethasone, ibuprofen) the number of therapeutics available for direct inclusion into the host β-CD cavity, serving as guest molecules is reduced. The modification of β-CD using various structures (*e.g.*, adamantane, azobenzene,

etc.,) or polymers (*e.g.*, PEG, PEI, etc.,), which on the one side can improve the solubility of therapeutic molecules and the stability of inclusion complexes and, on the other can decrease the affinity of the macromolecular self-assembled system in biological environment, promoting the dissociation process, represents a popular strategy in delivery systems (Hu et al., 2014; Sun et al., 2016).

Adamantane (Ad) moiety has been extensively used *per se* or in combination with other spacers as guest molecule for construction supramolecular assemblies (Kretschmann et al., 2007) owing to its capability to form robust inclusion complexes with β-CD through noncovalent interaction of adamantly groups and hydrophobic cavity of the host system, supplementary decreasing the affinity of macromolecular self-assembly carrier in water ($K\ 1 \times 10^5\ M^{-1}$) (Hu et al., 2014). For example, it was demonstrated that amantadine, an anti-Parkinson and antiviral drug, is able to form with amphiphilic β-CD, stable molecular aggregates mediated by coulomb interactions, which may be used as drug delivery system for HPTS (8-hydroxypyrene-1,3,6-trisulfonic acid). The potency of supramolecular nanoparticle to protect and deliver in a controlled manner the encapsulated HTPS was reflected in the release profile report, which highlighted that after 360 min the release kinetics of HTPS from supramolecular nanoparticle was 8-fold diminished than that of free HTPS (80%) (Sun et al., 2016). Another approach is to decorate the therapeutic cargo with Ad through conjugation, obtaining a prodrug that will be able to ensure the required β-CD – Ad interactions for linkage between the cargo and carrier and will eliminate the molecular steric requirements endurable by the β-CD cavity. Using this strategy, Hu (Hu et al., 2012) and Fan (Fan et al., 2012) have managed to engineer supramolecular carriers capable to efficient co-deliver a non-viral gene (DNA or siRNA) along with a chemotherapeutic agent (doxorubicin-DOX or paclitaxel-PX) with high potency in cancer management. The host prodrugs, consisting of adamantyl-conjugated DOX or PX, were encapsulated within the cavity of guest β-CD crosslinked by the polycation (PEI), followed by the formulation of supramolecular nanoparticles in the presence of non-viral genes. The superiority of the system in effective inhibition of tumor growth *in vivo* was corelated with a synergistic therapeutic effect which arose from the simultaneous and sustained release of non-viral genes along with chemotherapeutics mediated by host-guest interaction.

The modification of β-CD based nanoparticles with different flexible spacers, *e.g.*, poly(ethylene glycol) containing and adamantyl end (Ad-PEG) represents a more feasible and widely reported strategy in the literature, considering the amphiphilic nature of Ad-PEG, the advantages of this system are originated from the incorporation of hydrophobic Ad within the β-CD cavity while the hydrophilic PEG chains are located on the surface of the particles, increasing the hydrophilicity of the system and circumventing the insolubility problems.

Another approach relies in the surface modification of β-CDs by grafting various aliphatic chains (*e.g.*, hydroxypropyl, etc.,) or alkyl chains (Gèze et al., 2009) on either the primary or the secondary face of the glucopyranose units, generating amphiphilic or more hydrophilic derivatives (*e.g.*, hydroxypropyl-β-Cyclodextrin (HPβ-CD) an FDA approved hydrophilic excipient (Strickley, 2004)), that are biologically better tolerated and are able to increase the intimate contact of CDs-based system with biological membranes as well as improve and modulate the release kinetics of cargoes, notably enhancing the drug absorption in biological environment (Gould & Scott, 2005; Varan et al., 2017). For instance, Pons-Faudoa and co-workers (Pons-Faudoa et al., 2019) have demonstrated the contribution of HPβ-CD, in improving the solubility and pharmacokinetics of cabotegravir (CAB), an integrase strand transfer inhibitor, by developing a subcutaneously implantable nanofluidic device with predictable pharmacokinetics for sustained delivery of CAB-HPβ-CD complexes in HIV pre-exposure prophylaxis. The *in vitro* release studies showed a 5.44-fold higher release rate CAB-HPβ-CD complexes-filled implants when comparing to implants filled with standard CAB counterparts. This sustained release of formulated CAB from nanofluidic implant was able to attain and maintain clinically relevant plasma drug concentrations 2 times above the protein-adjusted concentration which was one month longer that in the case of standard CAB, leading to an inhibition of 90% of viral replication, while the predictable pharmacokinetics features can foresee the drug depletion necessities, device replacement or refilling.

Recently many research studies have demonstrated that geraniol (GER), an acyclic monoterpene plant metabolite owing to high affinity for various brain receptors, has an important contribution in the treatment of neurodegenerative diseases in mammalians, but the irritant effects on the mucosa when is delivered to the central nervous system *via* nose-to-brain route hinder its full exploitation in biomedicine (de Oliveira Junior et al., 2020; Pavan et al., 2018). Aiming to engineer a nanocarrier that will be capable for directly and safely delivery of GER to the central nervous system, circumventing the above-mentioned problems, Truzzi and co-workers (Truzzi et al., 2021) have formulated 1:1 GER-CD inclusion complexes using native β-CD and its hydrophilic derivative HPβ-CD, comparatively investigating the *in vivo* biocompatibility with nasal mucosae and drug bioavailability into cerebrospinal fluid. Beside the solubility and drug entrapment efficiency, the characteristics of designed formulations were comparable, while the *in vivo* experiments highlighted the detection of un unexpected high amount of GER (100-fold higher) in the cerebrospinal fluid after βCD-based complexes administration compared to that achieved after HPβ-CD-based complexes. The authors have hypothesized that the different structure and solubility of complexes may be underlying factors in the *in vivo* behavior of nanocarriers. The lipophilic βCD-based aggregates were able to fast penetrate the mucosal layer, ensuring a high release GER rate in the cerebrospinal fluid, while the HPβ-CD-based complexes, because of their high hydrophilicity were prone to be cleared from the nasal cavity, prior to their complete penetration through the mucus layer. Further on the authors foresee the *in vivo* studies on models of neurodegenerative diseases to demonstrate, not only the efficacy of the formulations, but also the dosage required to induce therapeutic response. Besides, owing to its ability to bind and solubilize hydrophobic molecules HPβ-CD (Strickley, 2004; Zimmer et al., 2016) and cyclodextrin polymers (CDP) (Cantuti-Castelvetri et al., 2018) have shown a great potential in the treatment of cholesterol-related diseases and multiple sclerosis by solubilizing plaque cholesterol without inducing significant cytotoxic and ototoxic effects *in vivo* in mouse model with atherosclerosis (Kim et al., 2020) or may penetrate the mouse retina and alter the retinal cholesterol homeostasis through endocytosis after oral gavage (El-Darzi et al., 2021).

3.2. Discovering a target. Affinity-mediated controlled drug delivery from CDs-based nanoparticles

Targeted delivery is recognized as more viable drug delivery approach characterized by high specificity to desired site (*e.g.*, cells, tissue, organ) and improved delivery efficiency (Hu et al., 2014). The targeting features of carriers are frequently obtained by their surface modification/coupling with targeting motifs, which are capable to assure a specificity/affinity of the functionalized nanoformulated system for a particular targeted site and efficiently deliver the therapeutics to the desired destination, ensuring thus a high curative efficiency and safety with minimal site effects (Ghitman et al., 2022; Webber & Langer, 2017). In this regard, supramolecular design provides an extensive freedom to incorporate a variety of targeting units/motifs, often in a modular fashion during the self-assembly process, while controlling the component ratios offers the opportunity to tune the density of targeting units or to combine multiple targeting moieties, according to the addressed target-specific drug delivery issues (Webber & Langer, 2017). In some scenarios modification of CDs with advanced functionality exhibits superior performances in specific diseases, *e.g.*, cancer therapy, various CNS disorders, representing a very promising research area for biomedicine and pharmaceutical industry.

Folic acid (FA) (Ang et al., 2014), RGD (Arg-Gly-Asp)-peptides

(Quan et al., 2010; Wang et al., 2010) or transferrin (Davis et al., 2010) are only few examples of targeting motifs that have been combined with supramolecular CDs-based carriers to impart the targeting specificity towards various type of cancerous cells in cancer therapy.

Since folic acid receptors are particularly overexpressed on the surface of 40% of solid tumors (Kurosawa et al., 2018), being insignificant on normal tissue, the formulation of folate-drug delivery systems that are capable to enter tumor through receptor-mediated endocytosis avoiding non-specific effects on healthy tissue are of particular interest in cancer management. For instance, Ang et al. (2014) relied on a supramolecular self-assembly approach driven by the host–guest complexation between β-CD and adamantane (AD) for tumor-targeted delivery of doxorubicin (DOX), integrating the folic acid (FA) as targeting motif. The group performed a detailed *in vitro* investigation of tumor targeting performances of DOX-loaded nanoparticles, observing a high specificity for targeting toward the cancerous cells. Then, the *in vivo* studied performed on tumor bearing nude mice showed that after 25 days of treatment, the functionalized formulations presented better capability to inhibit the tumor growth than standard nanoparticles, owing to their tumor targeted specificity that improved the therapeutic effects of DOX. Recently, aiming to improve the bioavailability, biosafety, and loading capacity of curcumin, Hong and co-workers (Hong et al., 2021) have managed to construct a folate receptor-targeted nanoparticle (FA-Cur-NPs) for specific delivery to cervical cancer tissue, by conjugating folic acid with β-CD-ε-PCL copolymer. The formulated FA-Cur-NPs were capable to load a high amount of chemotherapeutic, owing to the cyclic structure of β-CD (EE = 95.64 ±0.92%), and then release it in a rapid manner in the tumor microenvironment conditions *in vitro* (pH 6.4). The authors have proved the contribution of targeting agent in Fa-mediated endocytosis pathways by the superior uptake of FA-Cur-NPs on HeLa cells cultured *in vitro* registered in fluorescent microscopy and flow cytometry, followed by their more efficient accumulation in the tumor sites *in vivo* and *ex vivo* in HeLa xenograft mouse model experiments. This inference was further confirmed by the *in vivo* biodistribution and antitumor efficacy along with the H&E (hematoxylin-eosin) staining studies, which highlighted the superior tumor inhibitory effect of FA-Cur-NPs owing to both EPR effect and marked accumulation in the tumor site, respectively their potency for improving cancer therapy through active targeting and controllable release.

In another work, reported by Li et al. (2018) the targeting specificity of aptamers (oligonucleotides) and supramolecular self-assembly principle were used to construct a nanocarrier for targeted delivery and combination chemotherapy. Two antitumor drugs-doxorubicin (DOX) and docetaxel (DTX) were encapsulated within β-CD polymer (poly-β-CD) nanocarrier *via* host-guest interactions, while two aptamers, sgc8c and Zyl, specific for suspension cell line (human leukemia cell line), respectively for adherent cell line (human hematoma cell line) were used as targeted recognition elements. According to the results, both therapeutics presented a pH-controllable release profile, with high susceptibility to tumor acidic environment. The significant selective cytotoxicity toward selected cancerous cells was correlated with the ability of aptamers to specifically recognize the corresponding sites of cytomembrane followed by the endocytosis of nanoparticles into the tumor cells, where the formulated systems presented a good synergistic antitumor activity originated from the combination of therapeutics. Although no data about the *in vivo* behavior, these nanoparticles are considered a useful platform for targeted drug delivery systems with synergetic antitumor activity. Guo et al. (2017) have used the concept of gene delivery therapy to develop an antibody targeted CDs-based nanoparticle (NP) for efficient delivery of siRNA to silence BRD4 in leukemia stem cells, through IL-3Rα antigen-mediated cellular uptake in KG1 cells. The clinical prospective of antibody-tagged CDs nanocarriers as efficient non-viral vectors of therapeutic siRNA in the treatment of AML was sustained by exploring the *in vitro* mechanistic studies, revealing the effective knockdown of BRD4 mediated by the targeted formulation at both mRNA and protein levels in IL-3Rα positive KG1 cells and in *ex vivo* primary acute myeloid leukemia (AML) patient derived samples, leading to myeloid differentiation, induced leukemia apoptosis, thus reducing blast proliferation. Beside the great progresses registered in this field, the problems related to poor solubility of chemotherapeutic in biological environments still remain a challenge in efficient management of cancer therapy. In this context, Wang et team (Wang et al., 2021) have evaluated the antitumor activity of scutellarein (SCU) (flavonoid with chemotherapeutic properties) loaded-niosome nanoparticles (β-CD-CL-Scu-cRGD) by targeting integrin αvβ3 *via* cRGD ligand in colon cancer. The authors have noted a high proliferation potency and apoptosis of cRGD-decorated niosome loaded with SCU on LoVo cells cultivated *in vitro*, as well as a significant efficiency to inhibit the growth of colon cancer transplantation tumors *in vivo* in mice, through targeting integrin receptors mediated endocytosis, suppressing the expression of Ki67 (protein associated with tumor differentiation and metastasis) and αvβ3 (can disturb the angiogenesis).

Hyaluronic acid (HA), a glycosaminoglycan, the major constituent of the extracellular matrix with important contribution in tissue organization and fundamental biological processes (*e.g.*, cell growth, proliferation, differentiation and organ structure stability) (Liang et al., 2016) is also exploited as targeting motif owing to high affinity toward CD44 (membrane glycoprotein) and RHAMM (hyaluronate-mediated motility) receptors overexpressed on the membrane of tumor cells (Gupta et al., 2019). Starting from these premises Singh et al. (2021) have combined the biological and targeting features of HA along with the drug delivery abilities of β-CD to generate a supramolecular HA-β-CD biopolymer as promising carrier for targeted delivery of chemotherapeutic agents, through single step grafting the β-CD onto HA chains, following by the loading of chemotherapeutic agent (DOX) and fluorescent model of drug (Rhodamine B) within the cavity of β-CD component. Beside the excellent loading capacity of both drugs, which was 9-times and 31-times higher in the case of DOX (46.6 ± 2.0 mg/g) respectively Rhodamine B (31.1 ± 1.7 mg/g) as compared to β-CD alone the proposed supramolecular model presented a pH-dependent drug release profile. The affinity of HA toward CD44 receptors, respectively the selective targeting ability of HA-β-CD to tumor cells was validated *in vitro* on HeLa and MCF-7cancer cells, with different CD44 expression amounts on the membranes. The specific accumulation of DOX in the cell nuclei and the incorporation of Rhodamine B within the cytoplasm around the cell nuclei detected in CLMS analyses was correlated to cell membrane CD44 receptor-mediated internalization, confirming the drug delivery efficacy of HA-β-CD. Further, the plasma pharmacokinetic and drug biodistribution studies on mice revealed a slower drug clearance along with a significantly higher bioavailability of formulated DOX within the tumor tissue (314 ± 55), than free DOX (152 ± 42) after 12 hours, confirming that HA-β-CD can facilitate targeted delivery and sustained release of Dox to the tumor tissue (Fig. 3, A).

The blood-brain barrier (BBB) is a diffusion barrier with important contribution in the homeostasis and protection of central nervous system (CNS), owing to its high semipermeable properties (Banks, 2009; Mulvihill et al., 2020). Considering that the delivery of therapeutic agents to the CNS is modulated by blood–brain interfaces, the management of CNS related diseases represents currently one of the main challenges in both academic and clinical research. In this way, the literature reports a wide range of drug delivery systems (*e.g.*, saturable transport systems (Kastin & Pan, 2008), transport vectors (Choudhari et al., 2021), liposomes and micelles (Juhairiyah & de Lange, 2021; Shi et al., 2017)) with different architectures and functionalities, which are capable to overcome the constraints imposed by BBB through different mechanisms, delivering the encapsulated therapeutics across blood–brain interfaces to the targeted site with minimal side effects (Ahlawat et al., 2020; Dong, 2018; Pandit et al., 2020; W. Zhang et al., 2021). Among these strategies, it is documented that CD-based carriers may modulate the drug-transport properties across lipophilic membranes through different mechanisms that may alter the membrane fluidity and

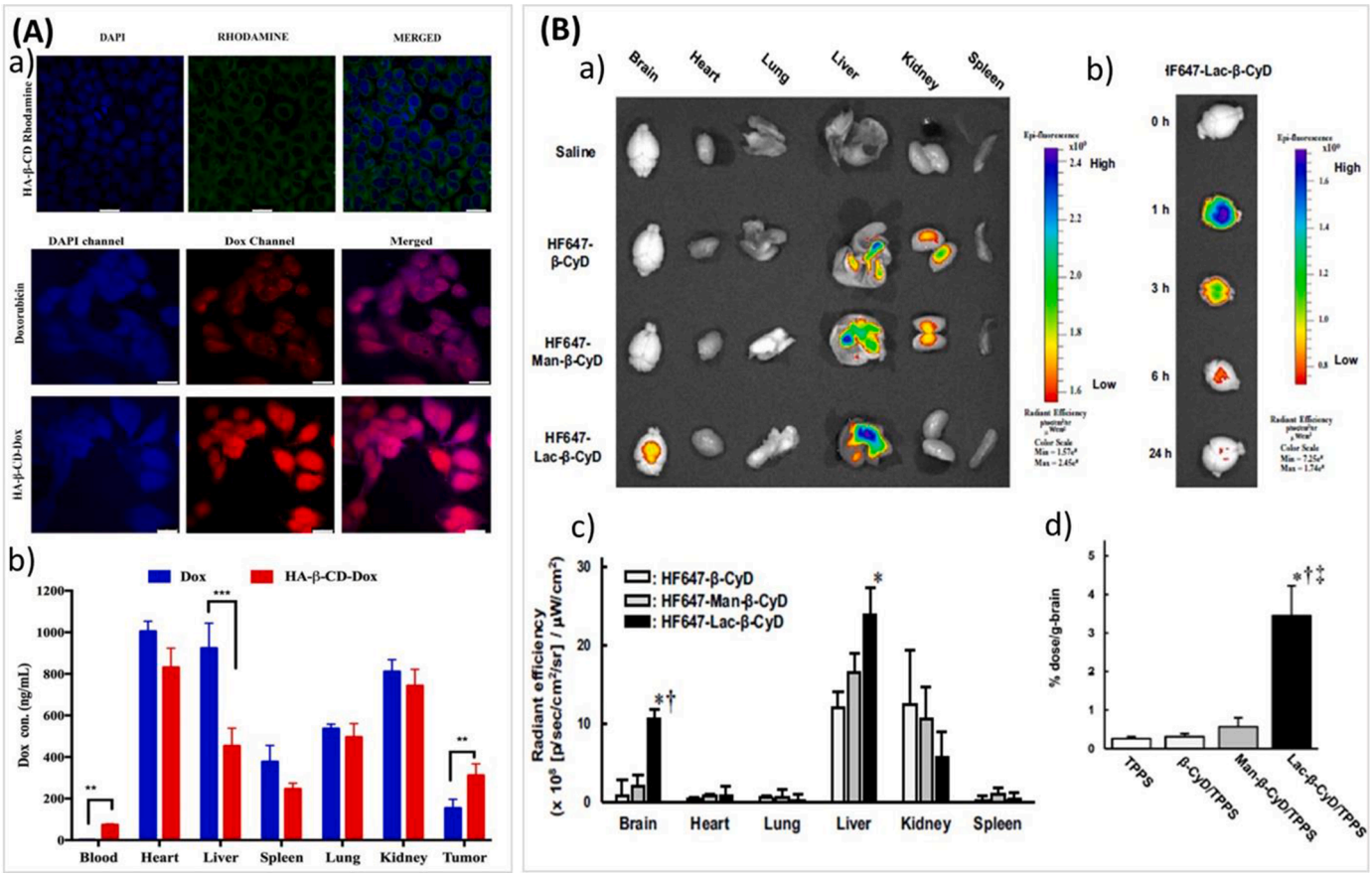

Fig 3. (A) – a) - The confocal laser scanning microscopy (CLSM) images of HeLa cells after 4 h of incubation with Rhodamine-B-loaded HA-β-CD and Dox and Dox-loaded HA-β-CD. The cell nuclei are stained with DAPI (blue fluorescence). Rhodamine B (green fluorescence) and Dox (red fluorescence) are visible. Scale bar is 25 μm; b) – The biodistribution of Dox in the tumor tissue and main organs 12 h after intravenous injection of HA-β-CD-Dox and free Dox, where $p < 0.002$ (**) in the blood samples and tumor tissue and < 0.0001 (***) in the liver of the mice (n = 3) (Reproduced with permission from (Singh et al., 2021)); (B) – Biodistribution of HF647-Lac-β-CyD after intravenous injection to mice, a, b, c) - Organ levels of HF647-Lac-β-CyD after intravenous injection in mice detected by IVIS. This figure shows the representative image for n=3; d) Brain levels of Lac-β-CyD/TPPS complex after its intravenous injection to mice (Reproduced with permission from (Yokoyama et al., 2020)).

lower its barrier function, therefore enhancing drug absorption through biological barriers (Coisne et al., 2016; Liu et al., 2021). In this regard, a significant work was done by Gill and co-workers who have designed quaternary ammonium β-CD (QA-CD) (Gil et al., 2009) and β-CD-poly (β-aminoester) (Gil et al., 2012) nanoparticles capable to improve the DOX delivery across the intact BBB endothelium. The authors claimed that owing to their small size (less than 88 nm) the nanoparticles are proficient to permeate the BBB *via* endogenous endocytosis and transcytosis pathways without affecting the integrity of endothelial cells, thus 2-fold increasing the permeability of DOX-loaded QA-CD nanoparticles throughout the BBB endothelium than control samples (Gil et al., 2009). Furthermore, in the case of β-CD-poly(β-aminoester) nanocarriers, beside high DOX loading efficiency (86 %) and preservation of the *in vitro* BBB models integrity, it was noted a much higher permeability and a more slowed and controlled release capacity of DOX, which lasted at least one month as compared to control samples (Gil et al., 2012).

Although CD-based nanoparticles can penetrate through BBB barrier, their targeted delivery to a specific site of CNS or into the neurons in a particular CNS disorder still remains a challenge due to their hydrophobicity and relatively high molecular weight (aprox.1000 Da). Aiming to formulate an optimal nanocarrier that will efficiently deliver the bioactive agents into de brain, being capable to reach the neurons, Yokoyama et al. (2020) have formulated various sugar-appended β-CDs (β-CyDs) using six different types of monosaccharide (mannose, N-acetyl-glucosamine, galactose, glucose, lactose and maltose) as brain targeting ligands. The *in vitro* analyses showed that among the investigated ligands, lactose-appended β-CyD (Lac-β-CyD) presented the highest affinity to hCMEC/D3 cells (human brain endothelial cells) significantly facilitating the cellular uptake of encapsulated model of drug TPPS (tetraphenyl porphyrin tetra sulfonic acid), as well as a high potency to permeate the human BBB models. The *in vivo* investigations confirmed the preferential intracranial accumulation of Lac-β-CyD (4.6% of the injected dose), particularly in the parenchyma and neurons of mouse brain after crossing the BBB barrier, while the biodistribution results revealed that, beside the brain, a high amount of Lac-β-CyD was also detected in the liver and kidney of mouse (Fig. 3, B). The authors have hypothesized that this preferential accumulation may be correlated with a high level of galectin-1 overexpressed in these organs, but the precise expression level of galectin-1 in each organ under selected experimental conditions was unclear. Hence, further experiments should clearly debrief the connection between the expression levels of galectin-1 in various organs and accumulation of Lac-appended-β-CyD formulations.

3.3. *Smart carriers. Stimuli-responsive CDs-based nanoparticles for controlled drug release*

In the context of "precision medicine", despite the various physiological changes that may occur in the organism during the treatment process, an efficient drug delivery system must ideally accomplish the on-demand release of the encapsulated therapeutic according to various environments of the disease/physiology or the dynamic process of the organism itself, potentially improving the selectivity, specificity and

therapeutic efficacy of therapeutic agents (Lin et al., 2021; Tian et al., 2021). Within this framework, (bio)stimuli-responsive nanoparticles have been recognized as potent multifunctional drug delivery systems that may increase the therapeutic efficiency and minimize side effects by selectively releasing the encapsulated therapeutics according to the requirements of the targeted location and in an accurate and well-controlled profile upon triggering by disease-associated pathophysiological signals or specific transporting pathways, avoiding the premature release of the encapsulated therapeutic during the distribution within biological environments (Tian et al., 2021; Zhang & Ma, 2013). CDs-based nano-assemblies and their derivatives have attracted widespread attention as stimuli-triggered drug carriers, since they can control drug release in a spatiotemporal manner and can achieve tunable drug release according to targeted physiological or pathological conditions (Peng et al., 2017; Zhang & Ma, 2013), owing to the dynamic of supramolecular interactions that may respond to various stimuli, under certain circumstances, generating different reversible structural changes of supramolecular formulations (dissociation and/or association processes) (Engel et al., 2018; Schmidt & Barner-Kowollik, 2017). These influencing circumstances may be broadly divided into exogenous stimuli (*e.g.*, ultrasound, magnetic stimulus, electrical stimulus, and light) or endogenous stimuli (*e.g.*, enzyme, active oxygen species, temperature, ions, and pH) (Peng et al., 2017; Yu & Lee, 2020; Zhang & Ma, 2013). The biological performances along with the influencing stimuli and targeted applications of current different smart stimuli-responsive CDs-based nanocarriers are summarized in Table 2.

3.3.1. Light-responsive CDs-based nanoparticles (exogenous)

Among the external factors, light represents one of the most versatile, relatively noninvasive and "bio-friendly" stimulus that can be easily controlled and manipulated in space or time (Tian et al., 2021). Since the specific wavelength of light (*e.g.*, UV, visible, NIR) and power are the main factors that trigger the cargoes release, while the tissue penetration depth and phototoxicity of the light employed are parameters that defined the safety of the designed system, their accurate modulation may generate smart photosensitive nanocariers capable to release therapeutic cargo "on demand" with precise spatiotemporal control and reduced side effects (Jia et al., 2018; Shanmugam et al., 2014). Generally, the formulation of light-responsive nanocarriers is based on the incorporation of photochromic molecules (*e.g.*, azobenzene and its derivatives) that undergo reversible isomerization when exposed to specific wavelength radiation, acting as "gates" or "switches" for the release of encapsulated cargoes (Bléger & Hecht, 2015; Jia et al., 2018). Zou et al. (2007) have described a non-covalent amphiphile driven by host-guest interactions between CDs and azobenzene-containing molecule (3C18-Azo) with optical switchable self-assembly behavior. Similar work was later reported by Li et al. (2012), while Mei's team (Mei et al., 2012) has managed to construct a supramolecular nanoparticle through β-CD-modified hollow MSNs covered with an amphiphilic copolymer with a *trans*-azobenzene structure that could release Ibuprofen in a ''release-stop-release'' manner by converting light irradiation from UV to VIS Wang (Wang & Wu, 2016) and Bian (Bian et al., 2019) have managed to photocontrol and improve the release profile of drugs from mesoporous silica nanoparticles (MSNs) by the means of photo-responsive supramolecular valves constructed of tetra-ortho-methoxy-substituted azobenzene and β-CD (mAzo/β-CD) grafted on the surface of nanocarriers. The authors claimed that light irradiation may trigger the release of encapsulated drugs by opening the photosensitive supramolecular valves that close the nanopores of MSNs based on a mechanism of transforming the isomerism of β-CD and changing the conformation of mAzo groups. In another complex study, Han et al. (2020) have combined targeting ability of MMP-9-sensitive peptide and light stimulus to formulate matrix metalloproteinase (MMP)-sensitive supramolecular nanoparticles (MMP-S NPs) with enhanced photodynamic antibacterial effect against biofilm-associated bacterial keratitis. The supramolecular nanocarriers were designed *via* host-guest self-assembly of chlorin e6 (Ce6) conjugated β-cyclodextrin (β-CD) prodrug (β-CD-Ce6) activated with MMP-9-sensitive peptide. The overexpressed MMP-9 in the keratitis microenvironment triggered the removal of protective peptide, thus promoting the penetration of the nanoparticles in biofilms and their bind to Gram-negative bacteria *P. aeruginosa.* The *in vivo* studies performed on mouse corneas with *P. aeruginosa*-infected keratitis, validated the efficiency of nanocarriers in killing bacteria through destroying the bacterial membrane owing to the *in situ* photodynamic activation of reactive oxygen species (ROS) generated under light irradiation. The histological analyses revealed the ability of nanocarriers to prevent the further damages of corneal tissues through inhibiting the inflammatory response in mice cornea, respectively their photodynamic antibacterial potency in management of bacterial keratitis.

3.3.2. pH-responsive CDs-based nanoparticles

Considering that the disparate tissues and organelles as well as their pathophysiological states are characterized by their environmental pH (Gao et al., 2010; Li et al., 2020), smart CDs-based nanocarriers with pH environmental responsiveness features, according to a particular pH gradient, capable to insure a more efficient delivery of therapeutics into the extracellular fluid or cytosol (Shen et al., 2008) are particularly important to therapeutic delivery field. Generally, the pH-triggered nanocarriers can be engineered employing three key-strategies: (1) incorporation of charge shifting polymers; (2) using pH (acid) degradable linkages as pendant functionality or (3) pH (acid) labile linkages to generate crosslinked particles, and their pH responsiveness may occur through physicochemical changes to their structure or surface characteristics, disassembling or releasing the encapsulated therapeutic molecules (Deirram et al., 2019; Gao et al., 2010). Liang and co-workers (Liang et al., 2018) have reported the formulation of a pH-responsive and sustained release supramolecular system for adenosine 5′-triphosphate (ATP) based on electrostatic interactions between sulfato-β-CD and polyethylenimine (PEI). Owing to the different protonation degree of PEI under various pH values, the formulations presented a good pH-responsive assembly/disassembly behavior as well as loading/sustained release abilities towards encapsulated biomolecules. In another study Yang et al. (2018) have integrated the pH sensitiveness of poly (β-amino ester) (PAE) with host-guest recognition of β-CD along with hydrophilicity of adamantul-terminated polyethylene glycol (PEG-AD) into a supramolecular micelle that could effectively encapsulate and then release in a pH-controllable manner the chemotherapeutic curcumin (CUR). The remarkable pH-responsiveness of micelles was originated from the transformation of hydrophobic PAE core to hydrophilic form in acid media, generating structural and morphological changes of carriers and triggering a twice higher drug unloading efficiency in weak acidic medium (pH=5.5) as compared to physiological one (pH=7.4). Besides, the micelles showed a good biosafety and a satisfactory inhibition efficiency of mouse sarcoma both *in vitro* and *in vivo* at a relatively high CUR dose (40 mg/kg). Then, Sawant with Bamane (Sawant & Bamane, 2018) have synthesized PEG and β-CD surface functionalized luminescent zinc oxide nanoparticles which showed high loading payload of hydrophobic CUR and increased pH-sensitiveness of drug delivery and release to cancer cells, respectively high *in vitro* antibacterial activity on *S Aureus* and apoptosis effect on MCF-7 cells. Further, aiming to extend the application of bio-based products in nanomedicine, Yang et al. (2020b) have employed the host–guest strategy to assembly biocompatible cellulose-based supramolecular nanoparticles from adamantane (Ad)-grafted carboxyethyl hydroxyethyl cellulose and β-CD-grafted glycerol ethoxylate, subsequently co-assembled with doxorubicin (DOX)-decorated CD (DOX-SNPs) as potent translational platform for chemotherapy and personalized nanomedicine. Based on high binding affinity of Ad and CD the team has managed to load a high amount of DOX within the nanocarriers (DLE = 94.16%) as well as to significantly improve their inhibitory effect on HeLa cells, owing to their pH-responsive release behavior originated from the acid-labile

Table 2
Stimuli-responsive CD-based nanocarriers as potent strategy in smart nanomedicine.

Supramolecular nanocarrier	*Stimuli mode*	*Drug*	*EE/ DLE (%)*	*Release efficiency*	*Targeted application*	*Therapeutic performances* *In vitro*	*In vivo*	*Ref.*
MSNs-mAzo/β-CD valves	Red/ NIR-light	DOX	3.21wt	~38% under red light and ~3% in dark	Drug delivery	-	-	(Wang & Wu, 2016)
MSNs-β-CD/Azo-PDMAEMA valves	Visible-light	CA	-	56 % upon green light and 7% without light	Cancer therapy	-	-	(Bian et al., 2019)
Chlorin e6-conjugated β-CD/ Ad-MMP-SPEPs NPs	Visible-light	C e6	-	-	PDT of bacterial keratitis	Excellent bactericidal rate (99.4% and 99.997%, against planktonic *P. aeruginosa* after 4 and 8 min of irradiation).	High antibacterial efficiency with low inflammatory response after 7 days of topical application on mouse corneas with *P. aeruginosa* infected keratitis; low long-term toxicity on major organs after 30 days of treatment.	(Han et al., 2020)
β-CD-poly(β-amino ester)/Ad-PEG micelles	pH 5.5	CUR	85.00	80% at pH 5.5, 65% at pH 6.5 and 40% at pH 7.4	Cancer therapy	Important antiproliferative effect on S180 cells, 15 μg/mL Cur-loaded micelles decreased the cells viability to 24.58% with IC50 = 5.07 μg/mL	CUR-loaded micelles (CUR 40 mg/kg) led to a 62.14% tumor inhibition in S180 tumor bearing mice 16 days post-treatment	(Yang et al., 2018)
β-CD-PEG surface functionalized ZnO NPs	pH 4.8	CUR	85.00	~88% at pH 4.8 and 50% at blood pH	Cancer therapy	Higher antibacterial activity than free Cur on *S. Aureus*; up to 85 % inhibition growth of MCF-7 cells.	-	(Sawant & Bamane, 2018)
CEHEC-Ad/β-CD-grafted GE NPs	pH 5.0	DOX	~ 94	52.0 % at pH 5.0 and 19.8 % at pH 7.4	Tumor therapy, personalized medicine	Good biocompatibility along with enhanced anticancer activity against HeLa cells after 24 h (~34.3 % viable cells at DOX-SNPs, DOX10 μg/mL	-	(Yang et al., 2020b)
Benzimidazole-PCL/ β-CD terminated dextran micelles	pH 5.5	DOX	46.48	up to 90% at pH 5.5 and less than 40% at pH 7.4	Intelligent drug delivery Tumor therapy	Improved apoptosis effect on HepG2 cells culture (~ 30% viable cells after 72 h); 2-fold enhanced the intracellular DOX release	-	(Zhang et al., 2013)
Benzimidazole-PEG/ β-CD-modified PLLA micelles	pH 5.5	DOX	27.5	~90 % at pH 5.5 and 30% at pH 7.4	Cancer therapy	Enhanced cytotoxicity against HepG2 and HeLa cells with the IC50 values of 0.29 and 0.53, after 72h	Improved antitumor activity with no obvious systemic toxicity in BALB/ c nude mice bearing HepG2 xenografts after 16 days of treatment.	(Zhang et al., 2015b)
Alg-β-CD/mPEG-Fc/ α-CD NPs	Redox H_2O_2	BSA	66.7	80% from Fc-containing NPs, 20% without oxidizable Fc	Diabetes, immunotherapy	Good biocompatibility, High affinity to CT26 cells with high cell internalization efficiency number of NPs after 4 h of incubation	-	(Dong et al., 2018)
MC11-PEI-β-CD/ Ad-SS-PEG NPs	Redox ROS, GSH	pDNA	-	-	Gene delivery in cancer therapy	High transfection efficiency in HeLa, HepG2 and SKOV3 cells; fast endosomal escape and strong gene expression	Notably improved transfection efficacy (the highest luciferase expression 7.3×10^4 RLU/ mg) in tumor-bearing mouse after systemic injection	(Ping et al., 2013)
MNP–S–S–PEI/β-CD nanoreservoirs	Redox DTI, GSH	CPT	5 mg	~80 % in the presence of DTI reducing agent	Chemotherapy magnetic resonance imaging	Severely inhibition the growth of HepG2 cells after 24 h; could efficiently induced DNA cleavage and cell apoptosis.	-	(Luo et al., 2012)
TPPC6-SS-Ada/PEG-β-CD micelles	Redox GSH	PRH	-	70% under GSH and less that 10% without GSH	Photodynamic therapy	No dark cytotoxicity; great cytotoxic effect against MCF-7 culture after 20 min of visible light exposure (400 mW/cm2)	-	(Liu et al., 2015)
PEG/PNIPAM/β-CD-MNPs	temp, H_2O_2 or pH	DOX	73%	89% under 25 °C and H_2O_2	Cancer treatment	A DOX concentration-dependent cytotoxic effect on A549 cells after 72 h	-	(Zhang et al., 2015a)
Dex-TMBA/ PEG-imine-β-CD NPs	Dual-pH	DOX	26.01 wt	85% at pH 5.3	Cancer treatment	Great biocompatibility, improved DOX doze-dependent toxicity on HeLa and HepG-2 cells; high internalization at pH 6.8	-	(Wang et al., 2016)
poly(α-CD)/ β-CD-Azo-Ace NPs	UV/ pH dual	MTX	21.3	65% at pH 5.0 upon UV in the half day	Cancer therapy	High COS7 cellular viability even at high dose (1000 μg/ mL)	-	(Dai & Zhang, 2018)

(*continued on next page*)

Table 2 (*continued*)

Supramolecular nanocarrier	*Stimuli mode*	*Drug*	*EE/ DLE (%)*	*Release efficiency*	*Targeted application*	*Therapeutic performances* *In vitro*	*In vivo*	*Ref.*
MSNs-wrapped poly (β-CD)-functionalized with Ad-PEG-FA or Ad-PEG-LA, Ad-PEI	pH/ Redox GSH	DOX	29.0	77.1% at pH 5.0 and DTTT reducing agent	Cancer chemotherapy	Enhanced intracellular release of DOX in HepG2 cells under pH/redox stimuli; high anti-tumor activity against HepG2, HeLa, MCF-7 and MCF-7/ADR cells along with good biocompatibility; high transfection efficiency on HEK293T and HeLa cells	-	(Liu et al., 2018)
mPEG-β-CD/Fc-CPT micells	Dual redox ROS/ GSH	CPT	14.7 wt	Hipper fast release under GSH, 78.9% under H_2O_2 in 48h	Cancer therapy	Low cytotoxicity on HLF cells as compared to that on A549 cells where the level of GSH is higher; high biocompatibility	~ 3-fold high inhibition of the tumor growth on S180 sarcoma tumor implanted mice	(Kang et al., 2017)
MSN-ss-CD/GAP NPs	Light/ redox dual	DOX	62.8	55.4% in the presence of UV and GHS and 16.9% in 150 h without stimuli	Anti-cancer treatment	High biocompatibility, efficient delivery of DOX into HepG2 cells along with great cytotoxicity (33.2% viable cells owing to overexpression of GHS) and high apoptotic effect (48.43% after UV) as compared with HeLa and COS7 cell culture	-	(Wu et al., 2019)
CD-PEG/ Azo-PC carrier	Redox/ light dual	DOX	30.4	<55% under GHS/UV and >20% in 48 h in standard conditions	Cancer therapy	Spontaneous drug release and selective cytotoxicity for SCOV3 cancer cells with reduced toxicity on normal HEK293T cells	-	(Li et al., 2019a,b)
Star polymer β-CD-PNIPAM/BM-PCL micelles	Temp/ pH dual	DOX	77.21	100% at 37 °C/ pH 5.2 and 48.6% at 25 °C;	Anti-cancer therapy	Excellent biocompatibility (98% at up to 1.0 mg/m micelles) along with DOX dose-dependent cytotoxic effect on HeLa cells	-	(Zhou et al., 2018b)
HA-β-CD/Cur-Pt (Cur-Pt) NPs	pH/ esterase dual	CUR-PT		5 % at pH 5, 16 % at pH 7 in 48 h without esterase; 85 % under pH 5 and esterase	Cancer therapy	High anticancer activity on PC-3 and A549 cells along with good biocompatibility on normal LO-2 cells.	-	(Bai et al., 2020)
Fc-PCL/β-CD-Las-POEGMA micelles	Dual-redox ROS/ GSH	DOX	56.3	95% under DTT and NaClO and 20% in standard condition in 72h	Cancer therapy	Great hemocompatibility and biocompatibility; high cytotoxicity in Bel-7402 cells	3-fold high DOX amount in tumor, low distribution in other major organs and excellent inhibition tumor effect on Bel-7402 tumor-bearing BALB/c mice 16 days after treatment	(Peng et al., 2021)
GO-Cys- CD-PEG nanocarriers	pH/ redox dual	DOX	94.58	78.2% at pH 5.3 under GSH in 72 h; 65.2% at pH 5.3 and 37.6% at pH 7.4 without GSH	Cancer therapy	High biocompatibility after 48 h, increased cytotoxicity against HepG2 cells and enhanced cellular uptake and nuclear delivery of DOX	-	(Borandeh et al., 2021)

MSNs - mesoporous silica nanoparticles; CD - Cyclodextrin; Azo-PDMAEMA - mAzo-containing amphiphilic copolymer poly{6-[(2,6-dimethoxyphenyl)azo-4-(2′,6′dimethoxy)phenoxy]propyl dimethylaminoethyl methacrylate-random-poly(2-(N,N-dimethylaminoethyl) methacrylate); Ad-MMP-S PEPs - MMP-9-sensitive peptides (YGRKKKRRQRRR-GPLGVRG-EEEEEE) terminated with adamantane (Ad); PEI- polyethyleneimine; CEHEC - carboxyethyl hydroxyethyl cellulose; BM-PCL - benzimidazole (BM) modified poly(ε-caprolactone); Fc- ferrocene; SS- disulfide bond; TPPC6-SS-Ada - adamantane-terminated porphyrin derivative bearing disulfide bond; PNIPAM - poly(N-isopropylacrylamide); TMBA - 2,4,6-trimethoxybenzaldehyde; GAP- azobenzene/galactose-grafted polymer; HA- hyaluronic acid; POEGMA - poly(oligo ethylene glycol) methacrylate; GO- graphene oxide; PRH. – porphyrin.

hydrazone bonds in CD-DOX. The nanoparticles internalization in HeLa cells through endocytosis, along with the endo/lysosome pH-triggered DOX escape into the nuclei were validated through CLMS images, highlighting slight reduced red fluorescence intensity in the case of cells incubated with DOX-SNPs as compared to free DOX that could rapidly enter cells through diffusion (Fig. 4, A).

3.3.3. *Redox-responsive CDs-based nanoparticles*

Electrofunctional materials receptive to modified electronic states are named electrically switchable materials or redox stimulated systems (Wankar et al., 2020). This type of self-assembled carriers has potential in controllable delivery and release in physiological environments, in which redox reactions are widely and constantly presented, overcoming the pharmacokinetic pitfalls observed in conventional drug delivery and leveraging the site-specific delivery properties (Mollazadeh et al., 2021), shows an enormous enthusiasm of scientists in the field of smart drug delivery. Commonly, these vehicles embody modified polymers conjugated to reducible or oxidizable (redox-responsive) linkers/molecules self-assembled into redox-responsive nanoparticles (Li et al., 2020). Ferrocene (Fc), also known as cyclopentadienyl iron, water-insoluble organometallic compound (Gu et al., 2018; Li et al., 2020), is a ubiquitous molecule in the design of dynamic redox switching nanoparticles owing to redox-sensing properties originated from the reversible one-electron oxidation to the ferrocenium cation as well as its host-guest

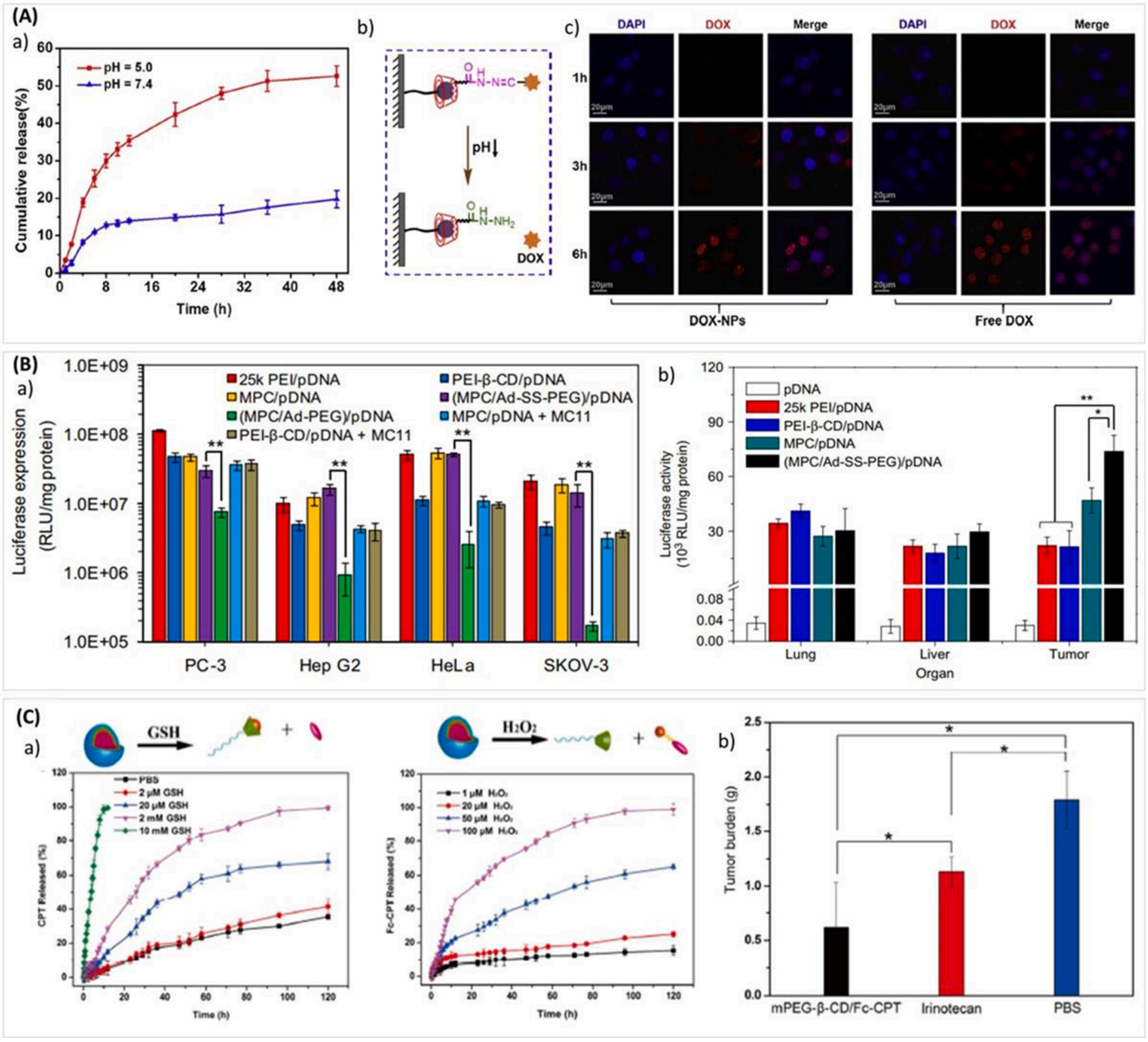

Fig. 4. (A) – a) - *In vitro* DOX release from DOX-SNPs in release medium at pH 7.4 and 5.0; b) - Schematic illustration for the acid-catalyzed hydrolysis of hydrazone bonds inducing the fast release of DOX from DOX-SNPs; c) - CLSM images of Hela cells incubated with DOX-SNPs and free DOX for 1, 3, and 6 h, respectively. For each panel, images from left to right show cell nuclei stained by DAPI (blue), DOX fluorescence (red) and merged images (Reproduced with permission from (Yang et al., 2020b)); (B) – a) - *In vitro* luciferase gene expression in four types of carcinoma cells transfected with various polyplexes at N/P ratio of 25. PEI polyplexes at N/P of 10 were used as a control. PC-3 cell lines were used as a FGFR-negative control, whereas Hep G2, HeLa and SKOV-3 was used as the FGFR-positive cell lines; b) - Luciferase expression in different organs 48 h after the systemic injection of different polymer/pGL3-Luc complexes ((n = 3, *P < 0.05, **P < 0.01) (Reproduced with permission from (Ping et al., 2013)); (C) – a) – Release profiles of CPT from the mPEG-β-CD/Fc-CPT supramolecular complex micelles at different GSH and H2O2 concentrations; b) - *In vivo* antitumor efficiency of mPEG-β-CD/Fc-CPT complexes and irinotecan to KM mice inoculated with S180 sarcoma (*p < 0.05) (Reproduced with permission from (Kang et al., 2017)).

interactions with β-CDs as reversible ferrocene/ ferricinium redox couple (Fernández et al., 2019; Wankar et al., 2020). Ergo, the reduced Fc state is a good guest for CDs, this affinity is practically completely lost through oxidation in the presence of oxidizing agents or by electrochemistry, this behavior being a great inspiration in the formulation of redox-responsive systems. For example, Mejia-Ariza et al. (2015) have constructed size-controlled and redox-switchable supramolecular nanoparticles (SNPs) using positively charged CD-grafted poly(ethylene imine) as host, positively charged Fc-terminated PAMAM dendrimer as multivalent guest and a series of monovalent stabilizers. The team has proven the key role of ionic strength in controlling the aggregate growth through finetuning the ratio of multivalent and monovalent interactions, as well as the contribution of Fc in the redox-triggered assembly/disassembly properties of SNPs. Later, Hao and co-workers (Hao et al., 2016) have shown that owing to redox chemistry of Fc, supramolecular vesicle based on Fc-Cholesterol and β-CD present reversible redox-responsive features capable of transforming between nonionic and cationic vesicles. Following a similar approach, Dong et al. (2018) have proposed a new design of β-CD-based nanoparticles (NPs) that released Bovine serum albumin (BSA) *via* glucose-responsive gate by

embedding sodium alginate with β-CD modified (Alg-β-CD) and methoxypolyethylene glycol (mPEG-Fc) containing Fc uncharged end-capping into a self-assembled structure. The formulated systems presented spherical uniform structure with constant BSA loading content that could be fractionated in the presence of hydrogen peroxide (H_2O_2) to release BSA. Further studies have found that the BSA-entrapped NPs may present a glucose responsive behavior in the sugar (GOD) containing environment, thus achieving a BSA delayed drug-release profile and representing a promising strategy for diabetes or immunotherapy.

Different kinds of cleavable disulfide bonds (-SS-) in the presence of elevated reactive oxygen species (ROS) and glutathione concentration (GSH) are among commonly used stimuli-responsive bonds to formulate redox drug delivery systems (Guo et al., 2018; Yang et al., 2020a). Since ROS and GSH are prevalent in organisms, being usually abnormally expressed under pathological conditions, *e.g.*, modified biochemistry of cancerous tissue, the use of disulfide bonds in carriers boots the redox sensitivity, thus allowing the delivery system to detach the loaded cargoes rapidly, only if they reach the site of tumor tissue or targeted cells, under specific circumstances like endosomal lysis (Hu et al., 2014; Li et al., 2020).

Albeit PEGylation represents one of the most efficient strategies to improve the serum stability of drug delivery systems, it may mitigate the transfection efficiency of polycations as can reduce the charge-mediated cellular uptake (Li et al., 2020). Aiming to overcome these problems, Ping et al. (2013) have proposed an alternative FGFR-mediated, PEG detachable gene nanocarriers with reduction sensitivity for safe and efficient delivery of therapeutic DNA. The guest segment consisting of PEG and adamantyl group linked by a disulfide bond (Ad-SS-PEG) along with the host group based on peptide-modified PEI−βCD (MPC) were self-assembled into nanoparticles with redox-detachable PEG corona (MPC/Ad-SS-PEG). Owing to sensitive disulfide bond that collapsed and detached the PEG during endosomal lysis, the formulated PEG-detachable vectors presented a significantly improved transfection efficiency in FGFR-positive various cancerous cell lines (HeLa, HepG2 and SKOV3) and high ability to mediate the endosomal escape that may induce a strong gene expression *in vitro,* along with high potency to facilitate tumor-targeted gene delivery in SCOV-3 tumor-bearing mouse model, reaching the highest level of luciferase expression (7.3×10^4 RLU/mg) in tumor tissue after 48 h systemic injection (Fig. 4, B). In another interesting research, Luo et al. (2012) have proven the great responsive potential of grafted-β-CD/PEI with cleavable disulfide linkers on magnetic nanoparticles to the reducing milieu of cytoplasm for intracellular hydrophobic anticancer camptothecin delivery *via* endosomal escape. The formulated complexes showed an improved endocytosis efficiency along with a remarkable apoptosis effect on HepaG2 cells culture, as well as the prospect to be used as smart nanocarriers with redox and magnetic dual-responsive behavior. Further, a hierarchically organized redox-responsive supramolecular structure based on PEG-β-CD and adamantane-terminated porphyrin derivatives bearing a disulfide bond (TPPC6-SS-Ada) with potential application in photodynamic therapy was described by Liu et al. (2015). Based on the *in vitro* release studies, the authors have shown the reduction-responsive release behavior of micelles and the modulation of porphyrin release kinetics through the GSH addition. Intracellular uptake indicated that photosensitizers micelles could be effectively up-taken by MCF-7 cells where they presented a significant phototoxic effect owing to the presence of disulfide bonds which are vulnerable to high intracellular level of GSH, thus releasing an efficient amount of porphyrin that induced high photosensitization effect.

In the framework of redox-responsive smart CDs-based drug delivery systems a valuable contribution has been done by the pioneer work of Marcus E. Brewster dedicated to the development of brain-targeting CDs-based formulations, including their chemical and theoretical characterization, preclinical and clinical testing. His concept is driven by the incorporation of a redox-targetor within the CDs formulations that undergoes enzymatic transformation drastically modifying their physicochemical properties, leading to significant improvements in CNS access by making the molecule more lipophilic and allowing its diffusion through the BBB, as well as providing a more sustained release by "locking" the molecule behind BBB through switching it into a hydrophilic intermediate (Hershberger et al., 2021).

3.3.4. *Multi-stimuli-responsive CDs-based nanoparticles*

Generally, multi-stimuli-responsive drug delivery systems combine various stimuli responsive motifs into one nano-entity, offering an appealing quality for therapeutic delivery by ensuring better specificity and amenability to various factors in the organism as well as releasing of therapeutic agents exclusively in the presence of a distinct combination of stimuli to achieve the desired release kinetics, respectively optimal therapeutic efficiency limiting the cytotoxicity (Hershberger et al., 2021; Tian et al., 2021). Supramolecular self-assembly of CDs and various materials with exogenous or endogenous stimuli-sensitiveness (polymers, inorganic nanoparticles, etc.), generating compelling smart and intelligent CDs-based drug delivery systems have sparked increasing interest to drug delivery filed. For instance, based on redox-switchable host–guest interaction between the β-CD and Fc groups, Tan and co-workers (Tan et al., 2015) have reported a carrier system capable of electrical and UV dual-stimulated release of size-selected cargos from β-CD-covered mesoporous silica nanoparticles, while Li et al. (2016) have formulated dual-responsive colloidal microcapsules *via* layer-by-layer assembly method on solid templates that could be disassembled into nanocomponents upon competitive molecular addition or at low pH. Moreover, in a recent study targeting to engineer smart nanocarriers with potential clinical translation and scale-up production, Peng et al. (2021) have proposed a one-pot robust strategy to engineer dual-redox sensitive supramolecular carriers with programmable DOX release, by self-crosslinking a multifunctional β-CD with Fc molecule and lipoic acids (LAs)-decorated primary and secondary faces for reversible *in situ* crosslinking by the reducible disulfide links. The *in vitro* investigations showed that the resulted nanocarriers present enhanced colloidal stability and high DOX loading capacity along with a programmable drug release originated from the destruction of the micelles that was triggered by a simultaneous adoption of intracellular GSH and ROS. According to MTT results, the DOX-loaded micelles showed a great cytotoxic activity (IC50 of 2.94 ± 0.25 μg/mL) as compared to free DOX (6.00 ± 0.56 μg/mL) in Bel-7402 cancer liver cells, as well as reduced side effects on L02 normal liver cells. The further *in vivo* investigations in Bel-7402 tumor-bearing BALB/c mice confirmed the efficient accumulation of micelles in tumor *via* EPR effect (biodistribution results) and the enhanced therapeutic efficiency along with reduced systematic toxicity, sustaining their great potential for practical applications and clinical translations. Aiming to overcome the problems related to conventional chemotherapy pH and UV dual responsive supramolecular nanoparticle based on host−guest inclusion complexation interactions between poly(α-CD) and acetal-modified β-CD-azobenzene or β-CD-graf t-poly(2-(dimethylamino)ethyl methacrylate) (β-CD-g-PDMAEMA) and azobenzene modified poly(ε-caprolactone) (Azo-PCL), have been also designed and investigated as potent smart chemotherapies (Dai & Zhang, 2018; Zhang et al., 2020). In another complex study, Wang with team (Wang et al., 2016) have designed a dual pH-responsive carrier based on 2,4,6-trimethoxybenzaldehyde modified dextran (Dex-TMBA) and mPEG-imine-β-CD able to respond to both extracellular and intracellular pH environments to simultaneously enhance cellular uptake and promote acid-triggered intracellular chemotherapeutic release. The *in vitro* experiments showed that under neutral conditions the carriers can efficiently load the DOX, promote the cellular internalization, owing to positively surface charge in tumor extracellular pH (~6.8) and release the drug in tumor intracellular environment and subcellular compartments (~5.3) when their disassembly occurred. Applying the same strategy, the *in vitro* effectiveness and accurateness of light/redox dual-responsive formulations based on β-CD-gated MSN

Azo/galactose-grafted polymer (MSN-ss-CD/GAP) (Wu et al., 2019) or β-CD-PEG self-assembled Azo-PCL (CPAP) (Li et al., 2019a,b) for efficient DOX delivery in different cancerous cells (HepG2 cells and SKOV3 cells) was studied and confirmed. Further, Liu et al (Liu et al., 2018) have proposed a modular strategy for designing multi-functional, pH/redox dual responsive DOX-loaded mesoporous silica nanoparticles (MSN) wrapped with poly(β-CD) *via* pyridine-disulfide bonds, capable to rapidly released DOX in lysosomal pH/redox microenvironment, potently killing drug-resistant cancer cells. Considering the tumor heterogeneity, the authors have proven the simplicity and effectiveness of this approach in endowing the nanocarriers with various customized functions (*i.e.*, cell-targeting capability, gene co-delivery property and imaging function), respectively the potency as smart drug delivery system for personalized chemotherapy. Following the same idea, dual redox and bio-relevant supramolecular complex micelles based on host-guest interaction of camptothecin modified Fc derivative (Fc-CPT) *via* dithioether bond and β-CD-methoxy polyethylene glycol (β-CD-mPEG) were constructed by Kang et al (Kang et al., 2017). The authors have done a detailed *in vitro* and *in vivo* investigation pointing a drug loading of micelles nearly 14.7 wt % along with a significantly hyper-fast redox-responsive CPT release in the tumor microenvironment. Moreover, the carriers presented a low level of cytotoxicity, good proliferation inhibition of A549 cancer cells and high performances to deliver CPT producing a 3-fold inhibition of the tumor growth (Fig. 4, C).

The construction of three dimensional supramolecular, biocompatible, pH/redox dual-responsive GO-Cys-CD-PEG nanocarrier by functionalization of graphene oxide (GO) with β-CD using cystamine (Cys) as a disulfide bearing linker and then PEGylated through the host-guest interactions of β-CD with PEG-Ad for efficient loading and specific controlled release of DOX was reported for the first time by Borandeh et al (Borandeh et al., 2021). The authors stated that Cys-disulfide bond induced the reduction-sensitive character into the nanocarrier and β-CD grafting improved GO dispersion, drug loading efficiency (to 94.58%) and reduced the toxicity of the system while the PEGylation step increased the GO solubility, stability as well as reduced its toxicity. Beside a stimuli-responsiveness DOX release behavior (under acidic milieu of cancer cells and in response to GSH simulating intracellular redox environment), the systems presented good cytocompatibility (90%, trypan blue dye exclusion assay) along with a significant cytotoxicity in HepG2 cells, which was corelated with the contribution of PEG corona in improving the dispersibility of nanocarriers in the culture medium, a prerequisite for successful drug delivery.

Considering that multi-stimuli responsive nanoparticles can offer the option to fine-tune the response to each stimulus independently, providing a high proper spatiotemporal control upon the delivered therapeutic, PEG/PNIPAM-coated multi-stimuli-responsive magneto-micelles with high DOX loading and stimuli-triggered drug release that can be modulated by one stimulus or by a combination of temperature, H_2O_2 and pH, were constructed by Zhang et al (Zhang et al., 2015a).

4. Performances of CDs-based nano-assemblies as smart multifunctional nanocarriers

The careful selection of structures that are involved in the construction of the nanoparticles matrix, significantly improves their potential as drug carriers (Schmidt & Barner-Kowollik, 2017), while the choice of the appropriate delivery system for a particular therapeutic agent is critical in achieving both the optimal bioavailability and the expected therapeutic efficiency. Albeit CDs-based nanoparticles have registered a great progress in various field of (bio)medicine, cancer nanomedicine received the greatest attention, because the efficiency of chemotherapy is often hampered by the development of drug resistance in time (Goldie, 2001); thus, the development of innovative and efficient chemotherapy remain a great challenging task in both academia and clinic. The recent advances of CDs-based assemblies as drug co-delivery systems, gene delivery vectors or theranostics are described in this section.

4.1. CDs-based nano-assemblies as cooperative co-delivery systems

Generally, co-delivery systems are capable to transport simultaneously different therapeutics agents that exert synergistic therapeutic effects on the targeted tissue/cells, substantially improving the treatment efficiency (Hu et al., 2011; Li et al., 2012a; Zhang et al., 2019). The literature reports a great number of research studies that use various CDs-based nanoparticles for cooperative co-delivery of a gene and a chemotherapeutic agent to reverse the multidrug resistance in cancer cells. As potent co-delivery system with ability to carry both chemotherapeutic agent and gene in an integrated formulation, the nanocarrier must be capable to load the drug *via* host-guest interaction and condense gene into positively charged complexes and suitable size for endocytosis. Ergo, rationally designed cationic supramolecular nanoparticles based on PEI-CDs (PEI crosslinked by CDs) *per se* or functionalized with targeted moieties have proven their potency as cooperative co-delivery systems for DOX and p-DNA (Hu et al., 2011), PTX and survivin shRNA (Hu et al., 2012), or PTX and p53 gene (Zhao et al., 2014) capable to deliver the encapsulated agents to various targeted cancer cells simultaneously, ensuring high bioavailability of chemotherapeutic drug along with efficient gene transfection, respectively combined/synergistic therapeutic effects both *in vitro* and *in vivo*. Yang et al (Yang et al., 2015) have successfully self-assembled amine-attached β-CD-centered hyperbranched polyglycerol and linear adamantine terminated octadecane into nano-sized vesicles for co-delivery of DOX and condensed DNA. The CLMS analyses confirmed the ability of vesicles to efficiently co-deliver the two payloads into the nuclei of COS7 cells through endocytosis, as well as the low influence of DOX loaded on the *in vitro* gene transfection. In another research study, Xiong and co-workers (Xiong et al., 2017) have proposed a new hyaluronic acid-coated cationic supramolecular nanoparticle based on β-CD-conjugated poly-l-lysine for co-delivery of oligoRNA and DOX targeting hepatocellular carcinoma (HCC). The formulated systems showed a great cytotoxicity against HCC cells, significantly inhibiting their proliferation after cellular internalization through CD44 receptor-mediated endocytosis, while their strong hepatoma-targeting capability was validated through distribution studies that highlighted the preferential accumulation in the tumor following their administration in HCC tumor-bearing mice. Aiming to reverse the multidrug resistance of HeLa cells, Li et al (Li et al., 2012a) have embedded chemotherapy and gene silencing into multifunctional quantum dots (QDs) functionalized by β-CD coupled to amino acids (L-Arg-or L-His) formulations that can be simultaneous loaded with DOX and siRNA for targeting the MDR1 gene and real-time tracked after the administration. The authors have investigated the effectiveness of the complexes on doxorubicin-resistant cervical carcinoma cell line (HeLa/DOX cells), noticing that co-administration and co-localization of mdr1 siRNA and DOX may promote the synergistic effects of the chemotherapeutic and gene therapy agents, leading to reduced levels of MDR1 gene expression, enhanced intracellular DOX accumulation and an increased potency of Dox to induce a higher apoptosis in HeLa/Dox cells as compared to free DOX. In a further report Liu et al (Liu et al., 2014) have managed to construct a biocompatible star-shaped β-CD-poly(L-lysine) dendron derivative as co-delivery system for Docetaxel (DOC) and siRNA plasmid (pMR3) with potential application in nasopharyngeal cancer therapy, capable to significantly decrease invasive capacity of HNE-1 cells by inducing a higher apoptosis effect than each therapy alone. A core-stabilized mixed micellar system consisting of β-CD conjugated poly(lactic acid)-b-poly(ethylene glycol) and DL-thioctic acid terminated PLA-mPEG nanocarrier that could efficiently co-deliver and release DOX and fluorescein isothiocyanate labeled adamantane in the same tumor cells, improving the bioavailability of drugs, were reported by Li and team (Li et al., 2014). In another study, Rahmani and

co-workers (Rahmani et al., 2021) proposed a pH-sensitive biodegradable β-CD-grafted poly maleate-block-PLGA micelle loaded with DOX and Conferone (CON) for triggering apoptosis of metastatic human breast cancer cells. The author hypothesized that the multifunctional structure may afford a multidrug loading capacity along with a pH-responsive sustained release, while the selected nano-combination form could show a synergic effect and induce apoptosis to MDA-MB-231 cells. The cytotoxicity results sustained the combinatorial antitumor effect of co-loaded micelles (the lowest IC50 = 0.259 μg/mL) that was originated from a synergistic effect of therapeutics, inhibition of P-gp expression and DOX efflux by CONF in MDA-MB-231 cells, whereas the cell cycle and apoptosis test showed a severe disturbance of cell cycle leading to an exceptional apoptosis (up to 98%) that was confirmed with real-time PCR (at gene level) and western blotting (at protein level), proving the p27, p53, Bax/Bcl-2; caspase-9; caspase-7 and caspase-3, intrinsic mitochondrial apoptosis pathway. Based on the promising *in vitro* results the authors foresee *in vivo* application of the micelles, encouraging the scientific community to consider this mechanism in clinical studies for the development of alternative therapeutic way to benefit cancer patients worldwide.

In recent years, it has been found that the combination of chemotherapy and phototherapy into multifunctional smart nanocarriers that are environment-responsive and tumor site-selective, represent another thriving approach used in improving the therapeutic efficiency in cancer management. For instance, aiming to design novel phototherapeutic nanoassemblies, Conte et al (Conte et al., 2014) have proposed a nanosystem based on α-CD suitable for delivering highly hydrophobic photosensitizing ZnPc (Zinc (II) phthalocyanine) to cancer cells, which under irradiation induce important photobiological activity on HeLa cells and may be suitable in photodynamic therapy (PDT) of solid tumors. Having the same motivation, Zhang and co-workers (Zhang et al., 2018) have constructed a multifunctional self-assembled nanoparticle based on β-CD-functionalized hyaluronic acid (HA) and Ad linked-disulfide bond CPT/near-infrared absorbing dye IR825 conjugate (CPT-HA@IR825) as smart nanocarrier for combinational photothermal-chemotherapy of cancer. The presence of HA affords the stability and biocompatibility of colloids while the instability of disulfide bond under reducing environment assures the release of conjugated drug and the recovery of fluorescence emission, transferring the absorbed light into local heat through IR825, key-parameter in photothermal therapy. According to the *in vitro* results, the formulated nanoparticles can be rapidly internalized by HeLa, MCF-7, and U14 cancer cells, release the encapsulated drug and exercise an efficient anticancer activity under NIR light irradiation. Additionally, the *in vivo* evaluations

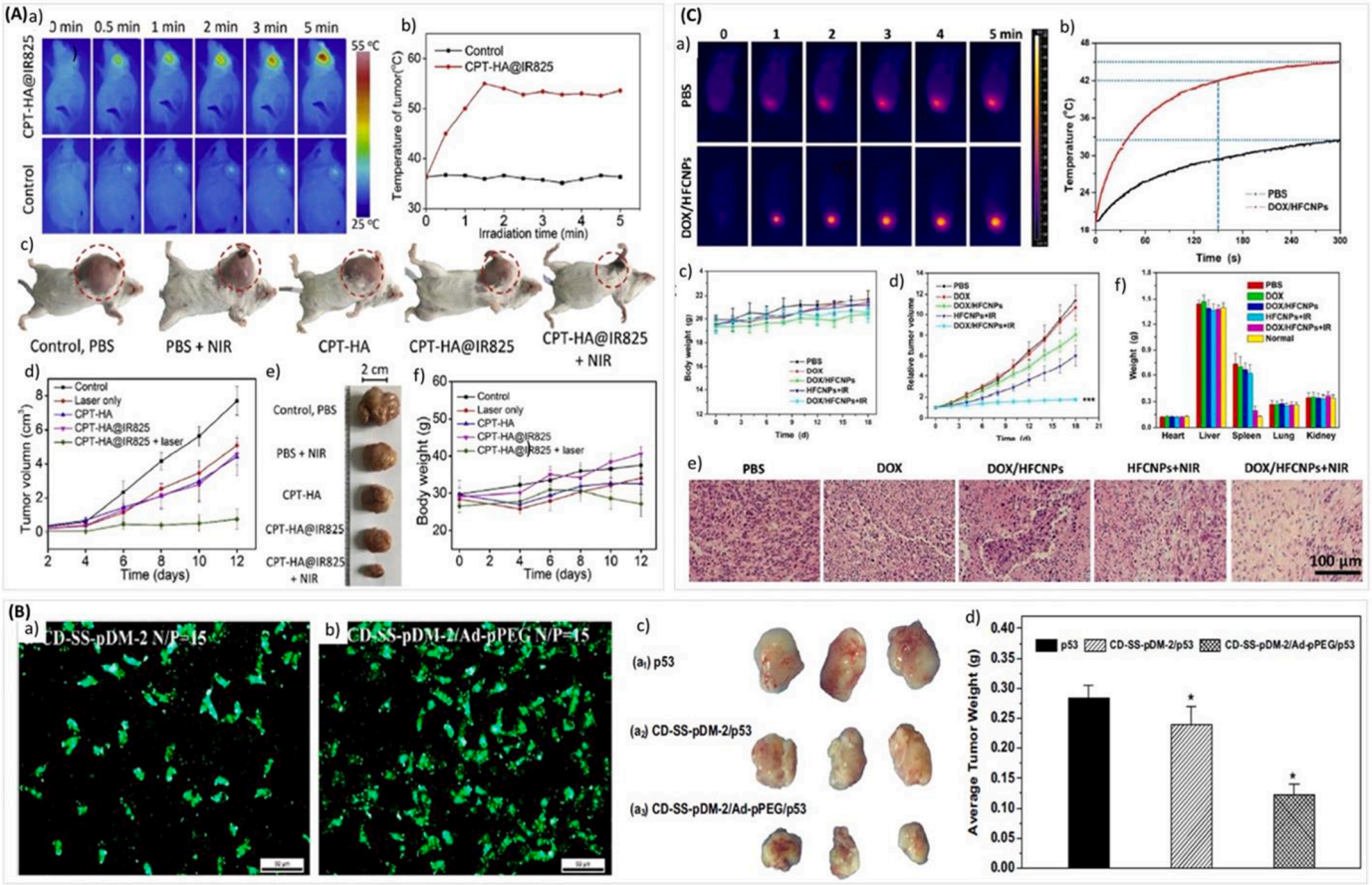

Fig. 5. (A) – *In vivo* combined photothermal-chemotherapy. a) - Infrared thermal images of U14 tumor-bearing mice treated with saline or intravenous injection of CPT-HA@IR825 nanoparticle suspension for different periods of laser irradiation time; b) - Maximum temperature profiles of the irradiated tumor region after the treatment with saline or CPT-HA@IR825 nanoparticle suspension as a function of the irradiation time; c) - Representative photographs of U14 tumor-bearing mice at day 12 after various treatments; d) - Time-dependent tumor growth curves of different groups after various treatments; e) - Excised tumors from representative euthanized mice; f) Time-dependent body weight curves of the mice after various treatments (Reproduced with permission from (Zhang et al., 2018)); (B) – a, b) - Cellular internalization of CD-SS-pDM-2/pDNA and CD-SS-pDM-2/Ad-pPEG/pDNA complexes at N/P ratio of 15 in HepG2 cells; c) - Photo-images of antitumoral therapeutic effects of polycations with p53 in female balb/c nude mice after intra-tumoral injection complexes at 30 mg p53; d) - weights of dissected tumor tissues 2 weeks later after the different treatment (Reproduced with permission from (Hu et al., 2013)); (C) – a) - *In vivo* thermal images of PBS or DOX/HFCNPs group at 1, 2, 3, 4, and 5 min; b) - *In vivo* temperature rising curve; c) - The curve of body weight in the treatment period; d)- Tumor volume in the treatment period ($p<0.001$); e) - H & E staining images; f) - Organ weight in various groups after treatment (Reproduced with permission from (Song et al., 2018)).

showed that CPT-HA@IR825 may accumulate at the tumor region after blood circulation and effectively convert irradiated light into heat for photothermal therapy, determining a significant tumor regression on tumor U14-bearing mice 12 days after treatment, successfully proving their high potency in combining photothermal-chemotherapy of cancer (Fig. 5, A). The construction of pH-sensitive acetalated β-CD nanoparticle loaded with DOX and coated with the amphiphilic zinc phthalocyanine ZnPc-(PEG)5 with both PDT and PTT ability with application in antitumor therapy, has been reported for the first time by Zheng et al (Zheng et al., 2021). The formulated systems presented an excellent stability and pH-responsive drug release features along with a remarkable anticancer activity originated from the synergy of chemotherapy and phototherapy cytotoxic effects, acting through a mechanism of inducing more intracellular reactive oxygen species and lowering the mitochondrial potential as well as interfering with mitochondrial and lysosomal functions. A significant tumor targeting ability, prominent antitumor activity, and reduced side effects were noted when the designed nanoparticles were investigated *in vivo* on tumor-bearing mice. In another work a high-efficiency drug and gene co-delivery carrier, based on supramolecular inclusion between β-CD-PEI600 and PCL-HPG-B as co-delivery system for DOX and pMMP-9, capable to improve the therapeutic outcomes in cancer therapy, was constructed by Zhou et al (Zhou et al., 2018a). Beside non-toxicity and excellent blood compatibility, the formulated co-delivery systems presented an improved inhibition effect on MCF-7 cells proliferation and migration *in vitro* as well as the suppression effect on MCF-7 tumors *in vivo*, suggesting their potency as co-delivery carriers in combined therapy to tumors.

4.2. CDs-based nano-assemblies as non-viral vectors for gene delivery

Gene therapy is defined as the delivery of genetic material into the nucleus of specific cells, aiming to facilitate/promote gene expression of desired therapeutic protein and is recognized as a revolutionary strategy in the treatment of various diseases. (McMahon et al., 2012; Mou et al., 2016). Generally, the genes carriage systems are classified into viral (*e.g.*, retroviruses, adenoviruses, etc.) and non-viral vectors (polymeric based nanoparticles), and particularly favoring and exploiting the non-viral vectors that may overcome the shortcomings related to the use of viral vectors (Jones et al., 2013; Thomas et al., 2003). It is well known that in the presence of a cationic or cationic-amphiphile polymers the polyanionic nucleic acids undergo self-assembly into nanoscale particles, known as polyplexes and lipoplexes. Although the loaded genetic material is protected in biological environment and is targeted to the site of action, the transfection efficiency is inferior to that of viral carriers, while their heavily charged nature might rise some toxicity issues (Antoniuk & Amiel, 2016). In this context, CDs-based carriers are appealing to gene delivery applications not only owing to their versatility and affinity to nucleic acid but also to their ability to overcome the issues related to high-charged carriers (Lai, 2014), being extensively used as non-viral vectors to improve gene editing, replacement, and modulation within cells through the delivery of nuclei acids (*i.e.*, DNA and RNA) (Mousazadeh et al., 2021). Considering that the direct interaction between CDs and nucleic acids is very week, their combination with cell-penetrating nucleic acid carriers (cationic polymers) or their structure modification for improving the interactions of CD polymers and nucleic acid fragments are widely encountered in the literature (Mousazadeh et al., 2021). One important example of using CDs-based nanoparticles as gene carriers is the work reported by Hu et al. (Hu et al., 2013) who have designed a supramolecular pseudo-block (CD-SS-pDM-2/Ad-pPEG) gene carrier by assembling bioreducible β-CD-cored star poly (2-dimethyl amino) ethyl methacrylate (pPEGEEMA) and Ad-PEG *via* the host–guest interaction. The nanoparticles were obtained following the conjugation of plasmid DNA (p53) to the polycation, which were subsequently coated with PEG for serum stability. The authors observed that neither condensing properties nor release performances of pseudo-block carriers were impacted following the Ad-PEG coating when comparing with the starting star carriers. Beside the reduced toxicity, a significant improvement of the cellular internalization and gene transfection efficiency *in vitro* on HepG2 and COS7 cell culture, was noted. Then, the *in vivo* anti-tumor activity and immunobiological analyses highlighted the higher potency of pseudo-block carriers to efficiently deliver p53 into tumor tissues and subsequently inhibit tumor growth in mice (Fig. 5, B). Dong et al (Dong et al., 2011) have developed a novel class of gene delivery non-viral vectors with high transfection efficiency of pDNA in COS 7 cells based on charge-tunable supramolecular dendritic polymers by combining two different cationic β-CD derivative and adamantane modified hyperbranched polyglycerol. Further, the author (Dong et al., 2016) has used the dynamics of supramolecular chemistry between DMEDA-β-CD and Ad-modified dimethylamino-azobenzene, to formulate a dual responsive supramolecular nanocarrier that can achieve a unique morphological transition combining with a cooperative optical variation in response to pH and light stimuli. The formulated carriers showed excellent low cytotoxicity and effective DNA condensation ability, respectively their potency to be used in gene delivery and bioimaging. In another work, McMahon and co-workers (McMahon et al., 2012) have developed a galactosylated amphiphilic CDs gene delivery system capable to induce substantial improved transfection of asialoglycoprotein receptor-bearing HepG2 cells as compared to non-targeted colloids, owing to high affinity of galactose targeting moiety to HepG2 cells. Aiming to optimize the structural features of supramolecular non-viral vectors that further enhance transfection efficacy, Yasen's group (Yasen et al., 2017) have integrated the inherent biodegradability of supramolecular polymers with biocompatibility and biostability of covalent polymers through the fabrication of a cationic N,N-dimethyl ethylenediamine (DMEDA)-functionalized supramolecular block copolymer based on host-guest interaction between β-CD-PEG and DMEDA-β-CD/Ad-PEHA that showed a high transfection efficacy in cancer cells owing to unique molecular structure and physiochemical properties, greatly improving pDNA binding ability and biostability

4.3. CDs-based nano-assemblies in theranostics

Theranostics represent an emerging therapeutic paradigm that enables synchronized execution and achievement of disease diagnosis, therapy, and instantaneous monitoring of advancement treatment and efficacy, using one pharmaceutical agent (Gadade & Pekamwar, 2020; Jo et al., 2016). Taking the advantages of multifarious design and ability in monitoring the biodistribution of therapeutics and providing an imaging guided therapy, stimuli responsive CDs-based nanocarriers have emerged as attractive candidates for the construction of multifunctional theranostics in cancer therapy that may tackle the issues related to drug resistance and toxicity (Yao et al., 2019). Considering that magnetic nanoparticles (MNPs) have attracted a particular interest in tracer agents and magnetic resonance imaging (MRI) contrast agents, the surface functionalization of MNPs with CDs-containing polymers is a common strategy to improve both the biocompatibility and stability as well as their loading capacity for different hydrophobic drugs (*e.g.*, diclofenac (Oroujeni et al., 2018)). Having this in mind, Cha et al (Cha et al., 2017) have proposed a new theranostic nano-platform by modifying MNPs with CDs-containing star-shaped poly(2-(dimethylamino) ethyl methacrylate) (PDMAEMA) following by the encapsulation of reduced glutathione (GSH) through association with CD-containing star polymers. The formulated nanocarriers presented higher GSH association capacity, improved stability in simulated biological media along with a pH-sensitive GSH release profile, low cytotoxic response and good T1MRI features, being considered as promising theranostic nano-platform. Aiming to formulate a multifunctional nanocarrier that beside therapeutic and diagnostic features will assure a targeted stimuli responsive release of multiple drugs, Das and co-workers (Das et al., 2019) have conjugated a series of functionalities on the MNPs using

β-CD as carrier for both hydrophilic (DOX-HCl) and hydrophobic (CUR) anticancer drugs. Based on detailed in *vitro* screening, the authors have demonstrated the superlative release of DOX under acidic tumor microenvironment (release studies), enhanced cellular internalization owing to folic acid functionalization (fluorescence imaging) as well as their accumulation driven by magnet near tumor site, assuring the required therapeutic temperature for destruction of cancerous cells, respectively their applicability in hyperthermia therapy. Further, these results were supported by the *in vivo* studies, showing a significant tumor regression when drug loaded nanoconjugates were injected into the animals (aprox.3-fold tumor decrement as compared to DOX). In another study Zarepour et al (Zarepour et al., 2019) have approached the same strategy to design biocompatible and pH-responsive theranostic nanocapsule able to assure an on/off switching release pattern of DOX, and efficient anticancer activity for simultaneous diagnosis and therapy. Song's group (Song et al., 2018) have reported the development of DOX-loaded β-HPCD functionalized Fe_3O_4/carbon nanoparticles (HFCNPs) for pH/near infrared (NIR)-responsive drug release, magnetic resonance/NIR fluorescence (MR/NIRFL) imaging-guided combined chemo/photothermal therapy. The formulated systems, beside high DOX entrapment efficiency showed excellent heat-generating ability and controllable pH- and NIR-responsive DOX release profile. Further, based on MR and NIRFL images the authors proved the preferential accumulation and prolonged retention-time of HFCNPs in the tumor region. Through the proposed design, the authors have managed to remarkable improve the chemotherapeutic outcomes both *in vitro* and *in vivo* (significant tumor inhibition in tumor-bearing mice as compared to each therapy alone (Fig. 5, C), owing to a synergetic chemo/-photothermal therapy effect under NIR irradiation that promoted drug permeation through inducing heating, suggesting the feasibility of nanoparticles as smart and efficient multimodal cancer targeted nanotheranostics. Lin et al (Lin et al., 2017) have reported the development and testing of a novel unimolecular micelle-GNPs-drug nanohybrid system based on the star polymer β-CD-(PLA-PDMAEMAPEtOxMA) as pH-responsive nanocomposite for anticancer drug delivery and computed tomography (CT) imaging. The versatility and potency of nanocarriers in theranostics applications was proven through a series of *in vitro* and *in vivo* experiments that revealed the superior anticancer efficacy and effective CT imaging abilities. In an attempt to provide a more advanced theranostic solution for hepatic radioembolization therapies that could overcome the associated side-effects, van Leeuwen's group (Spa et al., 2018) has extended the window of theranostics nanocarriers by proposing and *in vivo* investigating the utility of a different pre-targeting approach based on multivalent supramolecular host-guest interactions between Ad and β-CD. The diagnostic macro albumin aggregate (MAA) was converted into pre-targeting vector through Adx-guest-functionalized-MAA for intravenous administration of radiolabeled β-CD-PIBMA-polymer that was further functionalized with therapeutic radioisotope (^{99m}Tc-$Cy5_{0.5}CD_{10}PIBMA_{39}$). The authors have monitored and quantified the interactions between MAA-Ad particles and $Cy5_{0.5}CD_{10}PIBMA_{39}$ using confocal microscopy and radioisotope-based binding experiments, while the *in vivo* distribution of $Cy5_{0.5}CD_{10}PIBMA_{39}$ was guided through the pre-administration of MAA-Ad, creating a direct link between the scout-scan (MAA-Ad) and delivery of therapy, which led to a 10-fold increase in accumulation of this system into the liver or lungs, compared to the control. Then, aiming to validate the potency of this system for translational theranostic pre-targeting, the team has further performed a detailed *in vivo* assessment of the stability of both developed complex and individual components by dual-isotope multiplexing in a pre-targeting model of experimental liver radioembolization, showing a twice higher intra-hepatic accumulation of vectors between 2 h and 44 h post-injection along with a stability *in situ* up to 44 h in serum (Welling et al., 2019). Yang et al. (2018) have managed to amplified ROS concentration selectively in cancer cells through a self-assembled theranostic nanosystem based on Ad-functionalized Ru (II) complexes and ROS-labile-CD modified thioketal linkers co-loaded with CPT and vitamin K3 (VK3-CPT@Ru-CD). Beside the selective and improved therapeutic effect with minimal side-effects originated from the amplification of cancer-specific ROS and cancer-specific drug release pattern, the systems presented a lightening up effect accompanied by the ROS-triggered drug release both *in vitro* and *in vivo*, suggesting their efficacy for real-time and spatial tracking of drug release. In another work Mortezazadeh et al. (2019) have reported the construction of a novel targeted MRI contrast agent by coating gadolinium oxide nanoparticles with β-CD based polyester and decorated by folic acid (FA) capable for selective intracellular accumulation into tumor cancer cells *in vitro* and *in vivo* with selective toxicity and acceptable blood compatibility. In another interesting work, Yu and co-workers (Yu et al., 2018) have developed theranostic shell-crosslinked nanoparticles (SCNPs) using a β-CD-based polyrotaxane (PDI-PCL-b--PEG-RGD⊃β-CD-NH_2) that can avoid premature drug leakage and achieve precisely controllable release, enhancing the maximum tolerated dose of the supramolecular nanomedicines. The *in vivo* anti-tumor results demonstrated that drug-loaded SCNPs are capable to completely eliminate the subcutaneous tumors after a single-dose injection. Combining chemotherapy and photothermal therapy, the systems showed an excellent anti-tumor performance against orthotopic breast cancer and ability to prevent lung metastasis along with negligible systemic toxicity, respectively their high potency for clinical translation.

5. Conclusion, challenges and perspectives

The main challenge in the pharmaceutical field will be represented in the future by obtaining systems for the release of pharmaceutically active substances as locally as possible in the affected cells, in small quantities that minimize the side effects on the body. Supramolecular architectures based on CDs and CD derivatives are ideal candidates for this desideratum, but there are still challenges that will need to be solved. One of the main problems is related to the production costs of these systems and the price of the intermediaries used in the synthesis. The supramolecular chemistry in its entirety remains a challenge for synthesis on an industrial scale due to the multiple stages involved in these processes with different reaction conditions and catalysts. Also, for large-scale syntheses, CDs and CD derivatives remain intermediate with a high production cost. These shortcomings can be solved with the help of chemical engineering, modular installation systems, versatile and interconnected, being able to make this production easier.

Another challenge is related to obtaining systems that respond to biological stimuli. Even at the laboratory level, currently, most of the stimuli used are simple compared to the biochemical complexity of an affected organ or organism. Moreover, not all tumors, for example, are characterized by the same local temperature increase or the same pH variation. Instead, the use of systems that respond to tumor markers or enzymes would be much more effective. Such systems still remain difficult to obtain, even in laboratory research. The simplest principle on which one could rely would be the synthesis of complex architectures, in which the release of the drug is made by the redox disintegration of the system under the action of a tumor marker. But this would involve the presence in the system of monoclonal antibodies that would respond to the presence of that marker. In addition to the cost issues and obtaining these antibodies, the challenge of their viability remains after a succession of chemical reactions leading to the synthesis of the system.

In the field of research of controlled drug release systems in general, we try to find perfect solutions for extremely specific physiological conditions. Currently, the technologies we have at laboratory level cannot fully simulate the multitude of physical and chemical parameters at the level of an affected organ, taking into account including age-related variables, existence of other diseases, local and time variation of complex parameters such as pH, temperature, existence of other chemical and biological species in the respective organ, or all these parameters existing in the blood or other organs (the road traveled by

the release system to the target organ). Moreover, in the case of cyclodextrins all these parameters are essential because of their chemical structure that can undergo a multitude of reactions such as partial/total hydrolysis, reactions to hydroxyl groups in mild/strong acid/basic medium. Besides the development of synthesis methods, in the future it will be necessary to develop laboratory technologies that allow the simulation of as many as possible of parameters to be able to make the transition from perspective to large-scale commercial products or at least to viable systems for clinical trials.

The successive stages of functionalization or modification of cyclodextrins to obtain complex supramolecular architectures will lead to another problem – after the release of the active substance, how the biological system degrades the supramolecular complex in environmental conditions in the body? A simple cyclodextrin by partial or total hydrolysis does not release toxic compounds, but through the use of linker molecules, functionalization with other species for a response from the part of the biological systems, the chemical structure becomes complex, and the mechanisms involved in the degradation of these systems, respectively the study of the compounds that are released will have to be carefully studied long before reaching the clinical testing phase.

Until now, from the multitude of synthesis performed by research systems, most of them are proof-of-concept, the field being still at the beginning of the road in terms of practical applications and synthesis on an industrial scale. Many issues, some of them previously presented need to be addressed before large scale production, fact which will lead to a total new generation of pharmaceuticals.

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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Supplementary materials

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