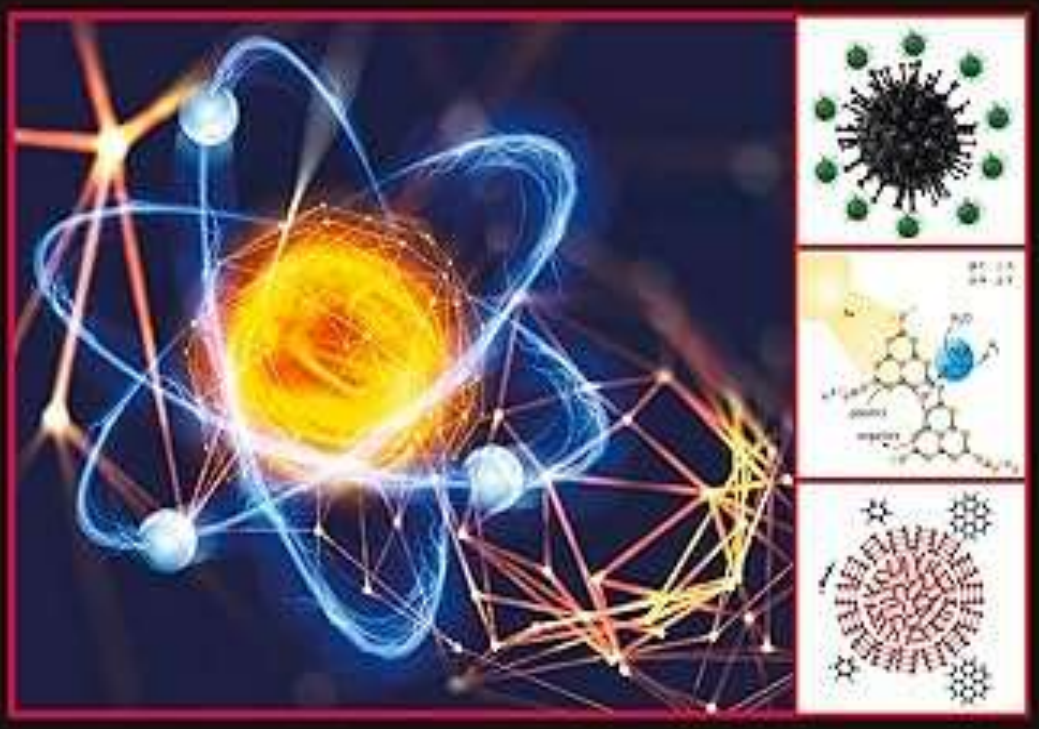
Progress in Biochemistry and Biotechnology

ADVANCES IN NANO AND BIOCHEMISTRY

Environmental and Biomedical Applications



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Milind Mohan Naik

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CHAPTER 18

Recent advances in supramolecular organic nanostructures for drug delivery applications

Kerba S. More, MSc, Harshad A. Mirgane, MSc, Vilas K. Gawade, MSc, Dinesh N. Nadimetla, MSc, Pooja V. Shreechippa, MSc and Sheshanath V. Bhosale, PhD
School of Chemical Sciences, Goa University, Taleigao, Goa, India

18.1 Introduction

Nowadays, nanomedicine and nano-delivery are rapidly growing and developing areas of science where nanomaterials are considered the diagnostic tool for delivering the therapeutic active agent to the targeted site. This emerging field has been used in treating various chronic diseases by target-oriented delivery of precise medicine. However, cancer is a major health issue and treatment of cancer is a concern of prime importance. There are various chemotherapies for cancer treatment, but many cancerous tumor cells are not inhibited by conventional chemotherapy, leading to poor therapeutic efficacy resulting in low survival rate. This mainly occurs because the drug may not be delivered to the particular targeted site or the proper distribution of the drug is not properly controlled. Hence, to overcome these limitations, drug delivery using nanotechnology has gained a lot of attention. In last 2 decades there is a great progress in the field of drug delivery system. Drug delivery system (DDS) is defined as the method by which a drug is delivered to a specific site safely and precisely during the correct period of time with the controlled release to the desired organs, cells, tissues, and other subcellular organs via various drug carrier. Drug delivery system has opened new horizons in multidisciplinary fields of science which includes biotechnology, pharmaceutical chemistry, biochemistry, physics, and medicine which has led to the rapid advancement in the field of controlled drug delivery system [1–3].

Usually in drug delivery system there are three important perspectives to be focused such as "drug design," "drug delivery," and "drug target." Another important thing is that, this drug delivery systems are designed to improve the solubility and maintain the chemical stability of the active agent's present in the drug, to increase the pharmacological activity, and further to reduce the side effect of the drug on the particular organ [4,5]. In the drug delivery system, nanocarriers play a very important role and acts as a vehicle in carrying forward the drug to the targeted site. There are several organic molecules,

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functionalized nanoparticles, polymeric nanoparticles, polymeric micelles, mesoporous silica particles, protein-based nanomaterial, quantum dot cluster, cyclodextrins metal organic frameworks, dendrimers, and so on which are used as carriers in drug delivery [6,7]. Coumarins are present in nature with a wide range of activities. Natural as well as synthetic coumarins have gained a lot of interest in the design of functional molecular nanostructures due to their unique biological, optical, and photochemical properties. Particular attention was paid toward the coumarins as an important skeleton for the drug designing as well as fluorescent probes for prodrug formation, decaying of prodrugs, metal detection, and diagnostic purpose. Drug delivery systems are also researched by scientists because of their ability to properly guide the drugs to target, lower the side/adverse effects, and keep drugs at a lower concentration for a longer period of time in the body by controlled release of drugs. For this purpose, different types of well-defined polymers with tailorable properties and different architectures were synthesized. Supramolecular self-assembly plays an important role in the formation of drug delivery systems such as dendrimers, nanoaggregates, or hydrogels. Coumarin belongs to the unique family used for the biomedical purposes because of their ease of synthesis with a wide range of substitution patterns, making them highly attractive and versatile for medicinal and biological applications. Coumarin possesses a wide range of biological activities such as anticancer activity, antimicrobial activity, antioxidant, and antiinflammatory activities, enzymatic inhibition activity, antineurodegenerative disease, and anticoagulant activity, thus making it a promising candidate for drug delivery systems [8,9]. Cyclodextrin (CD) was a naturally occurring oligosaccharide that was most widely used as excipients for pharmaceutical drugs as it could act as a molecular container for various ranges of guest molecules. Entrapping guest molecules in the internal cavity of CD could improve the solubility, bioavailability, and stability especially in chemotherapy as some of the anticancer, antibacterial, and antifungal drugs have low permeability and low aqueous solubility. So CD inclusion complex (IC) were mostly used for target drug delivery system (DDS) for various guests like antibiotics [10], bactericidal [11], antifungal [12], curcumin [13,14], and anticancer agents [15–17], thus showing fascinating results for DDS. Nanoparticulate drug delivery systems (DDSs) like organic and inorganic nanoparticles had been an integral part of development of an anticancer therapy. Such nanoparticle system exhibited enhanced properties like drug solubility, reducing drug side effects, protection of drug against degradation in blood stream, and drug delivery to target nuclear cell [18].

18.2 Synthetic pathways for small organic molecules as drug delivery agents

The important role of drug delivery systems (DDS) is to deliver a drug and maintain concentration of drug at particular target site. DDS are mostly designed to increase aqueous solubility, chemical stability, and nontoxic to biological cells, increase the therapeutic

effect of the drug, and moderate the side effects of the drug [7]. Recently nanoparticles have shown a great potential for DDS with the use of magnetic nanoparticles, niosomes, nanospheres, micelles, nanocapsules, nanoshells, solid–lipid nanoparticles, dendrimers, gold nanoparticles, and liposomes, which encapsulate the drugs, thus reduces toxicity and increases bioavailability (Fig. 18.1) [19]. It is a challenge to researchers to design organic molecules for DDS. Strategies for drug delivery include stimuli-responsive delivery, where drug is sensitive toward pH [20,21], enzyme [22–24], reactive oxygen species [25,26], redox [27,28], temperature [29,30], light [31], magnetic field, and ultrasound [32,33], electric potentials and mechanical force (Fig. 18.2) [34]. Co-delivery strategy is widely used for improvement of therapeutic effect by combination of photosensitizer and chemotherapeutic. Biomimetic drug delivery system strategy is mainly directed toward cell membrane-camouflaged nanoparticles, virus-like

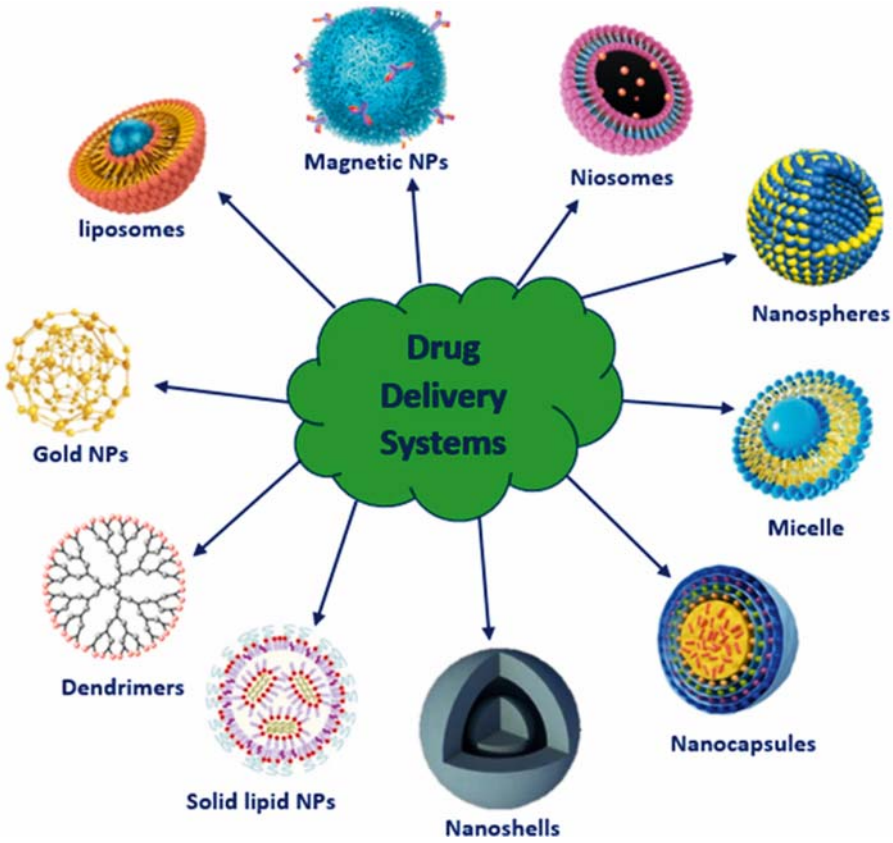


Figure 18.1 The various nanoparticles for drug delivery systems. *(The copyright permission from H. Aslam, S. Shukrullah, M.Y. Naz, H. Fatima, H. Hussain, S. Ullah, M.A. Assiri, Current and future perspectives of multifunctional magnetic nanoparticles based controlled drug delivery systems, J. Drug Deliv. Sci. Technol. 67 (2022) 102946. https://doi.org/10.1016/j.jddst.2021.102946, Elsevier Publisher.)*

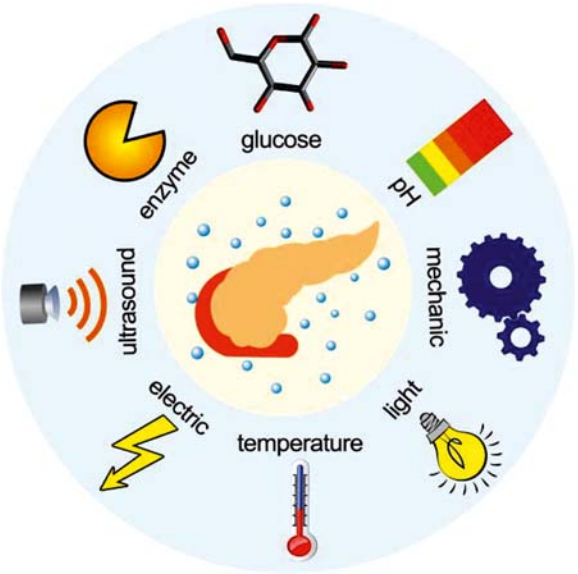


Figure 18.2 Schematic representation of stimuli-responsive drug delivery systems. *(The copyright permission from J. Yu, Y. Zhang, H. Bomba, Z. Gu, Stimuli-responsive delivery of therapeutics for diabetes treatment, Bioeng. Transl. Med. 1 (2016) 323–337. https://doi.org/10.1002/btm2.10036, John Wiley and Sons Publisher.)*

nanoparticles, lipoprotein-coated particles, cell penetrating nanoparticles. Keeping these strategies in mind, scientist have designed and synthesized many molecules for DDS, of which we have discussed mainly porphyrin, cyclodextrin, coumarin, few polymers, and some peptide in this book chapter.

18.3 Recent development in the field of drug delivery system

18.3.1 Porphyrin-based drug delivery system

The self-assembly of porphyrin derivatives with lipids, peptides, and polymers shows prominent application in photocatalytic pollutant degradation, photocurrent generation, and photosensitizers with multifunctional properties [18]. Herein, Bhosale et al. designed a system called Yoctowells with hydrophobic and hydrophilic receptors which are synthesized by two-step assembly approach of porphyrin and diamido bolaamphiphile which is bounded covalently to silica forming the special cavity as Yoctowells [35]. This yoctowells can be used as model for binding the small molecules of proteins and selective trapping of various solutes in water. However, this yoctowells was designed by combining covalently bound porphyrin to silica and bolaamphiphiles to porphyrin base [36]. This yoctowells has high affinity for formation of well filling like cavity "nanocrystal." Due to its rigidity and hydrophobicity, it shows outstanding activity to encapsulate different guest species. Modulations of these yoctowells provide wide application in many fields such as biology, material science, and medicines especially in drug delivery system [37]. Recently in 2014, Bhosale et al. reported two novel approaches which are

remarkable due to encapsulation of drug in yoctowells with magnetic silica nanoparticles for targeted drug delivery system and its reusability. Secondly, encapsulation of FDA-approved anticancer drug doxorubicin (DOX) or mitoxantrone (MTZ). The yoctowell cavities on magnetic silica nanoparticles are responsible for pH stimuli—responsive controlled released of drug molecules. Thus, research in yoctowell provides a potential and powerful tool in drug delivery and release of DOX or MTZ at the targeted site in future (Fig. 18.3) [38].

Ibuprofen (Ibp) is an antiinflammatory drug. To enhance the drug efficiency, it is important for the drug to reach the target cell, so drug carriers and transporters were used. Covalently linked fullerene (C_{60}) with porphyrin like transition metal (TM)-N4 clusters (TMN4C55) with nonsteroidal antiinflammatory Ibp drug were synthesized to investigate the interaction of drug with cluster. Transition metals like Fe, Co, and Ni used in cluster formation Ibp/TMN4C55 complex enhanced the adsorption of Ibp exhibiting shift of UV-visible spectra of complex toward lower wavelengths [39]. Pure nanocrystal form of drug can be utilized for photodynamic therapy by delivering hydrophobic drug 2-devinyl-2(1-hexyloxyethyl)pyropheophorbide (HPPH) and it is synthesized via reprecipitation method. There is no need of further stabilizer (surfactant) for HPPH nanocrystals because of their monodispersion and stability in aqueous solution. Cancer cells take the drug nanocrystals, as revealed by confocal microscopy. The quenching of fluorescence and photodynamic activity in aqueous suspension, both of these features were recovered in vitro and in vivo conditions, possibly due to serum albumin and nanocrystals

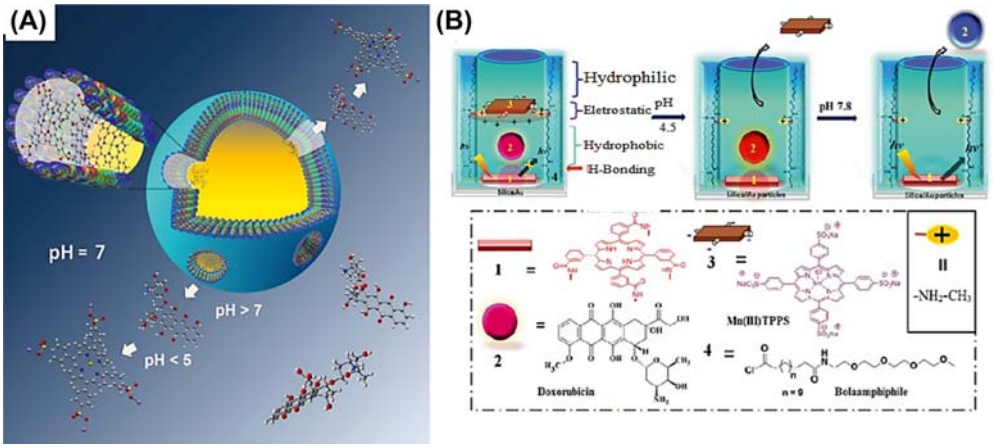


Figure 18.3 (A) Representation of schematic design of construction and release of bioactive molecules from porphyrin-based yoctowells. (B) Diagrammatic representation of illustrating the release process by pH stimuli at different pH with release of capping molecule at lower pH (4.5), secondly release of bioactive molecule at pH 7.8. *(The copyright permission from S.V. Bhosale, S.V. Bhosale, Yoctowells as a simple model system for the encapsulation and controlled release of bioactive molecules, Sci. Rep. 3 (2013) 1—8. https://doi.org/10.1038/srep01982, Springer nature.)*

interaction, forming the drug molecular system of nanocrystals. This was accomplished by recovery in existence of fetal bovine serum (FBS) or bovine serum albumin (BSA) [40]. The nanochemotherapeutic system with tetrasodium salt of meso-tetrakis-(4-sulfonatophenyl porphyrin (TPPS) shielded on gold nanoparticles (TPPS-AuNPs)) derived by Bera et al. which can avoid multidrug resistance (MDR), nontargeted delivery, and drug toxicity. The nanocarrier capability to internalize precisely to tumor cells than in normal cells followed by endocytosis leading to selective damage to the nucleus of diseased cells by antitumor drug doxorubicin (DOX). The nanoparticles exhibit outstanding stability and biocompatibility induced by embedment of TPPS on the gold nanosurface. The enhancement in retaining time of the drug within tumor cells is because of DOX-loaded nanocomposite (DOX@TPPS-AuNPs) which confirmed improved cellular uptake with suggestively reduced drug outflow in MDR brain cancer cells. The triggered release started by acidic pH with ~81% releasing capability leads to about 9 times superior strength for cellular apoptosis. Free DOX shows toxicity toward normal cell but drug-loaded TPPS-AuNPs show toxicity only toward cancer cell. Therefore, the outstanding features like huge drug encapsulation efficiency (~90%) with discerning targeting potential and acidic-pH-arbitrated intracellular release of DOX at the nucleus make TPPS-AuNPs a superior drug [41].

18.3.2 Coumarin-based drug delivery system

Many supramolecular organic nanostructures are co-assembled with amphiphilic materials loaded with hydrophobic moieties utilized for the sustained drug delivery or co-delivery of chemical drugs and therapeutic genes. Wang et al. developed a novel amphiphilic material based on low molecular weight polymers. This amphiphilic material is assembled with hydrophobic coumarin-anchored low generation dendrimers via hydrophobic interactions in aqueous solution. To develop an amphiphilic dendrimer-coumarin conjugate (G1-CM), coumarin was modified on generation 1 (G1) polyamidoamine (PAMAM) dendrimer. The synthesized nanostructures showed enhanced gene delivery and improved DNA binding with minimum toxicity on the transfected cells. In addition, the photoresponsive coumarin moieties on these nanostructures were cross-linked with each other upon UV light irradiation at 365 nm, and the cross-linked nanostructures were degraded on further irradiation at 254 nm (Fig. 18.4). The assembled nanoparticles also exhibited anticancer activity through a codelivery of 5-fluorouracil and a therapeutic gene delivery having encoding of tumor necrosis factor—related apoptosis-inducing ligand (TRAIL). These nanoparticles loaded with various drugs exhibited a light-responsive drug release and light-enhanced anticancer activities which provides a facile approach to develop light-responsive materials for the delivery of therapeutic genes and anticancer drugs [42].

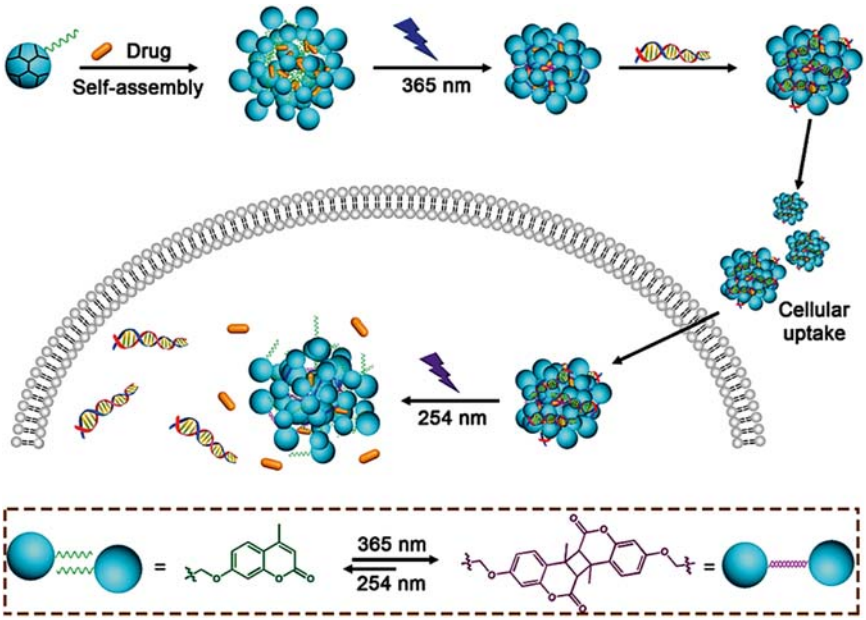
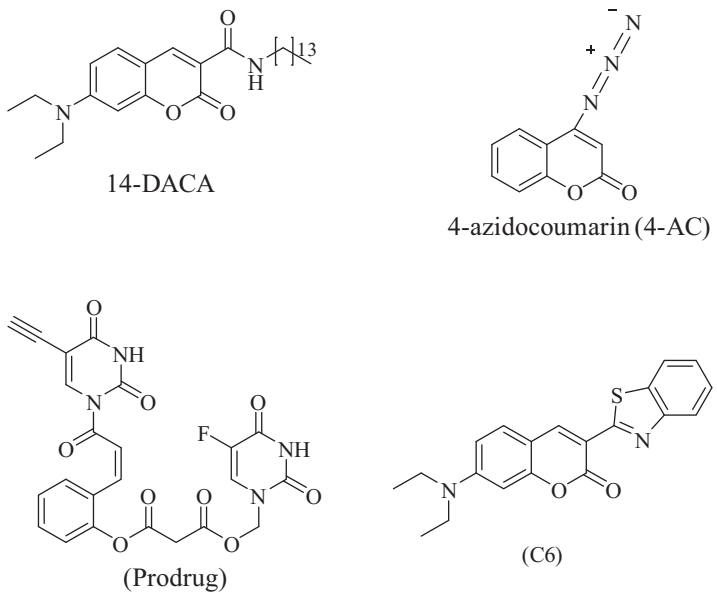


Figure 18.4 Self-assembly of coumarin-anchored low generation dendrimer for efficient gene delivery and light-responsive drug delivery. *(The copyright permission from H. Wang, W. Miao, F. Wang, Y. Cheng, A self-assembled coumarin-anchored dendrimer for efficient gene delivery and light-responsive drug delivery, Biomacromolecules 19 (2018) 2194−2201. https://doi.org/10.1021/acs.biomac.8b00246, The American Chemical Society Publisher.)*

Stefanello et al. developed a method for the synthesis of hyaluronic acid (HA)-based self-assembled nanogels with incorporation of poor water-soluble molecules in the inner hydrophobic core. The nanogels were formed by a temperature-induced self-assembly of light and thermoresponsive copolymers with HA derivatives. The coumarin moieties were incorporated within thermoresponsive ethylene glycol−based copolymers with their grafting onto HA as a photocleavable group. The copolymer was prepared by reversible addition−fragmentation chain transfer (RAFT) process from di(ethylene glycol) methyl ether methacrylate (DEGMA) and 6-bromo-4-hydroxymethyl-7-coumarinyl methacrylate (CMA) monomers. The CMA unit due to their hydrophobicity and photo lability plays a dual role as it increases the stability of the nanogels and induces their disassembly by light irradiation. In vitro biological studies of these nanogels demonstrated that the HA-m-poly (DEGMA-co-CMA) nanogels and their hydrophobic cargo were successfully internalized by HeLa cells in a concentration-dependent manner. The results indicate that coumarin-containing HA-based nanogels were promising drug delivery systems for anticancer chemotherapy [43,44]. Arjmand et al. developed a novel photolabile crosslinking nanocarriers which undergo complete cleavage of drug carriers under UV light irradiation. The cleavage of nanocarriers under photoirradiation are utilized as controlled drug delivery systems for

anticancer drugs. The photolabile nanocarriers were synthesized by one step synthesis via distillation precipitation polymerization (DPP) of 2-hydroxyethyl methacrylate (HEMA) with the new photolabile crosslinker 7-(allyloxy)-4-methyl-2*H*-chromen-2-one dimer, obtained from photodimerization of 7-(allyloxy)-4-methyl-2*H*-chromen-2-one. Photolabile crosslinked nanoparticles showed higher drug loading efficiency (DLE) than *N,N*′-methylenebisacrylamide (MBA) crosslinked particles because of the less drug aggregation. C_{10}, C_{15}, M_{10}, and M_{15} are the coding of the particles with 10 and 15 mol% of photolabile and MBA crosslinkers, respectively. These drug carriers are loaded with doxorubicin (DOX) and at different conditions these nanocarriers showed excellent drug release at acidic pH because of the protonation of primary amine of doxorubicin which makes the molecule more soluble. The cumulative drug release of M_{10} and M_{15} is higher than C_{10} and C_{15} at pH = 1 due to larger size of M_{10} and M_{15} than C_{10} and C_{15} [45]

Plajnsek et al. designed and synthesized a coumarin-based fluorescent probe, 7-(diethylamino)-2-oxo-*N*-tetradecyl-2*H*-chromene-3-carboxamide, 14-DACA (Scheme 18.1) to improve the visualization of nanoparticles within the cells. The coumarin chromophore is linked to a tetradecyl alkyl chain that results in lipophilicity and amphiphilic character of this probe. The probe 14-DACA exhibits excellent biocompatibility, and the solubility and the emission characteristics of this probe is insensitive toward the pH change. This new probe enables the possibility of spectral changes from green and red fluorescence and multicolor imaging in both living and fixed cells. Solid lipid nanoparticles (SLNs)

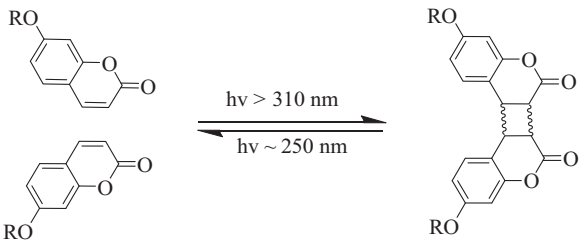


Scheme 18.1 Structures of coumarin derivatives.

labeled with 14-DACA (SLN-D) and 6-coumarin (SLN-C) were used to evaluate the trafficking and intracellular localization properties of nanoparticles [46].

Lin et al. designed and synthesized a novel coumarin functionalized mesoporous bioactive glasses (MBGs), having various biomedical applications, such as implants in clinical bone repair and regeneration materials, bioactive coatings of metallic implants, and in tissue engineering. This biomaterial exhibits a stable mesoporous structure with large pore volume and pore diameter, and surface area which is suitable for drug loading and possesses sustained drug release properties. In this material, an "open-close door system" was used in the photoswitchable controlled release of saddled/loaded drug molecules. Upon irradiation with UV light higher than 310 nm, this material induces the photodimerization of photoactive coumarin molecules to the pore of cyclobutane dimer. The loaded drug molecules can neither enter nor escape from the pores of the mesoporous bioactive glass. However, upon irradiation at ~250 nm the pores of the mesoporous bioactive glass's materials are opened, the coumarin dimer cleaves into the monomers of coumarin, and the guest molecules can be released (Scheme 18.2). This biomaterial with an "open-close door system" can be utilized in the photoswitchable controlled release of various drug molecules [47].

Wang et al. designed and synthesized a novel colorimetric, "turn-on" fluorescent probe 3-(benzo[d]thiazol-2-yl)-2-oxo-2*H*-chromen-7-yl (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl) carbonate, BC-OB having π-extended coumarin group as a fluorophore and a *p*-dihydroxyborylbenzyloxycarbonyl moiety, which is assembled with the coumarin fluorophore, as a reactive site for capture of hydrogen peroxide (H_2O_2) as shown in Fig. 18.5. This probe BC-OB exhibited excellent absorption and fluorescence spectrum with low detection limit (0.47 μM) with high fluorescence quantum yield ($\sqrt{} = 0.68$) both in solution and in living cells by regulating the intramolecular charge transfer (ICT) as shown in Fig. 18.6. The probe BC-OB also showed a stable fluorescent behavior at physiological pH and exhibited a good fluorescence response in both neutral and alkaline conditions. It can also be employed in the detection of endogenous H_2O_2 in RAW 264.7 cells (monocyte/macrophage-like cells, originating from Abelson leukemia virus transformed cell line derived from BALB/c



Scheme 18.2 Photoreversible dimerization cleavage of coumarin derivatives.

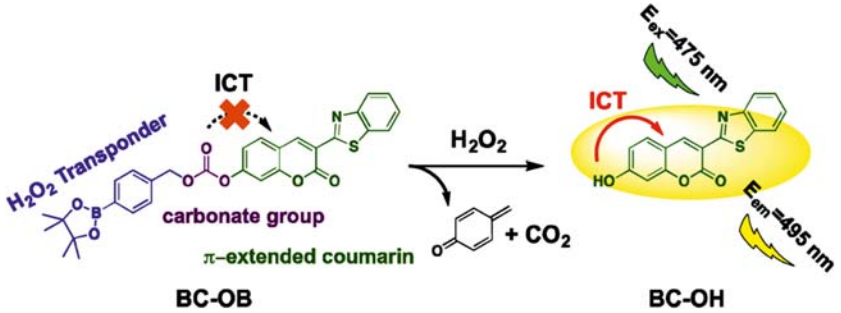


Figure 18.5 Design of a "turn-on" fluorescent probe BC-OB based on a π-extended coumarin fluorophore for H_2O_2 detection. *(The copyright permission from Y.B. Wang, H.Z. Luo, C.Y. Wang, Z.Q. Guo, W.H. Zhu, A turn-on fluorescent probe based on π-extended coumarin for imaging endogenous hydrogen peroxide in RAW 264.7 cells, J. Photochem. Photobiol. Chem. 414 (2021). https://doi.org/10.1016/j.jphotochem.2021.113270, Elsevier Publisher.)*

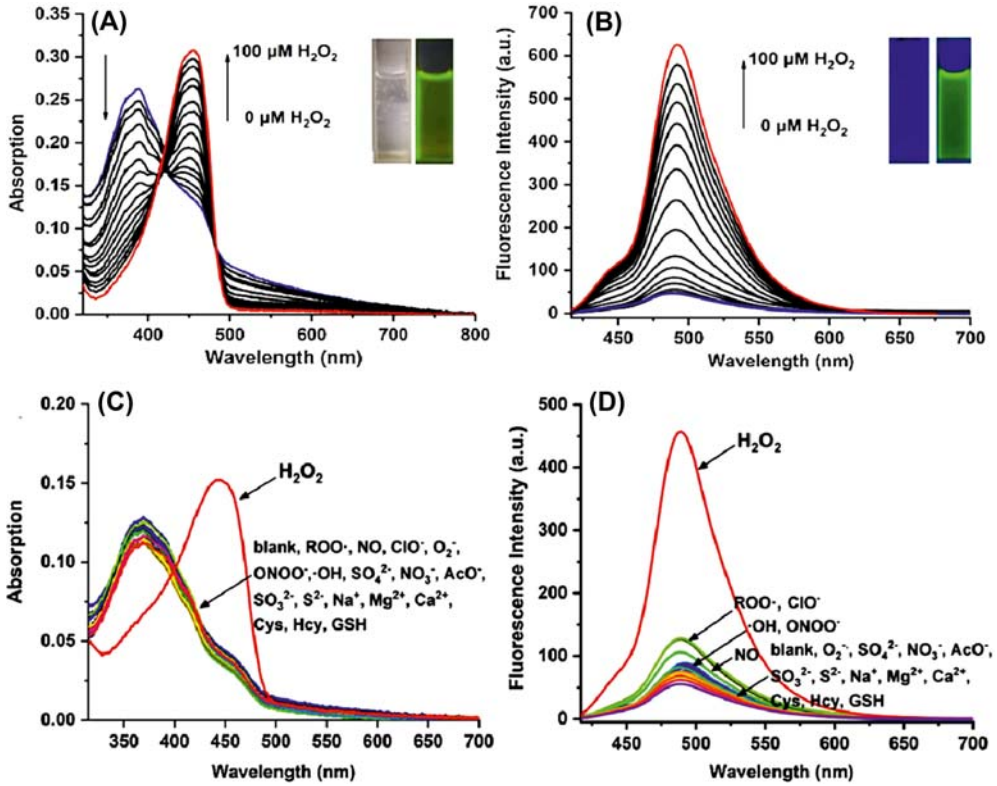


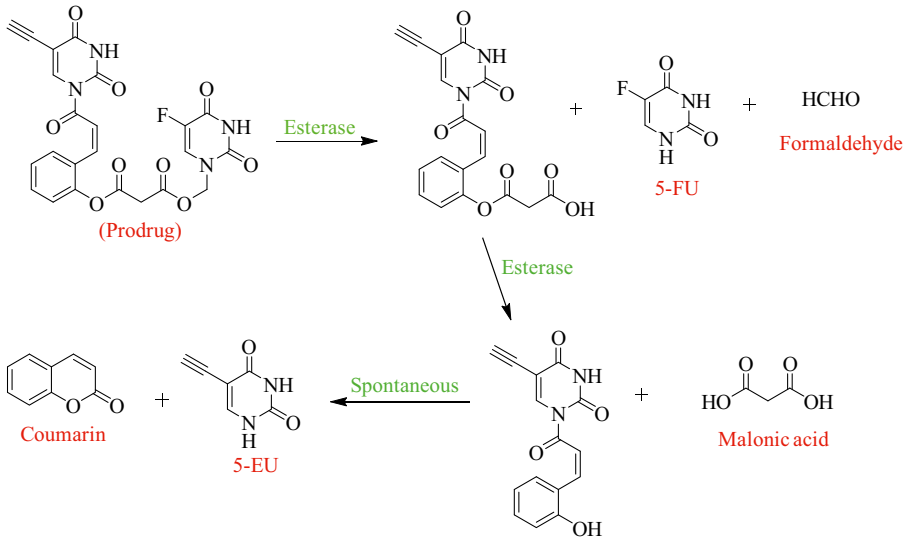
Figure 18.6 (A) UV-absorption and (B) fluorescence titration spectra of probe BC-OB (10 μM) with increasing equivalence of H_2O_2 (0—100 μM), (C) UV-absorption and (D) fluorescence spectra of probe BC-OB (10) in PBS buffer (20 mM, pH—7.4) with the representative species. *(The copyright permission from Y.B. Wang, H.Z. Luo, C.Y. Wang, Z.Q. Guo, W.H. Zhu, A turn-on fluorescent probe based on π-extended coumarin for imaging endogenous hydrogen peroxide in RAW 264.7 cells, J. Photochem. Photobiol. Chem. 414 (2021). https://doi.org/10.1016/j.jphotochem.2021.113270, Elsevier Publisher.)*

mice, an appropriate model of macrophages), so it possessed potential application as an efficient indicator for imaging H_2O_2 [48].

Paul et al. investigated the interaction of a novel fluorescent coumarin derivative 4-azidocoumarin (4-AC) with the relevant biomolecules or biomimicking molecules such as cyclodextrins (CDs) and serum albumins to demonstrate the microenvironment inside the biomolecules or biomimicking molecules (Scheme 18.1). The change in the microenvironment inside the CD cavity or protein nanocore after the incorporation of the coumarin fluorophore was studied by steady-state and time-resolved emission studies at 298 K by monitoring the enhancement in the emission of 4-AC which occurs due to interaction with all CD molecules and serum albumin (SA) proteins in an aqueous buffer medium of pH 7. The change in the photophysics of 4-AC in presence of CD and proteins had been utilized to determine the binding constants of the complexes and the binding sites of the CD and proteins with the fluorophore probing the emission enhancement of the bound ligand at 298 K. Thus, the modulation of the photophysics of 4-AC in the presence of different microheterogeneous environments might be utilized to show the effectiveness of the ligand for the targeted drug delivery systems [49].

Mustafa et al. designed and synthesized a coumarin-based prodrugs of 5-fluorouracil (5-FU) and 5-ethynyluracil (5-EU) which is utilized for the concurrent release of these two active drugs which results into the improvement of the therapeutic efficacy of both 5-fluorouracil and 5-ethynyluracil. The synthesized mutual prodrug was significantly stable in the HCl buffer (pH 1.2) and phosphate-buffered saline (pH 6.8) with half-lives of 33.19 and 18.13 h, respectively, obeying pseudo-first-order kinetics. Also, this prodrug was able to release the two active components in human serum with a half-life of 4.62 h obeying zero-order kinetics (Scheme 18.3). Therefore, the synthesized prodrug represents a promising oral prodrug of 5-fluorouracil and 5-ethynyluracil for the controlled release of drug molecules [50].

In recent times, the development of colloidal lipid drug delivery systems (DDS) and the location of the drug within the DDS with its protective potential and compatibility of the drug are of special interest. So, Finke et al. used a fluorescent coumarin dye (3-(2-benzothiazolyl)-*N,N*-diethylumbelliferylamine) coumarin C6, (3-(2-benzothiazolyl)-7-diethylamino)coumarin (Scheme 18.1), as a model drug to get information about the localization and trace the DDS (in vitro) by using the fluorescence spectroscopy. Pre-loading of C6 to the lipid matrix or post-loading of C6 to the readymade DDS after its processing leads to the localization of C6 in the interfacial layer in between the solid lipid nanoparticles (SLN) and an aqueous medium. In the pre-loading of C6, nanoemulsions disturbed in emulsion droplets causes a hypsochromic shift of the fluorescence spectrum. The larger surface area of emulsion droplets due to smaller size of droplets causes more interaction of C6 with the aqueous phase causing a bathochromic shift in fluorescence spectra. Along with this, the simulations of



Scheme 18.3 The hypothetical release of the drugs 5-FU and 5-EU from the prodrug in human serum.

fluorescence spectra were investigated to identify and precisely quantify the contribution of various species caused by the environment of fluorophore or protonation [51].

18.3.3 Cyclodextrin-based drug delivery systems

Cyclodextrins have a unique chemical structure with many potential sites, different cavity size, less toxic and low pharmacological activity which makes cyclodextrin as natural drug carrier [52]. Antibacterial activity of electrospun nanofibers was mostly restricted due to their low loading capacity of antibiotics. To synthesize oral delivery antibiotics, Topuz et al. had reported high drug loading nanofibers of natural excipients like cyclodextrin (CD) which showed better stability via forming inclusion complex (IC). Optimized bead-free CD concentrations led to the formation of ultrafine fibers by electrospinning of 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) with antibiotics like Gentamicin (GEN), Kanamycin (KAN), Chloramphenicol (CAP), and Ampicillin (AMP) to form IC from water (Fig. 18.7A–C). The highest antibiotic activity was observed for HP-β-CD@GEN subsequently followed by HP-β-CD@KAN and HP-β-CDAMP. Rapid dissolution of these IC in water and artificial saliva was due to the hydrophobic and uncross-linked nature of reported fibers. Such fibers could be used in fast-dissolving oral drugs with high loading capacity (Fig. 18.7D) [10].

Gao et al. fabricated thiophanate methyl/hydroxypropyl-beta-cyclodextrin (TM/HPβ-CD) nanofiber IC via electrospinning to enhance the water solubility of the TM. The water-insoluble bactericidal TM could cause dust pollution and harm the environment. In order to overcome such problems, TM/HPβ-CD beadles and

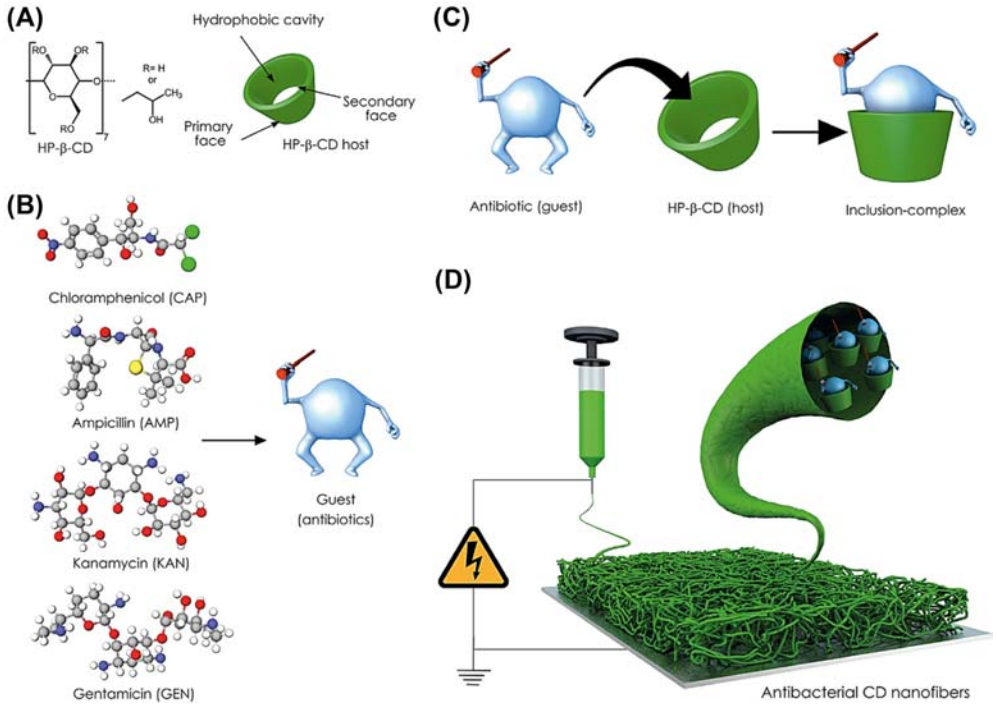


Figure 18.7 (A) Structure of HP-β-CD, (B) high potency antibiotics, (C) molecular models for IC of HP-β-CD with antibiotics, (D) diagrammatic electrospinning process. *(The copyright permission from F. Topuz, M.E. Kilic, E. Durgun, G. Szekely, Fast-dissolving antibacterial nanofibers of cyclodextrin/antibiotic inclusion complexes for oral drug delivery, J. Colloid Interface Sci. 585 (2021) 184–194. https://doi.org/10.1016/j.jcis.2020.11.072, Elsevier Publisher.)*

homogeneous nanofiber plays an important role via increasing solubility of TM. IC not only increases the solubility but also showed increased thermostability and antifungal activity of TM [11]. HPβ-CD was a widely used CD derivative. Compared to CD, HPβ-CD showed improved water solubility. The same group reported IC (thiram/hydroxypropyl-β-cyclodextrin) nanofiber capable drug delivery system (DDS) which comprised of water-insoluble dithiocarbamate fungicide, thiram drug incorporated in HPβ-CD. Proposed nanofibers have an excellent dissolution rate in water, thus antifungal activity with the thermal stability of the drug will be raised [12]. Curcumin (CUR) was a hydrophobic compound obtained from *Curcuma longa* having various applications including cancer therapy but due to poor solubility and less bioavailability, it showed limited applications. To overcome such drawbacks, Roozbehi et al. synthesized an enzyme-sensitive release system based on host–guest of β-CD and CUR. β-CD was the host with CUR as a model drug forming IC of β-CD-CUR/MAase, and the release system showed the response to enzyme maltogenic amylase (MAase).

CUR was incorporated with β-CD that showed in vitro 100% drug release capacity in presence of CD degrading MAase enzyme at the target site. Faster and higher drug delivery was showed in presence of enzyme due to degradation of IC but a comparatively slower rate was observed without degrading enzyme (Fig. 18.8) [13].

Curcumin is also one of the natural medicines having antibacterial properties, but it displays metabolic issues, aqueous insolubility, and biodegradation problems. β-CD inclusion complex with CUR could increase the aqueous solubility by 206 folds over pure CUR with a high association constant, therefore Arya et al. studied it as a drug delivery system. Also, interactions of CUR-β-CD (1:2) complex with 2,2-diphenyl-1-picrylhydrazyl (DPPH), serum proteins, amylase, trypsin, cathepsin B, and H. CUR-β-CD showed slow release of curcumin with DPPH/serum/enzyme. However, there was a fast release of curcumin without CD complex. Such host—guest complexes could delay the metabolic degradation by dehydrogenase by protecting diketo/keto-enol framework [14]. To develop a magnetic "smart" drug delivery system (DDS), Soleimani et al. synthesized β-CD-based supramolecular, pH, and reductive responsive magnetic nanohydrogel

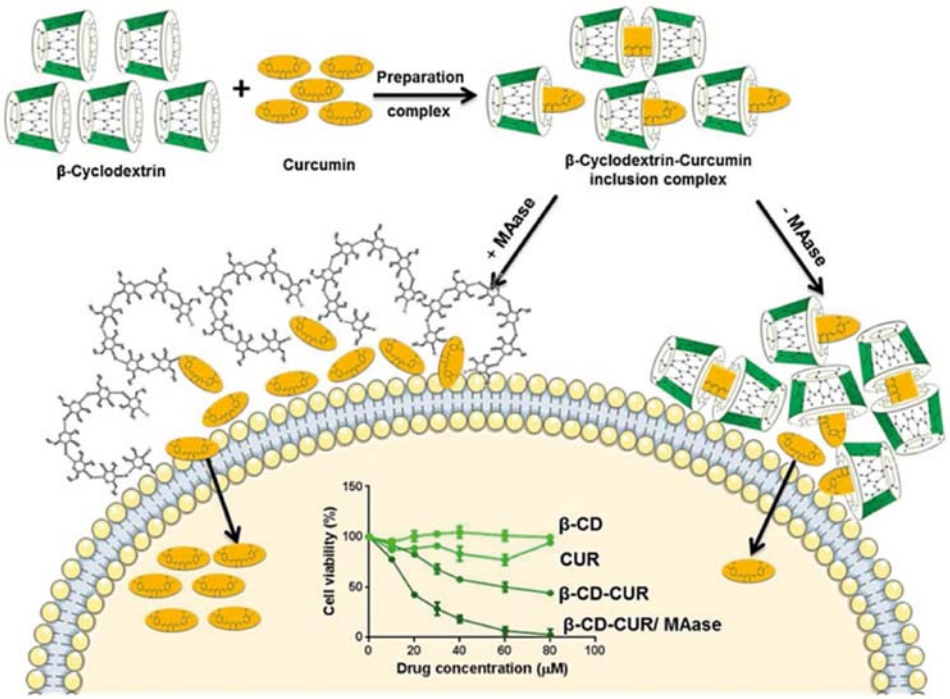


Figure 18.8 Proposed role of IC of β-CD-CUR/MAase with and without MAase. *(The copyright permission from S. Roozbehi, S. Dadashzadeh, R.H. Sajedi, An enzyme-mediated controlled release system for curcumin based on cyclodextrin/cyclodextrin degrading enzyme, Enzyme Microb. Technol. 144 (2021) 109727. https://doi.org/10.1016/j.enzmictec.2020.109727, Elsevier Publisher.)*

comprising of anticancer active drug Dox. Acetylated β-CD was grafted with 2-ethyl-2-oxazoline (EtOx) monomer consecutively linked crossly with amine-end capped Fe_3O_4 nanoparticles and cysteamine. Proposed DDS consisted of β-cyclodextrin grafted in PEtOx monomer which was further linked with Fe_3O_4 and cysteamine to form nanohydrogel which was capable of drug delivery. β-CD-g-$(PEtOx)_7/Fe_3O_4$ nanohydrogel loaded with the anticancer drug having loading capacity of ~74% could show pH and reduction-triggered release of the drug. A combination of hyperthermia and chemotherapy showed higher anticancer activity comparative to chemotherapy alone [15]. Al-Abboodi et al. fabricated the anticancer IC clausenidin/HPβ-CD (Clu/HPβ-CD) which has a higher solubility rate and constant drug release capacity. The intermolecular interactions and orientation of Clu within the hydrophobic HPβ-CD cavity via hydrogen bonding between host—guest made it more selective. Clu/HPβ-CD had a more cytotoxic effect on colon cancer cells and have reduced side effects observed on cell viability between normal and cancer cells. Clu/HPβ-CD showed reactive oxygen species—mediated cytotoxicity which ultimately enhances the anticancer activity of Clu. IC showed improved selectivity in DDS of anticancer Clu drug to only colon cancer cells without cytotoxicity [16]. Drugs having anticancer activity lacks aqueous solubility, therefore Suliman et al. synthesized an IC of diethyldithiocarbamate copper II (DDC-Cu) and HP or sulfobutyl ether beta-cyclodextrin (SBE) to enhance the solubility of anticancer drugs. By simply mixing DDC-Cu with CD at room temperature, the formed IC showed anticancer activity on chemoresistance triplet negative breast cancer cells (MDA-MB-231_{PAC10}) with 28 days stability [17]. CD-IC were widely used in target DDS nowadays. Antibacterial tedizolid drug lacked aqueous solubility but could show a progressive increase in antibacterial activity and dissolution rate when formed IC with HPβ-CD. IC (tedizolid-HPβ-CD) showed modified physicochemical properties with preserved pharmacological activity and was thus used for enhancement of physical and chemical properties of antibacterial drugs. Tedizolid-HPβ-CD showed increased dissolution rate and time while preserving a high permeation coefficient and high bactericidal activity. Tedizolid-HPβ-CD could be used as a delayed-release drug delivery system in chemotherapy in bacterial serious infections [53]. To increase the capacity of CD, Gonzalez et al. synthesized a polymeric cationic-CD derivative. Cationic-CD-based polymer (CCD/P) is capable of loading and transporting drugs more efficiently than a monomer unit. Gold-nanostars (AuNSs) incorporated in CD could load phenyl ethylamine (PEA) and piperine (PIP) showing effective colloidal stability. Such AuNSs formed a new AuNSs-CcD/P-PhEA-PIP nanosystem bearing 95 ± 7% loading capacity with increased colloidal stability [54].

18.3.4 Polymer, peptide, and AIE-active—based drug delivery systems

The peptide and protein drugs have higher specificity and potency, also less side effects compared to chemical drugs [7]. Most of the fluorescent nanomaterials used in the DDS

are inorganic quantum dots, fluorescent proteins, and organic molecules. But toxicity of fluorescent proteins and inorganic materials limited their biomedical application. However, organic dyes have high quantum yield, selectivity, and sensitivity [55]. In 2001, Tang and coworkers discovered a phenomenon called "aggregation-induced emission" (AIE) [56]. In this phenomenon molecules possess high fluorescence in aggregation state and no emission in dilute state. Because of these unique features, AIE molecules are used in chemical and biological applications. Ichikawa and Fukumori prepared microcapsule (MC) with air suspension coating technique having 100 μm diameter for positively thermosensitive drug release. The ethyl cellulose matrix comprised of nano-sized thermosensitive hydrogels used for composing thermosensitive coat. Carbazochrome sodium sulfonate (CCSS, a water-soluble model drug) particles were used for core layer of MC. The reversible change of shell thickness in water with response to environmental temperature change of the hydrogel particles consisted of newly synthesized composite latex with a poly(*N*-isopropylacrylamide (NIPAAm)) shell. The shrinkage of poly(NIPAAm) shells created many voids in the coat and thereby imparted higher water penetrability to the coat. This verified that MC showed a positive thermosensitive drug release: the release rate was remarkably improved at temperatures above a lower gel collapse point (temperature for complete deswelling) of 32°C. Composite latex particle content in the coat is a very important factor in thermosensitivity of drug release [57]. Zhang et al. designed 2,6-bis(hydroxymethyl)anilines with UV and redox-sensitive protecting groups. Chain-shattering polymeric therapeutics (CSPTs) was formed through these anilines as monomers which by condensation with bifunctional drugs and contact of external triggers resulted into whole drug release in chain-shattering manner by controlling trigger-responsive domains (TRDs). They detected pulsatile drug release in response to periodical drug release from CSPTs. After externally applied stimulations, the trigger-responsive cytotoxicity and in vivo antitumor efficacy of CSPTs and CSPTs having active control over drug release was observed [58]. Weber and coworker designed clinically licensed stimulus for human growth, i.e., stimuli-responsive hydrogels with pharmacologically controlled interactions among two proteins. In the release of therapeutic protein, the novobiocin concentration plays crucial role and for extended times ($t_{1/2} = 6$ h) hydrogels can be maintained in the plasma. Single oral dose of novobiocin above 0.15 mM can be obtained for 24−72 h which was demonstrated by clinical phase I study. As novobiocin is mainly located in the plasma, tissues supplied with blood (such as muscle) promised the best localization of the therapeutic cargo with trigger emphasized hydrogels. Thus, the trigger-inducible release hydrogel is proficient in biomedical applications [59].

Xiao et al. derived nanoparticles (NPs) for cancer thermo-chemotherapy by DNA self-assembly of targeted near-infrared-responsive gold nanoparticles. They mimic nature's ability of complementary strands of DNA to hybridize. For cancer therapy they constructed a DNA-based platform that can self-assemble into designed near-infrared

(NIR)-responsive NPs. There are three different functional components present in this DNA-based platform, such as (i) complementary DNA strands with its sequential CG base pairs which provide loading sites for Dox, (ii) the gold nanorod (NR) which serve not only as the model NIR light-to-heat transducer for cancer thermotherapy but also for the denaturation of DNA double helix upon NIR irradiation which leads to the triggered release of loaded drug for chemotherapy at the target site, and (iii) a polyethylene glycol (PEG) layer utilized to avoid the recognition of NPs by the immune system which extend the circulation half-life of the NPS. Through thermo-chemotherapy, they succeed to inhibit tumor growth possible by selectively transporting anticancer drugs to target cells, release them upon NIR irradiation by simple DNA self-assembly process. Rather than using intratumoral injection of NPs, their platform integrates targeting ligands through the DNA-assembly process and loading the drugs thereafter. Therefore, ligand density and drug loading can be fine-tuned and precisely controlled, which facilitates the optimization of NP biophysicochemical properties to achieve optimal biodistribution for synthetic administration [60]. Choi et al. constructed scheme for temperature-sensitive drug release with phase change materials (PCMs). This scheme has notable characteristics; uncomplicatedness in terms of construction method; quick response time to an ambient temperature; and no requirement to outside monitoring device due to precise release of the drug. The selection of suitable amalgamation of PCM and drug-encapsulating material helps to adapt initiation temperature and release pattern of drugs, respectively. They encapsulated FITC and protein conjugates rather than FITC-dextran which is having higher molecular weight. If drug is dissolved in suitably designated PCM, then encapsulation progression should have nothing to do with molecular weight. Fever causing temperature rise of body, inflammation, and among others can be promoted for drug release by PCM [61]. Aggregation-induced emission (AIE) and excited state intramolecular proton transfer (ESIPT) helped in fabrication of light-activated single component fluorescent organic nanoparticles for synergistic therapy by coupling tetraphenylethylene (TPE) with *p*-hydroxy phenacyl-chlorambucil (*p*HP-Cbl) for cellular imaging ability. The synthesized TPE-*p*HP-Cbl nanoparticles have certain advantages such as AIE activity with large Stokes shift, photoirradiation wavelength greater than 410 nm, and photodynamic therapeutic activity. Upon photolysis, the drug release from these nanoparticles occurred only in the aggregated state, which was confirmed by fluorescence color change from yellow to green. With visible light exposure, TPE-*p*HP-Cbl nanoparticles generated singlet oxygen as well as released anticancer drug chlorambucil. Nanoparticles show enhanced anticancer activity because of synergistic combination [62]. Fluorescent nanodiamond (FND) possessing peculiar features like less hazardous and physicochemical properties enhanced immense interest of researchers in the field of bioimaging and drug delivery. Though large-scale synthesis of FND was a challenge, Liu et al. synthesized luminescent nanodiamond having biomedical applications and AIE-active dyes rapidly through microwave-driven Diels—

Alder reaction. The synthesized FND (named as ND-poly(Phe-PEGMA-IA)) showing characteristic features like extensive fluorescence, high water dispersibility, desirable biocompatibility, and great stain performance was demonstrated by cell imaging. In the acidic environment precise release of cancer drug (cisplatin, DPP) loaded on ND-poly(Phe-PEGMA-IA) with 54.3% loading capacity proved importance of biological tracing and controlled drug delivery of ND-poly(Phe-PEGMA-IA) [55]. Dual FRET (fluorescence resonance energy transfer) process used for self-indicating cancer therapy. Wang et al. synthesized AIE-active polymer (FTP) and utilized to load doxorubicin (DOX) which is an anticancer drug. Strong fluorescence emission was observed via dual intramolecular FRET process by self-assembling of FTP polymer into nanoparticles (NPs) in aqueous solutions. The preferable colloidal solidity, hemolysis, and selective drug release with comparable in vivo antitumor effects to DOX.HCl is due to neutral surface charge and uniform particle size of 50 nm through drug DOX loading capacity 21.77% to FTP. Thus, promising platform for drug localization and release during the delivery can be monitored by FRET process among FTP (donor) and DOX (acceptor) as indicator for drug release in the in vitro and in vivo system (Fig. 18.9) [63]. The huge two-photon absorption (TPA) cross-section is due to increasing charge transfer in a π conjugated donor (D) and acceptor (A) systems. Relating to this phenomenon, Singh et al. constructed *p*-hydroxyphenacyl-based drug delivery systems (DDS) with good uncaging ability in the phototherapeutic window by incorporating naphthalene moiety

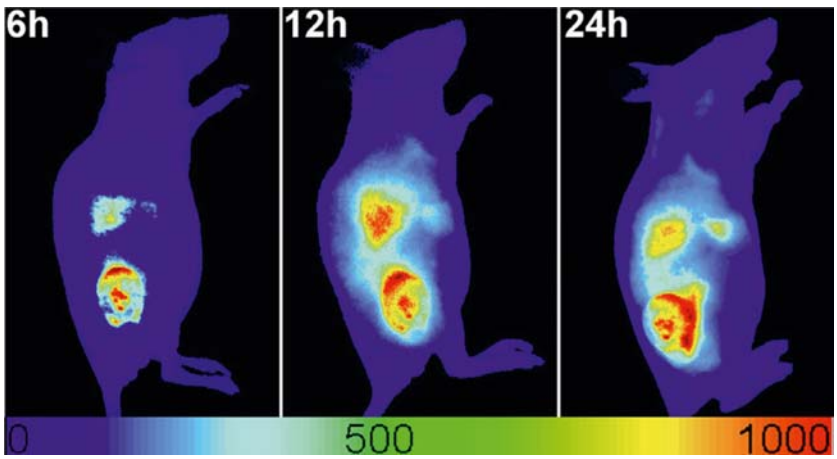


Figure 18.9 In vivo real-time fluorescence imaging of the MCF-7 tumor xenograft mice at 6, 12, and 24 h post intravenous injection of DiR-loaded FTP NPs. *(The copyright permission from C. Wang, Z. Wang, X. Zhao, F. Yu, Y. Quan, Y. Cheng, H. Yuan, DOX loaded aggregation-induced emission active polymeric nanoparticles as a fluorescence resonance energy transfer traceable drug delivery system for self-indicating cancer therapy, Acta Biomater. 85 (2019) 218–228. https://doi.org/10.1016/j.actbio.2018.12.020, Elsevier Publisher.)*

to the *p*-hydroxyphenacyl group. This led to strong charge transfer and absorption shifted toward red shift with increased two-photon uncaging cross section. The pHP-Naph-Cbl, i.e., the constructed photoresponsive DDS having extraordinary features, (1) display of AIE phenomenon; (2) two photon absorptions in the phototherapeutic window; (3) ESIPT process leading to large stokes shift; and (4) Drug release monitoring by different fluorescent color change [64]. For metastatic pancreatic cancer, gemcitabine (GEM) was the first-line drug since 1977 but due rapid deamination along with short plasma circulation time, it had limited clinical applications. However, use of prodrug could avoid deactivation of drug and could be used more efficiently. GEM was a nonfluorescent drug and hence cannot be detected in delivery or release process. Thus, GEM prodrug loaded in fluorescent dye such as TPE was used in monitoring of drug release and transport [65]. Qian and coworkers synthesized smart nanocarrier—based drug delivery system (STD-Nano-Micelle) which showed excellent application in theragnostic by targeting tumor in microenvironment, and in evaluating therapeutic response in vivo. STD-NM is functionalized with peptide and shows switch on AIE-active characteristics which can be used for in vivo imaging, tumor targeting, and apoptosis monitoring. The surface of micelle nanocarrier is functionalized with ST and TD peptide where ST comprising of pH-triggered targeting peptide STP (sequence: SKDEEWHKNNFPLSPG) AIE-active TPE derivative with caspase-3—responsive peptide linker (sequence: DEVD). TD tumor acidity—activated peptide comprises of cell penetrating peptide TAT and 2,3-dimethylmaleic anhydride (DA). This keeps the nanocarriers stealth and stable in normal physiological environment but activate in acidic environment [66].

The multifunctional antitumor drug was introduced on the enzyme-activated cell-penetrating peptide (CCP) which was further adsorbed on mesoporous silica ($mSiO_2$)-coated quantum dot (QDs) cluster surface which was capable of cellular and nuclear target drug delivery with controlled release of antitumor therapeutic agent like doxorubicin (DOX) into the nucleoplasm of tumor cell. Drug loaded with nanoparticles (QDs@$mSiO_2$) selectively localized the nucleus of tumor cells with prominent tumor cytotoxicity with limited side effects, particularly to the cells with antitumor drug resistant property. Nuclear-targeted drug delivery of QDs@$mSiO_2$ with DOX could be demonstrated by real-time cell-imaging as the fluorescence of QDs@$mSiO_2$ [67].

Pujals et al. stated the significance of cell-penetrating peptides (CPPs) self-assembly for CPP-facilitated intracellular drug delivery. CPP is known to be a proficient intracellular transport system. CPP internalization can be understood by following mechanistic pathway, first step of which involves interaction with extracellular matrix, second step is endocytosis, and lastly intracellular fate is reached depending on endocytosis type. Various methods are emerging for transport of drug molecules joined to a CPP which requires endosomal release of these positively charged amino acids, hydrophobicity, and/or amphipathicity mutual to CPPs. The self-assembly part into the cellular uptake of CPPs was defined by them. The aggregation of Sweet Arrow Peptides (SAP) CPP

confirmed by CD and TEM, which still is an internalized type and has up till now to be identified as either monomer or an aggregate. Mechanism of cellular internalization was identified by CPP shared property and its correlation to specific steps. So, extracellular matrix groups like sulfate, carboxylates, and phosphates are interacting firstly to positively charge. The factor responsible for CPP strong binding to the cell membrane or to enter a bilayer and attain endosomal release is hydrophobicity. Amphipathicity is due to maximal separation by CPPs [68]. The drug delivery field is broadened with certain peptides by observing peptides cross the eukaryotic cell membranes, and this evolution of peptides can be observed through rapid development in antitumoral, antiviral, or antibiotic drugs. The cell membrane crossed by proline-rich antibiotics demonstrated that peptide containing only proline residue (P_{14}) penetrates the cell membrane, albeit with low capability. Fernandez-Carneado et al. synthesized amphipathic peptides (VXLPPP)n (with n = one to three and X = His (H), Arg (R), Lys (K)) and investigated their capability to cross cell membranes. As the earlier mentioned γ-zein domain, they select Val (V) and Leu (L) by resemblance. The X residues cationic chains is for support interaction with phosphate diester anionic polar heads. The (VXLPPP)n family of peptides is proficient in case of its nonviral origin, amphipathic character, solubility in water, and absence of cytotoxic effect at high concentrations. With 5(6)-carboxyfluorescein as a marker method were introduced for labeling resin-bound peptides [69]. Hashida and coworker synthesized pure nanodrugs (PNDs) and investigated their anticancer properties. The reprecipitation method utilized for the preparation of SN-38 nanoparticles by them, and dimer containing carrier-free PNDs with effective cytotoxic activity. The enhanced cell permeability and good stability of aqueous dispersions play crucial role for dimer nanoparticles with combination [70]. Cathepsin B is the lysosomal cysteine protease and performs important physiological and pathological functions. Cathepsin B is considered as the most important factor in the formation, growth, invasion, and metastasis of various tumors such as melanoma, glioma, breast cancer, CRC, gastric cancer, lung cancer, and ovarian cancer. On account of these features cathepsin B is used as a platform which is loaded with active pharmaceutical and novel prodrug for targeted cancer treatment. Li and coworkers explored Cathepsin B-responsive nanodrug delivery system for diagnosis of the targeted malignant tumor [71]. There are several limitations also for the nanotechnology-based drug delivery systems, such as insufficient drug release, lack of real-time imaging, and poor tumor penetration. To overcome these impediments, Sheng et al. developed light-responsive nanodroplets as doxorubicin (DOX) nanocarriers containing perfluoropentane (PFP) and photoabsorber-indocyanine green (ICG) with lipid stabilized shell. These perfluorocarbon nanodroplets were upon laser irradiation resulted in transformation of phase or size of liquid PEP [72].

18.4 Summary and conclusion

The recent development in the drug delivery system is of prime importance and has gained lot of attention due to health-related problems. Now a days cancer is the serious health problem and its diagnosis and proper treatment at correct stage is required. There are wide range of nanomaterial that are used for diagnosis and to deliver drug to the targets but also there are several disadvantages such as lack of solubility, low stability, aggregate formation, side effects, lack of absorption, and reaching to the target site that limits the application of certain carriers for controlled drug release to the target. This chapter discusses the recent advances in nanomedicines and new technologies in the delivery of the drug via suitable carrier along with new diagnostic methodologies. In this chapter, we have introduced and discussed different organic molecules, such as porphyrins, coumarins, cyclodextrin, protein, and AIE-active based molecules and other polymeric nanoparticles for drug delivery system. We have also described various strategies and new approaches for design of new DDS carriers.

18.5 Challenges and future outlook

In the last few years, great progress has been achieved in designing the drug delivery strategies, construction techniques, and materials with improved bioavailability and biocompatibility. In fact, presently there are several formulated carriers for drug delivery that have different physicochemical and pharmacokinetic properties with various drawback such as improper dosage and undesirable side effects. There is also need for development in designing new strategies and formulation of drugs carrier for reducing the side effects. Another major problem with the use of nanoparticle is maintaining the size of the particle, complex synthesis strategies and solubility. To overcome the drawbacks while using nanoparticulate as a carrier for controlled drug release process, researcher mainly focused on synthesizing several organic and inorganic molecules which capable of efficient drug delivery system. Thus, it is important to strengthen the research in drug delivery and develop new synthetic approaches with good stability, solubility, and less side effects. Certainly, applying organic molecules in drug delivery requires frequent testing, revision, and rapid optimization.

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