Hollow Multicomponent Capsules for Biomedical Applications: A Comprehensive Review

Tanzeela Anis1 · Syed Mujtaba ul Hassan1 · Ahmat Khurshid2 · M. Fakhar-e-Alam3 · Faisal Shahzad1 · A. Ali4 · Jamil Ahmad1 · Nazia Hossain5

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Abstract
Hollow capsules with multi-shelled or multicomponent structures are essential materials for various applications. Biomedical applications like disease diagnosis, therapy, and monitoring have special significance as they aim to improve health conditions. This review demonstrated a comprehensive overview of hollow, multifunctional structures incorporating meaningful use of nanotechnology and its' unique prospects in medicine such as patient-specific treatment, multimodal imaging, multimodal therapy, simultaneous delivery of drugs and imaging probes, and actively targeted delivery. The internal hollow cavity provides safe and controlled drug release while also enabling transport of functional moieties to target sites. This review explored the performance of different organic, inorganic, and metallic multicomponent capsules that have been reported for biomedical applications, mainly diagnostic imaging and drug delivery. Material compositions, morphologies, and synthesis strategies involved in fabricating such multifunctional systems have been discussed in detail. It is expected that with time, more sophisticated and precise systems will come to light as the outcome of ongoing concentrated research efforts.

Keywords Multicomponent · Hollow structures · Drug delivery · Multimodal imaging · Theranostics · Combination therapy

Abbreviations

Chemicals

BSA · Bovine serum albumin
β-CD · Beta-cyclodextrin
Ce6 · Chlorin e6
CTAB · Cetyltrimethylammonium bromide
DDAB · Didodecyl dimethylammonium bromide
DEG · Diethylene glycol
DOX · Doxorubicin
FA · Folic acid
FBP · Flurbiprofen
FITC · Fluorescein 5(6)-isothiocyanate
GSH · Glutathione
HA · Hyaluronic acid
HF · Hydrofluoric acid
HSA · Human serum albumin
ICG · Indocyanine green
MH · Metformin hydrochloride
OA · Oleic acid
PAA · Poly (acrylic acid)
PAA-b-PI · Poly(acrylic acid-b-isoprene)
PAMAM d-PLL · Polyamidoaminodendron-poly(L-lysine)
## Introduction

The term ‘nanomaterial’ currently refers to materials having “discrete functional parts” with one or more dimensions of these parts in the 1–100 nm range. Concomitant is the term “nanoparticle” which is specific to entities with all three dimensions below 100 nm down to the atomic level (0.2 nm) [1, 2]. The upper threshold of 100 nm is scientifically arbitrary; it is mainly a marker to distinguish the broad size range where differences of physicochemical properties between bulk and nanomaterials become practically significant. It is this often-unprecedented change in properties comes across as the defining characteristic of nanomaterials in contrast with “conventional” bulk materials. Manipulating matter at this level has allowed researchers to play with the structure–property-application dynamics under the umbrella term of ‘nanotechnology.’

Besides other fields, nanotechnology has been actively intertwined with biomedical research for the last twenty years. Even advanced computational approaches such as machine learning are being employed to combine nanotechnology with medicine [3]. The sub-field of biomedical nanotechnology gained traction after the approval of the first nano-liposomal drug called Doxil by the Food and Drug Administration in 1995 [4]. Since then, researchers from around the world have been exploring the feasibility of using nanomaterials for diagnostic [5–9], therapeutic [10–17], and sometimes a combination for both purposes [18–22]. An emerging area of nanotechnology for biomedical applications is the development of multicomponent hollow capsules. Such platforms are engineered by incorporating nanosized particles (henceforth ‘nanoparticles’), functional nanoparticles, nanostructured particles, mesopores (2–50 nm), or nano-sized shell structures. A hollow cavity is present inside that reduces material consumption and allows encapsulation of different cargo material, including pharmaceuticals or biomolecules, for controlled and safe delivery. An encapsulating structure can also facilitate cargos' longer blood circulation time, depending on the used platform [23].

Hollow capsules can be modified by adding functional nanoparticles, drugs, or biomolecules like DNA and RNA inside. They can also be covered with such functional components as secondary shells or superficially attached nanoparticles that are much smaller in size than the primary capsule [24]. If superparamagnetic or ferromagnetic, functional nanoparticles can be used for magnetic guidance of nanocarriers’ path in vivo, as contrast agents in magnetic resonance imaging (MRI) or magnetic hyperthermia treatment [25, 26]. Other nanoparticles with photoluminescent

| Acronym | Description                     | Acronym | Description                     |
|---------|---------------------------------|---------|---------------------------------|
| PAN     | Polyacrylonitrile               | PTT     | Photothermal therapy            |
| PAZO    | Poly [1-[4-(3-carboxy-4-hydroxyphenylazo) benzenesulfonamido]-1, 2-ethanediyl] | SDT     | Sonodynamic therapy             |
| PBS     | Phosphate buffer saline          |         |                                 |
| PCPTF   | Poly (cyclotriphosphazene-cofluorescein) |         |                                 |
| PDADMAC | Poly(diallyldimethylammonium chloride) |         |                                 |
| PDDA    | Poly(diaryldimethylammonium chloride) |         |                                 |
| PEA     | Isopentyl acetate               |         |                                 |
| PEG     | Polyethylene glycol             |         |                                 |
| PEI     | Polyethylenimine                |         |                                 |
| PLGA    | Poly(lactic-co-glycolic acid)   |         |                                 |
| PMMA    | Poly (methyl methacrylate)      |         |                                 |
| P(MMA/DVB/AA) | Poly(methyl methacrylate/divinyl benzene/acrylic acid) | |                                 |
| P(MAA-co-EGDMA) | Poly(methacrylic acid-co-ethylene glycol dimethacrylate) | |                                 |
| PNIPAAm | Poly(N-isopropylacrylamide)     |         |                                 |
| PVA     | Polyvinyl alcohol               |         |                                 |
| RGD     | Arginylglycylaspartic acid      |         |                                 |
| TEOS    | Tetraethylorthosilicate         |         |                                 |
| HMSNs   | Hollow mesoporous silica nanopolymers |         |                                 |
| MC-GODs | Multi-carboxylic graphene quantum dots |         |                                 |
| mSiO₂   | Mesoporous silica               |         |                                 |
| OA-MNPs | Oleic-acid-capped magnetic nanopolymers |         |                                 |
| SPIONs  | Superparamagnetic iron oxide nanoparticles |         |                                 |
| U/DCNP  | Up/down conversion nanoparticles |         |                                 |
| CDT     | Chemodynamic therapy            |         |                                 |
| CLSM    | Confocal laser scanning microscopy |         |                                 |
| CT      | Computed tomography             |         |                                 |
| DDS     | Drug delivery system            |         |                                 |
| FDA     | Food and drug administration    |         |                                 |
| HIFU    | High intensity focused ultrasound therapy |         |                                 |
| LC      | Loading capacity                 |         |                                 |
| LbL     | Layer by layer                   |         |                                 |
| MOF     | Metal organic framework         |         |                                 |
| MRI     | Magnetic resonance imaging      |         |                                 |
| NP      | Nanoparticles                    |         |                                 |
| PDT     | Photodynamic therapy            |         |                                 |
| PET     | Positron emission tomography     |         |                                 |
properties can be used for in vivo optical imaging of tissues and cells [27, 28]. In drug delivery, hollow capsules with surfaces functionalized with biocompatible polymers (polyethylene glycol (PEG), for example [29]) or tumor-specific antigens are being studied for increasing in vivo biological targeting and response.

Surface functionalization plays a pivotal role in designing platforms with active targeting ability. Such functionalization involves surface coverage with tumor or cell-specific moieties [20]. It may also involve components that degrade in specific environments, e.g., low pH values found near tumors [30]. Opposed to active targeting is the passive targeting of tumors where enhanced permeability and retention effect is understood to cause relative accumulation of drug carriers at the tumor sites. This is made possible due to the leaky vasculature in the vicinity of tumors. Drug carriers flowing in the bloodstream are more likely to pass through the damaged vessels and tumor cells than other regions [31]. But more thorough studies have shown that this mechanism is more complex than initially understood [32].

Carefully developed multicomponent capsules can perform more than one function inside the body. Multimodal imaging capacity using two or more functional agents offers unique benefits [33–35]. For example, MRI contrast improving agents and PET contrast improving agents can be loaded on or in the capsules, and the capsule can then be used for both MRI and PET. Such strategies are employed to overcome individual limitations of each diagnostic technique, for instance, the low sensitivity of MRI and low spatial resolution of PET [36]. Other imaging modalities include CT, optical, and photothermal imaging. Combining imaging modalities this way also allows one-to-one image mapping, providing more details simultaneously.

Similarly, multiple therapeutic modalities can also be combined [37]. For example, the hollow structure enables increased capacity for drug loading as compared to solid nanoparticles. Besides drugs, sensitizer materials for photodynamic or photothermal therapy can also be loaded in or on the capsules [38–40]. Another interesting approach is to combine diagnostic modalities (such as imaging) with therapeutic modalities (drug delivery and cancer therapy) [41–44]. This approach is discussed under the domain of theranostics, a word coined by combining therapeutics and diagnostics.

When their size is in nano-scale, hollow capsules (referred to as ‘nanocapsules’) also provide added advantages. Directly, nanocapsules make good platforms for carrying drugs or other functional materials because of their capacity to carry more materials per gram of the platform material. An unconventionally high specific surface area, for example, leads to a higher density of electrostatically attached functional moieties or bonded antigens or proteins for targeted or controlled therapy [45]. Size comparable to biological molecules, such as proteins and DNA, also enables nanomaterials (particularly nanoparticles) to adopt similar biodistribution pathways as biomolecules [46]. Cellular uptake of drug carriers depends strongly on their size and shape [47, 48]. Indirectly, the variety of structures that can be achieved through an equally diverse set of synthesis methods makes a compelling case for their use in disease or patient-specific medicine. The inherent tunability of the synthesis methods leads to this variety in structure.

Notwithstanding all the exciting avenues of multifunctional hollow capsules, their applications have challenges and concerns. The idea of “killing two birds (or more than two in some highly engineered platforms) with one stone” is fascinating. Still, in practice, the efforts quickly fall to the arena of optimization and compromise. For example, when the same capsule system is designed to carry drugs and functional nanoparticles, the drug loading capacity is reduced compared to when the same capsule is employed only as a drug carrier. Fluorescence intensities of functional nanoparticles, magnetization values for paramagnetic species, heat generated by particles used for magnetic hyperthermia—all these factors are sometimes negatively affected by encapsulation of particles in another material devoid of such functionalities. Recently, the idea of theranostic platforms as a ‘paradigm shift’ has been critiqued for their inaccuracy and inutility [49]. It contended that a deeper look into the working definitions of theranostics does not support the novelty claim of related research efforts. However, it insufficiently addressed whether the term should retain its status in materials engineering efforts in theranostics.

Despite such challenges, the unique benefits of multipurpose hollow structures for biomedical applications compel a search to address the current problems and refine the technology for clinical use. This review discusses how this search has been carried forward, highlighting various applications, types of materials used, and synthesis strategies employed to fabricate hollow multicomponent structures. There has been a presence of literature reviews on the synthesis strategies of polymeric and inorganic hollow capsules [50–52], as well as reviews on the biomedical applications of nanocapsular structures [53–56]. Overviews of syntheses of polymeric hollow structures for cargo delivery and imaging is especially prevalent although silica has emerged as a potential alternative due to its favorable properties [57]. Apart from this, rational design strategy of preparing nanoplatfroms for cargo delivery has also been presented [58]. Herein, we present a wide-ranging literature overview of the last 22 years concerning hollow multicomponent, and hence potentially multifunctional, structures studied for biomedical applications ranging from drug delivery to imaging, therapy, and theranostics. The objective of this review is to explore and extract rational design approaches and
Multicomponent Structures: Categories and Types

Multicomponent hollow structures can be divided into three general categories. One category consists of structures with multiple shells around a hollow cavity. The second category consists of secondary functional nanoparticles embedded inside or stabilized on a hollow particle. A third auxiliary category involves hollow particles with functionalized surfaces through biocompatible polymers, target-specific moieties, and other biological markers. Figure 1 presents the advantages of hollow capsules with multicomponent shells for biomedical applications.

Multiple SHELLS

Multiple shells are composed of either shell of different materials grown on each other or shells of the same material grown on each other with voids present between the shells. The latter type is beneficial in controlled release. Drugs and functional molecules or nanoparticles can be embedded in each layer. In vivo, the encapsulated species are then released layer by layer in different spatial and temporal points.

Xu et al. reported multi-shelled Cu₂O hollow nanospheres through soft-templates of cetyltrimethylammonium bromide (CTAB). On varying the concentration of CTAB, double, triple, and quadruple-shelled Cu₂O hollow spheres were obtained. After removal of CTAB from between the shells, void@shell@void@shell type structures were obtained [59]. Multi-shelled silica has been prepared through both soft-templates and hard-templates with surface-protected etching. Zhang et al. reported multicelled silica based on the multivesicular templates removed after the growth of silica layers. The number of silica layers formed depended on the ratio of the two main monomers employed in the synthesis [60]. Another group reported the synthesis of multilamellar silica based on a similar strategy. They also found that the number of silica layers formed at the end depended on the ratio of the organic precursors used initially for templating [61]. Huang et al. prepared double and triple-shelled void@
silica@void@silica type structures using a complex template and a multi-step process of silica layer growth, surface protection, and subsequent etching [62]. Figure 2 presents examples of multi-shelled structures with the void between consecutive shells.

Multiple shells are also grown one over the other, followed by removal of the innermost core only. The lack of voids between layers differentiates such morphologies from those described earlier. Different shells then provide different functionalities or structural integrity to the capsules. Chaudhuri et al. reported Ag@Au shells prepared by hard-template synthesis using sulfur cores. After the growth of Ag and Au layers one by one on the sulfur core, the core was removed through calcination [63]. Multiple shells of metallic character have been synthesized through etching or galvanic exchange reactions. The mechanism of these galvanic exchange reactions is different from bulk galvanic reactions. Mostly, Ag templates are taken and etched with weak acids of the other metals to create bimetallic hollow nanoparticles. One such method has been explored by Mahmoud et al. to produce mono and bimetallic cubic nanocages. Different compositions were obtained using weak acids of different metals [64]. Gao et al. prepared Ag/Pt using the same strategy, but since the Ag template was prepared through a different method, the template and the resulting capsules were spherical [65]. Pd@Pt dendritic nanocapsules were reported by Wang et al., where the etching of core was done by concentrated nitric acid [66].

Inorganic triple-shelled hollow spheres of 250–300 nm diameter were reported by Lu et al. They used a self-template strategy where silica and calcium silicate layers were grown on magnetic iron oxide cores, followed by partial removal of the iron oxide core through calcination [67]. A nanocapsule of polymeric materials protected by thin calcium phosphate layers was prepared by Perkin et al. The thickness of the phosphate layer thickness was dependent on experimental parameters [68]. Most recently, Lv et al. reported double-shelled nanocapsules with inner Co3S4 and thin carbon outer shells. These were prepared using a hard templating route combined with hydrothermal synthesis [69]. The synthesis methods are discussed in detail in Sect. 4.

**Loading or Decoration with Functional Nanoparticles**

Hollow capsules with nanoparticles encapsulated in the shell or inside it are another multicomponent capsules. Li et al.
prepared “cage-like” hollow spheres of silica with large holes decorated with superparamagnetic iron oxide nanoparticles in a one-step synthesis method [70]. Another silica-based multicomponent capsule was reported using a soft template filled with iron oxide nanoparticles and fluorescent quantum dots. Silica was grown on the template through the sol–gel method. A single through-hole was produced in the silica shell when the soft template was removed under specified conditions. The embedded iron oxide NPs and quantum dots moved towards the edge and were embedded in the silica shell at the end [71]. Figure 3 presents TEM images of different capsule systems with functional nanoparticles embedded inside or stabilized on the surface of hollow shells.

Polymer-based capsules have been presented in depth by Dergunov et al. [54], and many examples have been reported besides it in many studies. Double-shelled capsules made of poly(methyl methacrylate/divinyl benzene/ acrylic acid) (P(MMA/DVB/AA) were synthesized by Wichaita et al. [72]. They encapsulated oleic acid (OA) capped magnetic nanoparticles and were able to tune the location of the OA-MNPs inside the capsule by changing initial monomer ratios. In another study, polymer shells based on poly(diallyldimethylammonium chloride) (PDADMAC) and poly[1-[4-(3-carboxy-4-hydroxyphenylazo) benzenesulfonamido]-1, 2-ethanediyl] (PAZO) were prepared through layer by layer assembly on a silica template. During the growth of polymer shells, up and down conversion nanoparticles (U/DCNPs) were embedded in the layers. The silica template was removed at the end, leaving behind polymer shells containing up and down conversion nanoparticles [73]. Another type of structure was reported by Fuchigami et al., where the polymeric shell of poly(diaryldimethylammonium chloride) (PDDA) was grown on a rigid silica template. After using the PDDA layer to grow FePt nanoparticles on the outermost surface, the core silica was removed, leaving behind PDDA@FePt NPs [74].

Inorganic multicomponent shells have also been prepared. Zn-doped Fe₃O₄ was synthesized by Saha et al., exhibiting improved magnetic character and hollow structure [75]. Zeng et al. reported three combinations of ZnO with metallic nanoparticles. ZnO with Au NPs, ZnO with Pt NPs, and ZnO with Au and Pt NPs were prepared with hollow spherical morphology [76]. Elongated capsules of mSiO₂ containing magnetic iron oxide core were prepared by Chen et al. [77]. Yang et al. reported Cu₂-xS hollow spheres which were decorated with gold nanoparticles [78].

Fig. 3 TEM images of different capsule systems with functional nanoparticles embedded inside or stabilized on the surface of hollow shells: a U/DCNPs entrapped between the layer-by-layer assembly of PDADMAC and PAZO polymers. Used with permission from [73]. Copyright 2018, WILEY; b Less than 10 nm FePt nanoparticles on hollow PDDA shells. Reprinted with permission from [74]. Copyright (2011) American Chemical Society. c Au and Pt nanoparticles embedded in ZnO hollow nanospheres. Reprinted with permission from [76]. Copyright (2008) American Chemical Society. d Fe₃O₄ nanoneedles entrapped in mSiO₂ capsular shells. Reprinted with permission from [77]. Copyright (2010) American Chemical Society.
showing a high target preference for gp60 receptors [81].
sules and covered them with human serum albumin (HSA),

Therefore, the drugs are readily taken exclusively.
solid. Hollow structures are favorable in this regard, for
are loaded in or on carrier particles that may be hollow or
availability, longer blood circulation time, and high loading
biocompatibility, targeted delivery, stimuli-responsiveness, controlled release, enhanced drug loading capability etc. She et al. demonstrated the need for suitable surface characteristics by functionalizing hollow, mesoporous silica capsules with different functional groups. Their loading ability for a particular drug and specific surface area varied noticeably along with the functional groups [79]. Bismuth selenide capsules were reported by Sun et al., who PEGylated the surface of prepared capsules and loaded it with a PDT agent, chlorin e6, along with an anticancer drug [80]. The hollow sphere assembly of Cu2−xS@Au NPs reported by Yang et al. was functionalized with multi-carboxylic graphene quantum dots (MC-GODs). These QDs acted as gatekeepers during cargo release from the capsules [78]. Xu et al. prepared MoS2 capsules and covered them with human serum albumin (HSA), showing a high target preference for gp60 receptors [81].

Biomedical Applications

Drug and Cargo Delivery

Conceptually, drug delivery is an endeavor to counter “free” drug administration problems. When a patient is administered a pharmaceutical drug, it eventually enters the bloodstream through different biological pathways; from there, it enters different tissues and cells, including the diseased ones like cancerous cells and tumors. This is also a limitation, for the drug reaches the diseased cells and tissues inclusively, not exclusively. Therefore, the drugs are readily taken up by healthy cells and can cause adverse effects [82, 83]. Another challenge in pharmacokinetics appears when the drug is cleared out of the system too rapidly, which compels administration of more frequent dosage. Until side effects to healthy cells and tissues are better addressed, the more frequent dosage is a cause for concern. In other scenarios, a drug may be hydrophobic and is not well-received by the human body. The answer to such challenges has shaped drug delivery systems (DDS).

A plethora of research has been conducted to synthesize drug-carrying platforms (simply, drug carriers) that show safety, biocompatibility, immuno-friendliness, good bioavailability, longer blood circulation time, and high loading capacity, among others other desirable characteristics. Drugs are loaded in or on carrier particles that may be hollow or solid. Hollow structures are favorable in this regard, for an internal cavity enables higher loading capacity. Longer blood circulation time and biocompatibility are facilitated via surface coverage with biocompatible polymers like PEG. PEG-coated drug carriers benefit biocompatibility and help in evading the immune system response, which gets rid of foreign entities.

Stealth through polymer coating is not the only way to ensure that the drug carrier reaches the region of interest. Targeted and stimuli-responsive deliveries are two other strategies used to facilitate cellular uptake of the carrier and controlled release of the cargo. Table 1 summarizes different hollow multicomponent platforms and their drug and cargo delivery performance.

Therapeutic Advantages of Delivery Systems

Loading Capacity As noted earlier, hollow structures inherently afford an advantage in drug delivery. In contrast to solid nano and microparticles, which can only carry drugs immobilized on their surfaces, hollow capsules can also carry cargo inside. There are several examples in the literature where a drug loading capacity (weight of loaded drug/total weight of capsules, usually expressed as a percentage) of more than 50% has been reported for hollow multicomponent structures.

Massoumi et al. [84] and Jahanban-Esfahlan et al. [85] recently reported polymeric nanocapsules, less than 50 nm in size, which showed DOX loading capacities of 71% 53%, respectively. Another example of high drug loading polymer capsules is available in a study by Hu et al. [86]. They prepared hollow poly(methacrylic acid-co-ethylene glycol dimethacrylate) (poly(MAA-co-EGDMA) capsules with a drug loading capacity of 52.4% for DOX.

Inorganic capsules with high loading capacities have also been reported. The most noteworthy is a hybrid PEGylated ZnO@CuO@Au NPs@RGD peptide capsule reported by Wang et al. which was said to have a loading efficiency of 187% [87]. However, it is not entirely clear from the stated procedure whether the value was the loading capacity or the loading (or encapsulation) efficiency because the subtle difference in the two has not been distinguished by the authors. In another study, 120 nm capsules of CuS modified with bovine serum albumin (BSA) and folic acid (FA) were loaded with indocyanine green (ICG) by Han et al. [88]. The system exhibited a maximum loading capability of 54.8%. A reason highlighted for this high drug loading was the affinity between ICG and the hydrophobic ends of the BSA protein. Hollow carbon spheres, 100 to 120 nm in size, with surfaces functionalized with PEI and PEG, could carry 48.2 mg of DOX in every gram of the functionalized carbon spheres [39].

Interestingly, hollow thioether-bridged organosilica capsules (240–310 nm) showed less loading capacity (50.9%) than their solid counterparts (LC of 78.2%) [89]. The size and composition being roughly the same, the
Table 1  Summary of hollow multicomponent capsules reported in the literature for drug delivery

| Sr. # | Hollow structure composition | Morphology | Drug/molecule loaded | Loading capacity | Encapsulation efficiency | Release performance | Cytotoxicity assay | References |
|-------|---------------------------|------------|---------------------|-----------------|------------------------|---------------------|-------------------|------------|
| 1     | PEG-lyted Fe₃O₄           | Long needle-like capsules | Doxorubicin         | 28.9 wt. %      | --                     | --                  | ca. 20% viability of SKBR-3 cells at DOX concentration of 10 µM | [109]     |
| 2     | Amino-functionalized SiO₂ | Spherical capsules with oriented pores | Flurbiprofen        | 1274 ± 59 mg/g  | --                     | ~80% released in ca. 5 h | --                | [90]       |
| 3     | Fe₃O₄@hollow@mSiO₂        | Elongated ovoidal capsule with encapsulated Fe₃O₄ needles | Doxorubicin         | 20%             | Up to 100%              | --                  | ~20% cell viability against MDF-7 cells at DOX-nanocapsules concentration of 20 µg/ml after 72 h | [77]       |
| 4     | mSiO₂                    | Double or triple-walled spheres | Doxorubicin and fluorescein 5(6)-isothiocyanate (FITC) | Double-shelled: 31.7 µg/mg | --                     | (In 50 h) Double-shelled: ~75% FITC in pH 7.2 | --                | [62]       |
|       |                           |            |                     | Triple-shelled: 14.6 µg/mg FITC and 30.8 µg/mg DOX |                    | ~6% FITC in pH 4.3 |                   |            |
|       |                           |            |                     |                 |                        | Triple-shelled: ~23% FITC in pH 7.2 |                   |            |
|       |                           |            |                     |                 |                        | ~0% FITC in pH 4.3   |                   |            |
|       |                           |            |                     |                 |                        | ~30% DOX in pH 4.3   |                   |            |
|       |                           |            |                     |                 |                        | ~5% DOX in pH 7.2    |                   |            |
| 5     | Fe₃O₄@SiO₂@CaSiO₄        | Triple-shelled spheres with hollow inner cavity | Ibuprofen          | 75 mg/g          | --                     | ~95% in 20 h (pH 7.4) | --                | [67]       |
| 6     | mSiO₂ with disulfide linkages and surface functionalized with tetraethylene glycol chains, α-cyclodextrin, and folic acid | Hollow spheres | Doxorubicin         | 20 wt.%          | --                     | ~75% redox-responsive release in GSH (glutathione) stimulus concentration of 10 mM in ca. 12 h | ~35% cell viability at 24 h against HeLa cells | [103]     |
| 7     | mSiO₂                    | Spherical Shell@hollow@shell@hollow… (2–7 shells) | Metformin hydrochloride (MH) | Double-shelled: 40.8 wt.% | --                     | 95% MH release in ca. 8 h in pH 6.8 | --                | [60]       |
| 8     | poly(cyclotriphosphazene-co-fluorescein) (PCTPF) | Spherical hollow capsule | Doxorubicin         | 26.2 wt.%        | --                     | ~60% at pH 5.5 in 12 days | ~50% cell viability against HeLa cells incubated with PCTPF-DOX at 50 µg/ml in 48 h | [91]       |
| 9     | mSiO₂ with –CH₃, –CN, –NH₂, –COOH functionalized surfaces | Spherical hollow capsule | 5-fluorouracil (5-FU) | 28.89% (HMSN-NH₂) | --                     | --                  | --                | [79]       |
| Sr. # | Hollow structure composition | Morphology | Drug/molecule loaded | Loading capacity | Encapsulation efficiency | Release performance | Cytotoxicity assay | References |
|------|-----------------------------|------------|---------------------|-----------------|--------------------------|---------------------|------------------|-----------|
| 10   | N-palmitoyl chitosan and Fe$_3$O$_4$ | Quasi-spherical hollow capsule with Fe$_3$O$_4$ particles inside | Doxorubicin | 1.54\% | 73\% | $\sim$85\% DOX released in ca. 120 h at pH 5.5 $\sim$70\% DOX released in ca. 120 h at pH 7.4 | – | [106] |
| 11   | CuS- bovine serum albumin–folic acid (BSA–FA) complex | Very rough spherical capsule | Indocyanine Green (ICG) | 54.8\% | – | $\sim$40\% ICG released in ca. 72 h in DMEM (high glucose) + 10\% fetal bovine serum (ICG release is pH independent) | $\sim$70\% HeLa cells viability with 4 µg/ml ICG concentration | [88] |
| 12   | Carbon with polyethyleneimine (PEI) and polyethylene glycol (PEG) | Brain-like spherical porous hollow nanocapsule (PHCN) | Doxorubicin | 482 µg/mg for DOX 86 µg/mg for BAG3-siRNA | – | (In 48 h, for DOX) 57.4\% release at pH 5 + NIR irradiation 55\% at pH 5 without NIR 16.6\% release at pH 7.4 + NIR 13.8\% release at pH 7.4 without NIR | $\sim$50\% cell viability for A549 cells with PHCNs-PEI-PEG@DOX capsules (482 µg DOX/mg PHCNs-PEI-PEG) with a carrier concentration of 50 µg/ml | [39] |
| 13   | mSiO$_2$-$\beta$-cyclodextrin-PEG conjugated adamantane (Ada) | Hollow spherical | Doxorubicin | 10–11 wt.% | – | (In 13 h) $\sim$80\% DOX release at pH 5 $\sim$50\% release at pH 6.8 $\sim$20\% release at pH 7.4 | $\sim$50\% cell viability of HepG2 in 24 h (pH 6.8) | [108] |
| 14   | poly(methacrylic acid-co-ethylene glycol dimethacrylate) (poly(MAA-co-EGDMA)) | Deflated moon like hollow capsules | Doxorubicin | 52.4 wt. % | – | (In 25 h) $\sim$24\% DOX released at pH 7.4 $\sim$5\% DOX released at pH 6.3 $\sim$2.5\% DOX released at pH 5.2 | $\sim$30\% cell viability of HeLa cells treated with DOX-capsules for 24 h | [86] |
| 15   | ZnSe:Mn/ZnS-SiO$_2$ | Spherical with quantum dots (QDs) embedded inside | Paclitaxel | 21 µg/mg (QDs+drug) | 63\% (QDs + drug) | $\sim$95\% paclitaxel released in 12 h | – | [22] |
| Sr. # | Hollow structure composition | Morphology | Drug/molecule loaded | Loading capacity | Encapsulation efficiency | Release performance | Cytotoxicity assay | References |
|-------|-----------------------------|------------|----------------------|-----------------|-------------------------|---------------------|------------------|------------|
| 16    | polyamidoamine dendron-poly(L-lysine) (PAMAM dendron-PLL) with disulfide bonds | Spherical | Doxorubicin | 4.1 ± 0.3% | 8.2 ± 0.5% | 10% DOX released in pH 5.5 in disulfide-bonded capsules in 24 h; ca. 10% DOX released in pH 7.4 in disulfide-bonded capsules in 24 h, ca. 95% cumulative; DOX released in next 8 h with most release in first two hours | Less than 5% HeLa cells viability for DOX-loaded (100 µg/ml), disulfide-bonded capsules with incubation times of 24, 32, and 48 h | [96] |
| 17    | Organosilica with thioether, benzene, or ethane bridges | Deflated balloon-shaped deformable structures | Doxorubicin | 509 µg/mg DOX loaded in thioether-bridged, PEGylated capsules | – | – | – | ca. 40% cell viability of MCF-7 cells at DOX concentration of 120 µg/ml after 24 h | [89] |
| 18    | Pectin-chitosan | Deflated round capsule | Doxorubicin hydrochloride | 20.32 ± 0.33% | 76.51 ± 1.53% | ca. 70% DOX.HCl released at pH 5 in 25 h; ca. 58% DOX.HCl released at pH 6 in 25 h; ca. 10% DOX.HCl released at pH 7.4 in 25 h | ca. 10% cell viability of HepG2 cells against DOX.HCl-loaded capsules | [98] |
| 19    | MoS₂-human albumin serum | Flexible, deflated, and wrinkled capsule | Doxorubicin | 27 wt.% | – | ca. 50% DOX released at pH 4 and laser irradiation for 6 h | Less than 20% cell viability of MCF-7 cells against DOX-loaded (30 µg/ml) capsules at a concentration of 10 µg/ml + NIR irradiation | [81] |
| 20    | Polymer-up and down conversion nanoparticles | Rough spherical capsules with embedded up and down conversion NPs | Doxorubicin | – | – | Less than 10% DOX released without irradiation in 3 h; ca. 50% DOX released with irradiation in 3 h | ca. 40% cell viability of U87-MG cells against DOX-loaded capsules under irradiation for 30 min | [73] |
| Sr. # | Hollow structure composition | Morphology | Drug/molecule loaded | Loading capacity | Encapsulation efficiency | Release performance | Cytotoxicity assay | References |
|-------|-------------------------------|------------|----------------------|------------------|-------------------------|---------------------|-------------------|------------|
| 21    | Poly(lactic-co-glycolic acid)-poly (vinyl alcohol)- Gd-DBCF (Gd-Ce6-folate modified bovine serum albumin complex) | Hollow spherical capsule with a halo ring outside | Doxorubicin and chlorin 36 (Ce6) | DOX: 0.87% Ce6: 0.79% | DOX: 78.1% Ce6: 95.3% | 1–2% release of DOX and Ce6 in 48 h at pH 6.5 and 7.4 ca. 35% Ce6 release in 48 h at pH 5 ca. 55% DOX release in 48 h at pH 5 | Less than 5% cell viability of MGC-803 cells against nanocapsules in 12 h with DOX (8.8 µg/ml) and Ce6 (8 µg/ml) | [97] |
| 22    | poly(methyl methacrylate/ divinyl benzene/acrylic acid) (P(MMA/DVB/AA) with Fe₃O₄ nanoparticles | Double-shelled spheres with embedded nanoparticles | Rhodamine B and fluorescein isothiocyanate (FITC) | –– | Qualitative assessment through imaging | – | – | [72] |
| 23    | Polypeptides (GSL12 and GSL16) | Nanocapsules (high aspect ratio) and nanospheres | Propidium iodide (PI) | ca. 50% PI encapsulated in nanocapsules after 40 h | ca. 95% PI released in 120 h (5 days) | – | – | [121] |
| 24    | Polysaccharides | Oil-filled, spherical polysaccharide shells | Camptothecin (CPT) | – | ca. 70% CPT released from monolayer capsules after 23 h ca. 23% release from bilayered capsules ca. 15% release from trilayered capsules | – | – | [122] |
| 25    | mCuS-PEG | Hollow, rough spheres | Doxorubicin and Ce6 | DOX: 5.24% Ce6: 15.34% | DOX: 32.12% Ce6: 40.46% | ca. 60% Ce6 release at pH 5 and 7.4 in 6 h ca. 90% DOX release at pH 5 in 6 h ca. 55% DOX release at pH 7.4 in 6 h Greater than 90% Ce6 and DOX release under irradiation in 100 min | Less than 10% cell viability of 4T1 cells and MCF-7 cells against laser irradiation and capsule treatment Capsule concentration of 200 µg/ml used (DOX: 10.48 µg/ml, Ce6: 30.68 µg/ml) ca. 10% cell viability of HeLa cells against laser irradiation and prepared capsules (DOX: 10 µg/ml, Ce6: 6.57 µg/ml) ca. 60% viability of same cells without laser irradiation | [95] |
| 26    | Bi₂Se₃-PEG | Hollow spheres | Doxorubicin and Ce6 | DOX: 18.1% Ce6: 11.9% | DOX: 20.1% Ce6: 13.6% | ca. 50% DOX release at pH 5 in 12 h ca. 80% DOX release with periodic irradiation in 12 h (lower amounts released at higher pH values in both conditions) | – | – | [80] |
| Sr. # | Hollow structure composition | Morphology | Drug/molecule loaded | Loading capacity | Encapsulation efficiency | Release performance | Cytotoxicity assay | References |
|-------|-------------------------------|------------|----------------------|-----------------|------------------------|--------------------|-------------------|------------|
| 27    | Co$_3$S$_4$-N doped carbon   | Hollow and rough spherical capsule with nanoparticle aggregates on surface | Doxorubicin | –                  | 87.2%                  | ca. 87% DOX released at pH 5 under irradiation in 12 h (lower amounts were released at pH 7.4 and at pH 5 without irradiation) | Less than 12% cell viability of HeLa cells against laser irradiated, DOX-loaded nanocomposite (concentration: 60 µg/ml) | [69]      |
| 28    | CuS-Au-multicarboxylic graphene carbon dots (MC-GODs) | Hollow, rough spheres | Doxorubicin | 28.4 wt. % | – | Less than 10% DOX release at pH 5.5, 7.4, 8.5 after 48 h with MC-GOD guards Up to 40% DOX release at pH 5.5 after 48 h without MC-GODs Ca. 90% DOX release in GSH medium (glutathione, 20 mM) after 48 h | ca. 0% cell viability of HeLa cells against prepared DOX-loaded nanocomposite (200 µg/ml) under laser irradiation | [78]      |
| 29    | Polyacrylic acid-PEG          | Irregular hollow capsule | Doxorubicin | 71%            | 83%                  | ca. 41% DOX release at pH 4 in 300 h (~12 days) (lower amounts released at higher pH values) | ca. 40% cell viability of MCF-7 cells against DOX-loaded capsules (200 µg/ml) after 48 h | [84]      |
| 30    | Polymethyl methacrylate (with functionalized surface with a block copolymer) | Round hollow capsule | Doxorubicin hydrochloride | 53%            | 62%                  | ca. 40% DOX release at pH 4.2 and temperature 41 °C in~ 300 h (~12 days) (lower amounts of DOX released at higher pH or lower temperature) | ca. 35% cell viability of MCF-7 cells against DOX-loaded capsules (100 µg/ml) after 48 h | [85]      |
| Sr. # | Hollow structure composition | Morphology | Drug/molecule loaded | Loading capacity | Encapsulation efficiency | Release performance | Cytotoxicity assay | References |
|-------|----------------------------|------------|---------------------|-----------------|--------------------------|--------------------|-------------------|------------|
| 31    | MIL-125-Ti MOFs functionalized with hyaluronic acid | Irregular spherical hollow capsule | Doxorubicin | 25-35% | – | ca. 75% DOX release at pH 5 after 24 h with 30% HA | ca. 20% cell viability of MCF-7 cells against DOX-loaded capsules (20 µg/ml) after 48 hrs | [92] |
|       |                            |            |                     |                 |                          | ca. 35% DOX release at pH 5 after 24 h without HA (lower amounts of DOX released at higher pH) | ca. 35% DOX release at pH 5 after 24 h with 30% HA (lower amounts of DOX released at higher pH) | |
| 32    | m-SiO$_2$-FA | Hollow spheres | Doxorubicin | 20.6 ± 2.1% | – | 85.2 ± 2.0% DOX release at pH 4 after 24 h with NIR irradiation (lower DOX release at higher pH and/or without NIR irradiation) | ca. 30% cell viability of SMMC-7721 cells against DOX-loaded capsules (1000 µg/ml) after 48 h | [93] |
| 33    | MnO$_2$-Au NPs | Hollow spheres | Doxorubicin | – | ca. 82% | ca. 90% DOX release at pH 4.5 after 12 h in presence of 5 mmol L$^{-1}$ GSH (lower DOX release at higher pH and lower amount of GSH) | – | [123] |
| 34    | ZnO-CuO-Au-PEG-RGD peptide | Hollow spherical capsules | Doxorubicin | 187% | – | ca. 65% DOX release at pH 5 after 24 h with NIR irradiation (lower DOX release at higher pH and/or without NIR irradiation) | ca. 2% cell viability of A549 cells against DOX-loaded capsules (200 µg/ml) with 2 W.cm$^{-2}$ laser irradiation (10 min) after 28 h | [87] |
| 35    | SiO$_2$-chitosan | Hollow spheres | Ce6 | 80.6% (pH 6) 33.8% (pH 7.4) | – | ca. 80% Ce6 release at pH 6 after ca. 8.5 h (lower Ce6 release at higher pH) | Less than 10% viability of *Staphylococcus aureus* bacteria against Ce6-loaded capsules (100 µg/ml) after 18 h | [124] |
difference could be attributed to starkly varied morphologies. The synthesized product in the hollow capsule did not retain the spacious hollow cavity; due to the complicated formation mechanism, the capsules had a pinched, deflated morphology with many concave surfaces. The potential advantage of an internal cavity was thus rendered moot; in addition to that, due to concavity, even the surface loading of the drug was not as efficient as obtained for solid organosilica spheres.

An exceptional drug loading capacity was found in a study by Wang et al. [90]. Here, 100 to 500 nm amino-functionalized silica capsules exhibited a very high capacity of 127.4 ± 59 for a flurbiprofen (FBP) drug. Morphologically, the capsules had a large internal cavity and oriented pore channels in the shell, which has been stated as the reason for high drug loading.

**Controlled or Sustained Release** Another advantage of using hollow delivery systems is the safe encapsulation of cargo inside, with varied and often-tunable drug release profiles. Huang et al. exemplified this with multi-shelled silica capsules [62]. In 50 h, the amounts of an imaging agent FITC (fluorescein 5(6)-isothiocyanate) released from double and triple-shelled capsules (at pH 7.2) were 75 and 23%, respectively.

Some studies reported capsules with slow-release characteristics where less than 50–60% of the cargo is released in more than two days. CuS capsules by Han et al. [88] showed around 40% ICG released in three days. Polymeric capsules synthesized by Massoumi et al. [84] and Jahanban-Esfahlan et al. [85] released nearly the same amount of DOX (41% and 40%, respectively) in about 12 days at a pH of 4 (approximately). PCTPF shells of 265 nm released ca. 60% DOX in acidic pH over 12 days [91]. Figure 4 presents the controlled release of cargo materials.

Short-term, quicker drug release from hollow structures has been presented as well. Although the amino-functionalized silica capsules reported by Wang et al. [90] displayed very high drug loading, most of the loaded FBP (ca. 80%) was released within the first five hours. The authors suggested that such drug release characteristics can be exploited by imparting stimuli-responsiveness to the system; a large amount of drug could be released only when the trigger is provided. This was illustrated by Zhao et al., where synthesized composite capsules showed less than 10% DOX release in three hours without the NIR light stimulus and around 50% release when the stimulus was provided [73]. There are many examples in literature where pH and NIR dependent drug release has been reported. Mostly, the results are reported for doxorubicin loading which shows enhanced drug release at lower pH, i.e. acidic environment, and under NIR irradiation [87, 92–94].
Notwithstanding potential applications, a high loading capacity and faster release profile in such structures raise an essential question: in what proportion is the loaded drug distributed among the internal cavity, the surface, and the pore channels in the case of porous shells? In general, studies reporting drug release behavior of different multicomponent hollow capsules do not address this question. Further work is needed to develop a methodology for characterizing the distribution of loaded cargo among shell surface, shell core, and the porous shell itself. This will be a meaningful contribution in assessing and comparing drug release profiles of various multicomponent platforms.

Zhang et al. also showed that connected pore channels, micropores, in this case, can facilitate faster drug release [60]. Around 95% of metformin hydrochloride (MH) was released within eight hours at pH 6.8. However, they showed that drug release could be slowed to some extent by incorporating a more significant number of shells, achieved in this case by altering precursor ratios. PEGylated CuS capsules prepared by Li et al. could release around 60% chlorin e6 (Ce6) and 90% DOX within 6 h in an acidic medium (pH 5) [95].

**Figure 4** Controlled release of cargo materials by adding more shells in the structure. Reprinted from [62], Copyright 2011, with permission from Elsevier. b varying pH levels of the environment. Used with permission from [84]. Copyright 2020, WILEY. c providing NIR light stimulus. Used with permission from [73]. Copyright 2018, WILEY

In another polymer-based system [97], less than 5% of MGC-803 cells survived after treatment with DOX loaded in the capsules. The DOX concentration was 8.8 µg/ml, and the incubation time was 12 h.

Cu$_2$S@Au NPs@MC-GODs system loaded with DOX displayed very promising therapeutic efficiency at a capsule concentration of 200 µg/ml [78]. Less than 5% of tested HeLa cells remained functioning after the treatment. At a drug concentration of 10 to 20 µg/ml, DOX. HCl loaded pectin/chitosan-based capsules have exhibited around 10% viability of HepG2 cells in 48 h [98]. Fe$_3$O$_4$@void@mSiO$_2$ capsules loaded with DOX showed comparable therapeutic performance with “free DOX” against MDF-7 cells in the same incubation period (72 h) [77]. Figure 5 presents examples of the promising therapeutic performance of DOX when loaded in capsular structures.

Sporadically, the literature shows that using hollow multicomponent structures may not always lead to better therapeutic performance. For example, in PCTPF shells carrying DOX as the anticancer drug, a high carrier concentration of 50 µg/ml could only kill around 50% of incubated HeLa cells after 48 h [91]. For a DOX concentration of 10 to 20 µg/ml, hollow functionalized carbon spheres yielded high cell viabilities for A549 cells after a 24 h incubation period. For a significant cell death of around 75%, the DOX concentration needed was 100 µg/ml [39]. ICG-loaded CuS-BSA-FA capsules, reported by Han et al., showed a mere 30% cell death of HeLa cells in 24 h [88]. The ICG concentration was 4 µg/ml.

**Therapeutic Efficacy** DOX-loaded hollow multicomponent capsules have shown a remarkable therapeutic performance against various cancer cell lines. In many cases, less than 20% cell viability has been reported after cytotoxicity assays. For polymeric capsules prepared by Teranishi et al., less than 5% of HeLa cells sustained viability after 24 to 48 h of incubation with the capsules [96].
It is clear that in qualifying drug and cargo delivery systems, special attention is necessary to the interplay between factors like loading capacity, release profiles, and therapeutic performance. Although systems reported by Han [88] and Sun et al. [91] exhibited substantial loading capacities (54.8% and 26.2%), their preliminary therapeutic performance as only drug carriers was subpar. A high loading capacity and a faster release rate, as discussed earlier, are also not functional unless modified with stimuli-responsive moieties. Therefore, hollow multicomponent structures for drug and cargo delivery must be designed to keep such design criteria (Fig. 6).

**Targeted Drug Delivery Systems**

Except for Ontak®, a protein-based targeted nanomedicine [99], targeted DDS is yet to gain approval for clinical use [100]. However, the preclinical research has been up-and-coming so far. Targeted delivery exploits the overexpression of specific receptors on the surface of cancerous cells (as opposed to healthy cells). These receptors’ respective ligands and functional groups are carefully selected to cover the DDS surface [101, 102]. In vivo, more DDS is then preferentially taken up by the diseased cells and tissue compared...
to non-targeted counterparts. This can lead to higher therapeutic efficiency per dose.

Luo et al. presented a sophisticated DDS based on surface-functionalized silica. Hollow mesoporous silica (HMSNs) was conjugated with a tumor-targeting complex composed of tetraethylene glycol chains, α-cyclodextrin, and folic acid. The complex was grafted through a disulfide bond on the silica particle’s surface. Folic acid was the targeting moiety for the folate receptors available in the tumor microenvironment. In vitro cellular uptake by HeLa cells was significantly enhanced for targeted HMSNs with folic acid conjugates. In vivo, HMSNs loaded with DOX showed active tumor inhibition after 21 days, whereas pure DOX failed to achieve tumor inhibition; the results were attributed to shorter circulation time of free DOX and its inability to reach tumor sites in large amounts due to non-selectivity [103]. Figure 7 presents TEM images, confocal laser scanning microscopy images (CLSM), and flow cytometry results showing active targeting ability of functionalized hollow mSiO2 and its increased cellular uptake by HeLa cells.

In another study, Han et al. covered the surface of hollow CuS particles with a complex of bovine serum albumin (BSA) and folic acid. BSA served as a biocompatible surface moiety and increased the loading capacity of indocyanine green (ICG) through hydrophobic interactions. Folic acid was introduced to facilitate targeting towards folate-receptor-containing tumor cells. It was found that cellular uptake by HeLa cells with overexpression of folate receptors was increased as compared to “folate-negative” A549 cells. The success of this strategy was further corroborated when HeLa cells were pre-treated with folic acid before exposure to CuS-BSA-FA carriers. Pre-treated HeLa cells showed reduced uptake; this showed that increased cellular uptake in non-treated cells was due to the presence of unengaged folate receptors, which readily allowed more uptake of FA-containing CuS carriers [88]. Figure 8 presented some examples of active targeting with folic acid that significantly increased cellular uptake by the FA-receptor-positive HeLa cells and decreased uptake by FA-receptor-negative A549 cells.

MoS2 hollow particles modified with human serum albumin (HSA) were prepared by Xu et al., which showed high tumor accumulation for MCF-7 cells. The presence of HSA was identified as one of the main reasons for increased uptake of the carriers by MCF-7 cells. This was evidenced by coincubating HSA with MCF-7 cells and prepared MoS2-HSA capsules. Qualitative results from fluorescence imaging showed much less uptake of capsules by MCF-7 cells when free HSA was supplied as well [81].

Folic acid and BSA were also used by Zhou et al. to modify PLGA-PVA based hollow capsules for tumor targeting. FA/BSA-modified capsules showed better tumor accumulation in gastric cancer cells (MGC-803 cells) and carried loaded DOX and Ce6 (chlorin e6) to the target site with higher precision. In comparison, free Ce6 failed to accumulate in the same concentration inside MGC-803 cells. When prepared capsules were accompanied with free folic acid, the cellular uptake reduced as free folic acid took up the receptor binding sites; consequently, fewer binding sites were available for capsules modified with FA/BSA, resulting in lower cellular uptake [97].

Wichaita et al. reported a polymer-based DDS with embedded magnetic nanoparticles functionalized with folic acid to increase tumor targetability. While non-targeted hollow magnetic capsules remained around the cell membrane of folate-receptor-positive HeLa cells, FA-modified capsules showed enhanced and deeper cellular uptake within 24 h of incubation. The mechanism was understood...
as folate receptor-mediated endocytosis, which could not be activated for non-targeted capsules [72].

**Stimuli-Responsive Drug Delivery Systems**

Stimuli-responsive DDS are designed to ensure that the drug carriers do not release the cargo prematurely in the bloodstream or into healthy tissues and cells. Strategies exist to utilize peculiar characteristics of tumors, such as acidic pH (6.5–7) in their microenvironment [100] and increased concentration of glutathione (GSH) inside cancerous cells [104]. Another strategy is to prepare light-sensitive structures which break apart or degrade under near-infrared (NIR) irradiation and release the loaded drugs [105]. Jahanban-Esfahlan et al. also presented a temperature-dependent drug delivery system prepared with polymethyl methacrylate (PMMA); here, surface functionalization with poly(acrylic acid) (PAA) and poly(N-isopropylacrylamide) (PNIPAAm) produced pH and temperature-dependent structures that directly affected the release amount of loaded drugs [85].

**pH-Responsive Delivery Systems** Huang et al. synthesized double and triple-shelled hollow carriers made of mesoporous silica that could aid in the controlled release of DOX. They demonstrated that while up to 40% DOX was released from the carriers into acidic phosphate buffer saline (pH 4.3) in around 15 days, only about 9% release was observed when the pH was 7.2. The same pattern was observed for a fluorescent molecule FITC (fluorescein 5(6)-isothiocyanate), where the release was negligibly minor at pH 4.3 but pronounced at pH 7.2 for triple-shelled silica capsules [62].

DOX release from a capsule made of poly(cyclotriphosphazene-co-fluorescein) (PCTPF) was studied by Sun et al. The release was found to be sustained and pH-dependent. DOX release was impeded in a more neutral pH of 7.4, where the maximum release amount was around 35% in the same period. The sustained release was attributed to the presence of mesochannels and favorable interactions between DOX and PCTPF [91].

Another study by Balan et al. using N-palmitoyl chitosan-based capsules supported the evidence by Sun et al. that DOX release was lowered in neutral pH of 7.4, as compared to pH value of 5.5. However, the morphology and composition of capsules were different, and the mesochannels were absent; therefore, the released amount was much higher (almost 100% release at pH 5.5, 80% at pH 7.4 in 6 days) as compared to Sun et al. The release profile was also distinguished, as a significant proportion of loaded drug was released in the first 30 h [106].

Inorganic hollow carbon nanospheres and their surfaces were functionalized with polyethyleneimine (PEI) and PEG. Drug loading and release study showed a highly pH-dependent release profile of DOX-loaded capsules. Where the maximum amount of drug release was only 13.8% for pH 7.4 in 2 days, 55% of DOX was released in the same period at pH 5 [39].

Bond cleavage due to a pH change is another strategy for pH-controlled release [107]. Liu et al. exemplified this by studying DOX release from a sophisticated mesoporous silica capsule assembly. The surface of the capsules was first decorated with beta-cyclodextrin (β-CD) through cleavable ester bonds. The β-CD decoration was further grafted with a conjugate of PEG and adamantane (Ada). The result was complex, with multiple pH response capabilities. In three simulated in vivo environments, namely, physiological (pH 7.4); tumor microenvironment (pH 6.8); and intracellular endosomes (pH 5), the capsules showed varied release profiles. DOX release from functionalized silica capsules was modest in physiological conditions (20%) and tumor microenvironment (34%) after 24 h. However, the release was significantly enhanced in endosomic conditions (pH 5), reaching almost 80% in 24 h. The same study also evidenced the increased cellular uptake of prepared carriers at lower pH (6.8). This is a valuable characteristic since the release is pronounced manifold once the carriers undergo endocytosis [108].

More DOX release at lower pH is a recurrent finding in drug delivery systems based on multicomponent hollow capsules [69, 78, 80, 81, 84, 85, 95, 97]. However, contrary evidence exists in a study by Hu et al. [86]. Here, an organic capsule made of poly(methacrylic acid-co-ethylene glycol dimethacrylate) (poly(MAA-co-EGDMA) was loaded with DOX, and the release profiles were obtained for three
different pH values (5.2, 6.3, and 7.4). Distinguishably, the highest amount of DOX release was at pH 7.4 (26%) in 48 h. The release was much lower at pH 6.3 (~5%) and 5.2 (~2%) in the same duration. This behavior was attributed to carboxyl groups on the capsules that are ionized at higher pH; the result is a swollen, open structure with more drug release. The authors suggested that the DDS may be useful for oral drug delivery; an acidic medium in the stomach would not trigger drug release and allow carriers to flow into regions of interest without much drug loss. Figure 9 presents mechanism of a pH dependent drug release in organic capsules.

Interestingly, Ji et al. prepared a pectin-chitosan-based capsule, which showed increased DOX release at lower pH (5 and 6) in a reversed state of affairs. The mechanism was similar but opposed in character. The ionized carboxyl groups in the outermost pectin shell were protonated at lower pH, leading to a swollen structure. The hydrodynamic size of the capsules was around 400 nm at a pH of 7.4 and increased to around 525 nm at pH 5. Looser structure aided in increased release of DOX molecules [98]. These studies show that surface charge, type of functional moieties, morphology, and chemical composition play a role in drug release characteristics of a multicomponent hollow DDS.

GSH-Responsive Delivery Systems Luo et al. presented a hollow mSiO₂ capsule capped with a [2]rotaxane assembly. This mechanical assembly was supported on the capsules’ surface through disulfide bonds. These disulfide linkers made the capsule sensitive to glutathione (GSH) concentration in the environment. Thus, when the capsules were loaded with DOX and exposed to a medium with a GSH concentration of 0, 1, and 10 mM, the highest drug release amount (around 85% in 24 h) was obtained for a concentration of 10 mM; at 0 mM, i.e., in the absence of GSH, the drug release was minimal (around 10% in 24 h). At high GSH concentrations, the disulfide bonds are cleaved, and the capping assembly is consequently removed, enabling the escape of drug molecules [103].

Another example of a GSH-responsive system was reported by Teranishi et al. They synthesized polyamidoamine dendron-poly(L-lysine) (PAMAM dendron-PLL) capsules with disulfide bonds. DOX release from synthesized capsules was significantly enhanced when the GSH concentration of the dialysis medium was increased from 10 µM to 0.5 mM after 24 h. Within the next 8 h, almost 80% of the loaded DOX was released with increased GSH concentration [96].

Fig. 9 Reversible pH-dependent protonation of amino groups and ionization of carboxyl groups leads to structural changes responsible for pH-controlled drug release. Reprinted from [98]. Copyright 2017, with permission from Elsevier
A GSH-sensitive switch was incorporated by Yang et al. in a multicomponent system based on Cu$_{2-x}$S and Au NPs. The capsules were capped by multi-carboxylic graphene quantum dots (MC-GODs) through a disulfide bond. In the absence of GSH, the MC-GODs acted as a gatekeeper and inhibited drug release under all physiologically relevant pH values (5.5, 7.4, and 8.5). However, in the presence of 0.5 to 20 mM GSH, the disulfide linkage between the capsule and the gatekeeper MC-GODs degraded and allowed prompt drug release [78]. Figure 10 presents some examples of gatekeeping performance of MC-GODs for DOX release.

NIR-Responsive Delivery Systems A “smart” NIR-responsive delivery system was designed according to the varied biodistribution behavior of smaller (less than 20 nm) and larger (100–200 nm) carriers. Since larger carriers tend to accumulate more tumors, the system initially had ~ 180 nm particles. And since quicker biodegradation and metabolism are required after the carriers have completed the intended tasks (drug release, imaging, etc.), the system could disintegrate into 20 nm-sized particles. This was achieved by incorporating 20 nm up and downconversion nanoparticles (U/DCNPs) in layer-by-layer assembled polymer shells. Upon reaching the target site and fulfilling the purpose of drug delivery, the upconversion NPs were triggered by NIR radiation; the energy was utilized by the Azo groups in the polymer shell, which underwent reversible isomerization repeatedly. This repeated movement led to degradation of the polymer structure, leaving behind the 20 nm nanoparticles, which were quickly metabolized. The downconversion luminescence was used for bioimaging [73].

Hollow PEGylated CuS particles which exhibited NIR-dependent drug release for DOX and chlorin e6 (Ce6) have been reported. The difference in drug release amount under dark (without NIR) and light (with NIR) conditions was noticeable. Over 90% of drug release was achieved for DOX and Ce6 in 100 min when seven 5-min cycles of NIR light were supplied to the carriers. In contrast, only 58.41% Ce6 and 43.78% DOX were released simultaneously without NIR irradiation [95]. Figure 11 presents NIR-responsive drug release and therapy exhibited by DOX-loaded capsules.

Similar NIR-dependent DOX release behavior was reported by Sun et al. from PEGylated Bi$_2$Se$_3$ capsules [80], by Lv et al. for multicomponent Co$_3$S$_4$ capsules [69], and by Xu et al. for MoS$_2$-based hollow carriers [81]. Du et al. showed that drug release from hollow carbon spheres functionalized with PEI and PEG is NIR dependent. However, the effect was much more modest under-tested irradiation time of 10 min. Less than 3% improvement in drug release amount was observed for pH values of 5 and 7.4 [39].

Multimodal Systems

Embedding more than one modality, whether therapeutic or diagnostic, has been an ambitious effort to design biomedical applications platforms. The advantages are apparent: combination therapy for cancer has proven more effective than singular therapies in many studies. Combination diagnostic imaging addresses limitations suffered by individual imaging techniques. Lastly, the combination of therapy and diagnostic modality (theranostics) seeks to eliminate the gap currently found in these two processes of clinical medicine. A necessary condition for theranostic platforms is complementary pharmacokinetics which ideally would have the platform sustained long enough to perform both its functions if needed but cleared quickly after that to avoid adverse response by the body.

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**Fig. 10** Gatekeeping performance of MC-GODs for DOX release showing considerably more release a in the absence of gatekeepers than b in their presence. Reprinted from [78]. Copyright 2020, with permission from Elsevier

[ Springer ]
Theranostic and Multimodal Imaging Platforms

Drug Delivery and MRI Contrast Enhancement Piao et al. reported Fe$_3$O$_4$-based hollow capsules for drug delivery which could be utilized for T2-MRI contrast enhancement [109]. The drug loading capacity of the prepared system was significant (28.9%). The cytotoxicity assay for SKBR-3 cells against DOX-loaded (10 µM) capsules was less than 20%. At the same time, the system exhibited T2-MRI contrast improvement by lowering the signal intensity with the increase in Fe concentration from 0 (very bright image) to 640 (very dark image) µM.

Another bimodal capsule contained Fe$_3$O$_4$ needle-like cores in hollow mSiO$_2$ capsules [77]. The presence of Fe$_3$O$_4$ core in mSiO$_2$ capsules allowed similar T2-MRI contrast enhancement as in the previous study. The therapeutic efficacy of DOX-loaded (20 µg/ml) capsules was noteworthy. However, the drug loading capacity of the capsules for DOX was lower (20%) than Fe$_3$O$_4$-based capsules. A reason for that was the difference in composition and structure. In the capsules prepared by Piao et al., the shell material imparted the magnetic character itself, whereas the internal cavity was hollow before drug loading. In the mSiO$_2$ capsules, the functional magnetic nanoneedles partially occupied the cavity, leaving lesser space for drug loading. This emphasizes the practical aspects of realizing multimodal systems, which often translate as a compromise on at least one of the modalities.

Drug Delivery and Optical Imaging Literature also shows bimodal systems with drug delivery and optical imaging capability. An inherently-fluorescent PCTPF capsule was reported by Sun et al. which could carry 26.2% DOX and slowly release it over 12 days. Its therapeutic performance was unexceptional, as noted earlier in Sect. 3.1.1.3. Nevertheless, being a hybrid organic–inorganic system composed of fluorescent dye molecules, the system showed added promise for optical imaging [91]. The fluorescent intensity of PCTPF shells was significant compared to that of “free” fluorescein.

Zhao et al. [73] incorporated both up and down conversion nanoparticles in a double-polymer capsule. While the UCDNPs luminescence was employed for breaking up the carrier into smaller parts for quicker clearance, downconversion luminescence of NaGdF$_4$:Nd@NaYF$_4$ nanoparticles was added for optical imaging. In vivo, the luminescence of the capsules could be retained for up to 12 h. A study by Huang et al. [62] showed that multiple-shelled SiO$_2$ capsules could carry FITC (fluorescein 5(6)-isothiocyanate) molecules for optical imaging. At the same time, their controlled drug-carrying ability for DOX was also demonstrated. However, data for simultaneous DOX and FITC loading were not available. Figure 12 presents some examples of NIR and MRI imaging of capsules.

Ultrasound Imaging and Therapy Hu et al. [86] demonstrated that PEGylated hollow poly(methacrylic acid-co-ethylene
glycol dimethacrylate) (poly(MAA-co-EGDMA) capsules could be used for both drug delivery and contrast enhancement in ultrasound imaging. The drug loading capacity was exceptionally high (52.4%), and the pH-controlled drug release could kill 70% of HeLa cells incubated with DOX-loaded capsules. Ultrasound contrast enhancement was also remarkable; the UI contrast steadily improved by increasing capsule concentration up to 0.8 mg/ml. In vivo, the capsules were found to increase contrast in a liver model quickly after administration (within 30 s) which remained available for some time.

High-intensity focused ultrasound therapy (HIFU) modality has been combined with MRI contrast enhancement in an organosilica capsule [110]. T2-MRI contrast enhancement was made possible by adding Fe3O4 NPs in the organosilica shell. To facilitate HIFU therapy, isopentyl acetate (PEA) was added to the internal cavity. The capsules exhibited a maximum magnetization of about 43 emu/g. MRI contrast improved till the tested Fe concentration of 0.16 mM; these results were corroborated through in vivo MR imaging. HIFU therapy using prepared capsules was studied through both ex vivo and in vivo models. Ex vivo, the ablated tumor volume was highest for the liver treated with organosilica capsules containing PEA. In vivo, cell death was much more pronounced for the capsules-treated group, although much more tumor ablation was achieved via intratumor injection (523.3 mm3) than intravenous injection (52.3 mm3).

**Multimodal Imaging** Lim et al. presented SiO2-based hollow capsules with peculiar morphology and multifunctionality [71]. The capsules were hollow and spherical and possessed a through-hole on their surface. Fe3O4 NPs and CdSe/ZnS quantum dots were embedded in the silica shell, which imparted both MR and optical imaging capability to the system. The capsules exhibited significant MR contrast improvement in dendritic cells; the capsules-labeled cells were then admitted to an in vivo mouse model where the MR contrast enhancement was persistent.

**Multimodal Therapy Platforms** Many examples of combination therapy exist in the literature that employs hollow multifunctional capsules. Han et al. [88] reported a functionalized CuS capsule loaded with ICG (indocyanine green, a phototherapy agent). ICG-loaded capsules, when irradiated with NIR light, brought forth the most exceptional results in cell viability tests for HeLa cells. The cell viability was nearly 0% at an ICG concentration of 4 µg/ml. Free ICG (at the same concentration) showed nearly 40% cell viability whereas capsules loaded with ICG (same concentration) without NIR irradiation showed approximately 70% cell viability. The remarkable performance was due to simultaneous PDT and PTT ensured through photothermal properties of CuS and ICG, photodynamic properties of ICG, and NIR laser irradiation. The combination PTT/PDT therapy through ICG-loaded CuS-BSA-FA capsules yielded almost complete cell death of HeLa cells at 4 µg/ml ICG concentration.

Combination PTT, CDT, and chemotherapy was explored using hollow PEGylated Cu9S8 capsules by Liu et al. [94]. Figure 13 shows the superior therapeutic efficacy of triple combination therapy as compared to bimodal or monomodal therapies. Cell viability of CT26 cells decreased enormously to less than 10%.
Triple combination therapy was also explored by Li et al. [95] using PEGylated CuS hollow spheres (PTT agent) as carriers for chlorin e6 (PDT agent) and DOX (chemotherapy agent). For both 4T1 and MCF-7 cells, the triple combination therapy yielded maximum necrosis at a carrier concentration of 200 µg/ml. More than 90% of cells were killed through combined photo-chemotherapy (PTT, PDT, and DOX), and all other combinations (or lack thereof) yielded more than 30% cell viability. In vivo, around 94.8% tumor inhibition was demonstrated for the therapy in a mouse model through NIR irradiation of Ce6 and DOX-loaded CuS capsules.

Porous carbon materials’ photothermal properties were utilized to design a chemo-phototherapeutic agent based on hollow carbon spheres [39]. The carbon spheres were functionalized and loaded with DOX and BAG3-siRNA for combined photothermal, chemoe, and gene therapy. Among all tested combinations, including control and individual therapy modes, the highest cell death (ca. 95%) occurred for the combination of all three therapeutic modalities. MoS2-HSA capsules reported by Xu et al. [81] exhibited capability for both photothermal and chemotherapy. The capsules showed a high photothermal efficiency (51.38%) along with a high drug loading capacity for DOX (27%). In cytotoxicity assay, only around 15% MCF-7 cells retained viability when treated with DOX-loaded capsules irradiated by NIR radiation. The system was also imparted targetability through HSA functionalization. These factors combined resulted in excellent tumor inhibition when the DOX-loaded capsules were tested in a breast cancer model in mice. Through NIR irradiation, photothermal activity was also introduced, leading to a relative tumor volume of only 0.27. Table 2 presents the examples of reported hollow multi-component capsules for multimodal biomedical applications.

**Advanced Multimodal Platforms**

Years of research efforts to engineer multimodal systems have led to substantial progress; the proof exists in advanced systems with as many as five different modalities available in the same platform. These systems are summarized in Table 2 with other multimodal biomedical systems. Zhou et al. [97] synthesized a hollow polymeric capsule with PLGA-PVA [poly(lactic-co-glycolic acid) and poly(vinyl alcohol)] with loaded chlorin e6 and DOX. A Gd and the folic acid-containing complex supported the capsule’s surface to impart magnetic character and targetability. The end product was a quad-modal platform with potential application in photothermotherapy and MR and fluorescence imaging. The study demonstrated several benefits of hollow multicomponent platforms. It showed that DOX release could be controlled and slowed by encapsulating it in the capsules; free DOX was retained in plasma and tumor for less than 15 h, whereas DOX-loaded capsules showed prolonged retention in both. The capsules also improved T1-MR contrast steadily up to a Gd concentration of 0.24 mM. Due to targetability and favorable size, the capsules showed high tumor accumulation and sustained retention up to 96 h, as confirmed by the NIR imaging capability of the platform. The combination of photodynamic and chemotherapy on a tumor model in mice yielded almost complete elimination of the tumor in 18 days. Figure 13 presented optical in vivo and ex vivo imaging of tumor in a mice model with at least 96 h retention time of fluorescence.

MnO$_2$ and DOX loaded and folate-functionalized Fe-based MOF hollow spheres, prepared by Zeng et al. [111], were also capable of bimodal therapy as well as MR contrast enhancement and fluorescent imaging through magnetic properties of MnO$_2$ and fluorescence properties of loaded chemotherapeutic drug DOX.
| Sr. No | Capsule composition | Morphology | Number of Modalities | Applications | References |
|--------|---------------------|------------|----------------------|--------------|------------|
| 1      | PEG-lyted Fe₃O₄     | Long needle-like capsules | 2 | Drug delivery, MRI contrast enhancement | [109] |
| 2      | SiO₂, CdSe/ZnS quantum dots, Fe₃O₄ | Hollow spheres with a through-surface hole | 2 | Optical imaging probe, MRI contrast enhancement | [71] |
| 3      | Fe₃O₄, mSiO₂        | Ovoidal capsules with encapsulated Fe₃O₄ needles, hollow cavity between Fe₃O₄ and mSiO₂ shell | 2 | Drug delivery, MRI contrast enhancement | [77] |
| 4      | mSiO₂               | Multi-shelled hollow spheres | 2 | Drug/cargo delivery, optical imaging probe | [62] |
| 5      | PCTPF: poly(cyclotriphosphazene-co-fluorescein) | Spherical hollow capsules | 2 | Drug delivery, optical imaging probe | [91] |
| 6      | CuS, bovine serum albumin (BSA), folic acid | Rough hollow spheres | 3 | Drug delivery, photodynamic and photothermal therapy (PDT and PTT) agent | [88] |
| 7      | Carbon with polyethyleneimine (PEI) and polyethylene glycol (PEG) | Brain-like spherical porous hollow nanocapsule (PHCN) | 2 | Drug and gene delivery, photothermal therapy agent (PTT) | [39] |
| 8      | poly(MAA-co-EGDMA); poly(methacrylic acid-co-ethylene glycol dimethacrylate) | Deflated moon like hollow capsules | 2 | Drug delivery, ultrasound imaging agent | [86] |
| 9      | Fe₃O₄, PEA, organosilica (TPM) PEA: Isopentyl acetate 3-(trimethoxysilyl)propyl methacrylate | Spheres with encapsulated Fe₃O₄ nanoparticles | 2 | High intensity focused ultrasound (HIFU) therapy agent, MRI contrast enhancement | [110] |
| 10     | MoS₂@HSA (human albumin serum) | Flexible, deflated, and wrinkled capsules | 2 | Drug delivery, photothermal therapy (PTT) agent | [81] |
| 11     | Polymer, up and down conversion nanoparticles (U/DCNPs) | Rough spherical capsules with embedded U/DCNPs | 2 | Drug delivery, optical imaging agent | [73] |
| 12     | PLGA, PVA, Gd-DBCF Poly(lactic-co-glycolic acid)-poly (vinyl alcohol) Gd-DBCF (Gd-Ce6-folate modified bovine serum albumin complex) | Hollow spherical capsule with a halo ring outside | 4 | Drug delivery, optical imaging agent, MRI contrast enhancement, PDT agent | [97] |
| 13     | mCuS, PEG | Rough hollow spheres | 4 | Drug delivery, PDT and PTT agent (chlorin e6 carrier) | [95] |
| 14     | Bi₂Se₃, PEG | Hollow spheres | 5 | Drug delivery, PDT/PTT agent, CT contrast enhancement, optical imaging probe | [80] |
| 15     | Co₂S₈, N doped carbon, functionalized surface | Hollow and rough spherical capsule with nanoparticle aggregates on surface | 5 | Drug delivery, PDT/PTT agent, MRI contrast enhancement, photothermal imaging probe | [69] |
| 16     | CuS, Au NPs, multicarboxylic graphene QDs | Hollow, rough spheres | 3 | Drug delivery, PTT agent, optical imaging and monitoring | [78] |
| 17     | m-SiO₂, folic acid | Hollow spheres | 2 | Drug delivery, PTT agent | [93] |
| 18     | MnSiO₃ | Double-layered hollow cuboidal spheres | 3 | SDT, ultrasound imaging agent, MRI contrast enhancement | [125] |
| 19     | MnO₂, Au NPs | Hollow spherical capsules with nanoparticle aggregates on surface | 2 | Drug delivery, potential PTT | [123] |
| 20     | ZnO, CuO, Au, PEG, RGD peptide RGD (Arginylglycylaspartic acid) | Tri-layered hollow capsules of smaller crystallites | 5 | Drug delivery, PTT, PDT, MRI contrast enhancement, photothermal imaging probe | [87] |
A quintmodal platform with PDT, PTT, chemotherapy, optical imaging, and computed tomography (CT) imaging characteristics was reported by Sun et al. [80]. The platform consisted of PEGylated Bi$_2$Se$_3$ hollow spheres loaded with Ce6 and DOX. Bi$_2$Se$_3$ contributed photothermal properties and CT imaging contrast enhancement due to the high Z number (83) and X-ray attenuation coefficient (5.74 cm$^{-2}$/kg). The hollow cavity allowed the loading of a photosensitizing agent Ce6 (LC: 11.9 wt%) and an anticancer therapeutic agent DOX (LC: 18.1 wt%). It is noteworthy that drug loading capacity for either of the agents was compromised compared to other platforms; however, this compromise was balanced through the distinguished efficacy of the triple combination therapy. After treatment with the drug and Ce6-loaded capsules under NIR radiation, an in vivo tumor model showed total growth inhibition and reduction of relative tumor volume to around 0 in two weeks. All other treatment combinations (capsules + laser, free DOX, free Ce6 + laser, etc.) failed to cease tumor growth. CT contrast improvement was demonstrated in a limited capacity as we.

Another quintmodal platform recently reported was composed of a complex composition of ZnO, CuO, Au NPs, functionalized with PEG and RGD peptide. The platform, named as RGD@ZnO@CuO@Au@DOX hollow nanoparticles, was capable of tri-synergistic therapy as well as photothermal imaging and T1-MRI contrast enhancement. The experimental group employing all three therapies simultaneously was found to be the only one resulting in positive tumor inhibition, i.e. not only it slowed down tumor growth but also ablated the present tumor volume through synergistic therapy. The presence of Cu$^{2+}$ made MRI contrast enhancement possible through this multimodal platform. Whereas, presence of Au NPs made photothermal imaging and therapy viable [87].

Co$_3$S$_4$-based hollow spheres reported by Lv et al. [69] presented another advanced multimodal imaging and therapy system. The spheres were encapsulated in an N-doped carbon layer with PEGylated surface. The system could improve T2-MR contrast for Co concentration up to 0.8 mM. It also exhibited photothermal imaging characteristics. The platform showed excellent therapeutic performance in combination therapy by reducing the relative tumor volume to 0 in 12 days. In stark contrast, almost no tumor inhibition was observed for treatments with only chemotherapy (using DOX) or with NIR irradiation. Figure 14 presents the diagnostic performance of drug-loaded nano-capsules. Hollow Cu$_2$S$_3$ spheres decorated with Au NPs and DOX were presented as a bimodal therapy agent [78]. The platform could also be used for fluorescent imaging due to MC-GODs on the surface. MC-GODs also made the drug delivery stimuli-responsive, as mentioned in Sect. 3.1.3.2. In cytotoxicity assay, HeLa cells returned almost 0% cell viability when treated with NIR-irradiated, DOX-loaded capsules at a 200 μg/ml concentration. In vitro drug release in HeLa cells was monitored via MC-GODs and DOX fluorescent characteristics.

### Synthesis Strategies

Templating is the oft-reported method to produce hollow structures. A template is any expendable entity that provides a surface for the nucleation and growth of the shell components. Researchers have employed hard and soft templates to create hollow shells and capsules. Hard templates include solid entities such as inorganic silica nanoparticles, metallic nanoparticles, and even solid polymeric beads. The shape and size of the templates directly influence the size and morphology of the capsule obtained at the end. Soft templates based on polymeric micelles, vesicles, and gas and liquid bubbles are widely used. Figure 15 presents a schematic illustration of templating processes to synthesize hollow organic/inorganic shells.

Hard templates provide a rigid surface for shell growth and definite size and shape control. On the other hand, soft templates are not the first choice when precise size and shape control is a concern. However, the relative ease of removing soft templates after shell growth provides a rationale for creating hollow capsules. Nano-Kirkendall effect is also exploited in self-templated syntheses of metallic hollow capsules. Besides hard and soft templates, inorganic and metallic nanoparticles have been used as self-sacrificial templates.
to create hollow shells. Figure 16 presented a schematic illustration of strategies and methods employed to create hollow multicomponent capsules.

Second and higher-order shells, nanoparticles incorporated in the shells, nanoparticles supported outside the shells, all of these strategies introduce secondary components to make hollow capsular structure multicomponent.

Nanoparticles incorporated inside shells are either fabricated in situ or prepared separately before fabrication of the shells and embedded during the growth process of the shell. Nanoparticles and functional moieties can also be deposited or stabilized on the surface post-synthesis of the hollow shells.
Soft Templating

Perkin et al. synthesized polyacrylic acid shells further layered with calcium phosphate. The soft template used to create polymeric shells was based on poly(acrylic acid-\(b\)-isoprene) (PAA-\(b\)-PI) micelles. The shell was created by first cross-linking PAA on the outer edge of the micelles and then removing the PI core using a mixture of ozone and compressed air. CaCl\(_2\) and Na\(_2\)HPO\(_4\) were precursors to introduce Ca\(^{2+}\) and phosphate ions in a solution with PAA shells. The concentration of Ca\(^{2+}\) in the solution was kept very low to avoid precipitation. The carboxylate groups present in PAA at a low concentration provide a site for attracting Ca\(^{2+}\) cations followed by their neutralization through phosphate anions. This process creates a significantly impermeable inorganic layer around the organic inner shell [68].

Cetyltrimethylammonium bromide (CTAB) is a cationic surfactant molecule with an amphiphilic character. In aqueous environments, if the concentration of CTAB is above a critical value for given conditions (critical micelle concentration), the molecules self-assemble into temporary structures which are quasistatic, directing their hydrophobic, nonpolar ends inside and hydrophilic ends towards the aqueous environment outside [112]. Depending on various
Hard templates based on polymers, inorganic materials, and others. As such, they serve as templates for the nucleation of other nanoparticles. Xu et al. demonstrated the use of CTAB micelles and vesicles as templates for creating single and multishell Cu₂O hollow spheres. A CTAB concentration of 0.08 M was sufficient to create hollow spherical morphology, but monodisperse, uniform hollow spheres with single-crystalline shell were obtained at a concentration of 0.1 M. Dominantly double and triple-shelled product was obtained when CTAB concentration was increased to 0.13 M and 0.15 M, respectively and keeping other experimental parameters constant [59].

A dual-templated approach was reported by Zhang et al. where template-forming molecules were didodecyldimethylammonium bromide (DDAB) and CTAB. DDAB is a double-tailed amphiphile, so its structure was crucial in forming multilamellar vesicles on which silica could nucleate through the sol–gel process. Without sufficient DDAB, the CTAB assembled into longitudinal micelles and formed a solid silica sphere with “worm-like” pores. However, when enough DDAB is present (CTAB/DDAB ratio of 1:0.625), it forms multilamellar vesicles, driven by the increase of hydrophobic chain volume as a whole. A maximum of 7 shells were reported corresponding to CTAB/DDAB ratio of 1:0.625 [60].

Another method to create soft templates is creating emulsions using immiscible liquids and ultrasonication. The surfaces of small droplets of emulsified liquid serve as a nucleation site for the nanoparticles that later make up the shell. For example, an oil emulsion in diethylene glycol (DEG) was used with toluene in the oil phase. An anionic commercial surfactant was used to stabilize oil droplets in DEG. This oil phase was also loaded with hydrophobic iron oxide nanoparticles prepared separately. A sol–gel reaction using tetraethylorthosilicate (TEOS) as a precursor was employed to nucleate silica on the oil droplets. Through-surface holes were created in the silica as the shell shrank and toluene escaped from several points on the growing shell [70].

Bubble templates are another class of soft templates where ultrasonication creates gas bubbles in a liquid medium that can be stabilized using a surfactant and used as templates. Wang et al. used N-Lauroylsarcosine sodium as anionic surfactant and 3-aminopropyltrimethoxysilane (APMS) as a structure-directing agent in the bubble-templated synthesis of hollow mesoporous silica. APMS also served as a source of amine group for surface functionalization of the ordered mesopores in the end product. TEOS was used as a silica precursor [90].

**Hard Templating**

Hard templates based on polymers, inorganic materials, and metals are used for the nucleation and growth of nanoshells. These hard templates are removed through acid etching, surface-protected etching, or calcination at high temperatures. Polystyrene-based templates were reported by Huang et al. to create multishelled silica particles. The poly(styrene-co-styrene sulfonate) nanoparticles were synthesized separately, and silica was deposited through the sol–gel process using TEOS as the main precursor. Aminopropylmethoxyxilane (APTES) was used as an auxiliary precursor to aid bonding between styrene sulfonate and the formed silica layer [62].

30 nm polyacrylonitrile (PAN) nanoparticles were used as templates for forming Co₃S₄ shells by Lv et al. PAN templates were synthesized separately and were first covered with Co acetate hydroxide using cobalt acetate tetrahydrate as the precursor. The cobalt-based shell was converted to Co₃S₄ by hydrothermal treatment of PAN@Co acetate hydroxide with a sulfur precursor (thiacetamide). The hydrothermal treatment transformed PAN core to PAA (polyacrylic acid) by converting —CN to —COOH. Polyacrylic acid, being hydrophilic, was dissolved in the aqueous medium leaving behind a hollow Co₃S₄ shell structure [69].

Silica has also been employed as a template component in a silica@PDDA (polydiaryldimethylammonium chloride) template used to nucleate FePt nanoparticles before removing the silica core. NaOH aqueous solution was used to etch away silica at 70 °C for 1 h for core removal. PDDA shell formed on silica surface remained intact along with FePt NPs after NaOH etching [74].

The inorganic elemental sulfur template was used by Chaudhuri et al. to create Au and Ag/Au shells. In a suspension of sulfur nanoparticles, Ag or Au precursor was added in AgNO₃ and HAuCl₄ and reduced with NaBH₄. Successive addition and reduction of Ag precursor followed by that of Au yielded separate shells of Ag and Au on a sulfur core. The inorganic core was removed by calcination at 450 °C for 30 min [113].

**Self Templating**

Besides hard and soft templates, inorganic and metallic nanoparticles have been used as self-sacrificial templates to create hollow shells. Zeng et al. synthesized ZnO/Au, ZnO/Pt, and ZnO/Pt/Au hollow particles using a composite Zn@ZnO template. Weak acids of noble metal (Au and Pt) were used to etch away the active Zn metal core and nucleate small crystals of noble metals inside the ZnO shell [76].

In another study on the mechanism of hollowing metallic nanoparticles by galvanic exchange, Moreau et al. formed bimetallic Au/Ag hollow shells by treating solid citrate-capped Ag nanoparticles with HAuCl₄ acid. Such a method has been reported earlier and attributes the hollowing of the solid particles to either galvanic exchange reactions between metal and metal acids or to the nano-Kirkendall effect. In galvanic exchange, hollow structures are produced as for
every Au atom reduced, 3 Ag atoms are oxidized and etched away. This imbalance in ratio leads to a hollow structure. However, Moreau et al. suggested that their product was formed through a modified galvanic exchange, which they termed “nanoscale galvanic exchange” [114].

Inorganic templates of β-FeOOH were used by Piao et al. to prepare elongated needle-like haematite and magnetite capsules. The process was termed as the “wrap-bake-peel process”, β-FeOOH capsules were covered with a protective silica layer through sol–gel condensation, heated at 500 °C for 5 h to convert the oxy-hydroxide to Fe₂O₃ inside the silica layer. In a separate experiment for magnetite capsules, the Fe₂O₃ capsules were again heated at 500 °C for 10 h in a reducing mixed H₂-Ar environment. After conversion, haematite and magnetite capsules were obtained by removing silica with 0.1 M NaOH [109]. Solvothermal synthesis of Zn-doped Fe₃O₄ was described by Saha et al. to tune the magnetic properties of the iron oxide. The process was template-free, and hydroxides of Zn and Fe(III) obtained after the solvothermal treatment with urea were converted to hollow oxides at the end [75].

Layer-by-Layer Synthesis

Polyelectrolyte capsules are synthesized by a strategy called layer-by-layer (LbL) assembly. These methods use the alternative supply of precursors to deposit alternatively charged polymer layers on a template. Cuomo et al. produced chitosan-alginate by growing each layer on liposomes using a chitosan solution in acetic acid and sodium alginate. Zeta potential measurement was carried out against the amount of polyelectrolytes used to ensure charge neutrality on the surface [115, 116].

Itoh et al. [117] reported a chitosan-dextran sulfate capsule developed using a silica template. The silica nanoparticles were suspended in a polyelectrolyte solution of 1 mg/ml concentration in 1 M NaCl for 15 min. After washing, the silica templates were removed with diluted hydrofluoric acid (HF). Silica templates were also used in the LbL assembly of pectin and chitosan to form multishelled structures [98]. Here, silica templates were dispersed in acetic acid solution and then treated with 50 ml of 1 mg/ml chitosan or pectin solution to deposit the respective layer. The silica templates were later removed using an HF/NH₄F (2 M/8 M) buffer.

A summary of synthesis strategies, temperature requirements and obtained size and product, is provided in Table 3. Inorganic and organic capsules are often synthesized through hard or soft templating, whereas metallic capsules are more often produced through galvanic exchange reactions. LbL assembly is the preferred method for creating multiple shells of polymers with alternative electrostatic charges. SiO₂ has been employed as the template material more than any other material; the reason lies in its ease of fabrication, tunability afforded in its size and morphology, and its inorganic nature, which makes it a stable template with definite size and shape. Most capsules are smaller than 300 nm, and many are below 100 nm. The temperature requirements are more often than not below 100 °C and rarely exceed 500 °C. The morphology reported most frequently has been spherical due to the prevalence of wet chemical synthesis methods that generally yield spherical products to be used as templates. However, it has been argued that non-spherical carriers are better suited in significant aspects for biomedical applications [118–120].

Outlook and Future Prospects

Through nanotechnology, small-scale multicomponent structures are often translated into multifunctional structures. If they are hollow, then an added advantage of cargo delivery becomes inherently available. In biomedical applications such as drug and cargo delivery, combination cancer therapy, diagnostic imaging, and theranostics, hollow multicomponent structures have proven to be of great potential in pre-clinical studies. In this regard, earlier studies at the beginning of the twenty-first century started with hollow, surface-modified structures reported for potential drug delivery. With gradual understanding and progress in both clinical medicine and materials science, the platforms evolved with an increased number of modalities being offered in a single platform. Most recent efforts have reported five different therapeutic, and diagnostic modalities made possible through the deliberate selection of materials, synthesis methods, and functionalities. In materials, polymer and inorganic oxides (most frequently, SiO₂), sulfides, and selenides are preferred for shell materials of the capsules. Different functionalities are imparted through magnetite nanoparticles, superparamagnetic iron oxide nanoparticles (SPIONs), quantum dots, up and down conversion nanoparticles, and fluorescein labeling. Target selectivity is added through surface functionalization with proteins, folic acid, and otherspecies for cell-specific receptors. Hollow structures are fabricated mainly through layer-by-layer assembly and templating methods using hard, soft, or self-sacrificial templates. Metallic capsules are rarely explored for such applications but can be synthesized through galvanic exchange strategy and other methods.

Although various capsule compositions have been explored morphologically, the research has been confined to spherical capsules for a large part. Since literature provides a rationale for preferring non-spherical morphologies for biomedical applications, more research efforts must be concentrated towards new synthesis strategies, at least for template materials, which yield non-spherical products. Furthermore, the intricate design criteria spanning drug loading...
| Sr. # | Capsule composition | Synthesis strategies | Template material | Maximum Temperature (°C) | TEM/SEM size (nm) | References |
|-------|---------------------|----------------------|-------------------|--------------------------|-------------------|------------|
| 1     | Chitosan, dextran sulfate | Hard templating+Layer by layer assembly | Silica nanoparticle | Ambient | ~330 | [117] |
| 2     | Glucose oxidase | Hard templating | Anodized aluminum oxide (AAO) | Ambient | L = 1060 W = 101 | [127] |
| 3     | mSiO₂ | Hard templating+ surface protected etching | Polystyrene nanoparticles | 580 | 110 (double-shelled) 140 (triple-shelled) | [62] |
| 4     | PDDA@FePt NPs PDDA: poly(diaryldimethylammonium chloride) | Hard templating | Silica nanoparticles | 260 | 330 | [74] |
| 5     | Iron oxide@silica@calcium silicate | Self-templating + solvothermal + sol-gel + calcination | Iron oxide nanoparticles | 600 | 300 | [67] |
| 6     | mSiO₂ with functionalized surface | Hard templating+post-synthesis surface modification | Silica nanoparticles | 80 | 155±20 | [103] |
| 7     | PCTPF: poly(cyclotriphosphazene-co-fluorescein) | Hard templating | Silica nanoparticles | 40 | 265 | [91] |
| 8     | Ag@Au | Hard templating+hydrothermal+post-synthesis surface modification | Sulfur nanoparticles | 450 | 20–25 | [113] |
| 9     | mSiO₂ with functionalized surface | Hard templating+hydrothermal+post-synthesis surface modification | Eudragit S-100 nanoparticles | 150 | 120 | [79] |
| 10    | Carbon with functionalized surface | Hard templating | Silica nanoparticles | 500 | 100–120 | [39] |
| 11    | mSiO₂ with functionalized surface poly(MAA-co-EGDMA): poly(methacrylic acid-co-ethylene glycol dimethacrylate) | Hard templating | Silica nanoparticles | 80 | 120±13 | [108] |
| 12    | Hard templating | Hard templating | Silica particles | ~80 | 270±5 | [86] |
| 13    | Pectin, chitosan | Hard templating+layer by layer assembly | SiO₂-NH₂ | Ambient | ~18 | [98] |
| 14    | MoS₂@HSA (human albumin serum) | Hard templating | SiO₂-NH₂ | Ambient | 280 | [81] |
| 15    | Polymer@U/DCNPs (up and down conversion nanoparticles) | Hard templating | Silica particles | 280 | ~180 | [73] |
| 16    | Organosilica | Hard templating (in emulsion system) | Polystyrene nanoparticles | 120 | 100 | [128] |
| 17    | Co₃S₄@N-doped carbon with functionalized surface | Hard templating+hydrothermal | Polyacrylonitrile nanoparticles | 220 | 80–84 | [69] |
| 18    | (PAA-g-PEG) Polyacrylic acid-g-polyethylene glycol | Hard templating | MPS-SiO₂ nanoparticles | 80 | 30±10 | [84] |
Table 3 (continued)

| Sr. # | Capsule composition | Synthesis strategies | Template material | Maximum Temperature (°C) | TEM/SEM size (nm) | References |
|-------|---------------------|----------------------|-------------------|--------------------------|------------------|------------|
| 19    | PMMA with functionalized surface (Polymethyl methacrylate) | Hard templating | MPS-SiO$_2$ nanoparticles MPS: 3-(trimethoxysilyl) propyl methacrylate | ~ 80 | 30 ± 15 | [85] |
| 20    | Copolymer@Au@SiO$_2$ | Soft templating | Lysine-cysteine diblock copoly-peptides | Ambient | 800–4000 | [129] |
| 21    | PAA@calcium phosphate Polyacrylic acid | Soft templating | PAA-b-PI core-shell micelles Poly(acrylic acid-b-isoprene) | Ambient | 55 ± 10 | [68] |
| 22    | Cu$_2$O | Soft templating | CTAB micelles and vesicles (cetyltrimethylammonium bromide) | 60 | 150–180 (double-shelled) 210–240 (triple-shelled) | [59] |
| 23    | SiO$_2$@Fe$_3$O$_4$ | Soft templating | Oil-in-DEG (diethylene glycol) microemulsion | 200–300 | 2000–3000 | [70] |
| 24    | SiO$_2$ CdSe/ZnS quantum dots, Fe$_3$O$_4$ | Soft templating | CHCl$_3$-in-water emulsion | 290 | 270 | [71] |
| 25    | SiO$_2$ with functionalized surface | Soft templating | Bubble templates | 80 | 100–500 | [90] |
| 26    | SiO$_2$ | Soft templating | CTAB and PFOE(2-(perfluoro-n-octyl)ethanol) (cetyltrimethylammonium bromide) | 550 | 50–200 (depending on no. of layers) | [61] |
| 27    | mSiO$_2$ | Soft templating | CTAB and DDAB (cetyltrimethylammonium bromide and didodecyldimethylammonium bromide) | 550 | 60–120 (depending on no. of layers) | [60] |
| 28    | N-palmitoyl chitosan, Fe$_3$O$_4$ | Soft templating | Water–oil–water emulsion | 40 ± 2 | 100–150 | [106] |
| 29    | ZnSe:Mn/ZnS QDs@SiO$_2$ with functionalized surface | Soft templating | Pluronic F127 micelles | 280 | Up to 45 | [22] |
| 30    | PLGA,PVA@Gd-DBCF complex Poly(lactic-co-glycolic acid), poly (vinyl alcohol)- | Soft templating | Water–oil–water emulsion | Ambient | 120–130 | [97] |
| 31    | P(MMA/DVB/AA)@Fe$_3$O$_4$ NPs poly(methyl methacrylate/divinyl benzene/acrylic acid) | Soft templating | Miniemulsion using hexadecane | 70 | 87.3–235 | [72] |
| 32    | Ag-Pt | Galvanic replacement | – | 60 | 100–150 | [65] |
| 33    | Au-Pt, Au–Pd, Pt-Pd | Galvanic replacement | Ag nanocubes | 140–150 | 80–90 | [64] |
| 34    | FePt | Galvanic replacement + wet chemical synthesis (reduction of Fe precursor) | – | Ambient | ~400 | [130] |
| 35    | Ag-Au | “Nanoscale” galvanic exchange | – | Ambient | 20 | [114] |
| Sr. # | Capsule composition | Synthesis strategies | Template material | Maximum Temperature (°C) | TEM/SEM size (nm) | References |
|-------|---------------------|----------------------|-------------------|--------------------------|------------------|------------|
| 36    | ZnO@Pt/Au NPs       | Self-templating + selective etching | Zn nanoparticles | 40 (templates were prepared by laser ablation) | 20–30 | [76] |
| 37    | Fe₂O₃/Fe₃O₄         | Self-templated wrap-bake-peel process | β-FeOOH | 500 | L – 100 | [109] |
| 38    | Fe₂O₃@void@mSiO₂    | Self-templated selective etching | Fe₂O₃ | 550 | L – 200–300 | D – 100–120 | [77] |
| 39    | Pd@Pt               | Self-templated selective etching | Pd | Ambient | 30 | [66] |
| 40    | Chitosan, alginate  | Layer by layer assembly | Liposomes | Ambient | 200–250 | [115] |
| 41    | CuS, bovine serum albumin (BSA), folic acid | Self templating | Cu₂O | Ambient | 120 | [88] |
| 42    | SiO₂@PDMAS@Au NPs PDMAS: dimethyl(methacryloxyethyl) ammonium propanesulfonate | Self templating | SiO₂ | – | ~200 | [131] |
| 43    | Fe₃O₄, PEA, organosilica (TPM) PEA: Isopenetyl acetate 3-(trimethoxysilyl)propyl methacrylate | Self-templating | Isopenetyl acetate (PEA) | 70 | 82 | [110] |
| 44    | Silk@Au NPs         | Hard templating + layer by layer assembly | PLGA Poly[lactic-co-(glycolic acid)] | – | 560–570 | [132] |
| 45    | Organosilica        | Self-templated etching | mSiO₂ | 60 | 240–310 | [89] |
| 46    | polyamidoamine dendron-poly(L-lysine) (PAMAM dendron-PLL) with disulfide bonds | Self assembly | – | Ambient | 180–200 | [96] |
| 47    | Zn-doped Fe₃O₄     | Solvothermal synthesis | – | 180 | 390 (for optimized dopant content) | [75] |
| 48    | Polypeptides (GSL12 and GSL16) | Self assembly | – | 80–90 | L – 100–600 | D – 80 | [121] |
| 49    | Polysaccharides (oil-filled) | Solvent shifting | – | Ambient | 100–230 (multicomponent) 96 (multishell) | [122] |
| 50    | mCuS@PEG            | Self templating | Cu₂O | 60 | ~165 | [95] |
| 51    | Bi₂Se₃@PEG          | Self templating | Bi₂O₃ | 150 | ~150–170 | [80] |
| 52    | CuS, Au NPs, graphene QDs | Self templating | Cu₂O | 200 | 100 | [78] |

For every study, the maximum temperature was specified as the highest temperature employed to prepare the capsules from the beginning to the end of the procedure.
capacity, drug release behavior, and therapeutic efficacy should be considered while putting together hollow multicomponent capsules for drug delivery. There is also a need for more detailed criteria and guidelines for designing multimodal systems. This may include assessing compromises in functionalities all combinations suffer in such platforms and identifying modalities that are ideally suited to be put together. Moreover, to accelerate the translation of synthesized products from pre-clinical to clinical research studies, more comparative studies should be carried out gauging the relative performance of similar platforms for a given biomedical application. Considering these points, research in this particular nanotechnology arena has a long way to go, but the recent progress illuminating its potential benefits has made the course sufficiently enticing.

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