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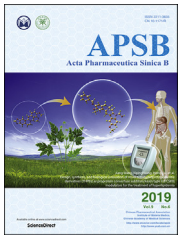

ANNUAL REVIEW

Recent progress in drug delivery

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Abstract Drug delivery systems (DDS) are defined as methods by which drugs are delivered to desired tissues, organs, cells and subcellular organs for drug release and absorption through a variety of drug carriers. Its usual purpose to improve the pharmacological activities of therapeutic drugs and to overcome problems such as limited solubility, drug aggregation, low bioavailability, poor biodistribution, lack of selectivity, or to reduce the side effects of therapeutic drugs. During 2015−2018, significant progress in the research on drug delivery systems has been achieved along with advances in related fields, such as pharmaceutical sciences, material sciences and biomedical sciences. This review provides a concise

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overview of current progress in this research area through its focus on the delivery strategies, construction techniques and specific examples. It is a valuable reference for pharmaceutical scientists who want to learn more about the design of drug delivery systems.

1. Introduction

Drug delivery systems (DDS) are used to transport therapeutic drugs in the body as needed to safely achieve the desired therapeutic effect. Such systems are usually designed to i) improve aqueous solubility and chemical stability of active agents, ii) increase pharmacological activity, and iii) reduce side effects. Modern drug delivery systems have undergone continuous progress since the 1950s, when the first sustained release formulation Dexedrine was introduced[1]. The goal of any drug delivery system is to provide and maintain therapeutic concentrations of drug at the target biological site.

Among present drug delivery systems, nanoparticles as carriers have shown great potential in recent years. The encapsulation of drugs in nanoparticles, including micelles, liposomes, dendrimers, nanocapsules, nanospheres and others, improves the therapeutic index and reduces the adverse side effects. For example, liposome drug delivery systems can improve bioavailability, increase efficacy and reduce toxicity. Several successful liposome-based drugs have been approved by the U. S. Food and Drug Administration (FDA), such as liposomal doxorubicin (Doxil®)[2] and liposomal amphotericin B (Ambisome®)[3].

This review focuses on the recent advances of drug delivery systems reported within 2015−2018. An extensive literature review was performed mainly using PubMed. In this review, we highlight the emerging strategies for drug delivery, and also emphasize the current construction techniques for delivery systems; specifically, several representative inorganic materials for delivery system and the delivery of biomacromolecules are also discussed.

2. Emerging strategies for drug delivery

2.1. Stimuli-responsive strategy

Currently, stimuli-responsive delivery has been the most attractive strategy in the field of drug delivery. This strategy has been actively explored in order to achieve the tumor-specific delivery and controlled release of their cargoes, where endogenous or exogenous triggers can be employed. The endogenous triggers including pH-sensitive[4], ROS (reactive oxygen species)-sensitive[5], redox-sensitive[6], enzyme-sensitive[7] and temperature-sensitive delivery strategies towards some disease sites like tumors[8]. Exogenous triggers include light-triggered[9] and temperature-triggered[10] strategies induced by exogenous methods. Magnetic-triggered[11], and X-ray triggered[12] delivery strategies have also been used in the design of stimuli-responsive systems. Ultrasound can also serve as a trigger for remote control of drug release deeply within the body. The use of focused ultrasound has the advantage of delivering spatially localized heat, thus improving site-specific controlled release by destabilizing the structure of such delivery systems[10].

Many stimuli-responsive systems containing sensitive segments can be used for delivering drugs to target tissue and achieving an on-demand drug release. The surface properties and nanostructures of stimuli-responsive nanoparticles can also be modulated through intrinsic or extrinsic stimuli for improving cellular uptake and enhancing penetration ability.

2.1.1. Controlled drug release by stimuli-responsive systems

In many circumstances, controlled release of drug at the target site is required for proper therapeutic effect and safety. This can be achieved by various stimuli. For instance, ultrasound-triggered release has been useful for on-demand control of local pain, as specific sonosensitizer can be activated to produce ROS. These products react with liposomal membranes through peroxidation of unsaturated membrane lipids to release drugs, allowing patients to self-manage the intensity and duration of local anesthesia. No systemic toxicity or tissue damage was detected[13]. It was shown that ultrasonic energy transferred to liposomes would cause a sonosensitizer to release ROS, peroxidating unsaturated lipids in the bilayers, leading to local release of anesthetics. An amphiphilic copolymer (PB-PEG) composed of pendant phenylboronic acid and methoxy poly(ethylene glycol) was designed to efficiently load doxorubicin (DOX), epirubicin (EPI), or irinotecan (IR) *via* donor−receptor coordination between the boron and nitrogen atoms[14]. The PB-PEG nanoparticles with a drug loading level of up to 49% exhibited an enhanced cytotoxicity as compared to traditional micelles through hydrophobic interaction. In another case, a prodrug of DOX (iPDOX) was prepared by attaching iRGD and DOX to pluronic P85 copolymer through a matrix metalloproteinase-2 (MMP-2)-labile peptide, and iPDOX was further encapsulated in the micelles consisting of acid-responsive poly(ethylene glycol)-*b*-poly(2-(hexamethyleneimino) ethyl methacrylate) (PEG-*b*-PHMA)[15]. The resulting nanoparticles were able to release iPDOX in tumoral acidic microenvironment (pH ∼6.8), and then iRGD facilitated subsequent tumor penetration and intracellular uptake of released DOX through peptide cleavage, thereby leading to preferable anticancer efficacy against MCF-7/ADR tumor-bearing nude mice[15]. Li et al.[16] employed poly(etherimide)-poly(lactic-*co*-glycolic acid) (PEI-PLGA) copolymer to load antiplatelet antibody R300 and DOX within the nanoparticles, which were further modified by a lipid shell layer inserted with matrix metalloproteinase 2 (MMP2)-cleavable peptides. These nanoparticles were found to deplete the platelet to enhance tumor permeability for effective DOX delivery. Cysteine-based poly-(disulfide amide) nanoparticles were designed to scavenge glutathione to inhibit detoxification of active Pt species, leading to the enhanced therapeutic index of Pt drugs against cisplatin-resistant tumors[17]. In addition to polymeric

micelles, polymeric vesicles as a drug vehicle have also been explored to provide hypoxia-responsive or redox-responsive drug delivery[18,19].

For drugs like photosensitizers, specific stimuli could be used to directly trigger their therapeutic effect. Recently, Guo et al.[20] fabricated the self-assembled nanoparticles consisting of PEGylated platinated boron dipyrromethene (Bodiplatin) with ultralow radiative transition. Upon single-wave light exposure, these nanoparticles generate both singlet oxygen through preferable singlet-to-triplet transition and photothermal conversion through nonradioactive decay, thus providing synergistic effect between photodynamic and photothermal treatments for tumor ablation. To further regulate the photoconversion of photosensitizers for cooperative cancer phototherapy, trimeric boron dipyrromethene (tri-BDP) within the nanoparticles were prepared to enhance nonradiative transition together with moderate singlet-to-triplet transition[21]. Thus, the polymeric tri-BDP nanoparticles caused dramatic tumor ablation through the dominant late apoptosis and moderate early apoptosis upon light irradiation[21].

2.1.2. *Enhanced uptake and penetration by stimuli-responsive systems*

The surface charge and moiety of nanoparticles can influence the interaction of delivery systems with cells and blood components[22], thus improving cellular uptake and penetration. To reduce opsonin adsorption and reticuloendothelial systems (RES) recognition, PEG is widely used as a surface layer of nanoparticles. However, PEG also reduces cellular uptake. To resolve this problem, one strategy the development of detachable PEG. After distribution into tumor, the PEG can be detached in acidic conditions[23], high level of GSH[3] and overexpressed enzymes[24]. The inner nanoparticle layer can be modified with ligands, such as cell penetrating peptides, to further improve cellular uptake[25]. Surface coating with charge-reversible groups is another method for improving drug delivery[26]. Particles with neutral or negative charge display long blood circulation time, whereas particles with positive charge show high cellular uptake.

As a basic rationale of nanoparticle-based drug delivery, the enhanced permeability and retention (EPR) effect is greatly influenced by the particle size and morphology. Generally, larger particles possess better retention but display less penetration, whereas smaller particles have poor retention but more penetration[27,28]. To achieve both higher tumor penetration and retention, various kinds of size-changeable nanoparticles have been developed. Shrinkable nanoparticles were fabricated by the small-sized nanoparticles with degradable crosslinkers or cores. For example, small-sized gold nanocluster (AuNC) and dendrigraft poly-lysine (DGL) with hyaluronic acid (HA) were used to form nanoparticles about 200 nm[29,30]. After extravasating tumor from microvessels, the nanoparticles can be retained around tumor vessels with minimal backflow to vessels. Subsequently, high levels of tumor-bearing hyaluronidase can degrade the HA thereby releasing the small-sized AuNC and DGL. These smaller particles can then deliver drug cargoes into deep tumor with good penetration.

For the size-shrinkable strategy, it would be useful to develop small-sized aggregable nanoparticles with good initial penetration capacity. The smaller size of the nanoparticles facilitates extravasation from tumor vessels into the deep tumor. The aggregation is thought to occur through click cycloaddition and the size is increased, limiting flow back to tumor vessels, with good retention[31]. Still, there are concerns for the protein corona generated on the surface of the nanoparticles when administered *in vivo*, which might influence nanoparticle aggregation[32] and have an effect on the final application of this strategy.

Alterations in the morphology of nanoparticles has also been used to improve tumor targeting for drug delivery. Normally, spherical particles display better tissue penetration, whereas nanotubes or fibers show better retention. Therefore, changing the particles from spherical to tubular would be useful in drug delivery. A peptide-based material, BP-KLVFF-His_6-PEG was developed with the capacity of forming nanoparticles in phosphate buffer solution[33] (Fig. 1). However, when the aqueous environment acidifies, the His_6 becomes hydrophilic, resulting in particle shift rearrangement to form nanofibers, showing long retention time up to 96 h.

To date, many polymeric nanoparticles have been constructed for cancer-targeted drug delivery, and a few clinical studies of these nanoparticles have been reported. Genexol® has been explored as a commercialized polymeric formulation for treatments of breast cancer, ovarian cancer, and non-small-cell lung cancer. Several polymeric micelles encapsulating chemotherapeutic drugs are also being evaluated under clinical trials. Subbiah et al.[34] developed a polymeric formulation of NC-6004 consisting of PEG-*b*-poly(α,β-aspartic acid) and cisplatin, which are being investigated under a phase III trial for the treatment of advanced metastatic pancreatic cancer. Although clinical studies of the polymeric nanoparticles still suffer from limited success, it is highly desired to focus on translational studies of these new therapeutic formulations for cancer nanomedicine.

2.2. *Co-delivery strategy and theranostics*

Combination therapy with various drugs is a common clinical practice in many diseases, but the optimization of PK profiles of the combined drugs for the best synergistic effect is not well demonstrated. Due to varying PK behaviors within the combinations, it is hard to obtain an optimal dose ratio that is often optimized by the cell-based tests[35]. Various delivery systems with identical PK properties (*e.g.*, liposomes) can be useful for co-delivery of drug combinations. Recently, the co-delivery strategy has made substantial progress, as evidenced by the landmark approval of liposomal combination (VYXEOS®) with co-encapsulation of daunorubicin and cytarabine in 2017 (Fig. 2). A potential application of co-delivery combination in cancer therapy is to overcome drug resistance[36,37] and metastasis[38].

Co-delivery of photosensitizer and chemotherapeutic agent has also been widely studied for improved therapeutic effect. Light-responsive polymeric nanoparticles have been assembled from tellurium-containing block polymer (PEG-PUTe-PEG), indocyanine green (ICG), and cisplatin through the coordination of platinum and tellurium[41]. Upon light exposure, ICG generated $^1O2$ to oxidize the tellurium for rapid drug release, and simultaneously produced photothermal effect, together affording synergistic thermo-chemotherapy. Aiming at synergistic cancer therapy, Zhang et al.[42] synthesized a prodrug of camptothecin and 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-α (HPPH) *via* a GSH-sensitive spacer. The polymeric micelles loading CPT-HPPH prodrug can efficiently accumulated at HCT116 tumors, demonstrating synergistic efficacy of chemotherapy and photodynamic therapy.

Nanoparticles have been used as co-delivery strategies for specific and personalized theranostics[43], combining therapeutic effects with diagnostics and prognostics, as well as image-guided

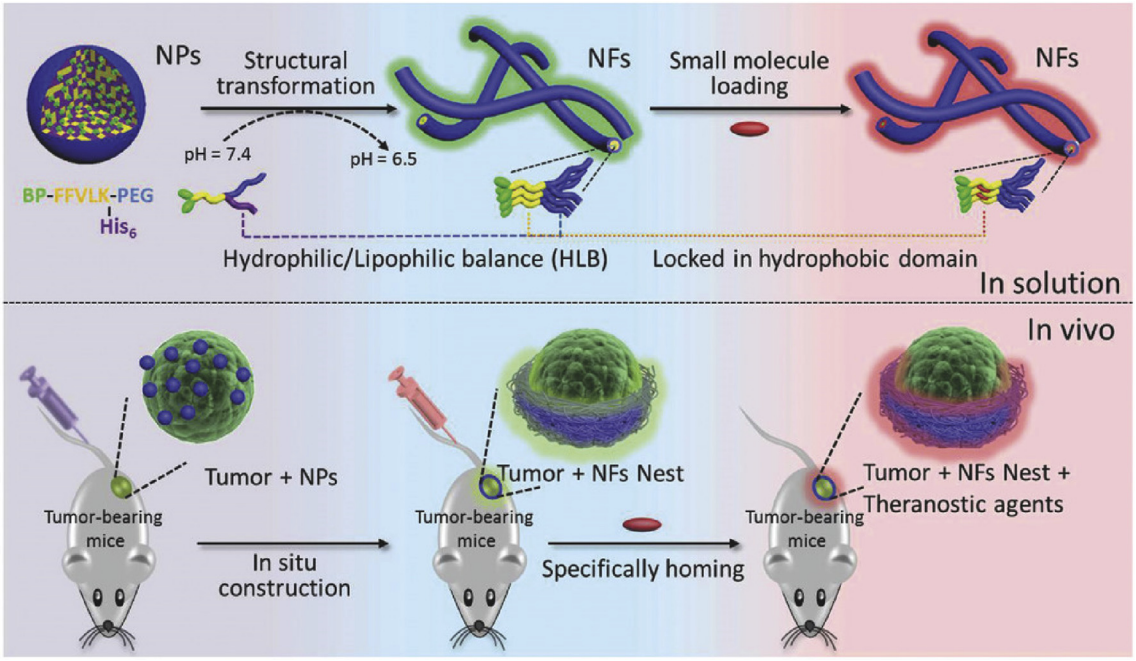

Figure 1 The schematic diagram of pH-triggered morphological transformation from self-assembled nanoparticles (NPs) to nanofibers (NFs) and a pre-nested host in a tumor where thermally sensitive drugs are located (Adapted from Ref. 33 with permission. Copyright © 2017 Wiley).

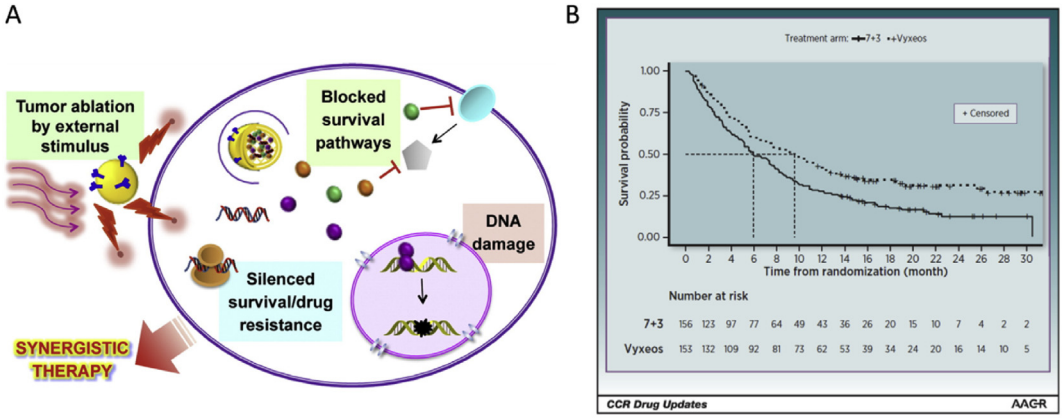

Figure 2 (A) The nanoparticle-based combination therapy. (B) Plasma drug concentrations after i.v. injection of the VYXEOS® liposomes and the free combo drugs in mice (Adapted from Ref. 39 with permission. Copyright © 2016, Elsevier and Ref. 40 with permission. Copyright © 2019, American Association for Cancer).

therapy, etc. For example, Tang's group[44] developed a pH-responsive bone-targeting drug delivery system. In this system, zoledronic acid and plumbagin were co-delivered with upconversion material gadolinium(III) in a mesoporous silica nanoparticle system, which could detect and treat early bone metastasis of breast cancer. Still, challenges exist for the co-delivery strategies for theranostics, such as their ability to provide high signal-to-background images[45]. Dysregulated pH, as a result of aberrant cancer metabolism, is emerging as a ubiquitous characteristic of cancer[46], and has been one of the highlights of DDS for generating high signal-to-background images for diagnostics and theranostics. Gao's group[47] pioneered the development of an ultra-pH sensitive (UPS) micellar theranostic nanoplatform with several unique properties, including tunable pH transition (pH_t spanning from 4.4 to 7.4), sharp pH responsiveness ($\Delta pH_{off/on} < 0.25$), ultrahigh fluorescence signal activation (up to 100-fold), and ultrafast pH response (<5 ms). This UPS theranostic technology has been successfully adopted for the imaging of a broad range of tumors by amplifying the tumor acidosis signals[48]. Moreover, a pH-activatable ICG-encoded nanosensor (PINS) based on the UPS systems has been fabricated for precise delineation of tumor margin. The real-time tumor-acidosis guided detection and surgery of solid tumors significantly prolonged mice survival after tumor resection[49]. The pH-responsive nanoplatform has also been applied for the efficient cytosolic delivery of antitumor agents, *e.g.*, anti-PD-1 antibody, for enhanced cancer therapy[50,51].

In addition to the conventional antitumor agents, photothermal therapy (PTT)[52,53] and photodynamic therapy (PDT)[54] are also widely adopted in theranostics. To avoid the poor signal-to-noise or even "false positive" results in conventional imaging

strategies, Yan's group[55] designed a dual-stimuli-responsive and reversibly activatable nanoprobe. Asymmetric cyanine and glycosyl-functionalized gold nanorods (AuNRs) served as the two building blocks linked by matrix metalloproteinases (MMPs)-specific peptide to achieve MMPs/pH synergistic and pH reversible activation. This nanoprobe could be activated only in tumor sites with negligible background and be implemented in fluorescence-guided photothermal therapy. During the PDT process, oxygen would be consumed to generate ROS, thus the cancer cells in hypoxic tumors are remarkably resistant to PDT. To overcome this limitation, an oxygen and Pt(II) self-generating multifunctional nanocomposite was proposed to reverse the hypoxia. Pt(IV) and chlorin e6 were loaded in the nanocomposite, induced by the near infrared (NIR) light to release Pt(II) and oxygen for the production of cytotoxic ROS and synergistic photochemo therapy to enhance antitumor efficacy[56]. Several other oxygen co-delivery PDT systems have been designed for enhanced anticancer efficacy[57].

Recently, great attention has been paid in the development of multifunctional and multimodality theranostic strategies for simultaneous cancer imaging, therapy and post-therapy monitoring, etc[58]. For example, a three-in-one system based on the porphyrin/camptothecin-floxuridine triad microbubbles (PCF-MBs) was established to act as not only a contrast agent for ultrasonic/fluorescence bimodal imaging but also a multimodal therapeutic agent for synergistic chemo-photodynamic therapy[59]. In addition, hollow manganese dioxide (H-MnO_2), as a biodegradable nanomaterial, was utilized to load Ce6 and DOX for tumor microenvironment (TME)-specifically imaging and modulating the hypoxic TME, which led to comprehensive anti-tumor efficacy and immune responses[33].

Mechanistic understanding of tumor biology has propelled the development of a variety of multifunctional strategies for the precise cancer theranostics[60–62]. Hence, it is of great importance to design stimuli-responsive drug delivery system dependent on the TME and external stimuli to selectively release therapeutic and imaging agents at the appropriate intervals and locations.

2.3. *Biomimetic delivery strategy*

Biomimetic drug delivery system (BDDS) is a novel strategy for nanosystems which works by mimicking the unique structures, functions and biosynthetic pathways of biological systems (the whole cells, structures or composition of cell membrane, and the natural budding processes of exosome)[63–65]. BDDS has advantages of high biocompatibility, low immunogenicity, long systematic circulation and lesion targeting[64–66]. It has been widely exploited for biomedical applications, including targeted delivery of therapeutics and diagnosis of diseases, tissue regeneration and wound healing, as well as cell microreactor and blood detoxification[67–71]. The development of such biomimetic systems is mainly focused on cell membrane-camouflaged nanoparticles, extracellular vesicles, lipoprotein-coated nanoparticles, virus-like nanoparticles, and others.

Cell membrane-coated nanoparticles are developed by cloaking natural cell membrane on synthetic nanoparticles, which preserves the properties of donor cells including long circulation, disease site targeting and immune evasion. Zhang's group[72] exploited erythrocyte membrane-coated nanogels to co-deliver paclitaxel and interleukin-2 for combinatorial immunochemotherapy. The biomimetic nanogels could responsively release drugs, improve drug penetration, and remodel the tumor microenvironment with enhanced antitumor effect. Cancer cell membrane-cloaked nanoparticles exhibited specific homologous-targeting property of cancer cells for targeted drug delivery and reserved tumor associated antigens for inducing multiantigenic immunity[73,74]. Inspired by the targeting ability of inflammatory neutrophils towards circulating tumor cells (CTCs), this neutrophil-mimicking nanoplatform showed selective depletion of CTCs and prevention of the formation of metastatic niches[75].

Extracellular vesicles (EVs) are nano-sized membrane vesicles mainly classified into exosomes (30−100 nm) and microvesicles (100−1000 nm, MVs), which are produced in different pathways. Both can mediate intercellular communication and regulate the occurrence and development of diseases. EVs have multiple advantages as drug delivery vesicles owing to their biocompatibility, low immunogenicity and intrinsic cell targeting properties. Wu et al.[76] constructed dendritic cells derived antigenic MVs packed with low-dose chemotherapeutic drug, which remarkably depressed the murine melanoma and hepatic ascites growth by the combination of direct cytotoxicity and increased infiltration of immune cells. Usman et al.[77] encapsulated CRISPR/Cas9 genome editing systems and microRNA into red blood cell derived EVs and demonstrated significantly robust inhibition of target gene in leukemia and breast cancer models.

Lipoprotein-coated nanoparticles have also been extensively investigated with high biocompatibility and biomimetic properties. Nie's group[16] fabricated PEGylated phospholipid-enveloped polymeric nanoparticles for the depletion of tumor-associated platelets to enhance the vascular permeability and promote drug accumulation in tumor. Kuai et al.[78] fabricated high density lipoprotein-mimicking nanodiscs for efficient co-delivery of neoantigens and TLR9 agonist CpG-ODN to lymphoid nodes which induced robust adaptive immunity with remarkable tumor growth inhibition.

Virus-like nanoparticles generated from viruses were also investigated as distinct advantages in immunomodulation for their similar characteristics with antigen and adjuvant[79]. Similarly, empty cowpea mosaic virus-derived vesicles could be utilized as immunostimulatory reagents for activating neutrophils and eliciting enhanced antitumor immune responses with striking antitumor efficacy against various cancers[80].

BDDS has shown bright prospects in the field of biomedical application. However, just like all new-born technologies, there is still a multitude of problems to be solved before wide clinical application. These include the retention of biomimetic function or biological information, poor control of the encapsulation of chemical molecules or synthetic nanoparticles, the negative influence of *in vitro* modification or drug loading on biomimetic system itself, as well as difficulties in establishing a standardized protocol for their preparation, purification and storage[63,66,68]. In addition, it is noteworthy that allogeneic or xenogeneic biological components involved in this kind of nanovesicles formulation may cause immunogenic and/or safety concerns.

2.4. *Ligand-modified target drug delivery strategy*

Ligand-mediated target drug delivery strategy could provide improvements in various characteristics including permeation across physiologic barriers[81], penetration into target sites[82], internalization by target cells[83], and specific subcellular locations[84], etc. Originating from this strategy, the antibody−drug conjugate (ADC) has seen several marketed products, such as brentuximab vedotin[85], gemtuzumab ozogamicin[86] and trastuzumab

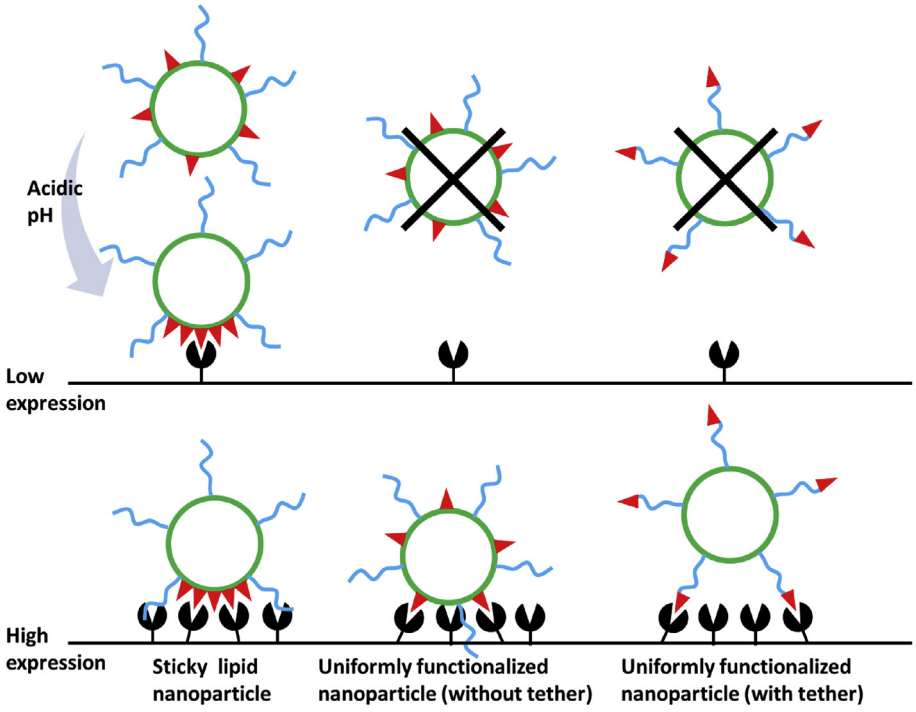

Figure 3 Schematic diagram of pH-tunable sticky vesicles, conventional uniformly functionalized nanoparticle with or without tether (PEG), and their affinity towards target cells with different receptor expressions.

emtansine[87], demonstrating the scientific significance and clinical value of ligand-mediated targeting.

The optimization of DDS has pursued the miniaturization, stability, efficiency and safety of the current design of the targeting moiety, paralleling the *de novo* optimization of the lead compound, with in-depth and interdisciplinary cooperation of chemicobiology, computational chemistry and structural biology. For example, Giralt and Teixidó's groups[88] reported the optimization of apamin for brain-targeting drug delivery. Apamin is a nature-derived bicyclic neurotoxin with proven ability to cross the blood−brain barrier (BBB). Based on the structure−function relationship, a minimized MiniAp-4 molecule was developed, with the toxic sites replaced by substituents, modifications of the bicyclic structure, and disulfide bond replaced by a lactam bond. The optimized molecule possessed even superior BBB-penetration ability *vs.* that of the parental peptide, with lowered toxicity, improved tolerance of proteases and easy preparation.

After entering systemic circulation, drug delivery systems commonly interact with various plasma macromolecules, resulting in the as-reported "protein corona". Therefore, the influence of ligand modification on their surface properties must be considered in the optimal design of targeting moieties. Guan et al.[89] reported that stabilized ^{D}CDX ligand of nAChR was liable for IgM absorption in blood circulation, inducing rapid liposome clearance. With computer-aided peptide design, a short and stable peptidomimetic ligand D8 was developed with reduced positive net charge, attenuated IgM absorption, enhanced immunocompatibility, prolonged circulation and preserved bioactivity.

In most conventional ligand-modified delivery systems, the targeting moieties distribute uniformly on the vehicle surface, with only a small proportion participating in the interaction with target cells, causing limited recognition ability as well as incomplete utilization of ligand materials. Sempkowski et al.[90] reported when aiming at target cells with relatively low receptor expressions ($<2 \times 10^5$ copies/cell), or at target tissues with heterogeneity (*e.g.*, tumor), the increased requirement of ligand density would largely restrict the application of targeted delivery. This group's approach was to construct "sticky" lipid nanoparticles with ligands changing into clusters in response to acidic pH, providing significantly enhanced recognition of target cells (Fig. 3). Lateral phase separation of lipids such as DPPS exhibited environmentally responsive lipid heterogeneities, forming clustered microdomains of ligands conjugated to these lipids. This increased ligand density and recognition in target tissues in acidic environments, and reduced specific interactions with normal cells with low receptor expressions.

Besides direct modification on the vehicle surface, a new strategy has been developed for the presentation of ligands. In this approach, the cavity formed by molecular imprinting acts as a recognition molecule to match the target receptor. Taking p32 receptor as template molecule, Zhang et al.[91] used conformational epitope imprinting to fabricate a targeted delivery system *via* one-pot synthesis with the fabricated cavity as stable targeting moiety, providing strong affinity towards the target protein as well as controllable modification density. As a mature and controllable technology, molecular imprinting might see further application in targets which could hardly be recognized. The folate receptor (FR) is highly expressed in various malignancies, with intense research and application in targeted delivery. However, endogenous folate in human body imposes restrictions on FR-targeted delivery, *e.g.*, folate-free medium and low folate diet are usually required in the *in vitro* and *in vivo* experiments to avoid competitive binding. With molecular imprinting, Liu et al.[92] adopted the non-folate-binding sites in FR as templates, giving rise to optimized ligands with high affinity and unaffected by endogenous molecules. This study provides new strategies for the targeted delivery system based on endogenous ligands.

3. Emerging techniques for drug delivery

Advances in other specific technologies have also improved modern drug delivery systems. Several of these are discussed below.

3.1. 3D printing-based drug delivery technology

3D printing is a layer-by-layer process technology capable of producing 3D drug delivery formulations from digital designs. 3D printing has been termed as an "additive manufacturing" technology by the American Society of Mechanical Engineers[93]. Sachs and Cima[94] published the first 3D printing drug paper in 1996. As compared with conventional technology, 3D printing possesses unique advantages for fabrication of complex, personalized and on-demand products. These advantages are crucial to improve the safety, efficacy, and accessibility of medicines[95]. In the past 3 years, 3D printing technology has made breakthroughs in the field of personalized medicine.

Fused deposition modeling (FDM) is the most widely used 3D printing technology for the preparation of special drug dosage forms. Goyanes et al.[96] first proposed the concept of FDM 3D printing tablet in 2014. Thereafter, FDM-based 3D printing technology has been applied for the fabrication of various drug delivery formulations including fast or controlled release tablets[97,98], time delayed capsules[99], multilayer capsules[100], T type intrauterine implant system[101], personalized percutaneous patch[102], and drug-eluting stents or implants[103]. For example, Gaisford's group[104] reported the fabrication of fast release tablets using FDM 3D printing. The drug release profiles of the tablets could be readily modified by adjusting the printing parameters.

For fabrication of controlled drug delivery formulations, Pan's group[105] reported a double-chamber drug delivery device by combining FDM 3D printing with HME. They formulated glipizide (anti-diabetes drug)-loaded drug delivery tablets with a dual-nozzle 3D printer, and formulated a double-chamber device composed of a tablet embedded within a larger tablet, each chamber contains different amount of glipizide. The double-chamber design can facilitate both fast and delayed drug release by reasonably adjusting drug distribution in the chambers, which is promising for on-demand drug delivery. Similarly, Rantanen's group[106] reported a customized approach to modify the drug release kinetics for flexible dosing and precision medication. They first co-extruded nitrofurantoin, Metolose® and polylactic acid into filaments with up to 40% Metolose® content, and subsequently 3D printed the filaments into model disk geometries. Nitrofurantoin release from the disks could be coordinately adjusted by Metolose® loading, with increased drug release for higher Metolose® loads. This study demonstrated the potential of drug-loaded feed materials for 3D printing of precision drug products with tailored drug release characteristics.

For the fabrication of drug-loaded eluent, Sandler's group[103] reported drug-containing T-shaped prototypes of intrauterine system (IUS) by using 3D printing. The drug release profiles from the printed devices were faster than that from the corresponding filaments due to decreased drug crystallinity in IUS, and the differences in the external/internal structure and geometry between the products. This study demonstrated that 3D printing is applicable for developing drug-containing IUS and might open new avenues for the fabrication of controlled release implantable devices.

Overall, 3D printing is unique for the preparation of personalized biomedical devices, which is emerging as a novel process technology for development of novel drug delivery formulations and drug-loaded devices on demand. Up to May of 2016, FDA had approved more than 85 personalized medical products including one orally disintegrating 3D printing drug, levetiracetam tablets (trade name of SPRITAM®)[107]. On 5th of December, 2017, the FDA released the world's first technical guideline "Technical Guideline for Additive Manufactured Medical Devices" for 3D printing of biomedical products. In the "Made in China 2025" Plan issued by the State Council of China, extensive efforts have been devoted to 3D printing, particularly, in the fields of biomedicine and high-performance biomedical devices. Given the unique advantage of 3D printing to develop complex products, 3D printing should be of wide application for personalized medicine.

3.2. Microneedle-based transdermal drug delivery technology

Microneedle (MN) technology has greatly accelerated the development of transdermal drug delivery system (TDDS). Due to the microscale size of the needles, the microneedle is able to penetrate the stratum corneum barrier of the transdermal delivery systems without reaching the nerve fibres and blood vessels. Therefore, the MN is painless and convenient in its application with the ability to avoid hepatic first pass metabolism as well as realize sustained release[108]. MNs are classified into solid MN, coated MN, dissolving MN and hollow MN according to the shape and use of MNs. Each of the MN has pros and cons. A solid MN punctures the surface of the skin, and then drugs can be applied to the skin for slow diffusion of drug through the pores and into the body. Although it can prevent pathogenic infection, the drug delivery effect is low. Coated MN is used to coat a water-soluble drug. The MN is attached to the skin, the drug is quickly delivered to the skin, and then the MN is removed. It is suited to deliver a very small fixed amount of drug, but the remaining MN is dangerous because it can infect other people[109]. Dissolving MN is suitable for many biomacromolecules and vaccines, since sustained release of antigen from MN could induce a better cellular immune response than fast release[110]. Dissolving MN improves the disadvantages of the coated MN by delivering large doses of drug, but it is difficult to transfer a fixed amount of drug[111]. Many techniques have been developed on the basis of dissolving MN, such as tip-concentrated MN, rapidly dissolving MN, double-layered MN, according to specific requirements[112]. Hollow-shaped MN has a hollow core inside the needles where the drug is released. Owing to precision control for drug delivery, hollow MN has been a promising strategy for both bolus and basal insulin administration[113]. Several hollow microneedle-based/assisted products have been approved and produced commercially used for clinic such as BD Soluvia™ and MicronJet 600™ as influenza vaccines[114]. The current fourth-generation self-adjustable TDDS based on MN technology could precisely control the amount and duration of drug release in response to the pathophysiological condition of patient.

Some coated MN can self-regulate through the environment, and two strategies can be used for developing self-adjustable MNs, mainly on the basis of the dissolving MN. One is represented by Kim[115,116], in which wearable biosensors and advanced transdermal delivery schemes are seamlessly integrated. This kind of design is not really "smart" and the drug release relies on external stimuli control. The other is closed-loop drug delivery strategies, also known as smart patch, which can intelligently

govern the drug release kinetics in response to the fluctuation of physiological parameters. The following are several examples of glucose-responsive insulin smart patches. One imitating the function of pancreatic cells loaded with insulin and glucose oxidase (GOx) enzyme has been developed with hypoxia-sensitive hyaluronic acid conjugated with 2-nitroimidazole. Under hypoxic conditions, 2-nitroimidazole is converted to hydrophilic 2-aminoimidazoles through bioreduction and thereby induces insulin release[117]. Another smart patch uses dual-responsive (hypoxia and H_2O_2) vesicles fabricated by self-assembly of hypoxia and dual-sensitive diblock co-polymers, which shows a pulsatile release of insulin and efficiently regulates the blood glucose in type I diabetic mice for 10 h[118]. Another patch reported by Tong et al.[119] uses a system which integrates glucose- and H_2O_2-responsive polymeric vehicles. After transdermal administration to diabetic rats, the insulin release was controlled from glucose- and H_2O_2-responsive elements. A smart thrombin-responsive MN system was described in which heparin release was successfully triggered by thrombin-cleavable peptides interlinked within hyaluronic acid hydrogel scaffolds in the presence of rising thrombin levels[120].

Although a large amount of literature claimed safety and non-irritation of MNs, several clinical phase I studies reported that skin irritation and patch application uniformity are still major obstacles[121,122]. The MN applicator and its parameter settings have crucial roles for MN penetration and subsequent dissolution into skin. The next-generation transdermal drug delivery system will plausibly be a single device of multi-functional integration. In addition, patient-tailored transdermal drug delivery will be very likely available in the foreseeable future with the development of co-application between sensing and therapy.

3.3. *Nanocrystals*

Unlike polymeric nanoparticle formulations, nanocrystal suspensions are generally stabilized by surfactants or polymeric steric stabilizers, and their particles are composed of 100% active pharmaceutical ingredients (APIs) without any carriers or vehicles. A reduction in particle size leads to an increase in dissolution rate due to an increased surface area and an enhancement in saturation solubility of the drug. Therefore, the nanosuspension approach can be very advantageous for poorly water-soluble drugs with size-related dissolution limitations. Several clinical available products using nanocrystals technique have been approved, such as the Rapamune, TriCor, Emend, Megace ES, Triglide, Cesamet, Theodur, Naprelan, and Invega sustenn[123].

The use of nanocrystals substantially reduces the amount of excipients needed in the formulation compared to other nanocarriers, and thus ultra-high loading capacity is easily achieved. Therefore, nanocrystals are considered as the ideal candidates for i.v. delivery, and several poorly water-soluble drugs have been formulated as nanocrystals for i.v. administration[124–128]. However, during the development of drug nanocrystals for i.v. administration, one must keep in mind that the nanosuspensions are usually surface modified just by stabilizer adsorption, so the stabilizer may rapidly shed off from the nanocrystal surface and the hydrophobic interface would be exposed upon enter the blood stream, resulting in rapid recognition of opsonin proteins and rapid elimination *via* phagocytic cells.

With the aid of better adhesion to mucosal surfaces, nanocrystals are frequently applied to mucosal route of administration, including pulmonary and ophthalmic[129–132]. For pulmonary drug delivery, rapid drug dissolution following inhalation is necessary; otherwise the atomized particles could be cleared away through mucociliary transport. Optimization of local bioavailability of inhaled nanoparticles requires consideration of dissolution, particle aerodynamics and tissue penetration. Because the aerodynamic diameter of the respirable particles ranges from 1 to 5 μm, recently nano-in-microparticles are designed for deep lung deposition, with the purpose of reconciling the advantages of nanocrystals with the aerodynamics of small microparticles. Once nano-in-microparticles reach the alveolar surface, the micron skeleton (mainly sugars, *e.g.*, trehalose) easily dissolves in alveolar fluids and the drug nanocrystals are rapidly outwardly exposed[126].

Regarding ocular drug delivery, conventional formulations usually result in very low bioavailability (usually <5%) due to rapid blinking reflex and lacrimation. Accordingly, efforts have been made to prolong the retention of drugs. Romero et al.[133] prepared a cationic nanocrystal formulation containing dexamethasone acetate nanocrystals and polymyxin B for ophthalmic application, in which the generation of the positive charge was achieved by the addition of cationic excipients cetylpyridinium chloride and benzalkonium chloride. *In vitro* mucoadhesion test results showed the potential of increased mucoadhesion of such cationic nanocrystals compared to standard eye drop formulations.

Although many cosmetic products exploiting the nanocrystal principle are available on the market, dermal delivery of nanocrystals has not been widely used and there are no nanocrystal pharmaceutical products for dermal application in the market. Nanocrystal products were expected to achieve deep skin penetration of poorly soluble agents in a size-dependent manner[134]. Recently, Pireddu et al.[135] produced diclofenac acid nanocrystals as a novel approach to treat skin inflammation. *Ex vivo* transdermal delivery experiments demonstrated that nanocrystal formulation could produce a higher accumulation of diclofenac in the skin compared to the commercial formulation (Voltaren). Moreover, the nanosuspension provided an *in vivo* anti-inflammatory effect similar to that of a commercial formulation, but with a higher inhibition of myeloperoxidase activity in the damaged tissue (86%) *vs.* the commercial formulation (16%).

Various inventions have been described for the preparation of nanosuspensions[136,137]. Generally, these methods require expensive equipment, or use high power consumption processes. Recently, some simple and low-cost approaches have been reported[138–140]. Although most commercially available nanocrystal-based products are oral dosage formulations, recent work has reported use for i.v. administration. Unique advantages have also been found for delivery to the lung, eye and skin.

3.4. *Prodrug nanomedicines*

Prodrugs are bioreversible derivatives of drug molecules that are generally inactive but can be transformed into their active forms *via* chemical or enzyme-catalyzed reactions[141]. The prodrug nanomedicines (PNs) based on the molecular self-assembly of amphiphilic prodrugs were developed decades ago[142,143]. They were named as self-assembled drug delivery systems (SADDS), prodrug self-assemblies, or nanodrugs. The advantages of PNs over traditional drug carriers have led to increased interest in PNs in the fields of pharmaceutics and nanomedicine (Fig. 4). Anticancer and antiviral drugs are commonly used parent drugs for PN design[142,144–147]. For example, the anti-cancer prodrugs paclitaxel and gemcitabine have been widely studied due to their higher

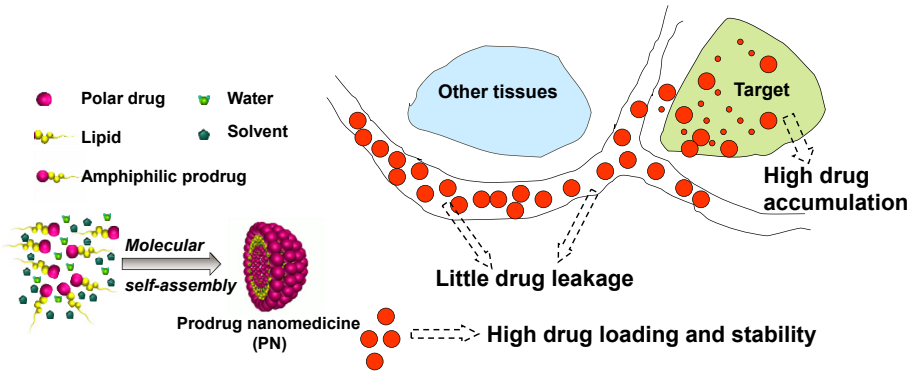

Figure 4 Formation and advantages of prodrug nanomedicines (PNs).

loading efficiency, stimuli-responsive drug release and enhanced therapeutic efficiency[144,148–150]. Clinically used prodrugs occupy about 5%–7% of the drugs approved worldwide[151].

Unlike traditional nanocarriers, both the chemical and physical stability of prodrugs in PNs are important. To enhance accumulation of parent drugs in target tissue, functional linkers are usually embedded in prodrug for tissue targeting[145], enzyme-triggered release[152], pH-triggered release[153], or redox-triggered release[150]. For instance, hepatocyte targeting of PNs was achieved by coating with D-galactide polyoxyethylene cetyl ether[152]. Lipid–CPT conjugate (CPT-SS-PA) was synthesized by conjugation of CPT and palmitic acid *via* a disulfide linker[154]. The results indicated that CPT-SS-PA SLN maintained chemical structural stability in simulated physiological environments but exhibited quick reduction-response release of CPT in the presence of DTT. In addition, pH-responsive prodrug system based on pH-sensitive amphiphilic diblock copolymer conjugated through acid-labile *cis*-aconityl moiety (mPEG-*b*-PAE-*cis*-DOX) have been fabricated which can self-assemble into DOX-conjugated PMs (DOX-*cis*-PMs)[148]. Antitumor experiments in tumor-bearing mice demonstrated that the pH-responsive nano-prodrug system effectively enhanced the therapeutic efficacy in comparison to free drug.

Prodrug nanomedicine self-assembled by amphiphilic prodrug usually achieves high drug loading and stability[153,155,156]. pH-responsive micellar nanoparticles are prepared by self-assembly of an amphiphilic poly(ethylene glycol)-acetal-paclitaxel (PEG-acetal-PTX) prodrug, and free PTX can be encapsulated in the hydrophobic core of the nanoparticles. These nanoparticles exhibit excellent storage stability for over 6 months under normal conditions, and have a high drug loading capacity of 60.3%[157]. The cRGD-decorated polymersomal mertansine prodrug (cRGD-PS-DM1) has been readily fabricated from cRGD-functionalized poly(ethylene glycol)-*b*-poly(trimethylene carbonate-*co*-dithiolane trimethylene carbonate) with simultaneous loading of mertansine (DM1) *via* thiol-disulfide exchange reaction and disulfide cross-linking of polymersomal membrane. The study showed that cRGD-PS-DM1 has high drug loading, superior stability, and fast responsive drug release[156].

As discussed above, PNs are continuing to develop as a popular DDS. As an interdisciplinary product, the study of PNs needs the participation of the scientists in multiple disciplines to achieve success of the design and molecular simulation of prodrugs and PNs, the preparation of them (especially large scale production), investigation of their properties and *in vitro/in vivo* behavior, and clinical studies.

4. Inorganic materials for drug delivery

Inorganic nanomaterials are also widely explored as potential materials for delivery systems[158–166] due to their unique and superior physicochemical properties, such as facile preparation/modification, good biocompatibility and storage stability[167]. Although many challenges need to be overcome, significant progress has been made in recent years based on various materials, *e.g.*, black phosphorus, mesoporous silica, metal-organic framework (MOF)[168], carbon nanomaterials[169], magnetic nanomaterials[170], as well as their combinations[171].

Mesoporous silica nanoparticles (MSNs) with unique properties have attracted increasing interest for drug delivery applications[172]. Zeng et al.[160] demonstrated a novel pH-responsive MSNs that is gated by the delivered DOX itself *via* a reversible covalent bond. The paradigm shift, caused by bypassing the use of auxiliary capping agents, could simplify inorganic nanomaterials and allow MSNs to function as intelligent drug carriers for therapy of cancer and other diseases. Cheng et al.[41] designed a cancer-targeted nanoparticle delivery system based on a DOX-gated MSN encapsulated with permeability glycoprotein (P-gp) small interfering RNA (siRNA) and a polydopamine (PDA) outer layer for DOX loading and folic acid decoration. The multifunctional nanoplatform tactfully integrates chemotherapy agents (DOX), gene (P-gp siRNA), and photothermal (PDA layer) substances in one delivery system. In another work, a nano-delivery system of D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS)-functionalized PDA-coated MSNs was designed for sustainable and pH-responsive delivery of DOX for therapy of drug-resistant non-small cell lung cancer[173]. The MSN-based drug delivery platforms are capable of delivering other hydrophilic and hydrophobic drugs or both (Fig. 5). Quan et al.[174] fabricated lactosaminated MSNs targeting the asialoglycoprotein receptor for anticancer drug delivery.

Although MSN is a promising carrier in drug delivery, the slow degradation and metabolism of MSN presently limit its use. In order to solve these problems, some novel mesoporous silica nanoparticles with rapid degradation rate have been synthesized. Zhao's group[175] developed uniform monodispersed three-dimensional dendritic mesoporous silica nanospheres with rapid simulated biodegradation, which were completely eliminated within 24 h. Choi and Kim[176] promoted the degradation of MSNs in a physiological condition by surface coating of polyethyleneimine (PEI) based on its proton-sponge effect. Efforts have been made to fabricate multi-stimuli responsive surfaces on MSN for environmentally sensitive, site-specific drug delivery

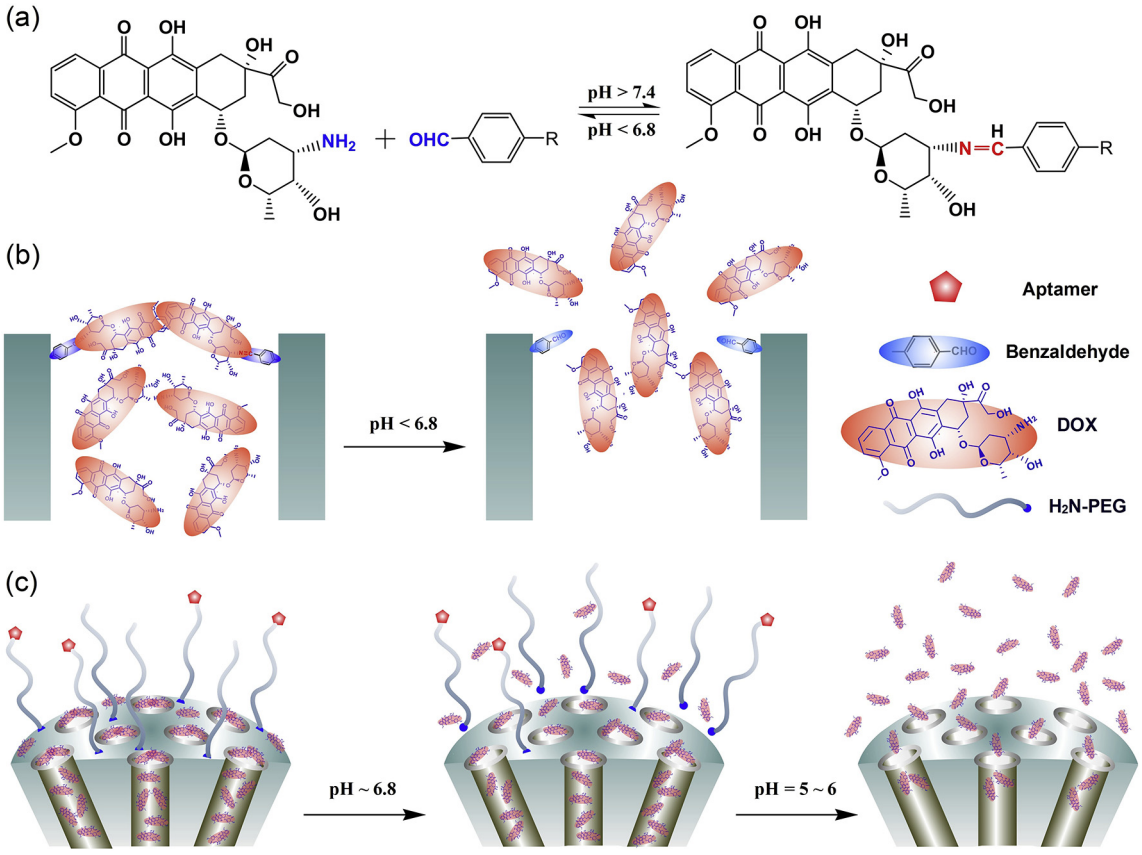

Figure 5 a) The dynamic interaction between DOX and benzaldehyde *via* pH-sensitive benzoic−imine bond. b) Schematic illustration of the drug DOX self-gated MSNs with pH-responsive drug release property. c) Dynamically PEGylated and DOX self-gated MSNs with site-specific drug release at weak acidic tumor tissue/cells.

with rapid degradation[159]. Wu's group[177] embedded the gelator within the mesopores of silica nanoparticles (MSNs) and formed low molecular weight gel (LMWG) as a gate to fabricate a dual pH and glucose responsive nano drug delivery system. Aiming at easy aggregation in saline buffers and limited circulation lifetime of MSNs, Su et al.[178] fabricated laser-responsive MSNs which supported RBC-mimetic nanoparticles with a long circulation time and controlled tumor drug release, to realize efficient anticancer drug delivery. Chai et al.[179] developed a red light (660 nm)-responsive drug delivery system based on low-cost cyclodextrin (CD)-gated MSNs containing a photodynamic therapy (PDT) photosensitizer (Chlorin e6, Ce6). The designed CD-gated MSNs are promising to improve the efficacy of PDT and chemotherapy while decreasing the side effects in cancer treatment.

Black phosphorus nanosheets (BPNS) are novel two-dimensional (2D) inorganic nanomaterials which are regarded as a promising candidate for drug delivery platform for synergistic chemo/gene/photothermal therapy[158]. Tao et al.[158] demonstrated the promising application of BPNSs as a robust drug delivery platform, thus opening up an exciting new research point of BP inorganic nanomaterials as a drug delivery carrier. In addition, Zhao et al.[180] elucidated the endocytosis pathways and intracellular trafficking of PEGylated BPNSs in cancer cells; this information is essential for understanding how BP and other emerging 2D inorganic nanomaterials can best be used for cancer theranostics. However, BP is very reactive to water and oxygen, leading to compositional and physical changes. The lack of water- and air-stability under ambient conditions impedes BP's progress in drug delivery applications. Zeng et al.[181] developed a simple polydopamine modification method to improve the stability and photothermal performance of bare BP nanosheets in order to fabricate a stable multifunctional co-delivery platform for the targeted synergistic chemo/gene/photothermal therapy against multidrug resistant cancer. Furthermore, other single atom nonmetal 2D inorganic nanomaterials have also shown considerable potential in DDS. In recent research, a type of ultrathin boron nanosheets (B NSs) was fabricated through a novel top-down method by coupling thermal oxidation etching and liquid exfoliation technologies. Based on the PEGylated B NSs, a novel photonic drug delivery system was explored, which exhibits multiple promising advantages for cancer therapy and imaging, including excellent biocompatibility, high drug-loading capacity, triggered drug release by NIR light and moderate acidic pH, and multimodal imaging properties (photothermal, photoacoustic, and fluorescence imaging)[161].

5. Gene drug delivery

With high selectivity and bioactivity, the gene drugs (such as siRNA, microRNA, pDNA and CRISPR/Cas9) have gained increasing attention, especially the successful marketing authorization application of siRNA-based drug (named Patisiran)[182−184]. However, in spite of the outstanding potential and rapid advances, only a few gene drug formulations have been applied to clinical

therapy. Poor pharmacokinetic properties are thought to contribute to limited efficacy of these formulations, which include low stability in the circulation, poor tissue-targeting ability and degradation in lysosomes[183]. To combat these severe challenges, various delivery strategies have been developed to improve clinical application of gene drug.

In order to improve the gene delivery stability in circulation, PEGylation, one of the most common approaches, can enhance colloidal stability and reduce opsonization and clearance by the mononuclear phagocyte system (MPS). Chen's group[185] developed pH-triggered PEGylated nanoparticles, in which the negatively charged siRNA was complexed by PEI and PLG to form the siRNA-loaded complex and further tightened by PEG. The PEG corona was stable during circulation but could be detached at tumor sites for facilitating the cellular uptake. In addition, researchers also attempted to encapsulate gene drug in the core of nanoparticles[144,186]. Sarett et al.[144] reported that siRNA hydrophobization through conjugation to palmitic acid could entrap siRNA in the hydrophobic core to improve stability, *in vivo* pharmacokinetics, and tumor gene silencing of PEGylated nanopolyplexes (siPA-NPs) compared with unmodified siRNA. Furthermore, Zou et al.[186] designed peptide-functionalized reversibly crosslinked chimaeric polymersomes, in which siRNA was completely and tightly loaded into the aqueous lumen. In contrast to common polycationic systems, the siRNA-loaded polymersomes were stable in blood circulation and had a low systemic toxicity due to disulfide crosslinking of the polymersomal membrane and effective stealth by PEG on the outer surface.

For improving cellular uptake of gene drug, some naturally available substances have been widely used in some work due to their natural internalization pathway through receptor-mediated endocytosis. Li et al.[187] selected unmodified human apoferritin to encapsulate siRNA and achieve high transfection efficiency in human tumorigenic cells, human primary mesenchymal stem cells (hMSC) and peripheral blood mononuclear cells (PBMCs) at low siRNA concentrations (10 nmol/L). Additionally, cell penetrating peptides are also used to efficiently carry gene drug into cells which are not depend on classical endocytosis. Xu et al.[188] developed a NP platform that could achieve TME pH-triggered rapid disassembly of NPs and exposure of tumor cell-targeting and penetrating peptide TCPA/siRNA complexes for enhanced cell uptake. Moreover, surface charge switchable nanoparticle is another common approach to improve cellular uptake. Wang et al.[189] developed nanoparticles by conjugating 2,3-dimethylmaleic anhydride (DMMA) molecules to the surface amines of PLGA-PEI micelles and used to delivery siRNAs. The nanoparticles remained negatively charged in physiological condition and positive surface charge was converted to facilitate cellular uptake of siRNAs due to tumor-acidity-activated shedding of DMMA.

After cell internalization, most of siRNA are trapped in the endosomes and further transported to late endosomes/lysosomes[190]. In order to improve gene silencing efficiency, some functional materials have been widely used to enhance endosomal escape and release therapeutic cargoes into the cytoplasm. He et al.[191] constructed lipid-based liquid crystalline nanoparticles that can perform high-efficient endosomal membrane fusion induced by the conformational transition of lipids in the intracellular acidic environment, resulting in direct release of free siRNA into cytoplasm. Wang et al.[192] present a novel strategy by using near-infrared (NIR) laser irradiation to activate "bomb-like" nanoparticle to generate heat by the coencapsulated ICG and then to produce CO_2 and NH_3 gases from the coencapsulated ammonium bicarbonate (NH_4HCO_3), which helps to efficiently break the endosomes/lysosomes and enhance the cytosolic release of the encapsulated miR-34a. He et al.[193] reported a hybrid nanoparticulate system based on a cationic helical polypeptide PPABLG for the efficient delivery of TNF-α siRNA. The pore formation feature of PPABLG was used to facilitate the direct translocation of cell membrane, as well as endosomal escape of TNF-α siRNA.

6. Peptide and protein drug delivery

Peptide and protein drugs, including antibodies and vaccines, increased rapidly among the novel therapeutics in the past three decades[194]. Compared with chemical drugs, peptides and proteins possess higher specificity and potency, as well as less adverse effects. However, they are significantly different in the physicochemical and biological properties with chemical molecules, primarily involving large molecular weight, poor stability, and low permeability, which lead to the limitation of their formulations.

Parenteral administration is the first choice for clinical application of peptides and proteins due to their intrinsic properties. Therapeutic proteins have increasingly been developed as subcutaneous injection, a route which offers many significant practical benefits[195]. Peptides and proteins are prone to degradation by enzymes and therefore usually have short half-lives *in vivo*. Encapsulation into micro- or nanoparticles with biocompatible and absorbable polymers can provide protection and sustained release for these extremely vulnerable macromolecules to achieve prolonged efficacy[196]. An alternative strategy is loading peptides and proteins into *in situ* forming depots, which can be injected as viscous liquids and subsequently solidified to hydrogels triggered by the local microenvironment[197] or to implants driven by self-assembly[198]. The common characteristic of these delivery systems is ease of preparation and administration with a standard syringe. Payloads can be released for several weeks.

Great efforts have also been paid for non-invasive delivery of peptides and proteins, among which oral administration is of most interest to improve patient compliance. Oral administration is a preferred method for drug delivery, though achieving effective drug delivery of biomacromolecules is especially challenging due to the multiple absorption barriers presented in the gastrointestinal (GI) tract including the harsh GI environment for biomacromolecules, the trap of mucus and the impermeability of epithelial cells. Proper encapsulation by delivery systems could provide protection for the biomacromolecules, and help to bypass the absorption barriers.

Peppas's group[198] recently reviewed the challenges to deliver peptide and protein orally, and discussed the possible approaches. These include the aid of permeation enhancers, protease inhibitors, and polymeric or polysaccharide carriers. Although the oral bioavailability has been significant improved by these approaches, it is often limited to 0.5%−1.0% in clinical trials compared to i.v. or s.c. administration[199]. A typical example is oral administration of semaglutide in a tablet formulation with the absorption enhancer *N*-[8-(2-hydroxybenzoyl)amino] caprylate (SNAC). Microenvironment-responsive hydrogel allowed for protection of protein in the stomach but release in the small intestine. Therefore, this seems to be a promising oral peptide and protein carrier[200]. Self-emulsifying drug delivery system

(SEDDS) was employed to deliver hydrophilic peptides and proteins in the presence of hydrophobic ion-pairing agents, and showed an oral bioavailability at least in the single digit percentage range[201]. The functionalized nanocarriers were also the potential candidates of oral macromolecule delivery systems[202].

For overcoming the barriers of mucus, mucus-adhesive NPs (MAPs) and mucus-penetrating NPs (MPPs) have been developed, and results have revealed that MPPs diffused more freely than MAPs, exhibiting improved distribution and access to the absorptive epithelium[203,204]. In addition, shape and elasticity are also reported to affect mucus diffusion[205,206]. For overcoming the barriers of epithelial cells, exploiting receptor/transporter-mediated pathways, such as neonatal Fc receptor (FcRn), transferrin receptor (TfR), and apical sodium-dependent bile acid transporter (ASBT), have also exhibited enhanced cellular internalization and improved permeability of loaded therapeutics[207−209]. It is worth noting that an increasing number of studies realize that the properties required for efficient mucus penetration are typically unsuitable for cellular internalization. Thus, NPs with the capacity to overcome both the mucus and epithelial cell barriers have been extensively explored[210]. Additionally, with further understanding of the physiology of epithelium, researchers are now developing NPs capable of overcoming intracellular barriers, such as lysosome-escape and exocytosis at the basolateral membranes[207,211].

Oral delivery of proteins has made significant progress, and several oral insulin and glucagon-likepeptide1 (GLP-1) analogue formulations are under clinical trials[212,213]. For example, Diasome has developed a liposomal formulation, which has been shown in phase 2 human studies to be very effective in lowering blood glucose levels in Type 1 and Type 2 diabetic patients using very low amounts of oral insulin.

Oral inhalation provides the opportunity for drugs to target the respiratory tract or alternatively be absorbed in the lung for systemic delivery. Inhalation is a particularly attractive route for peptides and proteins. One inhaled dornase alfa (Pulmozyme) and two inhaled insulin (Exubera and Afrezza) have thus far been launched into the clinic. The relative bioavailability of insulin is 33% for Afrezza, almost double the value reported for Exubera[214]. Although Exubera was subsequently withdrawn from the market, more than a dozen of inhaled protein therapeutics have entered various clinical trials for treatment of respiratory or lung diseases[215]. Protein nebulization and excipients are important parameters for the inhaled formulations. The former modulates the aerodynamic profiles of aerosols, while the latter offer opportunities to stabilize the protein.

Except for respiratory tract mucosa, buccal[202], ocular[216], and nasal mucosa[217], are all the active targets for peptides and proteins delivery. For example, Oral-Lyn™, an oral insulin spray formulation, has been developed by Generex Biotechnology to deliver insulin through buccal mucosa. When compared to insulin injection administered subcutaneously, Oral-Lyn™ shows a faster onset of action and a shorter duration of action.

Macromolecules cannot penetrate the human skin without assistance. Fortunately, recent advances in polymeric microneedles paved a way for transdermal delivery of proteins and vaccines[218]. Especially bioresponsive microneedles can be triggered by the physiological signals[219], allowing the precise, on-demand release of protein therapeutics[220,221]. Nowadays, several clinical trials are ongoing to investigate the effectiveness of microneedles for protein drug delivery, and developers of related products are optimistic for success.

In recent years, immune checkpoint inhibitors (ICI) including peptides and antibodies, have made great progress in cancer immunotherapy by antagonizing immune checkpoint proteins, promoting the activation of T cells, thereby producing anti-tumor immune effects. However, due to the frequently occurring toxic side effects, the ICI delivery has become an important topic in this field. In view of this, Wang et al.[222] have recently used the design of novel biomaterials to deliver checkpoint inhibitor antibodies to the TME to improve therapeutic efficacy. For example, a biodegradable MN has been developed to control the delivery of anti-PD-1(aPD1) to melanoma, compared with free-form aPD1, MN enhanced the retention of aPD1 in tumor microenvironment and induced a strong immune response to melanoma in B16F10 mice. In addition, MN patches could also serve as a platform for the combined delivery of other immunocheckpoint inhibitors, such as anti-CTLA4 (aCTLA4)[223]. In general, the strategy of local melanoma treatment based on biodegradable MN improved the efficacy of immunocheckpoint inhibitors and reduces systemic toxicity. Additionally, checkpoint suppression in combination with other immunomodulators showed synergistically increased antitumor activity. Wang et al.[224] demonstrated a novel vector for controlling the release of anti-PD1 antibodies and CpG oligonucleotides (CpG ODNs) in response to postoperative inflammatory conditions. DNCs (DNA nano-cocoons) contained aPD1 and inflammatory reactive triglyceride monostearate (TGMS) nanoparticles caging a restriction enzyme inside, which could specifically divide DNCs into short fragments of CpG ODNs. After injecting TGMS nanoparticles into the tumor resection site, they are digested by inflammation-related proteases and lysed, releasing caged enzymes, which cleaved DNCs into CpG ODN and released aPD1. The CpG DNA-based carrier can not only serve as the treatment loading matrix of aPD1, but also be cut into another drug CpG fragment to the active DC by enzymes, so as to improve the therapeutic effect.

7. Future perspective of drug delivery research

In the past three years, great progress in novel DDS has been achieved in the delivery strategies, construction techniques, and potential materials for improving the bioavailability, biocompatibility and therapeutic index of drugs. In fact, many presently-formulated prescription drugs have unfavorable physicochemical and pharmacokinetic properties, along with various limitations on the dosage regimen and undesirable side effects in the conventional dosage form. The development of new drug delivery systems and new formulations would be potential and promising approaches for increasing these therapeutic indices and reducing side effects. However, it should not be neglected to balance druggability and functional design, as the clinical application should be the final focus of our work. Also, decades of experience in drug research and development has demonstrated that there would be no new pharmaceutical preparations without technological innovation. It is imperative to strengthen the research and development of innovative technologies and drug delivery systems within the pharmaceutical industry. Certainly, a novel technical invention becomes an innovative technology to be applied in drug delivery system, requiring long-term testing, revision and optimization.

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