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Supramolecular interaction in the action of drug delivery systems

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Complex diseases and diverse clinical needs necessitate drug delivery systems (DDSs), yet the current performance of DDSs is far from ideal. Supramolecular interactions play a pivotal role in various aspects of drug delivery, encompassing biocompatibility, drug loading, stability, crossing biological barriers, targeting, and controlled release. Nevertheless, despite having some understanding of the role of supramolecular interactions in drug delivery, their incorporation is frequently overlooked in the design and development of DDSs. This perspective provides a brief analysis of the involved supramolecular interactions in the action of drug delivery, with a primary emphasis on the DDSs employed in the clinic, mainly liposomes and polymers, and recognized phenomena in research, such as the protein corona. The supramolecular interactions implicated in various aspects of drug delivery systems, including biocompatibility, drug loading, stability, spatiotemporal distribution, and controlled release, were individually analyzed and discussed. This perspective aims to trigger a comprehensive and systematic consideration of supramolecular interactions in the further development of DDSs. Supramolecular interactions embody the true essence of the interplay between the majority of DDSs and biological systems.

1. Introduction

Diseases exhibit a wide range of complexity, as evidenced by their diverse etiologies, pathogeneses, and clinical manifestations.[1] This complexity is further highlighted by variations in the location of the disease.[2] The current paradigm in drug development primarily centers on designing agents effectively interacting with the intended biological target. Drug therapy, when utilized as a standalone intervention, has been found to be inadequate in addressing a wide range of clinical needs and may lead to various adverse effects and complications. Approximately 40% of approved drugs exhibit limitations such as inadequate water solubility, rapid metabolism, low permeability, and insufficient elimination.[3] Thus, while various routes of administration (such as oral, parenteral, inhaled, transdermal, vaginal, rectal) exist, drug delivery is required for many diseases to meet complex clinical needs.[4]

Drug delivery encompasses the various methods, formulations, production methods, storage systems and technologies used to transport a pharmaceutical compound to its intended site of action to produce the desired therapeutic effect.[5] Since the first controlled-release formulation was approved in the 1950s,[6] drug delivery systems have been widely used in various medical fields, including cardiology, ophthalmology, endocrinology, oncology, pulmonology, immunology, and pain management.[7] Drug delivery systems can increase efficacy by targeting specific locations and controlling drug release, improve patient compliance by reducing dosages and administration invasiveness, and potentially lower drug doses needed.[8] Drug delivery is vital for human health and has rapidly expanded, benefiting millions of patients and becoming a multi-billion dollar industry.[9] However, current drug delivery strategies have not yet reached the level of specificity and efficacy envisioned by Paul Ehrlich's concept of the "magic bullet".[10] The drug delivery system faces challenges stemming from the complex and diverse improvement needs in current clinical practice.[11]

Different disease conditions and drug requirements result in diverse, even opposite, needs for ongoing improvement of clinical treatment methods. Some clinical needs are general such as improving therapeutic efficacy, mitigating adverse effects and decreasing the necessary drug dosage. In some cases, new administration methods need to be devised as patients are uncomfortable due to invasive and/or too frequent dosing. Certain drugs, such as nucleic acid drugs, are highly unstable *in vivo*, necessitating developing new methods to improve their stability. The effective treatment of many kinds of heterogeneous tumours needs personalized medicine through combination therapy.

Different clinical needs require drug delivery materials possessing all or partial capabilities of biocompatibility, efficiently and controllably loading drugs, maintaining structure and protecting drugs *in vivo*, crossing numerous biological barriers,

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tuning the spatiotemporal biological distribution, and selectively and controllably releasing drugs. Drug delivery is a multidisciplinary field that involves contributions from various fields such as material science, engineering, biology, and pharmaceutical science to develop and apply important concepts in the clinical setting. Particularly, the examination of supramolecular interactions is crucial in comprehending relationships between materials, drugs, and organisms, which would facilitate the advancement of drug delivery systems in all aspects. Supramolecular interactions are present in every stage of drug delivery systems, even if not intentionally designed, and should be considered in the design of all drug delivery systems. Clear and comprehensive summation could allow understanding the role of supramolecular interactions in the presently used drug delivery and designing new efficient and smart drug delivery systems for next-generation medical intervention.

In this perspective, we summarize the contribution of supramolecular interactions in drug delivery system, focusing on its contribution to the multiple objectives of drug delivery. The key objectives of a drug delivery system include good biocompatibility, attaining efficient and precise drug loading, robust stability prior to *in vivo* drug release, overcoming biological barriers, optimizing the spatiotemporal biodistribution, and controlled drug release. The supramolecular interactions involved in achieving these objectives were summarized and deliberated upon. The opportunities for future contributions and advances would be highlighted. Personal perspectives on utilizing supramolecular principles in drug carrier analysis and design will be included as appropriate. It serves to introduce drug delivery strategies on the market, ongoing clinical trials and in laboratory research. Currently, most drug delivery systems on the market or in clinical trials used the supramolecular unconsciously. Drug delivery systems *via* exquisite supramolecular design carried out by supramolecular chemists, to date, have not been fully evaluated clinically. Hence, the examples discussed in this perspective predominantly encompass liposomes and polymers, which widely employed in clinical applications, characterized by the involvement of supramolecular interactions. In contrast, macrocyclic delivery systems are comparatively less frequent. This review aims to call attention to the fields and act as an intellectual catalyst that takes current advances to the next step by, *e.g.*, attracting the attention of pharmaceutical chemists, physicians and preclinical researchers. Expectedly, researchers in the fields of molecular imaging and theranostics could also learn important lessons from the advances in supramolecular interactions in drug formulations as outlined in this perspective.

2. Supramolecular interactions between carriers and biomolecules influence biocompatibility

Biocompatibility denotes the capacity of a biomaterial to elicit the appropriate cellular or tissue response from the host in a given circumstance.[12] Introducing a material in body tissues can elicit various reactions, such as biomolecular corona, immune responses, inflammatory, and the subsequent repair processes, all of which are intricately intertwined with supramolecular interactions.[12] Annually, hospitals in the United States experience more than 770 000 occurrences of injury or death due to adverse drug events.[13] Drug delivery systems aim to minimize discomfort caused by the system or its insertion method.

Good biocompatibility of all drug delivery system is the premise of their successful application. The security aspect of drug delivery systems involves both the safety of the delivered drug and the biocompatibility of the delivery system. Drug carriers are often characterized by challenges in their degradation, metabolism, and elimination, as well as potential issues with immunogenicity, toxicity, and other undesirable effects. Materials perceived as inert, such as those utilized as protective barriers or in drug delivery systems, can still have an effect on their surroundings.

Liposomes, created through self-assembly of natural, nontoxic phospholipids and cholesterol, are the most widely employed and effective drug delivery vehicles for various chemotherapeutic agents.[14] For example, Doxil, the first nanomedicine of the cytotoxic drug doxorubicin, employs liposome formulation and is marketed as a chemotherapy agent for several cancers.[15] Moreover, other drugs, including mifamurtide, cytarabine, and daunorubicin–vincristine, have also been loaded into liposomes and marketed as MEPACT, DepoCyt, and Onco-TCS, respectively.[16] Despite limited understanding, the successful application of liposomes is ascribed to their favourable supramolecular interactions with biological molecules *in vivo*, thereby showing remarkable biocompatibility (Fig. 1A). For instance, hydrophilic drugs encapsulated in liposomes can enter cells *via* the distinctive fusion of liposomes with the cell membrane of eukaryotic cell or bacteria[17] facilitated by

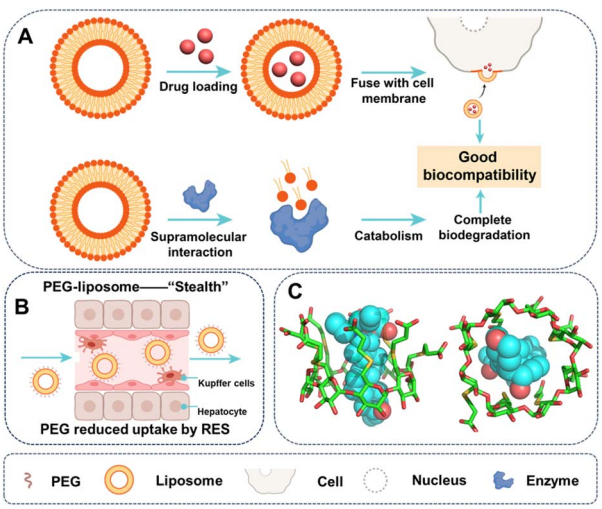

Fig. 1 Schematic illustration of (A) good biocompatibility of liposome due to proper supramolecular interaction with cell membrane and enzymes. (B) PEG modification reduced the uptake by RES through minimize the supramolecular interactions. (C) Crystal structure of the host–guest complex between the gamma-cyclodextrin derivative and rocuronium (CCDC: 172 247).

electrostatic interaction and hydrophobic interactions provided by fusogenic lipids. Furthermore, liposome could be recognized by relevant enzymes for complete biodegradation.[18]

Surface chemical modification of drug delivery systems,[19] such as PEGylation, can considerably enhance their biocompatibility by altering supramolecular interactions with biomolecules.[20,21] PEGylation could increase carrier solubility, shield the payload from plasma enzymes, prevent immune reactions, and reduce interaction with the reticuloendothelial system (RES) (Fig. 1B).[22–24] Since 1990, over 20 FDA-approved drugs have utilized PEGylation, including treatments for diseases such as severe combined immunodeficiency, hepatitis C, multiple sclerosis, and various cancers.[25] Although the mechanisms of PEGylation are not fully understood, it is conceivable that it provides physical blocking of the binding sites, and therefore decreased the supramolecular interactions, including electrostatic interactions and hydrogen bonding, which are dependent on the distance between the carrier and organism molecules. For instance, PEGylation of anti-p185^{HER2} antibody mitigates immune response, not by affecting its immune activity, but by diminishing the on rate in the binding kinetics.[26]

Supramolecular strategies provided various methods for improving the biocompatibility of drug delivery systems. One approach is to mitigate the toxicity of drugs to healthy tissues by utilizing host–guest inclusion interactions.[27,28] Macrocycles, such as cyclodextrin, are prominent subjects of study in the realm of supramolecular chemistry, and they have been used in pharmaceutical industry to enhance biocompatibility by mitigating side effect of drugs. The most effective and sophisticated example is Sugammadex, a gamma-cyclodextrin derivative marketed by Merck under the brand name Bridion.[29] Sugammadex complexed with rocuronium based on (1) augmented van der Waal and hydrophobic interactions resulting from extending the cavity depth of gamma-cyclodextrin and (2) improved electrostatic interaction through introducing carboxyl groups. The strong host–guest complexation ($K_a \sim 10^7$ M^{-1}) could reverse the effects of neuromuscular blocking agents such as rocuronium and vecuronium (Fig. 1C).[30] Another approach is the construction of drug delivery systems based on supramolecular assemblies, *e.g.* peptide hydrogels driven by hydrophobic interaction, electrostatic interactions, hydrogen bonding and $\pi\cdots\pi$ stacking, improving the compatibility of drugs.[31,32] However, synthetic or engineered drug delivery systems often face challenges of biocompatibility and immunogenicity, despite their ability to reduce drug toxicity to the carrier's level.[33] Insufficient knowledge about material–tissue interactions impedes the advancement of biocompatible materials. Therefore, developing liposome-like compatible carriers with a thorough comprehension of supramolecular interactions between carriers and organisms is essential. A comprehensive understanding of supramolecular interactions between carriers and organisms is required to create carriers that are comparable to liposomes in terms of compatibility.[34]

3. Efficient and precise drug loading based on supramolecular interactions

Efficient drug loading is a critical aspect of developing drug delivery systems. High drug loading efficiency in drug delivery system minimizes the need for carrier materials, reducing potential side effects and manufacturing costs in drug delivery systems.[35]

Amphiphilic supramolecular assemblies formed by conjugates of hydrophilic and hydrophobic drugs enable self-delivery of drugs, achieving notably high drug loading, up to approximately 100% (Fig. 2A).[36] A groundbreaking study produced an amphiphilic prodrug through the conjugation of the hydrophilic drug irinotecan, wherein the nitrogen of piperidine could be protonated and engage in interaction with water based on electrostatic interactions and hydrogen bonding, with the hydrophobic drug chlorambucil *via* a cleavable ester bond.[37] The carrier-free nanomedicine approach has been applied to the development of drug conjugates such as cisplatin–vorinostat[38] and erlotinib–curcumin.[39] Some drugs can be assembled into nanoparticles through noncovalent interactions, such as

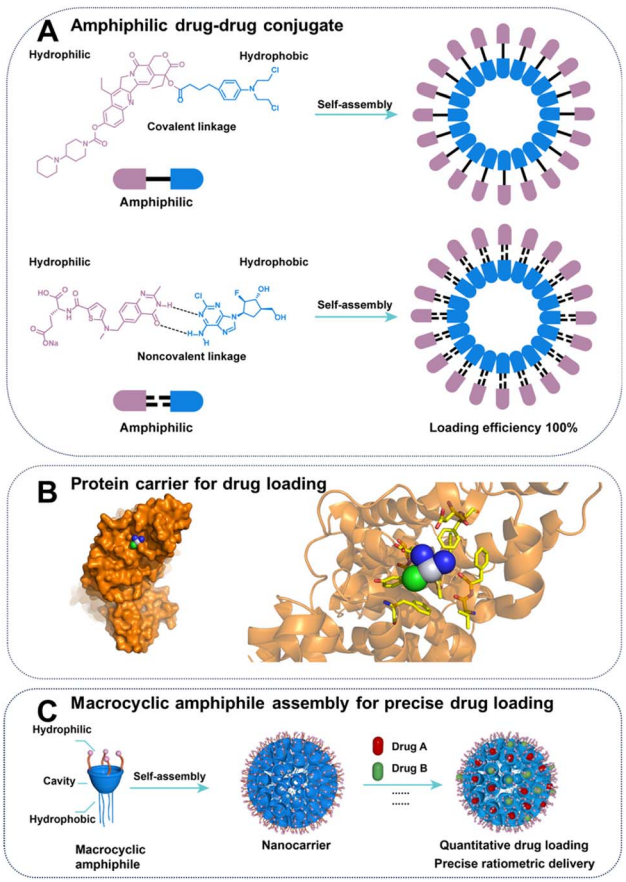

Fig. 2 Schematic illustration of (A) amphiphilic drug–drug conjugate strategy. (B) Crystal structure of albumin complexing with cisplatin (PDB ID:4S1Y). (C) Schematic illustration of the advantages of assembly of macrocyclic amphiphile for precise drug loading in combination therapy. Blue area: hydrophobic cavity and lower rim of macrocycles; pink area: hydrophilic upper rim of macrocycles.

the combination of hydrophilic clofarabine and hydrophobic raltitrexed, forming a supra-amphiphilic system that achieves ultra-high drug loading and self-delivery. Assembly of super-amphiphiles also facilitates self-delivery of drugs with high loading,[40] exemplified by hydrogen bond-mediated combination of hydrophilic clofarabine and hydrophobic raltitrexed.[41]

Drug delivery systems commonly employ porous carriers (*e.g.*, inorganic nanoparticles,[42,43] MOF,[44–46] hydrogel[47,48]) to mix with drug solutions, with drug loading primarily dependent on supramolecular interactions such as electrostatic and hydrophobic forces.[49] The low drug loading of drug delivery systems, usually only a few weight percent, were caused by not only the large molecular weight or size of the carrier, but also the absence of strong, specific interactions between the carrier and the drug. For example, although possessing high molecular weight, albumin, a protein host with specific binding sites still achieved high-efficiency loading of paclitaxel.[50] Abraxane, an albumin-bound nanoparticle formulation of paclitaxel, is a highly successful example of cancer nanomedicine, approved by the FDA for treating metastatic breast cancer with drug loading of approximately 10%.[51] The crystal structure of Abraxane has not been reported, but we can infer the supramolecular nature of its binding from the interaction of albumin with cisplatin (Fig. 2B).

Drug combinations that show synergy *in vitro* may not effectively accumulate in target tissues or cells *in vivo*, potentially limiting their clinical efficacy.[52] Clinical combination therapies often rely on empirical derivation, optimizing individual drug doses to their maximum tolerated levels, rather than on rational identification of synergistic drug doses.[53] Supramolecular assemblies have the potential to codelivery of drug combinations, in precise proportions, to the same tissue or cell, which can enhance the therapeutic effects.[54–56] Following injection, Vyxeos, a liposomal formulation containing a 5 : 1 ratio of cytarabine to daunorubicin, maintains the same drug ratio in bloodstream for a duration of 24 hours, contrasting with a rapid and independent elimination from plasma observed for a saline-based cocktail of the two drugs.[57,58] Currently, nanocarriers lack a means to accurately control drug ratios during loading and delivery, leading to inconsistencies between batches.[59] Host–guest complexation may provide quantitative drug loading at a given concentration due to a defined number of binding sites and measurable association constants.[60,61] Macrocyclic-amphiphile assemblies can load and deliver multiple drugs to tumours with precise ratios (Fig. 2C). For example, Liu *et al.* developed a drug carrier of assembles of an amphiphilic azocalixarene for complex with drug guests (paclitaxel and NLG919) based on electrostatic interactions provided by quaternary ammonium groups and hydrophobic interaction provided the deep hydrophobic cavity. Importantly, the ratio of the drugs loaded could be predicted by their binding constants and initial concentrations.[62]

Alternative drug delivery systems have the potential to offer increased capacity for drug transport. The drug delivery system NK911, composed of copolymer of PEG and polyaspartic acid, in which doxorubicin molecules were partially attached to the side chain of aspartic acid as the hydrophobic core of the micelles. Notably, the micelles can also load free doxorubicin drug component, and formed the formulation named NK911 for treatment of metastatic pancreatic cancer.[63,64] NK105, a micelle-based carrier containing paclitaxel, has been evaluated for treatment of pancreatic, colonic, and gastric tumours.[65–67]

At ambient temperature, the majority of processes dominated by supramolecular interactions, such as hydrogen bonding, π stacking, and van der Waal interactions, are dynamic and reversible, owing to the significantly lower Gibbs energy barrier compared to chemical reactions. The phenomena would simplify material construction by leveraging spontaneity, modularity, and self-correcting abilities, thereby reducing batch-to-batch inconsistencies.[68] Although numerous assemblies, including liposomes and lipid nanoparticles are in kinetic traps, their sizes can be conventionally standardized through post-drug loading extrusion processes, leveraging the dynamic and reversible characteristics of noncovalent interactions. For water-soluble siRNA, lipid nanoparticle formulations can be prepared by rapidly mixing lipid components in ethanol with an aqueous drug solution at specific pH and flow rates, triggering *in situ* self-assembly driven by hydrophobic interactions and drug loading through forming inverted micellar structures surrounding siRNA caused by the electrostatic interactions between cationic lipids and siRNA.[69] The approach has enabled the reproducible and scalable production of lipid nanoparticle-mRNA formulations, demonstrating exceptional encapsulation efficiency and uniform size distribution.

4. Stable drug delivery systems need minimizing improper supramolecular interactions before drug release at lesion site

There are at least two factors that control the stability of drug delivery formulation. The primary consideration is to minimize the undesirable drug leakage, a crucial requirement for all drug delivery systems. The second consideration is that certain drugs are unstable *in vivo* and require protection by their carrier. This section provides a summary of the advancements made in enhancing the stability of drug delivery formulations through the utilization of supramolecular approaches.

Drug carriers may become unstable under the harsh conditions encountered during circulation, such as biomolecular coronas, blood flow, phagocytic cells, and excretion. The disintegration of drug carriers primarily stems from the competitive supramolecular interactions of various biological entities in bodily fluids, potentially impacting the state of molecular assemblies.[70] In biological fluids, almost all nanomaterials are enveloped by a biomolecular corona caused by inevitable noncovalent associations with proteins, lipids, nucleic acids, and metabolites.[71,72] Biomolecular corona, particularly protein corona, would modify physiochemical characteristics of nanoparticle surface, and therefore alter their interactions with biosystems and determine their ultimate fate (Fig. 3A).[73,74] Protein corona patterns can unpredictably alter nanoparticle outcomes, such as uptake,[75] biodistribution,[76]

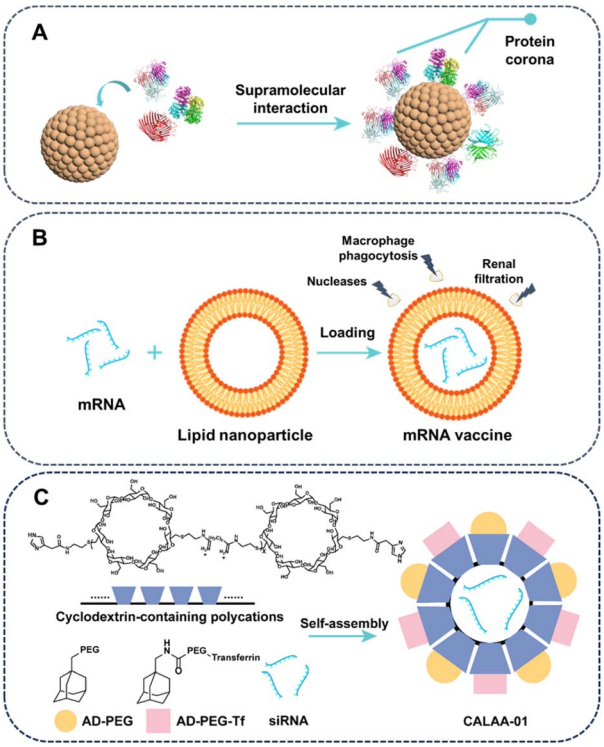

Fig. 3 Schematic illustration of (A) protein corona formation through supramolecular interactions between nanoparticles and proteins, (B) protection of mRNA by nanocarriers of lipid nanoparticles in mRNA vaccine, and (C) the self-assembling nanoparticle system CALAA-01.

immunological responses[77] and toxicity,[78] posing challenges for nanomedicine. Due to the dynamic nature of the supramolecular interactions, ambient factors like pH and ionic strength influence the corona profile and conformational changes of proteins binding onto the surface of nanocarriers. Additionally, weak noncovalent interactions enable the transient binding of numerous functional epitopes on the corona to multiple membrane receptors, thereby leading to subsequent biological effects, including the activation of cytosolic signal transduction.[79] Notably, nanoparticles can be designed to recruit plasma proteins that are beneficial to drug delivery. For example, surface modification of liposomes with a short amyloid β-derived peptide, resulting in forming plasma apolipoprotein corona-coated liposomes that can effectively target brain tissue.[80] The multifaceted roles of recognition of corona proteins in pharmacokinetics, immunoregulatory signalling, and gene expression are still not fully understood. Deciphering impact of corona protein pattern on cell internalization, tissue and organ distribution, and inflammatory cytokine secretion presents a challenge. Insufficient understanding of protein-carrier binding modes, especially for clinically used nanoparticles, hampers identification of general trends in protein corona dynamics and their relationship to paradoxical biological impacts, impeding reproducible nanomedicine development.[81,82]

Numerous short-lived drugs exhibit inherent *in vivo* instability caused by various factors, with RNA, such as messenger RNA (mRNA) and small interfering RNA (siRNA), being a quintessential example. To elicit therapeutic efficacy, mRNA molecules must target specific cells precisely and produce sufficient requisite proteins. However, extracellular nucleases, macrophage phagocytosis, and renal filtration promptly degrade and remove mRNA, with a scant 0.01% of extravasated mRNAs entering target cells.[83] Leveraging drug delivery advancements, various materials are devised to deliver mRNA *in vivo*, safeguarding it from rapid degradation by ubiquitous RNases.[84,85] In the triumphant Pfizer/BioNTech BNT162b2 and Moderna mRNA-1273 COVID-19 vaccines, lipid nanoparticles protecting mRNA through encapsulating the hydrophilic mRNA by noncovalent supramolecular interactions, such as hydrogen bonding and electrostatic interactions (Fig. 3B).[86,87] With the validation of vaccines against SARS-CoV-2 by Moderna and Pfizer-BioNTech, mRNA has shown immense potential for gene-editing and protein-based therapies.[88,89] Moreover, siRNA also faced the stability problem similar with mRNA, and exhibited biological half-life of less than an hour in human plasma. Remarkably, CALAA01, a self-assembling nanoparticle system involving the host–guest complexation between cyclodextrin-based polycations (CDP) and two guests (adamantane-PEG (AD-PEG) and adamantane-PEG-transferrin (AD-PEG-Tf)) based on hydrophobic interactions, demonstrated remarkable efficiency in protecting siRNA *in vivo* (Fig. 3C).[90] CALAA01 was the initial polymer-based siRNA nanomedicine to enter phase 1a/1b clinical trials in humans, although the trial was withdrawn due to dose-limiting toxicity caused by the instability of the transferrin targeting agent.[91]

The stability of drug carriers is profoundly affected by the interplay between their constituent materials and the surrounding environment. Carriers are cleared from the circulation mainly through interactions with reticuloendothelial system or mononuclear phagocyte system consisting phagocytes, monocytes and dendritic cells.[92] Cationic nanocarriers undergo rapid clearance, whereas neutral and slightly negative nanocarriers exhibit extended half-lives in the circulation.[93] In addition, adjuvants could co-assemble with nanoparticles to augment their stability.[94]

5. Supramolecular interactions for crossing biological barriers and regulating spatiotemporal biological distribution

Effective biodistribution and drug delivery is challenging as carriers encounter biological barriers of tissues that impede matter exchange, limiting their delivery to the target site (Fig. 4).[95] A meta-analysis of 232 data sets revealed that a median of only 0.7% of the injected dose of nanoparticles successfully entered a solid tumour in a mouse model.[95] Barriers can manifest as discernible physical structures, like skin, cornea, and gut, or less well-defined entities, such as the nerve's surrounding connective tissue. The extent and characteristics of barriers encountered by carriers, and strategies for surmounting them, are contingent upon tissue type, drug properties,

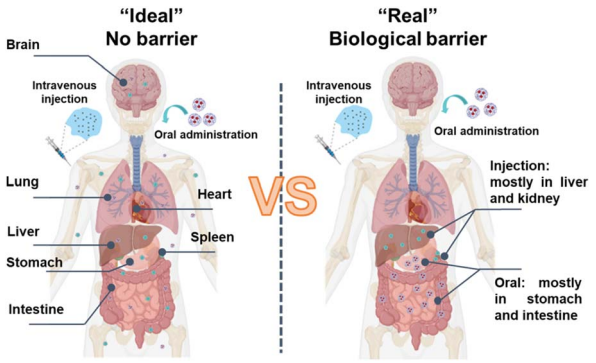

Fig. 4 Schematic illustration of drug distribution of in the absence ((left), a fictitious state) and presence ((right), real situation) of biological barriers.

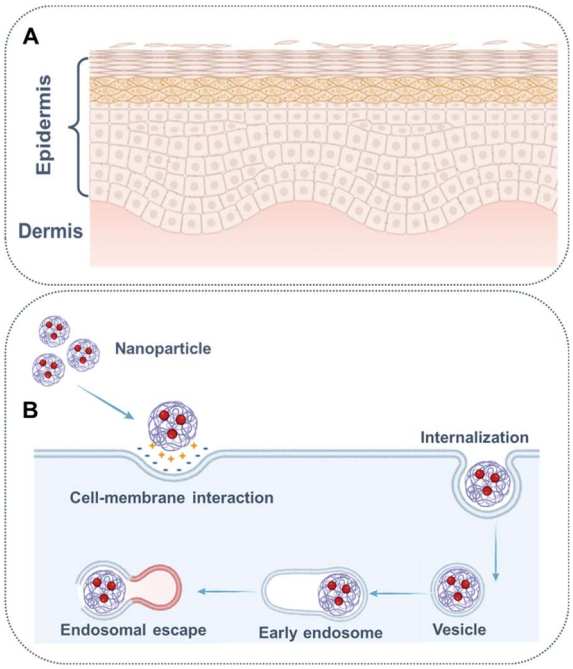

Fig. 5 Schematic illustration of (A) structure of skin and (B) internalization of nanoparticle and endosomal escape.

administration route and disease type and progression. The choice of administration routes can significantly impact organ distribution, expression kinetics, and therapeutic outcomes, a determination often guided by the properties of nanoparticles and therapeutic indications. Systemic administrations are commonly utilized due to the limitations of local delivery, which is typically restricted to diseases in easily accessible sites and frequently requires invasive procedures and intricate techniques. Drug delivery systems aim to facilitate the passage of drugs across barriers that would otherwise be insurmountable at safe and reasonable doses.

Transdermal drug administration aims to deliver drugs locally or systemically in a non-invasive manner.[96] The main barrier to drug permeation is the stratum corneum, comprising dead corneocytes (primarily cross-linked keratin) and lipids (mainly cholesterol and fatty acids) forming lamellar bilayers that occupy intercellular spaces (Fig. 5A).[97] The first type of chemical permeation enhancers (CPEs) is fluidizers, *e.g.* fatty acids, that enhance partition and diffusion coefficients by distributing into the lipid bilayers through hydrophobic interactions, facilitating the crossing of small molecules through the stratum corneum.[98] Extractors, another type of CPEs, predominantly remove lipids from the stratum corneum using solvent and surfactants, boosting the diffusion coefficient by creating pores. Moreover, transdermal drug delivery has provided valuable insights for drug delivery across other similar barriers, including CPEs for amplifying nerve penetration[99] and tympanic membrane permeability of drugs.[100] Transportation could be facilitated through receptor binding across the blood–brain barrier.[101] By altering keratin structure and disrupting lipid bilayers through supramolecular interactions with the stratum corneum,[102] Hyaluronic acid enhances the permeation of various small molecular drugs.[103] Low-molecular-weight chitosans improve the transdermal delivery of baicalin through dipole–dipole and van der Waals interactions with lipid bilayers.[104]

Human mucus consists of thick disulfide bond cross-linked fibers of hydrophilic mucin proteins, ranging from tens to hundreds of micrometers, entangled with DNA and glycoproteins.[105] Carriers employed for mucus-penetrating delivery usually possess hydrophilic properties and a neutral charge, unlike the properties needed for crossing the skin. Hydrophilic and neutrally charged PEG surface modification considerably enhanced polystyrene nanoparticle diffusion in mucus through reduced mucus interactions.[106] Additionally, coating nanoparticles containing acyclovir monophosphate with PEG-rich block copolymer poloxamer 407 significantly improved mucus penetration.[107] Inhaled vehicles have the potential to enhance pulmonary delivery, yet encounter barriers of mucus and pulmonary surfactant.[108]

Despite its popularity and acceptance, oral delivery encounters barriers in the gastrointestinal tract.[109] The gastrointestinal tract exhibits significant variations in pH levels and acidity.[109] Furthermore, a pronounced pH gradient across the mucosal barrier from neutral endothelial cell surfaces to acidic intestinal lumen exposes carriers to heightened vulnerability.[109] Macromolecule absorption in the GI tract, like insulin and antibodies, is challenging due to tight junctions between intestinal epithelial cells. Moreover, drug influx is countered by efflux transporters on GI epithelial cell membranes, like *p*-glycoprotein, actively expelling drugs post-enterocyte uptake. The transferrin pathway enables transepithelial movement in the intestines using transferrin-coated nanoparticles, which is valuable for treating colon cancer and irritable bowel disease with overexpressed transferrin receptors in the intestinal mucosa.[110]

After contacting target cells, carriers still face multiple barriers that hinder their uptake and intracellular trafficking, impacting functional delivery.[93] Anionic carriers may have difficulty contacting the cell surface due to repulsion. Cationic carriers, when excessively positively charged, have the potential

to inflict damage on the cell membrane and induce cytotoxicity.[111] Clathrin-mediated endocytosis, the main pathway for nanoparticle uptake, involves receptor–mediated interactions between nanoparticles and the clathrin-expressing regions of the cell membrane.[112] Stiffer NPs are often better internalized as their low energy barrier caused by the less tendency to deform during membrane internalization.[113]

For proper functionality, every drug must reach its designated target site, such as the nucleus (doxorubicin, platinum drugs), the cytosol, or the mitochondria, at therapeutic concentrations.[114] Upon endocytosis, nanoparticles are sequestered in endosomes that matured into lysosomes, greatly influencing the stability of both nanoparticles and drugs.[112] To evade degradation in lysosomes, materials need escape from the endosome by responding to acidic conditions and utilizing the proton sponge effect (Fig. 5B).[115] For example, within acidic endosomes, cationic polymers, such as poly(ethylene imine), acted as a proton sponge, which was partially protonation limited by the electrostatic repulsion, resulting in the bursting of the endosome and the escape of the cargos.[116,117] Furthermore, Zhang *et al.* developed an amphiphilic self-assemble of PpIX-PEG-$(KLAKLAK)_2$, wherein protoporphyrin IX (PpIX) was conjugated with the D-$(KLAKLAK)_2$ peptide by a PEG linker. The D-$(KLAKLAK)_2$ peptide moiety could target mitochondria through electrostatic interactions with negatively charged mitochondrial membrane, resulting in improved phtotodynamic therapy efficacy.[118]

6. Selective and controlled release of drugs through mechanism based on supramolecular interactions

Drug delivery systems often induce an immediate burst release, which not only results in the squandering of valuable drug cargo but also poses potential harm. For example, replacing polymeric microparticles with liposomes significantly reduces toxicity from the initial release of hydrophilic local anesthetics.[119] Accordingly, stimuli-responsive smart drug carriers that exhibit responsiveness to various physiological stimuli such as pH, redox, enzymes, temperature, and hypoxia, have emerged as a prominent focus in drug delivery research.[120] While sustained drug release patterns are commonly pursued in drug delivery systems, they may not meet the requirements of all drugs. For example, diabetics benefit from short bursts of insulin delivery.[121] This section will present the concept of controlled drug release through the implementation of supramolecular design.

Diseased microenvironments often exhibit different pH with normal tissues, such as the acidic pH in tumours or the fluctuating pH during wound healing stages.[122] Therefore, pH-sensitive platforms were developed to selectively release drugs under specific pH conditions. Hyperthermic wound sites can be targeted by temperature-responsive drug delivery systems.[123] Nutropin Depot represents a novel controlled-release system for the systemic administration of protein, achieved by encapsulating a coordination complex of zinc ions and human growth hormone within biodegradable microspheres.[124] This approach allows for sustained release of human growth hormone, facilitating the treatment of pituitary dwarfism through biweekly administration.

Corona formation can modulate drug release kinetics based on the physicochemical properties of a nanocarrier, the corona itself, and factors such as pH and temperature. However, the influence of corona on release kinetics of stimulus-responsive nanocarriers are still not well understood.[125] Future research should investigate the protein corona's role on stimulus-responsive nanocarriers. Understanding the protein corona's methodological implications would enhance the design of safe and efficient therapeutic nanomedicine.[126]

Supramolecular approaches have been widely utilized for controlled drug release in drug delivery.[127] By responding to microenvironments, such as low pH and hypoxia, the states of self-assembly and molecular recognition can be modulated, thus achieving controlled drug release.[128] Remarkably, supramolecular design enables tailored release of drugs or photosensitizers at tumour sites, *via* mechanisms of competitive host–guest complexation rather than chemical reactions, in response to biomarker molecules such as ATP, spermine, and bile acids.[129,130] For example, Zhang *et al.* reported a supramolecular chemotherapy system using the host–guest complex between oxaliplatin and cucurbit[7]uril driven by hydrogen bonding and hydrophobic interactions. Toxicity of the oxaliplatin was decreased by the host–guest complexation. Interestingly, cucurbit[7]uril could complex with spermine, which is overexpressed in tumor environments and essential to tumor growth, through the electrostatic interactions and hydrophobic interactions. The complexation between cucurbit[7]uril and spermine not only recovered the antitumor activity of oxaliplatin by competitive replacement, but also consumed the overexpressed spermine in tumor environments. Therefore, molecular recognitions based on supramolecular interactions will greatly enrich the types of stimuli and improve the spatiotemporal accuracy of response.

7. Conclusion and outlook

In conclusion, this perspective provides a summary of the supramolecular contributions in the action of drug delivery. It enables readers to see easily what has been accomplished to date, while giving a forward perspective into how and where the field is progressing and key challenges to be overcome in the future.

Based on our viewpoint from supramolecular chemists that continually advance the fundamental research and clinical translation of drug delivery systems, we highlighted the crucial and ubiquitous supramolecular interactions in the action of drug delivery. The importance of supramolecular principles is sometimes neglected, especially in drug delivery systems that not developed by supramolecular chemists. In this perspective, we depicted and emphasized the basic viewpoint by analysing the contribution of supramolecular interactions in the desired properties of drug delivery systems in detail. Therefore, the next personal viewpoint is that supramolecular principles should be

systematically considered in developing all drug delivery systems.

The utilization of supramolecular materials, fabricated by supramolecular chemists using commonly employed building blocks,[131] in the field of biomedicine is currently in its nascent stages. The majority of the research still focuses on employing macrocyclic host–guest systems for drug delivery,[132] such as combination therapy based on amphiphilic azocalixarenes[62] and CALAA01 based on cyclodextrins,[90] which were discussed in the main text. This is likely due to the significant enhancement of weak interactions through the macrocyclic effect, making macrocycles the preferred subjects of investigation for supramolecular chemists. Interestingly, these promising preliminary studies indicate that macrocycles have demonstrated distinctive advantages in drug delivery, encompassing molecular-level protection, and quantitative drug loading, and so on. Therefore, researchers and companies in the traditional biomedical field should pay greater attention to supramolecular systems, as they offer the potential to introduce highly specific intermolecular interactions and exert precise control over molecular entities. This capability could be crucial for developing next-generation drug delivery systems. This aspect of the research is currently limited to fundamental studies and is not extensively elaborated upon in this perspective. Interested readers are encouraged to refer to our previously published reviews on the subject.[133–135]

The field of nanomedicine typically necessitates the integration of various functions, yet this inevitably engenders heightened intricacies in nanomedicine formulations, presenting challenges in their clinical translation. The integrated utilization of molecular recognition and assembly in supramolecular design holds promise for the simple integration of multiple functionalities through the use of basic building blocks and components. This approach enables the construction of highly reproducible and multifunctional biomaterials, thereby facilitating the treatment of complex diseases. Our work on the construction of multifunctional materials using amphiphilic calixarenes for the treatment of rheumatoid arthritis serves as a testament to this point.[136]

The challenge of identifying effective approaches to assess the optimal properties of nanocarriers persists. The dynamic and reversible nature of supramolecular methodologies, coupled with the modular characteristics and quantitative drug loading provided by host–guest chemistry, enables the convenient and rapid assembly of a diverse array of precisely tailored drug delivery systems. This approach may facilitate the construction of high-throughput screening systems to obtain optimal parameters such as drug loading ratios and the number of targeting moieties.[137]

Author contributions

All authors contributed to the writing of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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