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Transformative Materials for Interfacial Drug Delivery

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Drug delivery systems (DDS) are designed to temporally and spatially control drug availability and activity. They assist in improving the balance between on-target therapeutic efficacy and off-target toxic side effects. DDS aid in overcoming biological barriers encountered by drug molecules upon applying them via various routes of administration. They are furthermore increasingly explored for modulating the interface between implanted (bio)medical materials and host tissue. Here, an overview of the biological barriers and host-material interfaces encountered by DDS upon oral, intravenous, and local administration is provided, and material engineering advances at different time and space scales to exemplify how current and future DDS can contribute to improved disease treatment are highlighted.

1. Introduction

Drug delivery systems (DDS) aim to improve therapeutic efficacy and reduce side effects. DDS offers several advantages over conventional free drug formulations. They can, for instance, protect unstable drugs, or aid in increasing the aqueous solubility of highly hydrophobic drugs. They furthermore help to control drug distribution and activation, thereby improving the pharmacokinetics and target site accumulation of small molecules.[1–3] Traditional examples in this regard are coated tablets or capsules that protect drugs from low pH or digestive

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enzymes in the stomach, or pegylated nanoparticles (NP) that are routinely used to encapsulate small molecule chemotherapeutics to increase their circulation half-life and tumor accumulation. DDS can be sub-categorized into systems that assist in better controlling the temporal aspects of drug activation and systems that help to spatially guide drug molecules to certain organs or pathological sites within the body (**Figure 1**).

Depending on the route of administration, drugs and DDS encounter multiple biological barriers. Oral delivery is, for example, hampered by the harsh acidic conditions in the stomach and by poor permeability across the intestinal epithelium. Upon intravenous (IV) delivery, nano- and micro-DDS delivery suffer from rapid clearance by the mononuclear phagocyte system, as well as from the structural integrity of vascular endothelium. For local administration, the presence of mucus, for example, in the airways and the vaginal tract, can lead to inefficient drug delivery. These and other biological barriers impede DDS performance and therapeutic efficacy.[4–7] Other than biological barriers, patient adherence to medication is often an overlooked barrier, which must be taken into consideration while designing DDS. Different approaches to overcome this barrier are highlighted in detail by Baryakova et al.[8]

To promote drug delivery across biological barriers, it is important to look at barriers not as hurdles, but as targetable, interactive, and adaptive interfaces. Interfacial drug delivery can be achieved in various different ways, and upon different routes of application (as well as via DDS integration in implants), with the overarching goal of temporally and spatially enhancing drug delivery and drug activity.[9–11] Novel materials and methods for interface modulation open up new directions for transformative DDS development and improved DDS performance.[12]

In this perspective, we discuss the biological barriers and in vivo interfaces that DDS encounter upon oral, IV, and local administration. We furthermore highlight recent advances in DDS engineering and bio-material interface modulation, which are together resulting in radical improvements in temporally and spatially targeted drug treatment.

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2. Oral Delivery

Oral drug delivery is generally the most preferred route of administration, because of its low patient burden, high dosing flexibility, high patient compliance, non-invasiveness, low cost, and low risk of disease transmission. The large surface area of the gastrointestinal tract (GI; >300 m^2; lined throughout with a viscous mucus layer) enables efficient small molecule drug absorption into the circulation.[13] Oral formulations are easily adaptable and highly versatile.[14] They exist in many forms including tablets, capsules, nanocrystals, and dispersions.[15,16]

2.1. Interfaces Encountered Upon Oral Administration

Drug absorption via the GI tract is a highly regulated process and is challenged by several barriers and interfaces (**Figure 2**A).[17–19] For a drug to eventually reach systemic circulation, it must avoid degradation in the fluid in the stomach, which is highly acidic and loaded with digestive enzymes. The drugs and DDS that manage to pass this first barrier should next traverse through the intestinal mucus layer—which serves as a pathogen trap[20,21]—before they can reach the epithelial cells, where tight junctions and membrane-embedded drug transport impede active or passive drug transport.[22–24] In the case of delivery to the terminal ileum or colon, the presence of microbiota affects drug transport as it is known to have a direct and indirect effect on drug metabolism.[25,26] Oral administration poses particular barriers and challenges to the delivery of biopharmaceuticals such as proteins and peptides. Recent medicinal chemistry and pharmaceutical technology advances, however, have made formidable progress toward next-generation oral drug delivery, as evidenced by the FDA (2019) and EMA (2020) approval of the oral glucagon-like peptide (GLP-1) agonist semaglutide.[27,28] This has been a stepping-stone for the use of oral peptide formulations, employing SNAC (i.e., sodium N-(8-[2-hydroxybenzoyl] amino) caprylate) as a permeation enhancer to promote absorption.

2.2. Modulating Interfaces Using Oral Drug Delivery Systems

2.2.1. Microneedles – Stomach

Microneedles are micron-sized needles commonly employed for transdermal delivery.[29,30] Microneedles breach the stratum corneum and enhance permeation across the skin to enable improved access to the systemic circulation.[31,32] Integrating microneedle technology in an ingestible capsule has also been employed to improve oral drug delivery.[33] An innovative approach in this regard is the development of a self-orienting microneedle applicator (SOMA) that can independently inject drugs into the gastric epithelial lining.[34] In a pig model, SOMA has already been employed for insulin,[34] adalimumab,[35] semaglutide,[35] epinephrine,[35] and mRNA nanoparticle delivery (Figure 2B).[36] In all setups, the SOMA-based microneedle platform substantially enhanced the delivery of both small and large molecules.[34,35] It was furthermore demonstrated that the microneedle device was safe, not showing any sign of tissue damage.[33] This technology was recently also tested in other parts

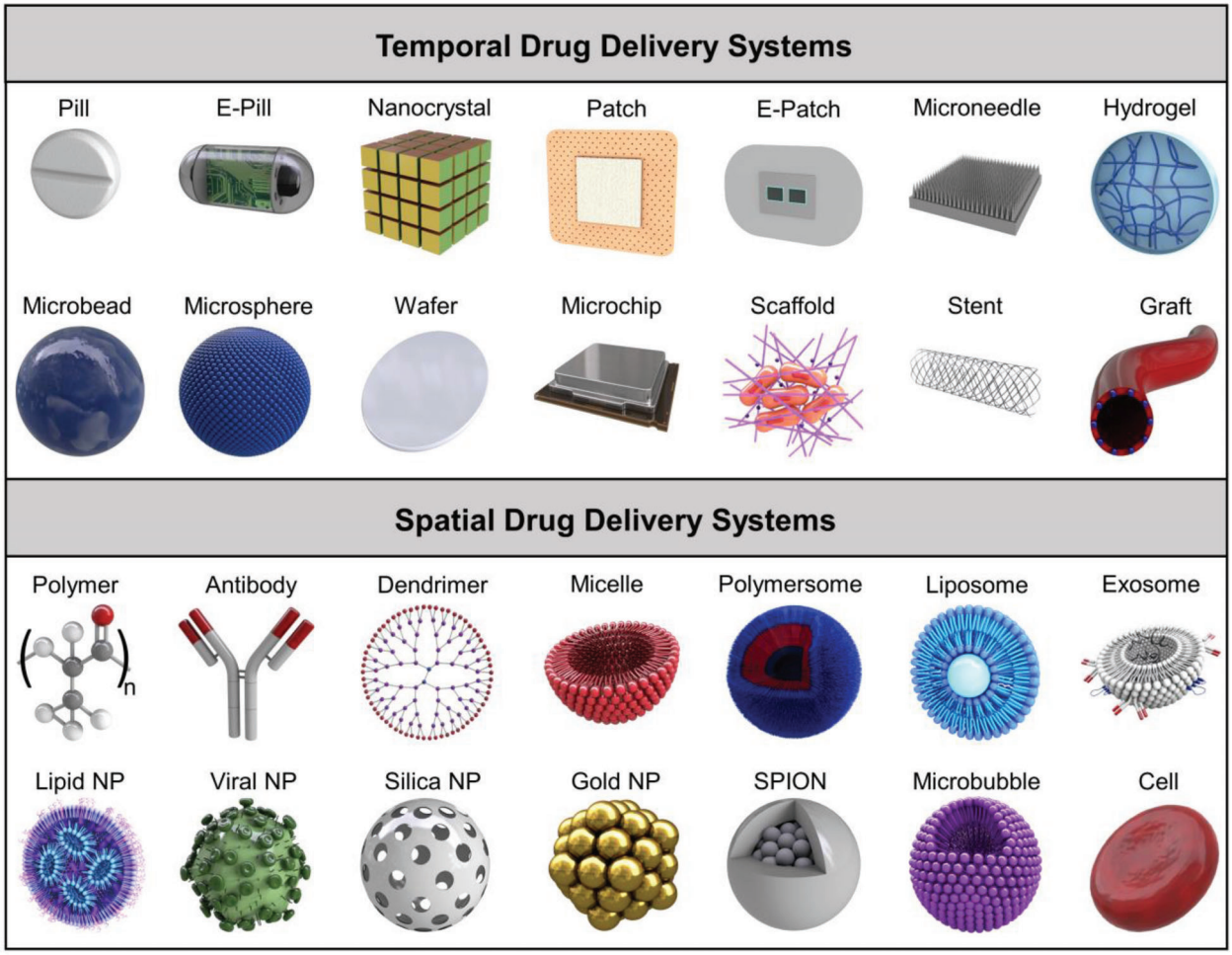

Figure 1. Overview of drug delivery systems used to overcome biological barriers and modulate interfaces. Temporally targeted DDS are generally applied orally or locally and aim to ensure drug activation at and for predefined periods of time. These include delayed release, sustained release, and triggerable release systems. Spatially targeted DDS are typically administered intravenously, and assist in improving the biodistribution, target site accumulation, and/or target cell uptake of drug molecules. It should be noted that categorization is meant to be representative, not exclusive. Thus, certain formulations included under temporal DDS (such as E-pills and beads) can also provide spatial improvements in drug delivery. Conversely, certain formulations listed as spatial DDS (such as liposomes or microbubbles) can also convey temporal control over drug delivery and activation.

of the GI tract, including the intestinal wall,[37,38] showcasing the promise of using self-orienting microneedle systems for novel applications in healthcare.

2.2.2. Mucoadhesive Devices – Intestinal Mucus

A major problem with oral peptide and protein delivery is dose dilution in the intestinal lumen and restricted transport of drugs across the mucosa, which is mainly composed of mucins and water. This can be tackled by using enteric coatings and mucoadhesive devices,[39,40] which dissolve only in the basic intestinal environment and promote high-concentration unidirectional drug release toward the mucosa (Figure 2C).[41,42] The presence of water in mucus can cause materials, such as polymers to swell, contributing to hydrogen bonding or electrostatic interaction between the polymers and mucin, thereby promoting adhesion. In such setups, optimized material hydration and swelling are needed.[43,44] A key example in this context is an enterically coated mucoadhesive capsule that contains both insulin and a permeation enhancer, and that was able to reduce blood glucose levels in rats.[45] Using the same technology, recombinant human granulocyte colony-stimulating factor was successfully delivered in dogs.[46] Moreover, micelles were recently coated with a mucoadhesive polymer to substantially improve the retention and delivery of curcumin (as a model drug with poor oral bioavailability) to the inflamed intestine (Figure 2C).[47] These preclinical studies demonstrate the potential of such devices to mediate mucus adhesion and drug delivery to and across the intestinal epithelium.

2.2.3. NP Permeation Enhancer – Epithelium

Upon being delivered in close proximity to the intestinal epithelium, drug molecules must either transcytose across epithelial

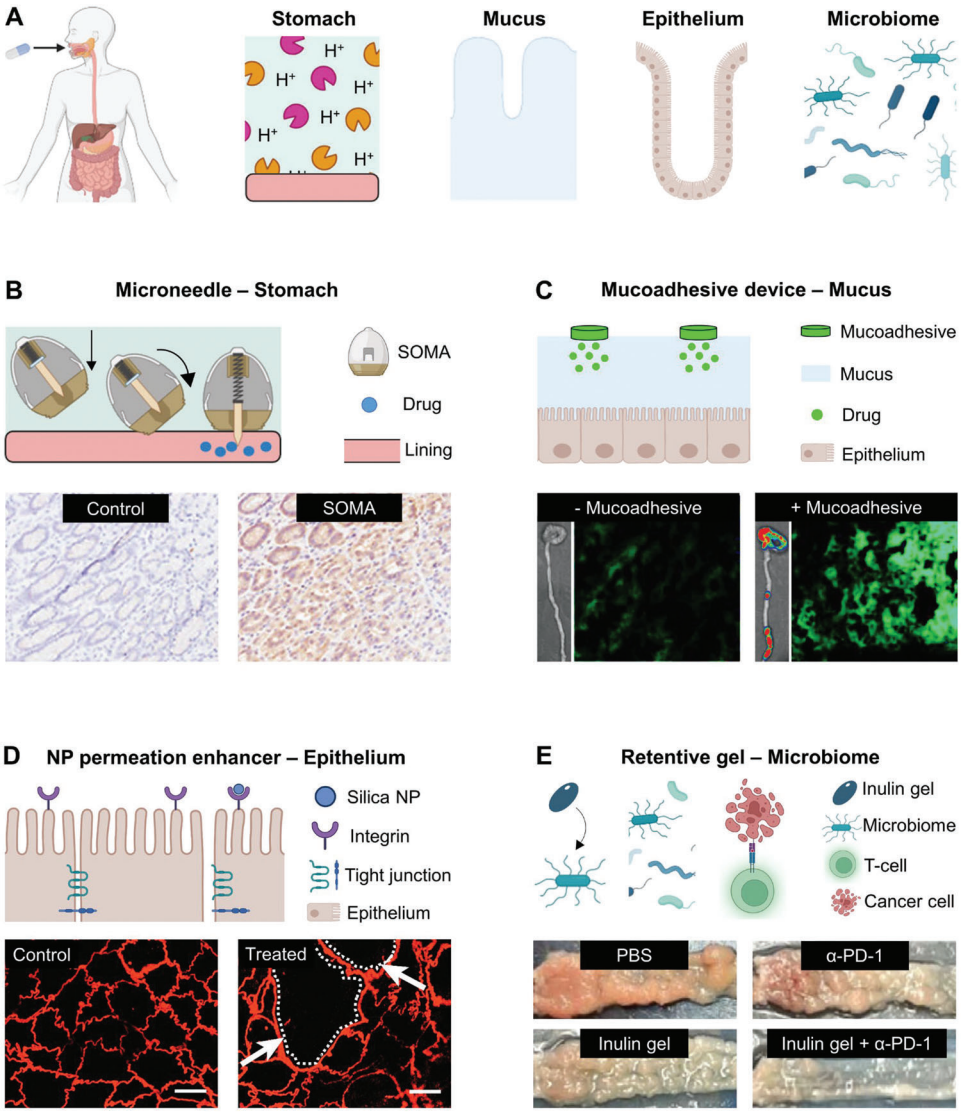

Figure 2. Drug delivery systems for modulating interfaces upon oral application. A) Schematic showing the key interfaces associated with oral drug delivery. B) Self-orienting microneedle applicator (SOMA) mimicking the shape of a tortoise localizes to the bottom of the stomach and autonomously orients its microneedles to mediate maximally efficient transepithelial drug delivery. In a pig model, SOMA efficiently delivered mRNA nanoparticles encoding for the Cre-recombinase to produce tdTomato fluorescence. Reproduced with permission.[36] Copyright 2022, Elsevier Inc. C) Mucoadhesive patches can be released from enterically coated capsules in the basic environment of the small intestine, followed by adhesion to mucus and subsequent intra-mucus drug payload release. In mice, micelles coated with mucoadhesive polymer enabled higher retention and enhanced curcumin (green) delivery to the small intestine. Reproduced with permission.[47] Copyright 2022, Elsevier B.V.. D) Negatively charged silica nanoparticles bind to integrin on intestinal epithelial cells, activate the myosin light chain kinase, and trigger the opening of tight junctions. Mice treated with anionic silica nanoparticles create cell clusters where the tight junction protein ZO-1 (red) is absent, indicating the opening of epithelial tight junctions in the dashed white area. Reproduced with permission.[55] Copyright 2019, Springer Nature. E) Prebiotics like inulin can be loaded in gel-based DDS to enhance drug delivery to microbiota and promote CD8$^+$ T cell responses when combined with checkpoint blockade cancer immunotherapy in mice bearing CT26 colon carcinoma. Reproduced with permission.[58] Copyright 2021, Springer Nature.

cells or traverse through the tight junctions connecting epithelial cells. The latter only permit passaging of very small molecules (<1 nm in size),[48] contributing to the notoriously poor systemic availability of large drug molecules such as peptides and proteins.[49] To improve trans-epithelial drug delivery in the GI tract, several physical and chemical permeation enhancers have been tested, which either target the transcellular or the paracellular route.[50–53] Contrary to the most commonly used enhancers, such as lipids, organic solvents, and polymers,[54] it was recently shown that negatively charged silica NP possess an inherent ability to act as a physicochemical permeation enhancer by binding to integrins on intestinal epithelial cells.[55] Integrins are involved in mediating the opening of tight junctions, and engaging them with anionic silica NP facilitated oral delivery of proteins such as insulin (Figure 2D). Other than silica NP, active transport of insulin-loaded polymeric NP modified with Fc fragments

to target FcRn expressed on intestinal epithelium has also been shown to improve oral protein delivery and efficient blood sugar control.[56] These and other NP engineering efforts are expected to play increasingly important roles in advancing oral drug delivery.

2.2.4. Retentive Gel – Microbiome

The increasingly obvious connection between the microbiome and human health suggests that modulation of gut microbiota holds enormous clinical potential, particularly because of its involvement in both innate and adaptive immune responses.[57] A pioneering study in this regard explored the oral administration of an inulin gel that modulates the microbiome by promoting the proliferation of commensal micro-organisms. This directed the metabolite-mediated differentiation of $CD8^+$ T cells toward stem-like $CD8^+$ T cells within the tumor microenvironment (TME), which synergized with α-PD-1 checkpoint blockade immunotherapy to improve anticancer efficacy in multiple mouse models (Figure 2E).[58] Beyond cancer, the composition and function of the microbiome are also prominently linked to autoimmune disorders, irritable bowel syndrome, and chronic liver diseases. Multiple proof-of-concept efforts demonstrate that drug delivery to target pharmaceutical modulation of the microbiome represents a viable therapeutic option for the prevention, management, and cure of various different diseases.[59–61]

Altogether, advances in drug delivery technology are increasingly enabling the oral delivery of agents other than small molecules including insulin (as a prototypic model compound) and biopharmaceuticals. Replacing drug injections with orally applicable drug formulations will not only lower patient burden and improve patient compliance but also reduce healthcare costs and improve chronic disease management. We are consequently confident that via steady progress in DDS engineering, the oral administration of peptides, proteins, and other biopharmaceuticals will gradually become feasible.

3. Intravenous Delivery

IV injection remains the standard procedure to apply highly potent drugs that cannot be given to patients via other routes of administration. Examples of this are traditional chemotherapeutics, antibodies, biopharmaceuticals, and cell therapies. IV injection helps to bypass key barriers associated with low stability, low absorption, and low bioavailability.

3.1. Interfaces Encountered Upon Intravenous Administration

Nanocarriers have emerged as suitable DDS for improving the biodistribution and therapeutic index of small-molecule chemotherapeutics, as evidenced by, for example, Doxil and Abraxane.[62,63] In terms of efficacy, however, they have to date offered only marginal improvements.[62,64] The target site accumulation and therapeutic efficacy of nanocarrier-associated drugs can be hindered by various nano-bio interfaces (**Figure 3**A).[65] In the bloodstream, serum proteins adsorb to the NP surface,[66,67] promoting phagocytic capture, reducing circulation times, and masking active targeting capabilities.[67,68] From the circulation, NP need to extravasate into diseased tissue, which in tumors and inflammatory disorders is mediated via the so-called enhanced permeability and retention (EPR) effect.[69] In diseases without leaky blood vessels, the endothelial lining constitutes a challenging barrier. After crossing the endothelium, IV-injected DDS furthermore has to penetrate through the tissue microenvironment, which in the case of cancer and many other chronic disorders constitutes yet another interface that needs to be surmounted to ensure efficient drug delivery and disease treatment.

3.2. Modulating Interfaces Using Intravenous Drug Delivery Systems

3.2.1. Nanoparticle – Blood

To avoid protein corona formation and improve NP circulation time, biodistribution, and target site accumulation, physicochemical properties have been extensively studied and refined, with dense PEGylation of the NP surface being a standard strategy.[70–72] Other examples include NP pre-coating with a supramolecularly constructed protein corona,[73,74] tuning NP elasticity,[75,76] and generating a biomimetic NP surface.[77–79] Alternatively, also strategies to intentionally interact with circulating immune cells to reach pathological target sites have been explored. In this context, it was demonstrated that RGD peptide-decorated lipid NP (LNP) are taken up by circulating neutrophils and monocytes in vivo. Due to the high motility and tumor/inflammation-homing propensity of these myeloid immune cells, RGD-NP efficiently hitchhiked to and into tumors and inflammatory lesions (Figure 3B).[80,81] Protein corona formation can also be beneficial—or even instrumental—for drug delivery. A prototypic example of this is the lipid NP that via LDL and HDL adsorption results in efficient hepatocyte targeting and uptake, to deliver siRNA (patisiran; Onpattro) and CRISPR-Cas9 components (NTLA-2001) for the treatment of hereditary transthyretin-mediated amyloidosis (hATTR).[82–86] Importantly, HDL/LDL-adsorption and hepatocyte-specific uptake are facilitated by the shedding of poly(ethylene glycol) (PEG) from the lipid NP bilayer, which is primarily integrated into these NP to prolong shelf-life stability (rather than to prolong in vivo circulation times).[87,88] Expanding beyond lipid NP and hATTR, fazirsiran, a DDS based on *N*-acetylgalactosamine conjugated to siRNA for hepatocyte-specific knockdown of mutant Z-AAT protein levels was recently successfully evaluated in patients with alpha-1 antitrypsin (AAT) deficiency.[89] In the advent of targeted epigenetic modifications,[90] CRISPR technology may in the future also be used to direct cell-fate decisions by transformative biomaterials in a controlled manner.

3.2.2. Microbubble – Endothelium

To overcome the vascular barrier in the case of non-fenestrated tissues and non-leaky pathologies, focused ultrasound (US) can be combined with microbubbles (MB) to generate shear forces near the endothelium, thereby promoting vessel permeability

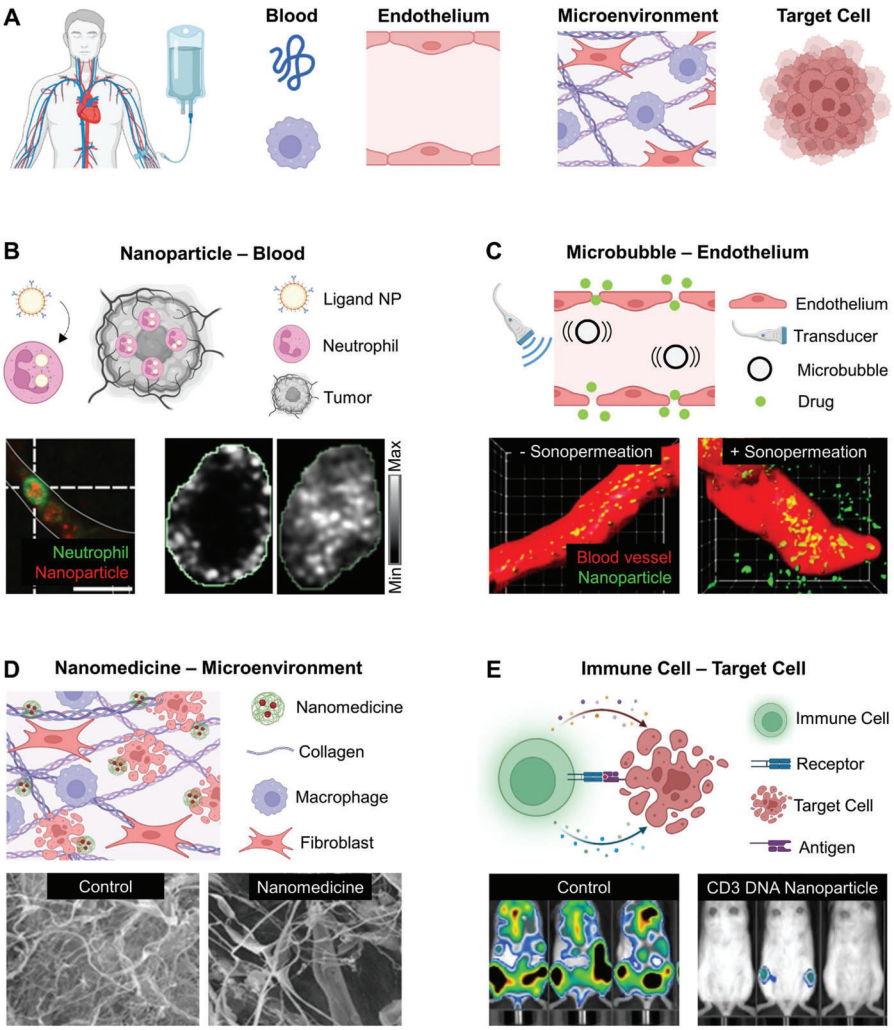

Figure 3. Drug delivery systems for modulating interfaces upon intravenous application. A) Scheme showing the interfaces faced upon intravenous DDS application. B) NP in the bloodstream can form a protein corona or directly engage with myeloid immune cells, like neutrophils, to assist delivery to and into tumors. Intravital microscopy shows that cRGD-targeted NP (red) hitchhike onto neutrophils (green). As revealed by positron emission tomography (PET) imaging, nanoparticles can hitchhike with neutrophils deep into tumor tissue even after their clearance from circulation. Reproduced with permission under the terms of the CC-BY 4.0 license.[80] Copyright 2020, the Authors. Published by the American Chemical Society. C) Microbubbles cavitate in the presence of ultrasound, generating shear forces near vascular endothelium. This promotes blood vessel permeability and drug delivery. In healthy mice, the combination of microbubbles and transcranial ultrasound enhanced the extravasation of 10 nm-sized polymeric DDS (green) across the BBB (red). Reproduced with permission under the terms of the CC-BY 4.0 license.[94] Copyright 2020, Ivyspring International Publishers. D) NP loaded with an ECM-degrading agent, like collagenase, can help to deplete the dense TME in pancreatic tumors in mice. Reproduced with permission.[104] Copyright 2019, American Chemical Society. E) Strategies to modify T cells with chimeric antigen receptors have demonstrated remarkable therapeutic outcomes. For instance, bioluminescence imaging demonstrated that CD3-targeted nanoparticles encapsulated with chimeric antigen receptor-encoding transgenes significantly suppressed tumor volume in a mouse leukemia model. Reproduced with permission.[111] Copyright 2017, Springer Nature Limited.

and drug extravasation (Figure 3C).[91–93] In this context, it has been shown that the concomitant use of MB and US can temporarily permeate the blood–brain barrier (BBB), to allow for the passaging of 10 and 100 nm-sized nanocarriers into the brain parenchyma (Figure 3C).[94] This concept, termed sonoporation or sonopermeation,[95,96] is increasingly validated in patients with high-end medical disorders including pancreatic cancer, glioblastoma, diffuse-intrinsic pontine glioma, Alzheimer's disease, and Parkinson's disease.[97–101] The spherical shape of the MB routinely used in such studies makes them flow in the center of blood vessels, reducing contact with the endothelium wall and resulting in suboptimal vessel permeability upon US insonation. Recent efforts demonstrate that also non-spherical MB can be generated, which flows to blood vessel walls, thereby enabling enhancement of trans-BBB drug delivery upon transcranial-focused US.[102]

3.2.3. Nanomedicine – Extracellular Microenvironment

The dense extracellular matrix (ECM) in the TME and in fibrotic diseases limits drug and DDS penetration and is generally associated with poor prognosis.[103] A common strategy to enhance

drug and DDS penetration is via degradation of the ECM (**Figure 3**D). In this context, pre-treatment of pancreatic tumors in mice with collagenase-loaded liposomes followed by administration of paclitaxel-loaded micelles resulted in a tumor size reduction of up to 87% compared to mice pre-treated with empty liposomes (Figure 3D).[104] Co-delivery of dexamethasone and docetaxel in DDS reduced ECM deposition, lowered the interstitial fluid pressure (IFP), and enhanced the accumulation and antitumor efficacy of docetaxel.[105] Similarly, a pH-responsive collagenase-loaded transcytosis gold NP facilitated NP penetration and sensitized pancreatic adenocarcinoma in mice to radiation therapy.[106] Such combination and co-formulation approaches are particularly useful for highly stromal cancers with dismal treatment prospects, and they may also hold potential for the treatment of fibrotic disorders.

3.2.4. Immune Cell – Target Cell

Cell-based therapies are gaining more and more traction as modalities for drug delivery and drug treatment.[12,107] Immunotherapy and chimeric antigen receptor (CAR) cell therapies are changing the face of cancer therapy.[108–110] To improve cancer immunotherapy outcomes, it is critical to understand how NP can be employed to prime and guide the immune system, and to promote CAR-T cell therapies. Particularly, the in vivo generation of CAR-T cells is interesting, which can be realized using DNA-NP or mRNA-loaded LNP.[111–114] For instance, in vivo T cell targeting with anti-CD3 antibody-modified DNA-NP loaded with a leukemia-specific 194-1BBz CAR efficiently programmed peripheral T cells, resulting in tumor regression with efficacies similar to adoptive T cell therapy (Figure 3E).[111] The concept of in situ generation of CAR-T cells has recently been extended toward restoring cardiac function upon infarction: CD5-targeted LNP containing mRNA encoding for a fibroblast activated protein (FAP)-based CAR were administered to mice with experimental cardiac fibrosis. This approach resulted in the elimination of FAP-expressing fibrogenic cells, thereby reducing cardiac fibrosis and improving the function of the heart.[102] The in situ generation of CAR-T cells in vivo is highly attractive,[115] because it does not require ex vivo cell expansion under GMP conditions, thereby making it more cost-effective. Furthermore, the transient nature of in vivo-produced CAR-T cells may limit toxicity, allows for dose adjustment, and enables repeated administration.

The field of IV drug delivery is currently expanding beyond conventional (i.e., chemotherapy and antibody) applications, toward designing NP and DDS that can target and modulate biological interfaces in vivo. Prominent and promising future directions in this regard range from the treatment of cancer and liver pathologies to the better management of chronic inflammatory and fibrotic disorders.

4. Local Delivery

Local delivery of drugs and local application (or integration) of DDS allows for sustained, time-controlled, and triggerable drug release at the site of action. It addresses limitations associated with low bioavailability, low tissue tropism, short target site retention, and unwanted systemic side effects. As a result, locally acting injectable or implantable DDS are widely studied for the treatment of many different diseases.[116–118]

4.1. Interfaces Encountered upon Local Administration

Locally applied DDS face challenges associated with appropriate time control and side effects to surrounding healthy tissues and organs.[116] Local anatomy and surrounding healthy tissues complicate local drug delivery. Nanoparticles, microspheres, microchips, implants, and stents are examples of systems used for local delivery. Major interfacial barriers faced by such DDS are mucus and host rejection reactions, that is, inflammation and fibrosis (Figure 4A). Several pioneering strategies to address and overcome such interfacial issues are discussed below.

4.2. Modulating Interfaces Using Local Drug Delivery Systems

4.2.1. Nanoparticle – Mucus

Mucus is a viscoelastic gel that is composed mainly of cross-linked and entangled mucin fibers, proteoglycans, and glycoproteins. As in the case of oral delivery, also locally applied DDS can be trapped in mucus layers, thereby limiting trans-mucosal drug delivery.[4] To overcome this, mucus-penetrating nanoparticles (MPN) have been engineered via dense surface-coating with PEG, to avoid mucus interactions and reach the epithelium (Figure 4B).[4] It was shown that upon intravaginal administration, acyclovir-loaded MPN diffused into the deepest mucus layers and efficiently reached the vaginal epithelium, thereby protecting animals against vaginal virus challenge (Figure 4B).[119] Analogously, inhalation of MPN loaded with dexamethasone enabled diffusion through airway mucus, improving drug distribution and retention, and reducing inflammation in a lung inflammation mouse model.[120] MPN has recently made significant advancements in the clinic. Kala Pharmaceuticals, for instance, has used MPN technology in two commercial products, namely Eysuvis and Inveltys. These contain the steroid drug loteprednol etabonate at different doses, the former indicated for short-term management of dry eye disease, and the latter for post-operative eye inflammation and pain.[121] These examples showcase the use of MPN as a versatile and potentially broadly applicable platform technology for local trans-mucosal drug delivery.

4.2.2. Microsphere – Stent

Stents are hollow cylindrical devices that are used for opening obstructed passageways such as blood vessels and airways. In the clinic, stents are oftentimes coated with drugs, such as paclitaxel or sirolimus, to block inflammatory/fibroblast cell proliferation and thereby prevent re-stenosis.[122] Stents have also been functionalized with drug-loaded microspheres, typically via their integration in (polymeric) coatings, to enable time-controlled and sustained local drug release at the target site (Figure 4C).[122] In a proof-of-concept study, gefitinib-loaded microspheres were prepared and shown to retain their characteristics even after embedding them in polyurethane airway stents. Under in vitro conditions, the microsphere-loaded stents released gefitinib in a sustained manner for up to 6 months (Figure 4C).[123] These efforts

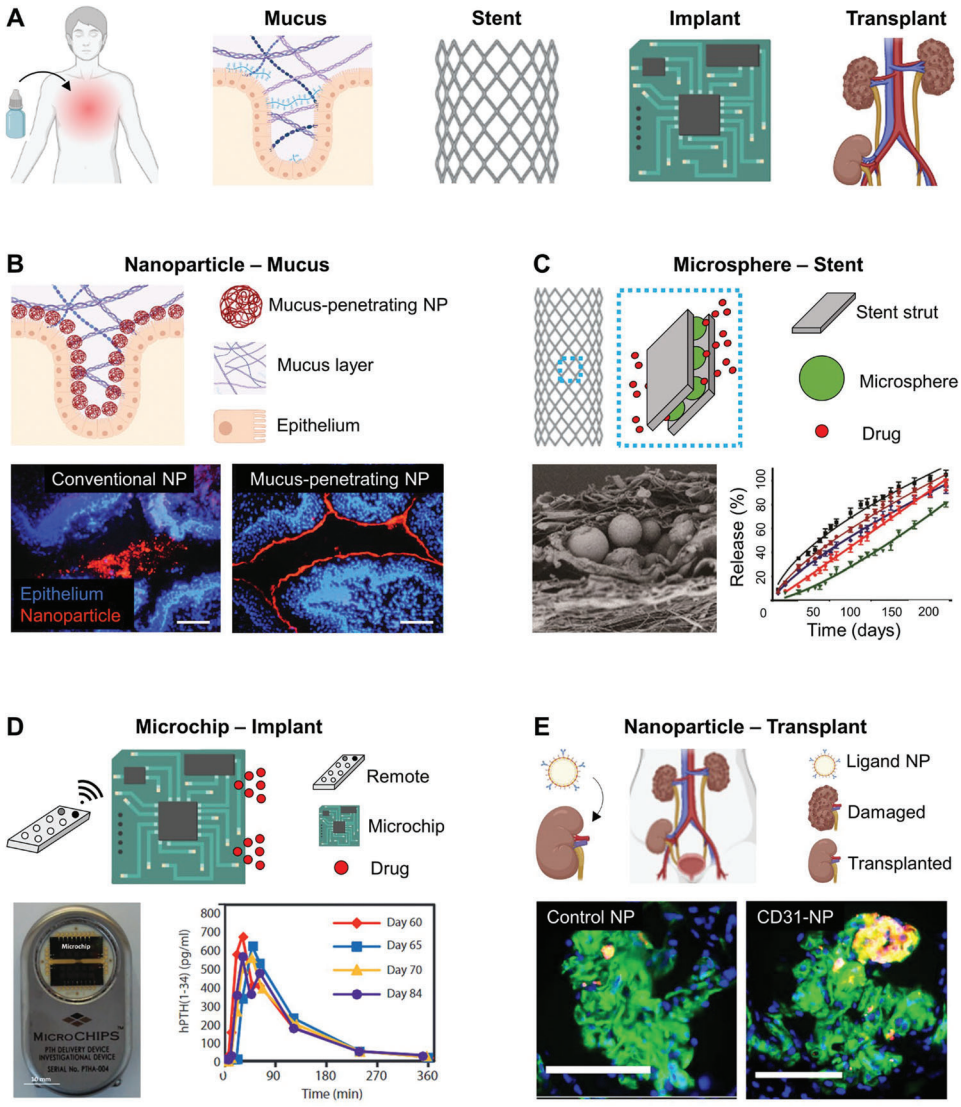

Figure 4. Drug delivery systems for modulating interfaces upon local application and implant integration. A) Scheme showing the interfaces encountered in local drug delivery. B) Mucus-penetrating nanoparticles (MPN) are densely surface-coated with poly(ethylene glycol) (PEG), enabling them to more efficiently pass through mesh spaces in the mucosa. Upon intravaginal administration, MPN (red) penetrated deep into the mucus and efficiently reached the epithelium (blue). Reproduced with permission.[119] Copyright 2012, The American Association for the Advancement of Science (AAAS). C) Stents with integrated microspheres allow for controlled local drug release inside tubular structures. Scanning electron microscopy shows that polymeric microspheres were embedded in the stent material, and zero-order release of microsphere-encapsulated gefitinib could be achieved for up to six months. Reproduced with permission.[123] Copyright 2017, Elsevier. D) Implantable devices can be wirelessly actuated by a remote controller, enabling on-demand drug release at a specific time and dose. The plasma concentration versus time curve demonstrates that an implanted microchip can efficiently deliver human parathyroid hormone once daily for up to 24 days to female patients suffering from osteoporosis. Reproduced with permission.[129] Copyright 2012, AAAS. E) Vascular targeted nanoparticles can be transfused through to ex vivo human kidneys to prevent transplant rejection. Immunofluorescence images show that anti-CD31-antibody functionalized nanoparticles (yellow) significantly enhanced vascular retention (green) when administered to isolated human kidneys during normothermic machine perfusion, thus indicating potential in promoting transplant acceptance. Reproduced with permission.[133] Copyright 2017, AAAS.

were extended by demonstrating that stent coatings containing docetaxel-loaded microspheres promoted re-endothelialization in vivo and mitigated restenosis in porcine coronary arteries.[124] A potential downside of these traditional stents is that the diffusion of drugs is limited to the walls of the tubular structures. To deliver drugs into deeper compartments, such as the submucosa, a kirigami-inspired stent was designed, which is composed of denticle-like needles integrated with a pneumatic actuator.[125] Upon pressurizing the actuator, the kirigami needles buckled outward and oriented perpendicular to the stent surface. This orientation facilitated the kirigami needles to be inserted deep into the esophageal and tracheal submucosa of pigs, enhancing local delivery via budesonide-loaded microspheres.[125] Thus, stent-embedded microspheres hold the potential to not only deliver

drugs locally within tubular structures but also to interfacial compartments further away from the tubular lining.

4.2.3. Microchip – Implant

Implants are devices that are inserted into patients to support, replicate and enhance the function of organs and tissues.[126,127] A battery-free implant that can be controlled wirelessly using a remote was developed to locally control temporal aspects of drug delivery.[128] After subcutaneous implantation, the device enables repetitive local drug delivery, and doses can easily be adapted by changing the number of actuations.[128] The system was used to deliver bromocriptine for type-2 diabetes in rats, as well as lisinopril for hypertension.[128] In a first-in-human clinical trial, an implantable microchip-based DDS was used to deliver human parathyroid hormone (hPTH) to eight post-menopausal women with osteoporosis. The chip was wirelessly programmed to deliver daily doses of hPTH for up to 24 days. It was found that hPTH released from the implanted DDS increased the level of the bone formation marker P1NP (Figure 4D).[129] A downside of implanted devices is that our bodies respond to them with inflammation and fibrosis, resulting in device failure. In this context, it has been shown that tuning the spherical dimension of implants can significantly reduce foreign-body responses.[130] The same group of authors also encapsulated crystalline GW2580 (i.e., a colony-stimulating factor 1 receptor inhibitor) in alginate microspheres, to suppress fibrosis when implanted intraperitoneally and subcutaneously in rodents and non-human primates.[131] Thus, implants and implant-embedded DDS can be engineered to assist in attenuating inflammation and fibrosis, thereby promoting long-term implant performance.

4.2.4. Nanoparticle – Transplant

Organ transplantation is needed for the treatment of patients with end-stage organ failure.[132] Key challenges associated with organ transplantation are lack of donors and post-transplant rejection.[133] In the case of kidneys, normothermic machine perfusion (NMP) holds promise for ex vivo organ preservation and assessment of functionality prior to transplantation.[132] Graft failure can be caused by inflammation, graft injury triggered by host anti-donor antibodies, and by ischemia-reperfusion injury.[133] The endothelial lining is a key target in transplant rejection, and DDS can be employed to engage with vascular endothelium to attenuate the transplant injury (Figure 4E).[134] In this context, NP functionalized with anti-CD31 antibodies were administered to isolated human kidneys during ex vivo NMP, resulting in enhanced vascular retention as compared to non-targeted NP (Figure 4E).[133] These efforts were extended by engineering a monobody adapter that enables anti-CD31 antibody-targeted NP to fully preserve their antigen-binding capability.[134] This technique resulted in higher vascular targeting by several orders of magnitude, exemplifying that vascular-targeted DDS are potentially suitable for preventing transplant rejection. Apart from locally targeting key cell types in transplants, recent efforts demonstrate that also systemic targeting of myeloid immune cells, for instance with lipid NP loaded with rapamycin to suppress trained immunity, holds promise to promote organ transplant acceptance and performance.[135]

Mucus-penetrating NP, stent-embedded microspheres, and externally actuatable microchips are increasingly impacting clinical practice. Local DDS may furthermore provide much-needed support in preventing rejection and promoting function upon organ transplantation. Such DDS are consequently considered valuable for realizing the next frontier in disease treatment.

5. Outlook

This perspective summarizes state-of-the-art DDS and strategies to target and modulate biological barriers and bio-material interfaces. The current generations and applications of DDS are becoming increasingly ingenious and transformative. They are gradually enabling time- and space-controlled delivery of small molecule therapeutics, as well as biopharmaceuticals, such as proteins and nucleic acids, which are more and more impacting day-to-day clinical practice. DDS are furthermore increasingly integrated in (tissue-engineered) implants and transplants, in order to reduce inflammation and fibrosis and to promote graft performance and function.

In this context, current developments are progressing from standard single-trigger-responsive DDS toward materials that are able to more autonomously respond to and act at pathological sites and bio-material interfaces. For this purpose, DDS has to be endowed with sensing capability, information processing capability, and drug release control capability. As such, ingested, injected, and implanted DDS may eventually become comparable to closed-loop insulin delivery systems, which integrate continuous glucose monitoring with app-controlled algorithms to determine the amount of insulin (analog) that needs to be administered via subcutaneous insulin infusion. It is anticipated that in the years to come, centimeter-sized closed-loop delivery systems will be more and more downscaled, toward materials that autonomously control drug activity at the milli-, micro-, and nanometer size range.

As the complexity of DDS (and DDS-containing implants) increases, challenges associated with their production and clinical translation also increase. By employing technologies, such as microfluidics and 3D printing, issues associated with large-scale manufacturing and customizable production can be addressed. Progress toward precision medicine and more efficient clinical translation will profit from establishing materials and methods for patient stratification, which assists in dealing with biological and patho/physiological heterogeneity. Such biomarker-based protocols are crucial in ensuring the success of clinical trials, and they are becoming more and more standard in drug and DDS development. Furthermore, with increasing progress in engineering advanced multi-component DDS (and drug-device combinations), the complexity of regulatory procedures also increases. This translational challenge requires intimate interactions between and efficient knowledge exchange by scientists coming from various different backgrounds—ranging from materials science and process engineering to regulatory science and medicine. Such concerted efforts, generating beyond-state-of-the-art solutions for drug delivery applications and bio-material interface modulation, are instrumental in realizing radical

improvements in the management of severe diseases for which no therapeutic options are currently available.

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Conflict of Interest

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