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Review Paper

From Conventional Formulations to Smart Nanomedicine: Advances in Targeted and Stimuli-Responsive Drug Delivery

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ABSTRACT

Advanced systems for drug delivery have evolved from basic dosage forms to engineered delivery platforms, that may enhance the solubility, biodistribution, therapeutic index, and release control of a drug. The current state of the art of lipid-based, polymeric, inorganic and biomimetic carriers is reviewed, with a focus on the influence of the composition, surface chemistry and loading strategy on the performance of the carriers through different routes of administration including transdermal, oral and CNS delivery. Lipid systems like liposomes, ethosomes, transferosomes, solid lipid nanoparticles and nanostructured lipid carriers are still the focus, as they can be applied to membrane-like transport and controlled release, and polymeric micelles, dendrimers and related systems bring programmability and better handling of poorly soluble drugs. The concept of passive delivery to smart, stimuli-responsive delivery is a key theme in the field. In recent years, more and more nanocarriers have been developed that are sensitive to biological conditions (pH, redox, enzymes, hypoxia) and/or external stimuli (temperature, light, magnetic field, ultrasound) in order to selectively release therapeutic agents at the pathological location. In parallel, targeting has been expanded from the enhanced permeability and retention effect to active ligand mediated delivery, and even to intracellular targeting (including organelle directed delivery). Growing interest in cancer, neurological disease, cardiovascular disease, and inflammatory indications, and the natural biocompatibility, low immunogenicity and useful tissue-homing properties of biomimetic systems, particularly extracellular vesicles and exosomes, adds another layer of interest. Central nervous system delivery is one of the most promising applications as nanocarriers can use several transportation pathways to cross the blood-brain barrier but there is still a lack of evidence in the clinical arena. Another active area, albeit with mixed human data, is oral delivery of macromolecules, which has seen only the single digit level gains with permeation enhancers—with gastrointestinal barrier being extremely difficult to penetrate in practice.

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INTRODUCTION

1. Background and Evolution of Drug Delivery

Drug delivery is no longer just about giving a molecule into the body. With modern nanomedicine, the delivery platform becomes an integral component of the therapeutic design due to its influence on solubility, circulation time, tissue distribution, uptake into cells, and the timing of release. The real challenge was to design advanced drug delivery systems to address the problem that many potent drugs are not biologically active but are poorly soluble, unstable in biological fluids, rapidly excreted, or simply not able to reach the desired site and localize at the appropriate concentration. To overcome these challenges, nanocarrier-based delivery systems have been developed which enables site-specific delivery, controlled release, pharmacokinetics improvements, biodistribution and safety[1][2].

The development of the field can be seen as a series of "exposure control" to "precision control". First sustained-release versions were developed to achieve smoother plasma concentration-time curves and less frequent dosing. This was a significant achievement, but the drug penetrated the body rather non selectively. The next generation added encapsulation and carrier mediated transport such as liposomes, lipid nanoparticles, and polymeric particles, which have been designed to protect the payload and to deliver to difficult tissues. The current generation is even more advanced; it incorporates the combination of carrier design, surface functionalization, and environmental responsiveness to enable the release of the drug when and where it is needed most. Today, however, the development of nanoplatforms is done not only to transport cargo, but to regulate its release based on disease biology[2][3][4].

Biopharmaceutical Limitations of Conventional Dosage Forms

The problem with the conventional dosage forms is not only technological, but also biopharmaceutical. Low aqueous solubility resulting in low dissolution and absorption, particularly for hydrophobic compounds. Enzymatic degradation and epithelial impermeability is a problem for large biologics. Pharmacologically active drugs in vitro could be less effective in vivo due to rapid clearance, tissue distribution, and/or inability to cross protected barriers (e.g., BBB). These are non-marginal points, and they determine if a molecule becomes a medicine. That's why advanced carriers are important. Nanocarriers such as lipid based and polymeric nanocarriers can provide protection against premature degradation, enhance apparent solubility of the drugs and enhance the duration of action at the target site.

A polymeric nanocarrier system is conveniently applicable when the problem is low solubility or early systemic clearance, and lipid-based systems are desirable if membrane compatibility and controlled transport are of relevance. A new alternative is exosome-based systems, which can also be delivered with low toxicity and low immunogenicity and have a natural membrane structure that may facilitate trafficking to specific cells[5][2].

The situation is aggravated by barrier physiology. Blood-brain barrier is a major challenge for all advanced platforms because most of the therapeutics cannot cross the BBB. Likewise, human oral bioavailability gains with orally administered macromolecules have been limited despite the encouraging in vitro results: one translation review of oral permeation enhancers details that gains have been frequently obtained only in the low single digits for human oral bioavailability[6]. One of the main drivers for the

evolution of the field to more advanced carrier systems was that gap between the elegant formulation and practical effectiveness.

Historical Generations of Delivery Systems: From Sustained to Smart Release

Drug delivery systems have evolved over the years and can be best characterized as a series of more and more specific attempts at control. The first generation focused on traditional dosage forms, with little control other than dosage and route. The second generation added sustained, controlled release; and matrix systems, coated particles, vesicular carriers, and lipid-based formulations for prolonged drug exposure and adherence. Although these systems provided greater convenience and minimized peak-trough variations, they were still largely passive release systems.

The third generation is about targeting and responsiveness. The carrier has been 'engineered' in that part of the world to have different behaviour in diseased tissue than healthy tissue. Nanocarriers may be stimuli responsive, and they can respond to endogenous stimuli, e.g., acidic pH, redox gradients, enzymes, and hypoxia, or to exogenous stimuli, e.g., temperature, light, magnetic fields, ultrasound and electric fields. They aim for not only delayed release, but on-demand release at the pathological site[3][4]. This is important for many diseases, particularly cancer and inflammatory disorders, which generate microenvironment that is distinct enough from normal tissues to be targeted for selective release.

Targeting has developed at the same time. In the past, passive targeting was attributed with increased permeability and retention, but the current thinking is more circumspect and more realistic – accumulation is not enough. Active targeting using ligands, peptides, antibodies, and small molecules can be used to enhance cellular uptake and tissue specificity. Meanwhile, the biomimetic delivery has been rising in popularity as extracellular vesicles and exosomes can transport nucleic acids, proteins, and small molecules while their intrinsic biocompatibility and low immunogenicity provide an added benefit. Targeting and release, and immune compatibility are no longer design add-ons—they are all considered design variables in the field [5].

Scope and Objectives of the Chapter

The chapter emphasizes the design rationale, functional classes and practical considerations for translating advanced drug delivery systems. It explores lipid based, polymeric, inorganic and biomimetic carriers, presents the methods of stimuli-responsive mechanisms to control release, and discusses tissue and organ-specific targeting of drug delivery systems. The chapter also covers the key biomedical applications of these systems including oncology, CNS delivery, oral macromolecule delivery to other applications where conventional formulations are still lacking[2][6][5].

Second is a translational objective. Cargo loading/release is not the only factor in formulation success. It also relies on critical quality attributes, repeatable characterization, scale up and immunological activity. Recent works in translational analysis have focused on the role of particle size, entrapment efficiency, polydispersity, surface charge, and membrane properties on in vivo performance, while recent works focused on regulatory aspects have focused on hemocompatibility, formation of protein corona, complement activation, and long-term toxicity [7][8].

The chapter is thus written from a product development point of view as well as from a materials point of view. It's not what carrier is the best one when it is the same, but what carrier is the best one when it isn't the same. Lipid systems are appealing where membrane transport and solubilization are the key factors. In cases where

structure flexibility and tunable release is required, polymeric systems become useful. When natural homing and low immunogenicity is important, exosomes are compelling. Where spatial or temporal accuracy is essential, then a stimuli-responsive system is most useful. The best take from the available literature is the realization that advanced drug delivery is no longer a fashion trend, but rather a fit. The field is moving toward platforms that not only work in theory, but are also clinically defensible and measurable, and easily scalable[2][3][8].

2. Lipid-Based Nanocarriers

The nanocarriers with lipid-based formulation occupy a central position in the advanced drug delivery as they are biocompatible, structurally versatile and adaptable to their delivery routes while maintaining a formulation logic similar to the physiological membranes. Conventional dosage forms do not always prove to be appealing because they lack targeting ability, low bioavailability and higher side effects, while the lipid systems can increase drug solubility, protect labile payloads and control drug release. Thus lipid carriers are not just used as a means of encapsulating drugs, but as a tool to alter drug pharmacokinetics, gain access to tissues, and minimize off-target exposure in current nanomedicine[9].

Vesicular Systems: Liposomes, Ethosomes, and Transferosomes

The most well-known class of lipid nanocarriers is the vesicular ones. The prototype is liposomes; their phospholipid bilayer allows the incorporation of both hydrophilic and lipophilic drugs, in the interior and exterior of the vesicles, respectively, in a way that is highly versatile to a variety of therapeutic classes. Their performance is affected by compositional factors like lipid type, cholesterol level, surface charge, and hydration conditions, which affect bilayer rigidity, leakage, circulation time and release behavior. In the broader literature, liposomes are always presented as a platform which can increase solubility, targeted delivery and/or bioavailability, while maintaining a biocompatible lipid interface[9][10].

The concept of liposomes is expanded on to that of ethosomes and transferosomes, which change the fluidity and deformability of the membrane. Ethosomes contain ethanol, which makes them more elastic in their bilayer structure, and enhances their interaction with biological membranes. Transferosomes are engineered to be extremely flexible in order to adapt to mechanical stresses and penetrate dense barrier structures more efficiently. In actual practice, these systems are most desirable when the membrane interaction is a significant issue, particularly in topical and transdermal drug delivery, where the emphasis is on the ability of the system to pass through the membrane and not merely to be encapsulated[11][10].

The important point to note is that these vesicular systems cannot be substituted. The broad platform is liposomes, the tuned to permeation enhancement is ethosomes, and the tuned to flexibility is transferosomes. Their usefulness is predicated on a compromise between rigidity and fluidity for a vesicle to interact productively with the barrier, and structural integrity before reaching the target site for a vesicle that is too fluid. Therefore, the role of the vesicular lipid delivery is still much more of a composition control exercise than of just ingredients mixing[10].

2.1. Lipid-Surfactant Mixed Micellar Systems

Related but separate are lipid-surfactant mixed systems. Rather than closed bilayer vesicles they are self-assembled aggregates where the surfactant fraction is used to solubilize hydrophobic drugs

and to stabilize the dispersed phase. They are most useful when the primary issue is aqueous insolubility, as opposed to a classical vesicle. Thus, mixed systems are useful for drugs that have to be better dispersed, have a lower interfacial tension, and are better thermodynamically compatible with the delivery vehicle.

Here, the key design concept is ratio optimisation. The surfactant-to-lipid ratio determines whether the system is stable as a nanocarrier or will drift towards instability, irritation, or payload expulsion. Excessive amounts of surfactant will result in insufficient solubilization of the drug, while excessive amounts of the drug will lead to less structural persistence. Therefore, in most cases, the formulation of mixed micelles is optimized in parallel with consideration of size, loading, colloidal stability and release behaviour. Although the actual platform may vary by product, the same design concept applies to both: the behaviour of the interfaces dictates the behaviour of the product, and the behaviour of the interfaces dictates the drug delivery performance of the product[9][2].

Surfactant-to-Lipid Ratio Optimization and Solubilization Dynamics

Optimization of ratio is not a parameter to be done for looks; it is a parameter that determines whether a lipid-surfactant system can keep a hydrophobic drug in solution long enough to have clinical value. The more surfactant that is added to a formulation the better it will wet and solubilize, although too much surfactant can cause problems with the carrier or tolerability issues. The most defensible formulation strategy is thus to determine the composition range over which the system is colloidally stable, has adequate drug levels, and is suitable for the specific route of administration[2][9][10].

Deformability and Intestinal/Lymphatic Transport Pathways

The importance of deformability is that unlike a simple membrane, a biological barrier is a dynamic and crowded interface with narrow paracellular spaces, mucus layers and rapidly evolving local conditions. Ethosomes and transferosomes are often mentioned in the context of transdermal delivery, as they are able to adapt more readily to the barrier architecture in topical systems. The same principle applies to oral and mucosal delivery, but the final delivery characteristics of the drug depend on numerous other factors such as interaction with the mucous membranes, enzymatic stability and epithelial permeability. The most secure guess is that the deformability enhances barrier interaction, and the particular route of absorption will depend on the drug, the carrier, and the route[10][11].

Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

The most proven non-vesicular lipid carriers are SLNs and NLCs, and in many aspects they are also the most formulation-pragmatic. They are appreciated due to their ability to include the drug within a solid or semi-solid lipid framework which protects against early drug degradation and facilitates slow release. The recent reviews generally explain liposomes, SLNs and NLCs as biocompatible, biodegradable and improving the solubility and bioavailability of therapeutic agents particularly for poorly water soluble as well as unstable therapeutic agents [9].

While the concept behind SLNs is simple, it has some limitations. The matrix is very ordered, restricting the loading of drugs and crystallization during storage may result in payload expulsion. The reason for the development of NLCs is just this problem. The NLCs, which are composed of solid and liquid lipids, have a less ordered internal

structure that allows for more active ingredient to be incorporated, increases loading efficiency and decreases the likelihood of expulsion during storage. This is a second-generation design that is one of the most helpful cases of a big translation issue with a small compositional solution[9][10].

These systems are particularly applicable to delivery via the skin or through the skin, where the lipid matrix may interact favourably with the lipids found in the skin. The importance of structural similarity between the carrier and the barrier to obtain transdermal effect is emphasized in the topical literature multiple times, and the encapsulation efficiency of SLNs, NLCs, liposomes, ethosomes and transferosomes have been used to support practical formulation development. Thus, lipid based nanocarriers are frequently the preferred choice when both physicochemical stabilization and a realistic barrier crossing route is required for a drug[11][10].

The most relevant variables from a design point of view for the different lipid nanocarriers are the composition of the lipids, the type of surfactant, the organization of the lipids in a bilayer or matrix, the size of the particles, the surface charge, the encapsulation efficiency and the release kinetics. These are not independent endpoints; they are connected outputs from the same formulation architecture. Thus, a successful lipid nanocarrier is one that involves the chemistry of the excipients, the physical structure of the carrier and the biology of the intended route coming together. Recent reviews also emphasize the growing need to implement QbD principles during the development of these systems in order to achieve the transition from proof of concept to reproducible manufacturing, as process flow, critical parameters, and stability controls all have an impact on the final product[10].

Liposomes offer wide versatility of encapsulation; ethosomes and transferosomes provide an improved interaction with membranes; mixed micellar systems enable solubilization of hydrophobic drugs; and SLNs/NLCs ensure protection of the drug matrix and controlled release. The most successful option is dependent on the physiochemical characteristics of the drug, the method of administration and the therapeutic challenge to be addressed. The technology that makes lipid-based nanocarriers so enduring in the field is that it is not a single technology but a family of tools that address various delivery requirements [2][9][10].

2.2 Polymeric Nanocarriers

Polymeric nanocarriers are some of the most versatile systems in the field of nanomedicine since their structure can be adjusted through polymer chemistry rather than relying on a single inherent material property. The most useful design feature is modularity: the core can be used to carry hydrophobic drugs, the shell helps to improve circulation and colloidal stability, and functional groups can be included in order to control targeting, release, and pharmacokinetics. In reality, this means that polymeric systems can be applied to small molecules, macromolecules, and combined payloads as well [12].

Core-shell polymeric micelles and the critical micelle concentration (CMC)

Polymeric micelles result from the self-assembly of amphiphilic polymers in water and only form when the concentration of the polymer is above the critical micelle concentration. The fact that the CMC is not a minor physicochemical point but rather a stability indicator should be noted, since a lower CMC usually means that the micelle is less likely to break down after being diluted in the bloodstream. Reviews always refer to micelles as nanoscale core-shell structures, generally in the size range of 10–100 nm, wherein the hydrophobic

core can solubilise poorly water-soluble drugs and the hydrophilic corona enhances dispersion and biocompatibility[13][12].

It is for this reason that micelles have continued to be used as a major platform in drug delivery; the core-shell structure of them allows for the incorporation of hydrophobic substances and their kinetic stability helps to prevent premature loss of the drug payload. When the principle is applied in actual formulations, it is frequently expanded by the use of targeting ligands or by employing mixed-polymer designs in order to enhance accumulation in tissues and decrease exposure to sites other than the target[12].

Dendrimers, nanospheres, and polymeric conjugates

Dendrimers have a special place within the family of polymeric nanocarriers since they are not just self-assembled particles; they are generation-controlled, hyperbranched macromolecules having a dense and highly ordered surface. The fact that their structure is compact and smaller than 10 nm gives them a large number of terminal groups which can be used for surface functionalisation, thus making them very useful for multivalent binding, the attachment of targeting ligands, and for the programmed loading of drugs[14][15]. PAMAM-type dendrimers are a typical example of this type, and the literature also indicates that they have been used as nanoconjugate systems for drug targeting with reduced toxicity.

One of the practical benefits of dendrimers is that they are capable of acting in more than one way at the same time; for example, they can encapsulate a payload, bind with nucleic acids, or deliver drugs by means of covalent conjugation. This versatility is the main reason why dendrimers are often mentioned together with nanospheres, micelles, nanogels, and vesicles in the context of broader polymeric nanomedicine[14].

The same principles can be applied in a more chemically precise way through the use of polymeric conjugates. Such systems achieve this by attaching therapeutic agents or functional groups to a polymer backbone, which in turn allows for a longer circulation time, better targeting, controlled release, and a reduction in immunogenicity. Because of these properties, they are particularly appealing in cases where the therapeutic window is narrow or when the drug is unstable on its own.

Inorganic and biomimetic delivery vehicles

Inorganic and biomimetic systems extend the range of possible designs beyond that of polymer chemistry; the inorganic ones provide structural rigidity as well as optical or magnetic properties and a high payload capacity, while the biomimetic ones offer natural membrane biology, endogenous communication pathways, and the ability to home in on tissue. Together, these two categories include some of the most promising concepts for modern nanodrug delivery in terms of potential translation[4][16].

Mesoporous Silica and Metallic Nanoparticles

Mesoporous silica nanoparticles are some of the most versatile inorganic carriers since they have a high surface area, a tunable pore size, a controllable morphology, and good biocompatibility. It is because of these characteristics that they are useful both for simple drug loading and for gated release, surface decoration, and theranostic design. Whenever reviews of MSNs are looked at, it is stressed that the pore structure and surface chemistry of these nanoparticles allow for the effective encapsulation, protection, and targeted delivery of therapeutic and diagnostic agents[16].

Metallic nanoparticles provide a number of different functions since they can enhance stability

during circulation, aid biodistribution, and be adapted for either passive or active targeting. Gold nanorods in particular are important because the main therapeutic value of them lies in their ability to generate heat which can be adjusted under near-infrared irradiation, this heat being able to be linked to drug release or photothermal therapy. To put it simply, the particle serves not only as a carrier but also as a transducer that transforms external energy into a local therapeutic effect[17].

Exosomes and Extracellular Vesicles

The exosomes and other extracellular vesicles discussed here are the most naturally occurring delivery systems in this section. They are tiny vesicles surrounded by a lipid bilayer membrane, which cells produce as part of normal cell-to-cell communication, and which naturally contain proteins, lipids, and nucleic acids. Because of their origin within the body, they have a significant advantage over a number of synthetic systems: they are generally regarded as having low toxicity and low immunogenicity together with intrinsic biocompatibility[4][18].

It is not just because they are well tolerated that they are attractive, but since they already have biological routing information. Reviews state that they have better organotropism, homing capacity, cellular uptake, and cargo release ability than a number of synthetic carriers. Further improvements in specificity and a reduction in endosome trapping can be achieved through surface engineering, which is the reason why exosomes are increasingly being considered as precision delivery platforms rather than merely as natural nanoparticles [4].

When it comes to design, current exosome engineering is concerned with three issues: defining the vesicle population, loading the cargo efficiently, and managing targeting during large-scale production. These constitute the genuine translational challenges, and it is important because although exosomes are in principle very elegant the way they operate is more complex than that of polymers or inorganic particles. Yet they are still a clear example of how biomimicry can enhance the specificity of delivery without having to give up biological compatibility[4][18].

Using a chapter-based approach, this method of classification is advantageous since it connects the type of material with its function. When it comes to tunability and the control of release, polymeric systems are most effective; inorganic carriers provide structural and physical transduction properties; and exosomes offer natural biodistribution and homing capabilities. The most suitable platform is not usually the one that appears to be the most advanced in theory, but rather the one whose material characteristics are appropriate for the drug, the disease, and the route of administration. Since this is just an initial review of the literature, a more in-depth examination could include additional primary studies focusing on generation-specific dendrimer chemistry, MSN gating strategies, and engineered exosome platforms.

Table 1. Classification of Advanced Nanocarrier Systems Based on Their Key Features, Applications, and Limitations

Nanocarrier Class	Key Idea	Why It Matters	Main Limitation
Core-shell polymeric micelles	Amphiphilic copolymers self-assemble above the CMC into nanoscale core-shell particles; the core loads hydrophobic drug and the shell stabilizes circulation.	Useful for improving solubility, stability, and controlled release.	Can dissociate on dilution, so CMC and kinetic stability matter.

Dendrimers and polymeric conjugates	Hyperbranched dendrimers and polymer-drug conjugates provide dense functional groups for multivalent loading and precise surface chemistry.	Useful for targeted delivery, controlled release, and reduced immunogenicity.	Synthesis, toxicity management, and translation can be complex.
Mesoporous silica nanoparticles	Highly porous silica particles with tunable pore size and large surface area support cargo loading and surface functionalization.	Useful for targeted, controlled, and theranostic delivery of drugs, genes, and proteins.	Clinical translation depends on reproducibility, biodistribution, and long-term safety.
Metallic nanoparticles, especially gold nanorods	Metal nanoparticles can convert external energy into local heating; gold nanorods are widely used for NIR-triggered release.	Useful for remote activation, photothermal therapy, and combined imaging-delivery platforms.	Toxicity, surface engineering, and scale-up remain important concerns.
Exosomes and extracellular vesicles	Natural lipid-bilayer vesicles carry proteins, lipids, and nucleic acids as part of cell communication.	Useful for biocompatible delivery with intrinsic homing and low immunogenicity.	Large-scale production, loading efficiency, and standardization are still difficult.

3. SMART AND STIMULI-RESPONSIVE DRUG DELIVERY SYSTEMS

Smart and stimuli-responsive drug-delivery systems are engineered to change their structure, surface chemistry, permeability, or degradation in response to a specific biological signal or externally applied stimulus. Responsive systems try to link delivery with location and timing, as opposed to conventional systems, which primarily offer passive protection and prolonged release. A formulation can be fairly stable when in circulation but can become larger, charged, altered in shape, or become chemically connected in some way following a process of acidity, enzymatic activity, redox conditions, heat, light, magnetic fields, or ultrasound. These changes can help to control release, expose a targeting ligand, facilitate endosomal escape or activate a therapeutic payload[19][3].

The major difference in the design is endogenous and exogenous stimuli. Endogenous systems are based on physiological and pathological differences that are already present within the body, while exogenous systems are based on a physical input in the body controlled by the clinician. Endogenous cues may supply autonomous activation but levels of activation are not the same in all tissues, patients and disease stages. The exogenous triggers provide greater control over the dose and treatment site, but they require appropriate equipment and a realistic approach to the delivery of energy to the treated tissue(20).

Endogenous stimuli-responsive systems

The pH-responsive delivery is especially important as pH changes are observed in the different compartments of the gastrointestinal tract, in tumors, in inflamed tissues, and in intracellular vesicles. Ionizable polymers and lipids can become protonated or ionized and change their charge and hydration; acid-labile bonds can cleave; pH-sensitive assemblies can swell, dissociate, or disrupt membranes. When the tumor environment is moderately acidic, the environment of endosomes and lysosomes is more acidic, thereby affording sequential opportunities for targeting to the extracellular environment and for release in the endolysosomal compartment. But the contrast between healthy and unhealthy tissue

might be too low or not distributed uniformly to ensure selective activation. Redox-responsive systems are based on differences between the extracellular fluids and the cytosol [21][3]

Polymerization, lipid anchoring, cross linking and drug conjugation can be achieved by incorporation of disulfide, diselenide and thioketal linkages. Once within the cell, the reducing environment can break susceptible bonds and facilitate the disassembly of carriers and/or release of cargo. In inflamed or tumor tissue, the complement target is provided by ROS. The selectivity is only apparent; activation may be influenced by extracellular thiols, and by variable glutathione and organelle redox conditions[3].

The accessibility and cleavage rate of the linker is thus as important as the nominal stimulus. Enzyme responsive systems are based on peptide, ester, glycosidic or other cleavable motifs, which are substrates for proteases, phospholipases, glycosidases, or disease-associated enzymes. The cleavage by enzymes can expose a ligand, break a gate in a nanoparticle, and/or detach a covalently linked drug. This approach is appealing when the disease process is associated with an over-expression of an enzyme in a specific compartment, but the expression of the enzyme is somewhat variable and may also be present in non-target tissues. Therefore

screening of purified enzyme solutions is not enough, activation should be tested in disease-relevant matrices and models that include other proteins and variable enzyme activity[22][3]

Table 2. Overview of endogenous stimuli-responsive drug delivery systems, highlighting the trigger mechanisms, typical material responses, therapeutic opportunities, and key limitations associated with pH, redox/ROS, enzymatic, hypoxia, and ATP-responsive systems.

Endogenous trigger	Typical material response	Main opportunity	Key limitation
pH	Protonation, charge change, swelling, acid-labile cleavage, membrane destabilization[21]	Tumor, gastrointestinal, endosomal, and lysosomal release	Narrow or heterogeneous pH differences may cause incomplete or off-target activation [3]
Redox / ROS	Disulfide or thioketal cleavage, oxidation, carrier disassembly [21]	Cytosolic release and disease-associated oxidative activation	Redox gradients vary by tissue, cell type, and compartment [3]
Enzymes	Peptide or polymer degradation; shell opening; ligand exposure[3]	Activation in tumours, infection, inflammation, or organelles	Enzyme abundance and activity are biologically heterogeneous[3]
Hypoxia / ATP	Reduction-triggered chemistry or ATP-sensitive structural switching [22]	Microenvironment-specific activation and intracellular sensing	Trigger distribution may not match carrier distribution [3]

Exogenous stimuli-responsive systems

Externally controlled delivery may be able to give fast, repeatable activation after administration. Thermoresponsive liposomes, polymers, micelles and hydrogels change their properties or phase behavior at the local heat. The light responsive materials can involve the use of photolabile bonds, photoisomerization, photothermal conversion, and/or photo dynamic generation of reactive oxygen species. Magnetic nanoparticles can be magnetically directed or heated under an alternating magnetic field and ultrasound can induce cavitation, acoustic streaming, sonoporation and/or thermal release. Such

modalities can also be used to couple therapy with imaging, forming theranostic systems[20].

The primary benefit of an external trigger is that exposure can be manipulated over time and in intensity. Its primary limitations are that the energy has to be delivered into the relevant tissue without causing unacceptable injury. However, light penetration is restricted, especially in the short wavelengths; magnetic heating is sensitive to the magnetic condition and properties of the particles; and ultrasound is sensitive to the frequency, pressure, and duration of exposure and to the interactions between the ultrasound and the tissue. Therefore, the trigger is an integral component of the product: formulation performance cannot be dissociated from the trigger device and treatment protocol.

Table 3. Overview of externally triggered stimuli-responsive drug delivery systems, highlighting the external triggers, release or targeting mechanisms, translational strengths, and principal constraints associated with heat-, light-, magnetic field-, and ultrasound-responsive systems.

External trigger	Release or targeting mechanism	Translational strength	Principal constraint
Heat	Lipid phase transition, polymer collapse, increased membrane permeabilit([21]	Can be integrated with local hyperthermia	Temperature must be spatially controlled to avoid tissue injury([21])
Light	Photocleavage, photothermal heating, photodynamic activation[20]	Remote and potentially repeatable on–off control	Limited penetration and wavelength-dependent safety([3])
Magnetic field	Guidance, vibration, or alternating-field heating[20]	Enables combined imaging and treatment	Field localization, particle retention, heating, and clearance must be controlled
Ultrasound	Cavitation, sonoporation, acoustic or thermal disruption[20]	Deep-tissue access and imaging compatibility	Exposure parameters must balance penetration, focality, and safety

Multistimuli designs and translation

The combination of different stimuli can lead to a sequential release. For instance, a carrier can stay stable in the blood, form a protective layer in the acidic environment of a tumour, shrink in order to penetrate more deeply, and then discharge its payload following redox cleavage in the cytosol. This kind of multi-stage approach takes into account the fact that accumulation, tissue penetration, cellular uptake, endosomal escape, and drug release represent different obstacles. However, each additional trigger introduces more formulation variables, more analytical assays, more possible points of failure, and greater regulatory complexity. The most convincing design is therefore not the most complicated one, but rather the simplest response sequence that resolves a well-documented delivery issue[22].

The translation is still the key challenge. When nanoparticles are present in biological fluids they form a protein corona, and the resulting changes in their composition, size, and charge can affect how they are taken up, how they are recognised by the immune system, their circulation time, and the way they are cleared. A study mentioned in a major review calculated that less than 1% of the dose of nanoparticles injected reached the tumour tissue, highlighting the discrepancy between beautiful in vitro release studies and actual in vivo

performance. It follows that development efforts should include the determination of trigger thresholds together with an assessment of pharmacokinetics, biodistribution, degradation, organ retention, and the integrity of the payload. Manufacturing processes must ensure control over particle size, surface characteristics, loading, the presence of any residual reagents, release behaviour, and consistency from batch to batch; safety issues could arise if residual initiators, stabilisers, or catalysts are not properly removed [3].

A number of responsive systems have now undergone clinical testing, such as those that respond to magnetic stimuli, to heat, to changes in pH, and to secretory phospholipase-A2, and ThermoDox was itself tested in conjunction with high-intensity focused ultrasound and radiofrequency ablation. However, these cases only show that the approach is feasible, not that it is universally effective. Further advances will rely on reproducible manufacturing processes, on validated combinations of device and formulation, on the use of biologically realistic models, and on selecting patients according to their measurable trigger biology[3].

CONCLUSION

The function of modern drug-delivery systems extends well beyond that of merely slowing down the release of a drug; their present role is to manage the entire exposure pathway of a therapeutic molecule. This includes solubilization, protection against degradation, circulation, biodistribution, tissue penetration, cellular uptake, intracellular trafficking, and release. It is necessary to adopt this broader approach because a drug's clinical performance depends not only on its pharmacological potency but also on whether sufficient quantities of it reach the right biological compartment while at the same time reducing exposure in other regions. Although lipid-based, polymeric, inorganic, and biomimetic carriers each deal with these challenges in different ways, no single type is generally superior to the others. The most appropriate carrier system will depend on the properties of the drug, the route of administration, the biological barrier in question, the required duration of exposure, and the acceptable safety margin.

Lipid-based systems are still worthwhile because their membrane-like structure allows them to solubilise, encapsulate, fuse and enable controlled drug transport. Polymeric systems on the other hand offer greater flexibility when it comes to their architecture, degradation, surface modification and responsiveness to stimuli. Inorganic and hybrid materials can provide imaging, photothermal, magnetic or catalytic functions, but their long-term behaviour and the way in which they are cleared from the body have to be carefully evaluated. Biomimetic systems, such as extracellular vesicles and exosomes, are attractive since they may provide biological compatibility, the ability to interact with cells, and tissue-homing properties that are difficult to obtain with synthetic materials. Yet these advantages should not be interpreted as proof that biomimetic carriers are automatically safer or more effective; new risks may arise because of their composition, which depends on their source, the variability in the amount of drug they carry, their sensitivity to storage, and the complexity of their manufacturing process, even though they do overcome some of the disadvantages of conventional nanoparticles.

The idea of stimuli-responsive drug delivery is a significant conceptual step since it associates the release of drugs with either the biology of the disease or with a controllable external intervention. Release can be activated at specific sites by endogenous signals such as acidity, redox conditions, enzymes, hypoxia, reactive oxygen species, and intracellular ATP, while temperature, light, magnetic fields, and ultrasound can offer

external control. Such systems have the potential to reduce premature leakage, enhance intracellular delivery, and allow for sequential control over several biological barriers. Nevertheless, a trigger is of any use only if there is a sufficient difference between the target and non-target compartments, if it reaches the carrier with adequate intensity, and if it gives a predictable response within the required therapeutic time frame. Tumour heterogeneity, variation in enzyme expression, the formation of the protein corona, immune clearance, and limited tissue penetration can diminish this apparent selectivity. Therefore, the stimulus sensitivity observed in buffer or in purified enzyme does not match selective drug release in a patient.

Care must also be exercised when interpreting targeting. Passive accumulation does not mean that effective delivery has taken place, and the enhanced permeability and retention effect differs from one type of tumour, one stage of disease, one vascular structure, and one stromal environment to another. Although active targeting ligands can increase receptor-mediated uptake, they do not remove the requirement for an adequate circulation time, tissue access, and intracellular processing. A carrier that gets to a tumour but stays close to the blood vessels, is quickly taken up by inactive cells, or fails to release its payload may result in only limited therapeutic benefit. The figure stating that less than 1% of an injected nanoparticle dose may reach tumour tissue shows just how great the delivery problem is and underscores the importance of assessing biodistribution rather than depending solely on data regarding cellular uptake or release.

The main point therefore relates to the issue of translation. An efficient advanced delivery system must be designed as a complete product and not just as a single nanoparticle. When designing it, all the following factors have to be considered: the composition of the formulation, the particle size, its surface charge, its morphology, the amount of drug it contains, the rate at which it releases the drug, the degradation products, the device's parameters, the route of administration, and the conditions for storage. Manufacturing should make sure that it produces reproducible critical quality attributes on a scale that is clinically relevant, and pharmacokinetic and biodistribution studies must verify that the carrier actually reaches and stays at the target site. The safety evaluation has to include hemocompatibility, activation of the complement system and the immune system, organ accumulation, oxidative stress, chronic toxicity, and the effects of repeated dosing. There also needs to be control over any residual catalysts, initiators, stabilisers, or other process-related impurities.

Several responsive platforms have now advanced to the stage of clinical evaluation, which shows that the field is moving beyond just theoretical research. However, clinical testing by itself does not demonstrate that a treatment will be effective across a wide population, and the fact that only a small number of cancer nanomedicines have been approved compared to the enormous amount of research carried out every year suggests that the process of turning research into practice is still selective. Future progress will depend on selecting indications in which both the biological barrier and the trigger can be measured, on using models that better represent the variety of human tissues, and on setting pharmacokinetic and pharmacodynamic endpoints that have clinical importance. The field should favour simpler systems with a clear mechanistic basis over those that are becoming increasingly complex because the additional functions included cannot consistently be manufactured, characterised, or controlled. Advanced drug delivery will only be able to realise its full potential when responsiveness, targeting, safety, and manufacturability are all treated as essential requirements of the final product. In this

view, nanocarriers are not merely carriers for drugs; they are engineered components of therapeutic systems and their value should be assessed according to the reliable benefit they give to patients and not merely on the complexity of their material composition.

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