



ISSN: 2231-3656

International Journal of Pharmacy and Industrial Research (IJPIR)

IJPIR | Vol. 16 | Issue 4 | Oct – Dec 2026

www.ijpir.com

DOI: <https://doi.org/10.61096/ijpir.v16.iss4.2026.1006-1024>

Stimuli-Responsive Nanocarriers for Targeted Drug Delivery: Formulation Design, Therapeutic Applications and Translational Challenges

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Published on:

15.10.2026

Published by:

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Abstract: Stimuli-responsive nanocarriers are designed to hold a drug securely during transport and to release it, or to change shape, surface charge or permeability, when they meet a defined biological cue or an externally applied form of energy. This review examines such systems from a pharmaceuticals perspective. Endogenous triggers (pH, glutathione, reactive oxygen species, enzymes, hypoxia and glucose) and exogenous triggers (light, ultrasound, heat, magnetic fields and ionising radiation) are discussed together with the lipidic, polymeric, inorganic, biomimetic and hybrid carriers built around them. Attention is given to trigger chemistry, payload compatibility, colloidal stability, biodistribution and release kinetics, and to applications in cancer, inflammatory bowel disease, infection, brain disease, diabetes and nucleic-acid delivery. Clinical-stage products, including thermosensitive liposomal doxorubicin, hafnium oxide nanoparticles, magnetic thermotherapy and implantable ultrasound devices, show that externally triggered approaches have reached patients, whereas purely biochemical triggers have yet to yield an approved product. The evidence indicates that responsiveness adds value only when the trigger shows a reproducible difference between diseased and normal tissue, the carrier stays intact until activated, and the whole drug-carrier-device system can be manufactured and used in routine care. A quality-by-design framework for defining critical material attributes, process parameters and release specifications is outlined, followed by recommendations for evaluation, reporting and trial design. Future progress is most likely to come from simpler platforms matched to a defined clinical need and supported by mechanistic pharmacokinetic and trigger-performance data.

Keywords: Stimuli-responsive nanocarriers; targeted drug delivery; controlled release; quality by design; clinical translation; pharmaceuticals

1. Introduction

A drug-delivery system has to put the right amount of drug at the right place for long enough to matter clinically. Conventional dosage forms rarely manage all three at once. Small molecules spread through the body, are cleared quickly or injure healthy tissue on the way, and biologics and nucleic acids are degraded, cross membranes poorly and are often lost inside the cell before they act. Nanocarriers were introduced to deal with these problems: they can improve solubility, shield labile molecules, change pharmacokinetics and carry more than one function in a single particle. The field has moved from liposomes and polymeric micelles to lipid nanoparticles, nanogels, inorganic particles, vesicle-inspired vehicles and hybrid constructs [1–3]. Better particle chemistry has not, however, guaranteed better delivery. Opsonisation,

uptake by the liver and spleen, limited transport across the endothelium, uneven perfusion and cell-specific uptake all reduce the dose that reaches diseased tissue, and the median fraction of an injected nanoparticle dose found in solid tumours is small [4–6].

Stimuli-responsive nanocarriers tackle part of this problem by separating stability in the circulation from release at the target. The particle is built to stay intact in blood and to change only after meeting a specific cue. Depending on the design, the change may free a physically entrapped drug, cleave a drug conjugate, expose a ligand, reverse the surface charge, swell a network, dismantle a micelle or generate heat locally. The cue may come from the disease itself, as with acidity, raised enzyme activity, oxidative stress or low oxygen, or from outside the body in the form of ultrasound, heat, light, magnetic fields or radiation [7,8]. The appeal is that timing is controlled in addition to location.

Whether a given design is useful depends on three conditions that are largely independent. The stimulus must differ enough between target and normal tissue, or be deliverable with sufficient spatial precision. The responsive reaction must proceed fast enough, and far enough, to change the free-drug concentration in a meaningful way. And the inactive carrier must be safe, stable and practical to make. Many systems that perform impressively in the laboratory fail the first condition in patients, because tumours and inflammatory lesions differ widely between individuals and over time in perfusion, pH, redox state and stromal density [9–11]. This mismatch helps explain why only a handful of responsive products have reached clinical testing, and why recent analyses of the clinical landscape point to poorly defined medical need, excessive material complexity, limited tissue penetration, restricted access to devices and economic constraints as recurring obstacles [12,13].

This review looks at stimuli-responsive nanocarriers mainly from the standpoint of pharmaceuticals rather than materials chemistry. We describe how carrier composition, trigger chemistry, particle architecture and manufacturing conditions together determine performance; compare the main endogenous and exogenous triggers; summarise applications in six disease areas; and set out the formulation, analytical and regulatory evidence that translation requires. Throughout, we treat a responsive nanocarrier as a single medicinal product whose trigger, carrier, route of administration, manufacturing process and any associated device have to be defined together from the start.

2. Design principles for stimuli-responsive nanocarriers

2.1 Defining responsiveness

A nanocarrier can be called stimuli-responsive when a defined input produces a purposeful, measurable change in its structure, physicochemical properties or drug-release behaviour. Formulations that simply release faster in a non-specific environment do not qualify. A useful system has three measurable properties: an activation threshold, a response rate and a release amplitude. For endogenous triggers the threshold must lie outside the normal physiological range, and for external triggers it must fall inside a range of energy that can be delivered safely. The response rate has to suit the pharmacological aim; a cytotoxic drug paired with local ablation may need to leave the carrier within minutes, whereas an anti-inflammatory agent in the colon may be better served by retention and release over several hours. The amplitude is the difference in drug release or exposure between triggered and untriggered conditions, and it is this difference, rather than the absolute release at the trigger condition, that predicts how selective the product will be.

2.2 From target product profile to trigger

Formulation work starts with a target product profile that fixes the disease, target tissue, route, payload, dose, desired onset and duration of action, acceptable size range, storage conditions and intended clinical workflow. The choice of stimulus follows from that profile. An acidic endosome is a dependable cue for intracellular delivery, whereas the small extracellular pH difference in a solid tumour is a weak sole trigger. Near-infrared light gives excellent temporal control in skin, the eye or endoscopically reachable mucosa, but not in deep tissue. Focused ultrasound reaches deep organs and can be guided by imaging, but acoustic settings, cavitation behaviour and operator technique then become part of the performance of the product [7,14].

2.3 Carrier selection and the coupling of attributes

The carrier is chosen next, on the basis of the drug and the intended release mechanism. Liposomes offer a biocompatible bilayer, with an aqueous core for hydrophilic solutes and a membrane compartment for lipophilic drugs; their response can be tuned with phase-transition lipids, acid-labile components or

enzyme-cleavable phospholipids. Polymeric micelles and nanoparticles accept a very wide range of cleavable bonds and responsive blocks, but their stability on dilution and their chain exchange need to be tested. Dendrimers allow multivalent functionalisation at the price of possible charge-related toxicity. Mesoporous silica, gold, iron oxide and other inorganic platforms supply optical, magnetic or thermal functions, while raising questions of degradability, persistence and impurity control. Biomimetic coatings and lipid–polymer hybrids may improve behaviour at the biological interface but add raw-material and analytical complexity [1,8].

Particle size, polydispersity, shape, surface charge, ligand density, drug loading and release profile cannot be optimised one at a time. A smaller particle may pass through capillaries more easily but is cleared by the kidney sooner and carries less drug. A cationic surface improves cell uptake and nucleic-acid complexation but also adsorbs more serum protein and activates complement. Ligands can raise binding to a cell population once the particle is in the tissue, yet they do nothing for a particle that never arrives. The term ‘active targeting’ therefore needs careful use: the largest determinant of exposure is still whether the carrier reaches the diseased compartment at all, and affinity matters only after that barrier has been crossed [9,10].

These interdependencies suggest a practical order of decisions (Fig. 1). One first chooses a disease with a justified trigger and an accessible target, then the simplest carrier that protects the payload and responds in the required window, then establishes the release mechanism, and only afterwards considers targeting or imaging functions that bring measurable added value. Following this order reduces the chance of ending up with a multifunctional particle that is scientifically elegant but cannot be reproduced, characterised or used in a clinic.

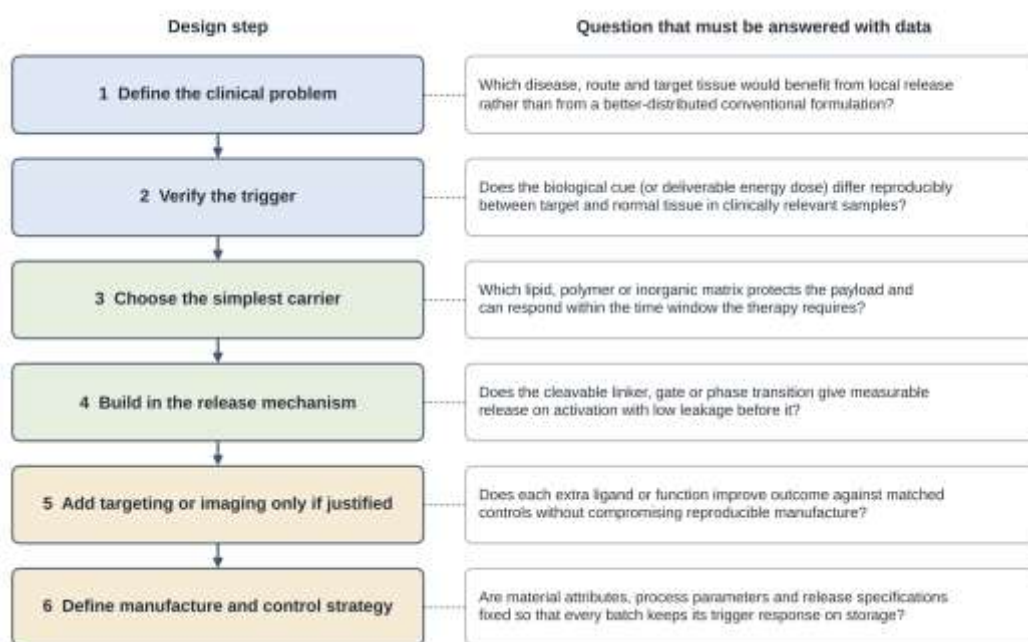


Fig 1: Design logic for a stimuli-responsive nanocarrier. Each step must be supported by data before further complexity is added.

3. Endogenous stimuli

Endogenous triggers exploit chemical differences that disease creates in the body. Their main attraction is that no equipment is needed; the main difficulty is that the difference between diseased and healthy tissue is often modest and varies from patient to patient. Fig. 2 summarises the endogenous and exogenous trigger classes discussed in this review and Table 1 compares the endogenous ones.

3.1 pH-responsive systems

Acidity is the most widely used endogenous cue because pH varies along the gastrointestinal tract and differs between normal tissue, the tumour interstitium and the endosomal and lysosomal compartments. Tumour extracellular pH is typically in the region of 6.5 compared with 7.4 in normal tissue, whereas endosomes and lysosomes acidify to about 5.5 and 5.0 respectively [15–17]. The extracellular gradient is

thus small and variable, and a poorly tuned polymer will not give a sharp response to it. The intracellular gradient is larger and more dependable, which is why pH-sensitive designs tend to work best after endocytosis. Common motifs include hydrazone, imine, acetal, orthoester and cis-aconityl bonds, together with polymers carrying tertiary amines or carboxylic acids. Protonation can swell a matrix, destabilise a membrane, drive a micelle-to-unimer transition or expose a positively charged, cell-interacting surface [16,17].

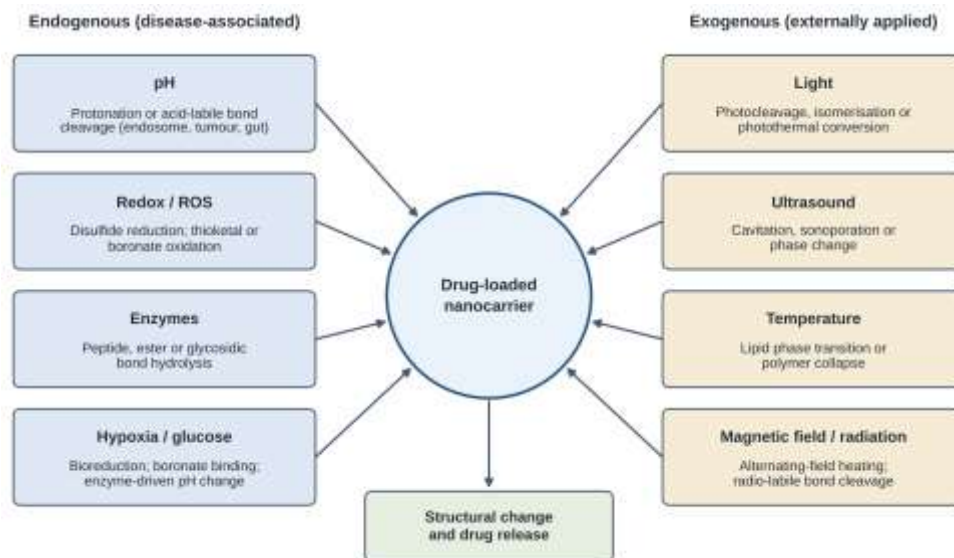


Fig 2: Endogenous and exogenous trigger classes and the events that lead to drug release from a nanocarrier. Abbreviations: ROS, reactive oxygen species.

In liposomes, pH sensitivity is usually introduced by inserting a fusogenic or ionisable lipid, or a pH-sensitive polymer, into the bilayer. Polymeric examples include poly(histidine), poly(β -amino ester), poly(2-diisopropylaminoethyl methacrylate) and chitosan derivatives. What counts is the apparent pKa of the finished nanocarrier, not that of the isolated monomer: hydrophobicity, polymer architecture, ionic strength and protein adsorption all shift the transition. Release should therefore be measured in media that represent blood, tumour interstitium and endolysosomal fluid at physiological ionic strength. An unbuffered experiment showing complete release at pH 5.0 can badly overstate what happens in vivo.

3.2 Redox- and ROS-responsive systems

The glutathione concentration inside cells (roughly 2–10 mM) is orders of magnitude above that in plasma and the extracellular space (roughly 2–20 μ M), and many tumours, inflamed tissues and infected lesions show further redox disturbance [17]. Disulfide and diselenide bonds are the standard way to couple a drug to a carrier or to crosslink one; reduction by glutathione cleaves them, leading to de-crosslinking, drug liberation or charge conversion. Oxidation-responsive materials use thioketal, thioether, boronate or selenium-containing groups that react with reactive oxygen species (ROS) [18]. The two approaches are not interchangeable. A reducing intracellular environment and extracellular oxidative stress are chemically and biologically different cues, and a system designed for one will not respond to the other.

Redox responsiveness is especially attractive for nucleic acids. A particle can stay cationic enough to condense RNA during preparation and transport, then lose its crosslinks after uptake and free its cargo in the cytosol. Cleavage alone cannot compensate for poor endosomal escape, however, and escape is generally inefficient. For small-molecule drugs, redox-cleavable prodrugs give a better-defined architecture than physical entrapment, provided that the linkage is stable in plasma and that the released species are identified. Measuring glutathione levels is not enough; response has to be shown in disease-relevant cells and compared with healthy controls.

3.3 Enzyme-responsive systems

Enzymes can offer more molecular specificity than pH. Matrix metalloproteinases, cathepsins, hyaluronidase, phospholipases, esterases, β -glucuronidase and bacterial enzymes have been used to cleave peptide, ester, glycosidic or phospholipid substrates built into outer shields, linkers, gates on mesoporous

particles or drug conjugates [19,20]. A typical example is a polyethylene glycol shell attached through an MMP-cleavable peptide, which detaches in the tumour matrix and uncovers a cell-penetrating surface; a hyaluronic-acid coating that is degraded by hyaluronidase in selected tumours or inflamed tissue works on the same principle.

The weakness of this approach is variability. Enzyme amount, localisation and activity depend on disease stage, tissue compartment and previous treatment, and an enzyme that is plentiful in a homogenised biopsy may be out of reach of an intravenously injected particle. Kinetic assays therefore need to be run in biological matrices and off-target tissues as well as in disease models, and the stability of the cleavable substrate during sterilisation and storage has to be confirmed. Enzyme sensitivity is most convincing when it is used to overcome a specific barrier, such as mucus penetration, unmasking of a ligand in the stroma or intracellular release, rather than included as a feature in its own right.

3.4 Hypoxia, glucose and other metabolic cues

Hypoxia-responsive carriers generally use nitroimidazole, azobenzene or quinone groups that are bioreduced at low oxygen tension; they may release a drug, consume oxygen or activate a prodrug [21]. The idea is relevant to poorly perfused solid tumours and to ischaemic disease, but severely hypoxic regions are, almost by definition, those that intravenous carriers reach least. Glucose-responsive platforms use glucose oxidase, phenylboronic acid or lectin competition to adjust insulin release to blood glucose. They are conceptually ideal for diabetes, but have to overcome protein fouling, variable diffusion in subcutaneous tissue and the need for very reliable response kinetics [22]. ATP, nitric oxide and inflammatory reactive species offer further possibilities, though each needs to be checked for disease specificity, measurability and sufficient concentration at the carrier's location.

Table 1. Principal endogenous triggers used in stimuli-responsive nanocarriers

Trigger	Disease-related cue	Typical responsive chemistry	Main advantage	Main limitation
pH	Tumour interstitium ~6.5 (normal 7.4); endosome ~5.5; lysosome ~5.0; gut segments	Protonation of amines or carboxylates; hydrazone, imine, acetal, orthoester and cis-aconityl cleavage	Reliable for endosomal release and oral site targeting	Extracellular gradient small and heterogeneous
Glutathione (reducing)	Intracellular ~2–10 mM vs extracellular ~2–20 μ M	Disulfide or diselenide reduction	Supports cytosolic unpacking and prodrug release	Requires cell entry and endosomal escape
ROS	Oxidative stress in inflammation, infection and cancer	Thioketal, thioether, boronate or selenium oxidation	Links release to inflammatory activity	Levels fluctuate; not disease-specific
Enzymes	MMPs, cathepsins, hyaluronidase, esterases, bacterial enzymes	Cleavage of peptide, ester, glycosidic or phospholipid substrates	High molecular specificity possible	Expression and accessibility vary between patients
Hypoxia / glucose	Low O ₂ tension; raised glucose in diabetes	Nitroimidazole, azobenzene or quinone bioreduction; boronate binding; glucose oxidase	Matches specialised tumour or metabolic niches	Hypoxic regions hard to reach; slow or variable kinetics

Abbreviations: MMP, matrix metalloproteinase; ROS, reactive oxygen species. Values are approximate and are given to illustrate the size of the gradient [15–17].

4. Exogenous stimuli

External triggers trade biological uncertainty for procedural complexity. The input can be scheduled, measured and repeated, but the nanocarrier, the energy source and the clinical procedure have to be developed and validated as one intervention. Table 2 compares the main modalities.

4.1 Light-responsive systems

Light provides direct temporal control and high spatial precision. Ultraviolet and visible wavelengths can drive photocleavage, photoisomerisation, crosslinking or photothermal conversion, whereas near-infrared (NIR) light penetrates tissue better and is preferred for biomedical use. Azobenzene and spiropyran groups change configuration, o-nitrobenzyl and coumarin groups can be cleaved, and photosensitisers generate ROS. Gold nanorods, carbon-based materials and some semiconducting particles convert absorbed light to heat, which can disrupt a carrier or promote diffusion of the drug [23,24].

The main formulation issue is the balance between optical response and biocompatibility. A higher chromophore content improves activation but may alter particle size, payload capacity and clearance. Photothermal heating has to be quantified in the formulation matrix and in tissue-like phantoms, not inferred from experiments in clear solution, and the clinician needs an illumination protocol that states wavelength, fluence, irradiance, duration and target depth. Light is realistic for skin, eye, oral cavity, bladder, cervix and lesions reachable through an endoscope, fibre or surgical field. The feasibility of the approach in humans has been shown with gold-silica nanoshells and MRI/ultrasound-fusion-guided laser ablation of localised prostate cancer in a pilot device study [25]. Claims of deep-tissue optical activation should be tempered by scattering, absorption and local heating limits.

4.2 Ultrasound-responsive systems

Focused ultrasound can be applied non-invasively to deep tissue and combined with real-time imaging. At low acoustic pressure it promotes stable cavitation and transient membrane permeability; at higher pressure it causes inertial cavitation, mechanical disruption and local heating. Microbubbles, nanobubbles, phase-change droplets, liposomes and polymeric particles have all been adapted for ultrasound-triggered release, and the field itself can increase vascular permeability and push payload across biological barriers [14,26,27].

With ultrasound, the pharmaceutical product cannot be separated from the acoustic protocol. Particle response depends on gas core, shell elasticity, size distribution, dissolved gas and temperature, as well as on frequency, pressure, duty cycle and pulse length, so a formulation that is effective at one set of laboratory settings may be inactive or unsafe at another. Solid tumours, blood-brain barrier modulation and local infection are logical targets because the trigger can be applied after imaging confirms the position of the lesion, but safety monitoring is needed to avoid vascular damage, excessive heating and off-target sonoporation. Nanobubbles also suffer a particular stability problem: the high Laplace pressure of a very small gas core favours dissolution during storage or circulation.

4.3 Thermo-responsive systems

Thermosensitive liposomes release their contents when the bilayer approaches its gel-to-liquid-crystalline transition, which is designed to fall in the mild-hyperthermia range, and temperature-sensitive polymers such as poly(N-isopropylacrylamide) dehydrate and collapse above their lower critical solution temperature. Heating can come from radiofrequency ablation, high-intensity focused ultrasound or magnetic hyperthermia. Lyso-thermosensitive liposomal doxorubicin (ThermoDox) is the most advanced example and is discussed in Section 9: the programme showed both the promise and the difficulty of the approach, because release depended on accurate and sufficiently long heating of the tissue as well as on formulation properties, local perfusion and trial design [28–30].

For heat-triggered products the transition temperature must be controlled tightly and re-verified after manufacture, sterilisation and storage. Retention of drug below the transition is as important as rapid release above it, and the target tissue has to be heated uniformly without harming adjacent structures. Mild-hyperthermia systems make sense where a heat source is already part of the clinical procedure, but the need for coordinated devices, imaging and treatment planning adds logistical and regulatory burden.

4.4 Magnetic fields and ionising radiation

Superparamagnetic iron oxide particles can be steered or heated by magnetic fields, although effective magnetic targeting in deep human tissue remains difficult. Alternating fields generate local heat, static fields may help retain particles near superficial targets, and the iron oxide core doubles as an imaging contrast agent. In the clinic, intratumoural injection of aminosilane-coated iron oxide particles followed by

alternating-field thermotherapy and radiotherapy has been studied in recurrent glioblastoma [31]. Radiation-responsive carriers use radio-labile linkers or radiation-generated ROS to trigger release and can be combined with radiotherapy. Hafnium oxide nanoparticles are the best-known clinical example of a radiation-linked strategy, although they act as radioenhancers rather than as drug carriers, and radiosensitisation should not be confused with drug release [32]. The value of these modalities depends on access to specialised hardware, on energy deposition in the intended tissue and on a demonstrated advantage over standard image-guided radiotherapy or hyperthermia.

Table 2. Externally controlled trigger modalities

Trigger	Mechanism	Suitable settings	Key development requirement	Principal limitation
Light	Photocleavage, photoisomerisation, photothermal heating, photodynamic ROS	Skin, eye, bladder, oral cavity, endoscopic or surgical lesions	Defined wavelength, fluence, irradiance and thermal safety	Limited penetration; scattering in deep tissue
Ultrasound	Cavitation, sonoporation, phase change, local heating	Deep tumours, brain, local infection	Acoustic parameter control, cavitation monitoring, device compatibility	Operator and equipment dependence; off-target mechanical effects
Temperature	Lipid phase transition or polymer collapse	Tissue adjacent to ablation; focused hyperthermia	Tight transition-temperature specification; thermal mapping	Non-uniform heating; added procedural complexity
Magnetic field	Magnetic navigation or alternating-field hyperthermia	Superficial or image-guided targets	Magnetic material safety; field characterisation	Limited depth and field gradient for targeting
Ionising radiation	Radio-labile cleavage, ROS generation, radiosensitisation	Radiotherapy-accessible tumours	Coordinated radiation dose and formulation performance	Does not by itself guarantee local drug release

Abbreviation: ROS, reactive oxygen species.

5. Carrier platforms and multi-stimuli designs

5.1 Lipid-based carriers

Lipid carriers are the most clinically familiar platforms. Liposomes, lipid nanoparticles, solid lipid nanoparticles and nanostructured lipid carriers can incorporate responsive lipids, cleavable PEG–lipid conjugates, redox-sensitive linkers or phase-transition components. Their strengths are biocompatible excipients, existing manufacturing experience and the ability to carry hydrophilic and hydrophobic molecules. Their weaknesses are leakage, phospholipid oxidation, drug–lipid interactions, complement activation and batch-to-batch variation in lamellarity or encapsulation [33]. Ionisable lipid nanoparticles have created a strong precedent for nucleic-acid delivery, and responsive designs can build on that experience, as long as the added functionality does not compromise RNA protection or endosomal escape [1,34].

5.2 Polymeric carriers

Polymeric carriers offer the greatest chemical flexibility. Amphiphilic block copolymers form micelles, biodegradable polyesters form nanoparticles, crosslinked networks form nanogels and dendritic structures

can present several drugs or ligands. Responsive blocks can be placed in the backbone, the side chains or the crosslinks; a disulfide-crosslinked nanogel, for instance, stays stable in the circulation but de-crosslinks after uptake. Micelles tend to dissociate on dilution unless the core is sufficiently hydrophobic or crosslinked, while excessive crosslinking can prevent release altogether. A rational design therefore needs measurements of critical micelle concentration, aggregation in plasma, cargo redistribution, degradation products and the relationship between crosslink density and response time.

5.3 Inorganic carriers

Inorganic materials are useful when therapy is coupled to imaging, optical, magnetic or catalytic function. Mesoporous silica allows high drug loading and can be capped with pH- or enzyme-labile gates; gold and copper sulfide are used in photothermal systems; iron oxide responds to magnetic fields; and metal–organic frameworks provide porous, degradable networks with tunable coordination chemistry. The principal concern is not cytotoxicity in a cell-culture assay but long-term biodisposition, dissolution, metabolites, interaction with the mononuclear phagocyte system and impurity control. The reason for including an inorganic component should be explicit, for example a unique ability to produce heat at tolerable energy exposure or to allow quantitative imaging.

5.4 Biomimetic and hybrid carriers

Biomimetic systems include cell-membrane-coated nanoparticles, exosome-inspired vesicles, protein carriers and bacterial or viral mimics. They may interact better with the biological interface, but source control, pathogen safety, reproducibility between batches and analytical characterisation remain major barriers. Hybrid systems combine, for example, a polymer core with a lipid shell, or place inorganic particles in a polymer matrix. They can integrate several trigger responses, yet every added interface is a new potential site of instability, so a hybrid design needs a specific therapeutic justification beyond novelty [35].

5.5 Multi-stimuli designs

Multi-stimuli carriers respond to two or more cues, in series or in parallel. One example is a pH-responsive outer shell that exposes an enzyme-cleavable linker and is followed by redox-mediated intracellular release; another is a thermosensitive liposome that also responds to ultrasound, allowing externally controlled heating and mechanical release. In principle, AND-type logic sharpens selectivity because release occurs only when both conditions are met. In practice each added function raises the number of critical material attributes and can create mismatched kinetics: if one response is incomplete the drug may never be released, and if the first step occurs prematurely in the circulation the second mechanism may be exposed too early [12,36].

Evaluating any of these platforms requires comparison with a non-responsive control of the same composition, a free-drug control and, where relevant, a single-responsive analogue. Without these comparators it is impossible to say whether an improved outcome comes from trigger activation, altered pharmacokinetics, carrier accumulation or an unrelated material effect. Table 3 summarises the main carrier classes.

Table 3. Comparison of carrier architectures for responsive delivery

.	Representative materials	Payload compatibility	Responsive design options	Main advantages	Main development risks
Lipidic	Liposomes, ionisable LNPs, SLNs, NLCs	Small molecules, proteins, nucleic acids	Thermosensitive bilayers, ionisable lipids, cleavable PEG-lipids	Familiar excipients; versatile encapsulation	Leakage, oxidation, complement activation, storage instability

Polymeric	Micelles, PLGA particles, nanogels, dendrimers	Hydrophobic drugs, proteins, nucleic acids	Cleavable backbones or crosslinks, ionisable blocks, swelling networks	Broad chemistry; controlled architecture	Dilution instability, residual solvents, polymer variability
Inorganic	Silica, gold, iron oxide, MOFs	Small molecules, imaging agents, combination payloads	Porous gates; photothermal, magnetic or radiation response	Optical and magnetic functions; high loading	Persistence, biodistribution, impurity control
Biomimetic	Membrane-coated particles, vesicles, protein carriers	Diverse payloads	Disease-recognition motifs with responsive core or shell	Biological interface advantages	Source control, lot consistency, pathogen safety
Hybrid	Lipid-polymer, polymer-inorganic, multicomponent	Combination payloads	Sequential or dual-trigger response	Complementary functions in one particle	High analytical and manufacturing complexity

Abbreviations: LNP, lipid nanoparticle; MOF, metal-organic framework; NLC, nanostructured lipid carrier; PEG, polyethylene glycol; PLGA, poly(lactic-co-glycolic acid); SLN, solid lipid nanoparticle.

6. Biological barriers, targeting claims and interpretation of performance

Nanocarrier performance is the outcome of a sequence of biological events, and a failure early in the sequence cannot be rescued by a clever release mechanism later. After administration, particles meet dilution, salts, plasma proteins, cells of the mononuclear phagocyte system and tissue-specific vascular barriers. Proteins adsorb within seconds to form a dynamic corona that changes colloidal stability, apparent surface charge, receptor recognition and uptake. A ligand on a freshly prepared particle may be partly masked *in vivo*, and a nominally neutral stealth coating may gradually desorb [35,37]. Because species differ in plasma protein composition and complement activity, these processes should be studied in human-relevant plasma where possible, and complement-mediated reactions should be considered early [33]. A carrier with excellent trigger response in buffer that is rapidly sequestered by the liver will not activate usefully at a distant target.

Size and architecture influence every step of this journey. Particles that are too large are trapped in the spleen or cannot cross vascular barriers; very small ones may carry little drug, be unstable or be filtered by the kidney. Shape, stiffness and surface hydration affect flow, cell interaction and phagocytic uptake. Tissue delivery should not be inferred from a single fluorescence image, because dyes detach, quench, redistribute to cells or persist after the drug has gone. Quantitative studies should distinguish total carrier-associated signal, intact carrier, released drug and pharmacologically active drug, using radiolabelling, mass spectrometry, microdialysis or orthogonal imaging, and their limitations should be stated [4,5].

The enhanced permeability and retention (EPR) effect deserves particular scepticism. Analyses of nanoparticle entry into tumours indicate that transport through endothelial cells, rather than passive leakage through gaps, may account for much of the entry in some models, and that human tumours vary widely in vessel permeability, perfusion, interstitial pressure and macrophage content [6,11]. Passive accumulation in one lesion therefore says little about accumulation in another lesion in the same patient.

Targeting is also best understood as a multistep process. Passive accumulation refers to access to diseased tissue through altered perfusion, permeability, drainage or local administration. Active targeting uses a ligand that binds a receptor, but it generally improves cell association after the carrier has already

arrived. High-affinity ligands can even reduce deep penetration by creating a binding-site barrier close to the vessel. The relevant question is whether the ligand increases therapeutically relevant intracellular exposure at a dose and time that change outcome. Receptor expression must be quantified in the intended patient population, including in normal tissues, and competitive binding, internalisation, shed receptors and interpatient variability should be taken into account [9,10,36].

Likewise, the link between activation and therapeutic effect has to be demonstrated rather than assumed. A pH-sensitive formulation may release rapidly at pH 5.0 and stay largely intact in the extracellular tumour environment. A redox-responsive system may release drug in cell lysate but not in the cytosol, where it is needed. An ultrasound-responsive particle may reach a lesion yet receive insufficient acoustic pressure in a deep, moving organ. Experiments should measure the activation event in a relevant context (linker cleavage, shell disruption, drug release or change in surface state), followed by evidence of intracellular availability and pharmacodynamic action. Matched non-responsive analogues are needed to isolate the contribution of the responsive element, and such evidence should precede any claim of precision delivery [7,38].

Model selection should reflect the clinical route and the disease barrier. Cell monolayers are useful for mechanism and cytotoxicity but rarely reproduce the extracellular matrix, tissue pressure, immune cells and vascular transport of human disease. Tumour spheroids, organoids, organ-on-chip systems, mucus-producing epithelial models, biofilms and ex vivo tissue provide intermediate evidence. Animal models remain necessary for pharmacokinetics and safety, and they predict better when tumour size, vascularity, immune status, route and procedure resemble the clinical situation. For externally triggered systems the animal study must reproduce the planned energy-delivery method; a superficial subcutaneous tumour cannot support a deep-tissue light-responsive product. The strongest packages combine complementary models rather than relying on one favourable assay [39].

Finally, heterogeneity of response should be treated as a clinical variable and not as experimental noise. If a carrier needs high glutathione, strong protease activity or a particular pH range, a biomarker may be needed to identify patients with a suitable microenvironment, through imaging probes, tissue assays or functional tests. This moves the field away from generic ‘smart’ nanomedicine towards a defined treatment for a defined biological context, and it avoids the common error of assuming that a disease label is itself a sufficient trigger. A formulation that works in a well-chosen subgroup can be more valuable than one designed for every patient that is effective in none.

7. Therapeutic applications

7.1 Cancer

Cancer is the largest application area, because chemotherapeutics, nucleic acids, immunomodulators and imaging agents all benefit from spatially restricted delivery. Tumours show acidic extracellular pH, high intracellular glutathione, oxidative stress, raised enzyme expression, hypoxia and abnormal vasculature, and each feature has inspired responsive carriers [17,40]. As discussed above, the EPR effect is not a universal clinical mechanism, so responsiveness is most useful when combined with a route or procedure that ensures local exposure, such as intratumoural administration, regional perfusion, image-guided injection or external ultrasound or heat [10,11].

pH-sensitive systems can promote endosomal release of doxorubicin, paclitaxel, platinum complexes or nucleic acids. Redox-responsive carriers can liberate cytotoxic drugs or siRNA after uptake, and enzyme-responsive systems can unmask a peptide, detach a protective shell or release drug in a protease-rich matrix. Hypoxia-responsive platforms have been explored for prodrugs and radiosensitisers in poorly oxygenated tumours [21]. Externally triggered strategies can be integrated with ablation, photothermal therapy, radiotherapy or ultrasound. Future cancer studies should stratify patients by trigger-relevant biology, include pharmacodynamic biomarkers and measure intratumoural free drug rather than total nanoparticle signal.

7.2 Inflammatory and autoimmune disorders

Inflamed tissue contains ROS, acidic regions, activated macrophages, proteases and altered vascular permeability, and responsive nanoparticles have been investigated for inflammatory bowel disease, rheumatoid arthritis, psoriasis and atherosclerosis. Oral delivery in ulcerative colitis and Crohn disease is particularly appealing, because pH, microbial enzymes and local oxidative stress can protect the drug during upper-gastrointestinal transit and release it in the colon. In preclinical models, polymeric particles, lipid carriers and hydrogels have delivered corticosteroids, aminosaliclates, immunosuppressants, nucleic

acids and biologics; an enema-delivered hydrogel that adhered preferentially to inflamed mucosa and retained drug there, and ROS-responsive particles that accumulated in inflamed colon, are representative examples [41,42]. Severe inflammation can, however, change luminal pH, fluid volume, transit, mucus turnover and epithelial permeability, so a formulation has to work across variable disease states and not only in a single idealised model.

7.3 Infectious disease

Infection can generate acidity, bacterial enzymes, biofilm matrix components and oxidative stress. Enzyme-responsive vehicles may be cleaved by bacterial lipases or β -lactamases, and pH-responsive systems may release antibiotics in an abscess or biofilm microenvironment, in principle raising local antimicrobial concentration while limiting systemic exposure. The challenge is specificity: ROS and low pH are also found in sterile inflammation, and enzyme expression differs between bacterial species and strains. Evaluation should therefore include biofilm models, infected-tissue models and normal microbiota. For many infections, local and inhaled routes are likely to offer clearer benefit than intravenous administration.

7.4 Neurological disease

The blood–brain barrier is a formidable obstacle to delivery. Ultrasound with circulating microbubbles can open it transiently and locally, creating a route for drugs, antibodies or nucleic acids. An implantable ultrasound device used with carboplatin in recurrent glioblastoma showed in a phase 1/2a trial of 15 patients that repeated opening was feasible and well tolerated [43], and a later phase I/II study of a nine-emitter device in 33 patients confirmed repeated opening in combination with carboplatin [44]. Redox- and enzyme-responsive systems may then assist intracellular release once the carrier is in the brain. The potential extends to glioma, neurodegeneration and lysosomal storage disorders, but safety is paramount, because excessive opening can cause haemorrhage, inflammation or neurotoxicity. A responsive carrier for the brain needs detailed neurobehavioural, histological and imaging evidence and an acoustic protocol that can be reproduced across centres.

7.5 Diabetes and metabolic disease

Glucose-responsive systems aim to modulate insulin availability according to glucose concentration. Phenylboronic acid derivatives bind cis-diols, glucose oxidase converts glucose to gluconic acid and locally lowers pH, and lectin-based systems rely on competitive binding. These mechanisms have been built into nanoparticles, hydrogels and microneedle patches; hypoxia-sensitive vesicles in a microneedle patch, for example, gave rapid glucose-responsive insulin release in diabetic mice [45]. The practical challenge is a response fast enough to prevent hyperglycaemia without causing delayed hypoglycaemia, and in vivo performance is influenced by subcutaneous diffusion, the foreign-body response, oxygen supply for the enzyme reaction and interpatient variation [22]. Stringent glucose-clamp-type studies and a fail-safe approach to dose release are required.

7.6 Nucleic-acid and combination delivery

Responsive lipid and polymeric nanocarriers can improve intracellular delivery of mRNA, siRNA, plasmid DNA and genome-editing components. Ionisation at low pH is already fundamental to the endosomal escape of several nucleic-acid nanoparticles [34], although imaging studies show that only a small fraction of delivered mRNA escapes, from specialised endosomal compartments [38]. Additional disulfide or acid-labile elements can promote unpacking in the cytosol. Combination systems may co-deliver a chemotherapeutic and a nucleic acid, or pair an immunomodulator with a photothermal agent. The obstacles are achieving the right intracellular ratios, avoiding mutual instability during manufacture and showing that co-delivery is better than separate products; release kinetics and biodistribution of each cargo must be measured independently.

8. Pharmaceutical development, characterisation and quality by design

8.1 Quality-by-design framework

A quality-by-design (QbD) approach is the logical way to develop responsive nanocarriers [46–48]. The target product profile defines the therapeutic objective and trigger conditions. Critical quality attributes (CQAs) commonly include particle size and distribution, morphology, surface chemistry, drug loading, encapsulation efficiency, free-drug content, trigger threshold, release kinetics in triggered and untriggered media, residual solvents, pH, osmolality, sterility, endotoxin, container compatibility and stability [49]. For

externally activated products the energy-delivery protocol and device settings may also be critical, because a change in ultrasound pressure or temperature profile can alter release as much as a change in lipid composition. Table 4 lists the main attributes and suitable analytical approaches.

Critical material attributes include polymer molecular weight and dispersity, lipid purity, linker identity, ligand density, buffer composition and, for biomimetic systems, the quality of biological source material. Critical process parameters depend on the manufacturing route. Microfluidic mixing controls particle size and nucleic-acid encapsulation in lipid nanoparticles; thin-film hydration and extrusion are used for liposomes; and nanoprecipitation, emulsification–solvent evaporation and self-assembly are common for polymeric systems. Each process can change drug location, degree of mixing, residual solvent, internal structure and responsive behaviour. Scale-up is not a simple increase in batch volume, because shear, mixing time, heat transfer and losses during sterile filtration may change the finished product [49].

8.2 Physicochemical characterisation

Characterisation must connect structure to performance. Dynamic light scattering gives rapid size measurement but should be complemented by nanoparticle tracking analysis, electron microscopy or cryogenic transmission electron microscopy when morphology and subpopulations matter. Zeta potential is an operational measurement that depends on medium composition and does not directly establish surface charge in vivo. Drug loading should be measured with a stability-indicating assay able to separate free and associated drug, and for nucleic acids, integrity, encapsulation, potency and impurity profile need orthogonal methods. Responsive behaviour should be assessed under stepwise trigger conditions and, where possible, in biologically relevant media containing proteins, enzymes or tissue-derived components.

8.3 Release testing

Release testing is frequently the weakest part of academic development. Dialysis is useful for screening, but membrane resistance and sink conditions can obscure the real release mechanism, and pharmacopoeial standards for colloidal carriers are lacking [50]. Better approaches include sample-and-separate methods, asymmetric flow field-flow fractionation, ultrafiltration with validated recovery, and real-time fluorescence methods calibrated against direct drug assays. A complete study measures baseline leakage in plasma-like conditions, the concentration–response curve for the trigger, response time, repeatability, the influence of the protein corona and release after storage. For ultrasound, light and heat systems, release should be coupled to independently verified acoustic, optical or thermal dose.

8.4 Biological evaluation

Biological characterisation should proceed in stages. In vitro work should use relevant trigger concentrations and compare normal with diseased cells, and three-dimensional spheroids, organoids, mucus models, biofilm models and patient-derived samples can reveal barriers invisible in monolayers. Ex vivo tissue experiments help quantify penetration and activation. Animal studies should include pharmacokinetics, whole-body biodistribution, free-drug concentration in the target, toxicology, immunological response and therapeutic outcome. A carrier signal alone is not proof of drug release; the most informative studies combine imaging of carrier distribution with an assay for released drug and a pharmacodynamic readout.

8.5 Sterility and shelf-life

Sterility and shelf-life need attention early. Filter sterilisation may not be possible for larger particles or aggregates, autoclaving can disrupt lipid and polymer structures, and aseptic processing is a manufacturing burden. Lyophilisation can improve stability but requires careful selection of cryoprotectants and proof of reconstitution behaviour. For responsive systems, the trigger threshold itself must remain stable over the shelf-life, so accelerated studies should examine leakage, aggregation, oxidation, linker cleavage and changes in trigger response, and real-time studies are needed in the final container closure [51]. These are not secondary tasks; they determine whether a promising system can become a dosage form.

Table 4. Critical quality attributes of responsive nanocarriers and suggested evaluation

Attribute	Why it matters	Illustrative analytical approach
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Particle size and distribution	Influences stability, filtration, clearance and tissue interaction	DLS plus NTA; electron microscopy for morphology
Cargo loading and free drug	Determines delivered dose and leakage risk	Validated chromatographic or spectroscopic assay after separation
Trigger threshold and response time	Defines selectivity and clinical control	Release study across a gradient of trigger concentration or energy
Baseline versus triggered release	Establishes retention in transit and therapeutic release	Biorelevant media with sample-and-separate methodology
Surface chemistry and ligand density	Affects protein corona, uptake and targeting	XPS, NMR, chromatography, fluorescence or immunoassay
Internal structure and morphology	Controls payload location and transition behaviour	Cryo-TEM, SAXS, AF4-MALS or related orthogonal methods
Sterility, endotoxin and stability	Essential for parenteral safety and shelf-life	Compendial microbiological methods; real-time and accelerated studies
Device-linked performance	Essential for light, ultrasound, heat and magnetic systems	Measured optical, acoustic or thermal dose coupled to release testing

Abbreviations: AF4-MALS, asymmetric flow field-flow fractionation with multi-angle light scattering; DLS, dynamic light scattering; NTA, nanoparticle tracking analysis; SAXS, small-angle X-ray scattering; TEM, transmission electron microscopy; XPS, X-ray photoelectron spectroscopy.

9. Clinical translation and regulatory considerations

9.1 Clinical experience to date

Clinical progress has been uneven, and the products that have advanced furthest are almost all externally triggered or locally administered (Table 5). The lessons are instructive. In the phase III HEAT trial, 701 patients with intermediate-size hepatocellular carcinoma received radiofrequency ablation with or without ThermoDox; the primary endpoint of progression-free survival was not improved (hazard ratio 0.96) [29]. A post hoc analysis suggested an overall-survival benefit in patients with a solitary lesion whose ablation lasted at least 45 minutes (hazard ratio 0.63; $n = 285$), which pointed to the heating procedure rather than the liposome as the variable that determined drug delivery [29,52]. A confirmatory phase III study (OPTIMA, NCT02112656) was designed around this finding; its sponsor reported in 2020 that an independent committee had found the prespecified futility boundary to be crossed at an interim analysis, and that follow-up would continue. The programme illustrates how the outcome of a trial of a triggered product depends on the delivery of the trigger as much as on the particle [28,30].

Other products show the same dependence on a procedure. NBTXR3, a hafnium oxide nanoparticle that enhances local radiation dose, was injected intratumorally before preoperative radiotherapy for soft-tissue sarcoma; in the phase 2–3 Act.In.Sarc trial ($n = 176$) the pathological complete response rate was 16% against 8% with radiotherapy alone [32], and the product received a CE mark in 2019. Magnetic thermotherapy with aminosilane-coated iron oxide particles obtained European approval in 2010 for glioblastoma after a single-arm study of 59 patients with recurrent disease reported a median overall survival of 13.4 months from recurrence [31]. Gold–silica nanoshells with NIR laser ablation were tolerated in a pilot study of localised prostate cancer [25], and ultrasound-mediated opening of the blood–brain barrier has been shown to be feasible in two early-phase glioblastoma trials [43,44]. None of these systems depends on a subtle biochemical gradient. Each pairs a well-defined carrier or device with an energy input that clinicians can control, in a setting where the dose can be applied directly to a visible lesion.

Table 5. Clinical-stage systems that depend on an external or local trigger

Product	Carrier and trigger	Setting and design	Reported finding	Lesson for development
ThermoDox (lyso-thermosensitive liposomal doxorubicin)	Thermosensitive liposome; mild hyperthermia from RFA	Phase III HEAT, intermediate-size HCC, n = 701	No PFS benefit (HR 0.96); post hoc OS benefit with RFA ≥ 45 min in solitary lesions (HR 0.63) [29,52]	Heating protocol is part of product performance
NBTR3 (Hensify)	Hafnium oxide nanoparticle; radiotherapy (radioenhancer)	Phase 2–3 Act.In.Sarc, soft-tissue sarcoma, n = 176	pCR 16% vs 8% with radiotherapy alone [32]	Intratumoural injection secures local exposure
NanoTherm	Aminosilane iron oxide; alternating magnetic field	Single-arm study, recurrent glioblastoma, n = 59	Median OS 13.4 months from recurrence [31]	Dependence on dedicated field applicator
AuroLase	Gold–silica nanoshell; NIR laser	Pilot device study, localised prostate cancer, 15 treated	Tolerated; most targeted lesions cancer-free at biopsy [25]	Light delivery feasible where access is direct
SonoCloud	Implanted ultrasound emitter with circulating microbubbles; carboplatin	Phase 1/2a (n = 15) and phase I/II (n = 33), recurrent glioblastoma	Repeated barrier opening feasible and tolerated [43,44]	Trigger can be repeated and imaged

Abbreviations: HCC, hepatocellular carcinoma; HR, hazard ratio; NIR, near-infrared; OS, overall survival; pCR, pathological complete response; PFS, progression-free survival; RFA, radiofrequency ablation.

9.2 Safety and regulatory evaluation

Safety assessment must address the intact carrier, the released drug, degradation products, impurities and any energy-delivery procedure. The mononuclear phagocyte system, complement, coagulation, cytokine release and accumulation in liver and spleen are the usual concerns. Surface properties change in vivo through protein-corona formation, with altered uptake and loss of targeting, and repeated dosing may provoke antibody formation or accelerated blood clearance. Inorganic components require long-term biodistribution and clearance studies, and biomimetic materials need controls for source, adventitious agents and lot consistency [33,37,51].

Regulatory evaluation is product-specific, but it builds on established principles of pharmaceutical quality, nonclinical safety and benefit–risk assessment. The ICH quality guidelines support a risk-based understanding of materials, manufacturing and control strategy [46–48], and regulators expect physicochemical characterisation, batch consistency, stability and biodistribution data, together with a justified relationship between critical quality attributes and clinical performance [53,54]. The development plan must also state whether a device is integral to the therapy; where external energy is essential to activation, co-development of drug product and device may be needed to avoid uncertainty in dose delivery.

9.3 Manufacturing economics

Economics matter as well. Responsive platforms that need rare materials, multistep synthesis, difficult purification or bespoke energy hardware may not suit broad indications. A more realistic route starts with diseases in which the trigger is accessible, the population is clearly defined and the clinical procedure already exists, for instance intravesical therapy, topical or ophthalmic treatment, locoregional oncology, endoscopic gastrointestinal delivery and image-guided ablation. In such settings therapeutic benefit can be demonstrated before systemic use in heterogeneous metastatic disease is attempted.

Overall, the development package should support a chain of evidence in which the chosen disease displays the intended trigger, the formulation senses it selectively, activation produces the required release, the released drug reaches its cellular target, benefit exceeds that of an appropriate comparator, and the product can be made reproducibly (Fig. 3). If any link is unsupported, additional carrier complexity cannot make up for the missing evidence.

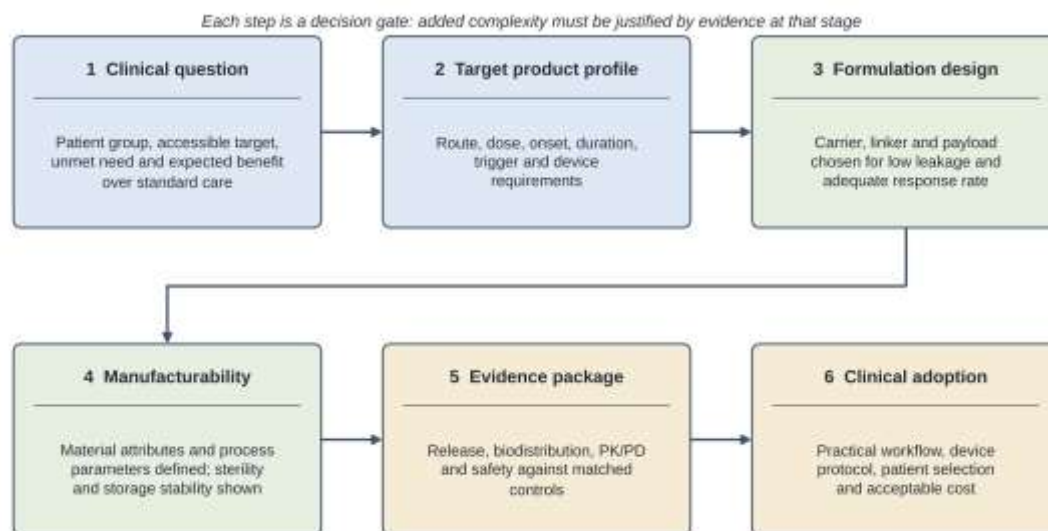


Fig. 3. Development pathway from clinical question to clinical adoption. Added carrier complexity should be justified at every stage. Abbreviations: PK/PD, pharmacokinetics/pharmacodynamics.

10. Discussion

10.1 Reading the clinical record

Considered together, the clinical experience reviewed above and the large preclinical literature give a consistent message. Responsiveness to a biochemical cue has been easy to demonstrate in vitro and hard to turn into a clinical advantage, largely because the cues that are easy to engineer (a mildly acidic extracellular space, elevated glutathione, overexpressed proteases) are not reproducibly different enough in patients. The products that have reached the clinic instead rely on an external energy source or a local procedure to fix both location and timing. This does not mean that endogenous triggers are unpromising. It means that they are best used where the gradient is large and measurable, as in the gastrointestinal tract and inside the endosome, or where a local route removes most of the biological uncertainty.

10.2 Trial design and patient selection

A first-in-human programme for a responsive nanocarrier should be planned around the clinical decision that the formulation is meant to improve. Early studies need more than conventional dose escalation: they should establish the pharmacokinetics of total and, where possible, released drug, confirm the feasibility and reproducibility of trigger delivery, monitor procedure-related toxicity and obtain pharmacodynamic evidence at the target. For products activated by a local procedure, sites need harmonised equipment, treatment planning and operator training, and the energy actually delivered, the target location and the timing relative to drug administration should be recorded. Without that information a negative efficacy result cannot distinguish product failure from failure of trigger delivery, as the HEAT experience shows [12,29].

Patient selection matters equally. A cancer trial should consider lesion accessibility, microenvironmental biomarkers, prior therapy, organ function and whether the carrier can plausibly reach the site. An inflammatory-bowel-disease programme should take account of disease location, stool frequency, mucosal severity, concurrent immunosuppression and gastrointestinal transit, and a brain-delivery programme must consider skull characteristics, imaging compatibility and baseline barrier integrity. Enrichment strategies should be justified prospectively, and exploratory biomarkers built into protocols so that exposure–response relationships can be analysed.

The choice of comparator determines how a trial can be interpreted. Depending on the question it may be standard treatment, the same drug in a clinically used nanocarrier, a non-responsive analogue or the procedure alone. A study of heat-triggered chemotherapy, for example, has to establish whether benefit

arises from the drug, the heat, their timing or carrier-mediated release, which may call for factorial or carefully stratified designs. Relevant outcomes include local drug exposure, durability of response, reduction in toxicity, patient-reported burden and feasibility in routine care as well as conventional radiological endpoints; a formulation that reduces hospital visits or allows delivery of a new cargo may be valuable even when its response rate matches that of a standard regimen.

Manufacturing comparability must also be maintained throughout development. A change in lipid source, polymer grade, mixing equipment, sterilisation process or container can alter particle attributes and trigger response, so bridging studies should compare biological activity, release kinetics and stability in addition to size and loading. Predefined control strategies, reference materials and stability-indicating assays reduce the risk that an apparent clinical difference is caused by product drift [46,47,49].

10.3 Standardised reporting

Data reporting needs to become more comparable between laboratories. As a minimum, a report should state the complete composition, active-drug content, size distribution, morphology, release method, trigger conditions, sample temperature, biological medium, storage history and matched controls. Trigger response should be expressed with both an absolute and a relative measure, such as the percentage released at a defined time, the difference from untriggered release and the stimulus dose–response relationship [50]. For external-energy systems, all relevant device settings and target geometry must be reported. Such practice would allow independent groups to reproduce findings, distinguish genuinely promising platforms from results driven by assay conditions and select formulations that merit costly animal studies and clinical development.

11. Conclusion

Stimuli-responsive nanocarriers offer a logical route to targeted drug delivery because they couple transport with controlled local release. Their success depends on how well disease biology, trigger chemistry, carrier architecture, payload, route of administration and clinical workflow fit together. pH-, redox- and enzyme-sensitive platforms are valuable where the biological gradient is large and reproducible, and ultrasound, heat, light, magnetic fields and radiation provide scheduled activation where device access and energy distribution can be controlled. Lipidic, polymeric, inorganic, biomimetic and hybrid carriers each have distinct advantages, and none is inherently superior.

From a pharmaceuticals standpoint, the decisive questions are whether the formulation remains stable until activated, releases drug at the intended rate afterwards, can be described by meaningful quality attributes and can be manufactured with reproducible performance. Clinical translation will favour simpler systems that address a specific unmet need, use well-characterised materials and are supported by strong comparative pharmacokinetic, biodistribution, safety and efficacy evidence. A disciplined quality-by-design approach can turn responsive nanocarriers from attractive experimental constructs into credible therapeutic products.

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