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Research Article

SMART PHARMACOSOMES: STIMULI-RESPONSIVE PLATFORMS FOR PRECISION DRUG TARGETING

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ABSTRACT

A sophisticated type of lipid-based drug delivery systems called stimuli-responsive pharmacosomes is intended to provide site-specific and regulated medication release. The active pharmaceutical ingredient is covalently bonded to phospholipids to generate self-assembling nanostructures with improved stability, solubility, and bioavailability, which are known as pharmacosomes. On-demand and targeted medication release at sick locations is made possible by the integration of stimuli-responsive mechanisms, which include external triggers like magnetic fields, light, ultrasound, and electric fields, as well as interior triggers like pH, redox potential, enzymes, and temperature. This review thoroughly examines the structural traits, materials, characterization methods, preparation processes, and therapeutic uses of stimuli-responsive pharmacosomes. Their function in the treatment of cancer, inflammatory conditions, neurological diseases, infectious diseases, and the transport of phytoconstituents is given particular attention. Additionally addressed are recent developments, legal issues, and prospects for the future, such as personalized treatment and smart systems enabled by nanotechnology. All things considered, stimuli-responsive pharmacosomes present a viable way to increase therapeutic effectiveness while lowering systemic toxicity.

Keywords: Pharmacosomes, Lipid-drug conjugates, Site-specific drug release, Smart nanocarriers, pH.

INTRODUCTION

Targeted systems that concentrate medication at the illness site while preserving healthy tissue are encouraged by the fact that many medications exhibit poor pharmacokinetics, off-target toxicity, and multidrug resistance, particularly in cancer. Targeted nanocarriers increase safety and efficacy by improving permeability, controlled release, and tumour selectivity (Semalty *et al*., 2009; Adhikari *et al*., 2017). First pass metabolism, quick elimination, varying plasma levels, and low patient compliance are issues with oral and injectable dose forms. Clinical benefit is limited by the low solubility, instability, and short duration of action of many active ingredients, particularly natural goods. In the 1960s, liposomes made it possible to encapsulate both hydrophilic and hydrophobic medications, enhancing their solubility, stability, and biocompatibility. PEGylated lipid nanoparticles for mRNA and siRNA, transferosomes, phytosomes, nanostructured lipid carriers, solid lipid nanoparticles, and self-nano emulsifying systems are examples of advanced lipid systems. Phytosomes, which covalently or ionically link bioactive with phospholipids to enhance absorption and stability, are conceptually similar to pharmacosomes, which are drug–phospholipid conjugates or complexes that form vesicular/lipid assemblies. These drug-lipid complexes get beyond the low bioavailability and poor permeability of a lot of small compounds and polar phytoconstituents. By enabling on-demand release at the disease microenvironment, "intelligent" or stimuli-responsive carriers (pH, redox, enzyme, temperature, and light) maximize local action and minimize systemic exposure. The extension of these concepts to pharmacosome designs is supported by the fact that stimuli-responsive liposomes and other nanocarriers already exhibit triggered release and enhanced selectivity in inflammatory and cancerous circumstances. Pharmacosomes are amphiphilic lipid drug conjugates in

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which phospholipids, usually phosphatidylcholine, and medicines containing an active hydrogen (e.g., -COOH, -OH, -NH_2) create a covalent connection to form a self-assembling lipid–drug complex. As lipoidal prodrugs, these systems fall under the category of lipid-based nanocarriers and are intended to increase the solubility, membrane affinity, and consequently the bioavailability of medications that are poorly absorbed Adhikari *et al*., 2017. Instead of being physically imprisoned, the drug is an essential component of the lipid matrix, in contrast to encapsulation systems (liposomes, niosomes). Pharmacosomes are micellar/lipoidal or non-vesicular aggregates that are created when a drug chemically conjugates with a lipid to produce amphiphiles that self-assemble in aqueous conditions. Depending on the drug lipid ratio and environment, the complex's hydrophobic fatty acyl or phospholipid part and more polar drug-containing head can form supramolecular structures including micelles, lamellae, or hexagonal phases. Even for highly polar medicines, significant loading is possible because to the covalent attachment, which reduces leakage. The creation of ester or amide bonds between the hydroxyl or amino groups of fatty acids or phospholipids and the active hydrogen-containing group of the medication (such as the carboxyl of NSAIDs or the hydroxyl groups of polyphenols). The formation of lipoidal prodrugs, which subsequently self-assemble into nanoscale lipid–drug conjugate particles, through the use of coupling agents (such as carbodiimides) or activated lipid derivatives. While the lipid moiety adheres to regular lipid metabolic routes, improving absorption and changing pharmacokinetics, endogenous esterases or amidases break the bond upon administration, renewing the parent drug.

Table1. Key unmet needs driving targeted drug delivery.

Issue with conventional therapy	Consequence	Nanocarrier advantage	Citations
Poor solubility, rapid clearance	Low bioavailability, frequent dosing	Solubilization, prolonged circulation	Chen Q *et al.,*2024)
Non-specific distribution	Systemic toxicity	Passive/active targeting to diseased tissue	(Cai W *et al.,*2018),
Biological barriers (skin, BBB, GIT)	Limited access to target	Lipid vesicles, SNEDDS, transdermal carriers	(Park H *et al.,*2021)

Drawbacks of Traditional Medication Administration Methods

Table 2. Key structural and functional contrasts among major lipid nanocarriers.

Feature	Pharmacosomes	Liposomes	Niosomes	Phytosomes	Citations
Basic nature	Covalent drug–lipid conjugate (lipoidal prodrug)	Phospholipid–cholesterol bilayer vesicles with entrapped drug	Non-ionic surfactant–cholesterol bilayer vesicles	Phytochemical–phospholipid complex forming vesicles	(Adhikari P *et al*., 2017)
Drug association	Chemically bound to lipid (minimal leakage)	Physically entrapped in aqueous core or bilayer	Physically entrapped in core or bilayer	Hydrogen bonded complex with polyphenolic phytochemicals	(Park H *et al*.,2021)
Main aims	Increase loading, stability, and bioavailability; reduce GI toxicity	Versatile systemic/topical delivery, targeting, controlled release	Cheaper, more stable alternative to liposomes	Enhance absorption and bioavailability of phytochemicals	(Su S, Kang P*et al.,*2020), (Edis Z *et al.,*2021)

Table 3. Core elements of a smart responsive delivery system.

Design aspect	Role in responsiveness	Examples	Citations
Stimulus-sensitive bond/group	Cleaves or changes conformation on trigger	pH-labile ester/hydrazone; disulfide (redox)	(Cheng R *et al.,*2024)
Responsive matrix/material	Swells, collapses, or degrades	Smart hydrogels, MOFs, polymers, liposomes	(Lee Y *et al.,*2017)
Targeting & accumulation	Ensures carrier reaches stimulus region	Tumour EPR, receptor targeting, cell-based carriers	(Luo Y *et al.,*2019)

In response to a trigger, smart DDSs change their bonds, permeability, or structure, resulting in carrier degradation or controlled drug release. Triggers can come from outside sources (such as light, heat, magnetic fields, ultrasound, and electric fields) or diseased microenvironments (such as enzymes, redox gradients, and acidic pH). This improves the therapeutic index and reduces off-target effects by enabling site-specific, on-demand, and frequently reversible drug release (Liu D *et al.,*2016; Sun T *et al.,*2023).

Take use of the biochemical and physicochemical variations between healthy and sick tissue: pH-responsive: Release is triggered by pH-labile linkers or swelling polymers; tumours, inflammatory tissue, and endosomes/lysosomes are more acidic. Redox-responsive: Tumours with high glutathione or ROS might release substances intracellularly thanks to disulfide or ROS-cleavable groups. Enzyme-responsive: Drugs are released when peptide or polymer segments are broken down by overexpressed enzymes (such as MMPs, proteases, and glycosidases). Additional internal cues, such as temperature micro gradients2 in certain tissues or tumours, ions, ATP, and glucose. The clinician uses this to achieve fine spatiotemporal control: Light (UV, visible, and NIR): Photo-thermal, photo-cleavable bonds, or photo-triggered hydrogels or liposomes. Thermosensitive liposomes, gels, and polymers that release medication when heated are examples of temperature/hyperthermia. Magnetic field: To initiate release and facilitate targeting, magnetic nanoparticles produce mechanical effects or local heat. Ultrasound: Promotes cavitation-induced release and penetration from particles, gels, or liposomes. For regulated release in particular tissues (such as the skin or eye), electric fields and others can alter permeability or redox states.

Table 4. Main internal triggers and design logic for smart pharmacosomes.

Trigger type	Key mechanism in conjugates	Typical disease context	Citations
pH	Protonation / cleavage of pH-labile bonds → destabilization and release	Tumours, inflamed tissue, endo/lysosomes	(Xu C *et al.,*2018)
Enzymes	Over expressed enzymes cleave peptide/ester linkers	Cancer (MMPs, cathepsins), RA, skin inflammation	(Lee Y *et al.,*2017)
Redox (GSH)	GSH reduces disulfide/other redox linkers → conjugate breakup	Solid tumours, redox-imbalanced tissues	(Luo Y *et al.,*2019)
Temperature	Local hyperthermia induces phase change of thermo-blocks	Solid tumours under focused heating	(Amin M*et al.,*2022)

Table 5. Comparison of main external triggers and carrier designs.

Stimulus	Main mechanism	Typical designs	Citations
Magnetic field	Local nano-hyperthermia, targeting	Magneto liposomes, magnetic polymersomes, hybrid NPs	(Oliveira H *et al.,*2013)
Ultrasound	Cavitation, heating, barrier opening	Liposomes, nanodroplets, microbubble–liposome complexes	(Refaai K *et al.,*2024)
Electric field	Conductive matrix switching, electroporation	Conductive hydrogels, melanin NPs, conductive polymers	(Qu J *et al.,*2018)

The components of polymerases, phospholipid–drug conjugate (PDC) vesicles, and smart liposomes are expanded upon by stimuli-responsive pharmacosomes. The lipid/phospholipid matrix, stimuli-sensitive polymers, and cleavable linkers/functional groups that convert the stimulus into drug release are the three main design decisions **(**Xu C *et al.,*2018; Luo Y *et al*. 2019). Traditional bilayers consist of cholesterol, sphingolipids, phosphatidylcholines, and phosphatidylethanolamines that produce biocompatible vesicles with a controllable phase-transition temperature (Tm) that regulates permeability. Lipids that is sensitive to pH: DOPE/POPE/DAPE with moderately acidic amphiphiles (cholesteryl hemi succinate, oleic acid, and N palmitoyl L homocysteine) produce membranes that collapse through protonation in acidic tumour/endolysosomal pH 3. Phospholipid drug conjugates (PDCs) are covalent drug–phospholipid structures that can be equipped with stimuli-responsive linkers for on-demand drug release. They self-assemble into nanovesicles. PDMAEMA, poly (acrylic acid), poly (methacrylic acid), and other amine/carboxyl polymers grafted to lipids or surfaces are examples of pH-responsive polyelectrolytes that offer charge switching, swelling, or membrane instability. Thermoresponsive polymers: LCST/UCST transitions for temperature-triggered release are made possible by N isopropylacrylamide and oligo (ethylene

glycol)-based blocks. Redox/other responsive blocks: polymers containing disulfides, modified by boronic acid, or degradable by enzymes produce crosslinked shells and multistimuli carriers that are highly stable in blood but quickly break down in target regions.

Table 6. Main material classes and linker chemistries enabling stimuli response.

Stimulus	Typical linker chemistries / groups	Role in pharmacosomes	Citations
pH	Hydrazone, acetal/ketal, imine, Ortho ester; ionizable acids/amines	Acid-triggered bond cleavage or protonation-driven destabilization	(Xu C *et al.,*2018)
Redox (GSH)	Disulfide, Di selenide	Cleaved in reductive cytosol → drug release	(Cao Z *et al.,*2019)
Enzymes	Peptide, ester, matrix metalloproteinase– or protease cleavable motifs	Site-specific drug detachment in enzyme-rich tumours	(Lee Y*et al.,*2017)
External (light, heat, electric)	Photocleavable bonds, thermosensitive blocks, redox-active groups (e.g., in conducting polymers)	Remote control of release and carrier properties	(Qu J *et al.,*2018)

Solvent Evaporation & Double Emulsion Methods Hydrophilic and hydrophobic medications can be encapsulated with controlled release using single and double emulsion solvent evaporation (o/w and w/o/w), which is commonly employed to create micro/nanoparticles from polymers like PLGA. Important factors that affect particle size, porosity, and loading include phase ratios, evaporation rate, stabilizer type and concentration (such as PVA, PVP), organic solvent (often chloroform/DCM), and others. Solvent extraction/evaporation-based microencapsulation is well-suited for large-scale production and works with a variety of stimuli-responsive polymer chemistries. Apart from the conventional methods like Thin Film Hydration and Ether/Ethanol Injection & Related Injection Methods there are some novel techniques are more accurate and reliable**.**

Table 7. Comparison of preparation routes and uses.

Approach	Key Advantages	Typical Use in Stimuli-Responsive DDS	Citations
Microfluidics	Narrow size, low batch variation	Stimuli-responsive liposomes/niosomes	(Ruiz A *et al.,*2022)
Co solvent evaporation (micelles)	Higher loading, solvent tunability	Hydrophobic drugs in responsive micelles	(Jia R *et al.,*2021),(Torres J *et al.,*2025)
Aqueous/fewer toxic solvents	Reduced organic solvent burden	"Greener" PLGA NPs, micelles, liposomes	(Vora L *et al.,*2023)

Dynamic light scattering (DLS) or nanoparticle tracking analysis are commonly used to quantify size and PDI; usual values for nanocarriers are ~40–500 nm with PDI ≤0.3–0.4. Colloidal stability is indicated by the zeta potential from electrophoretic light scattering; absolute values ≥30 mV (positive or negative) is often regarded as stable. Aggregation behaviour, absorption, and circulation time are all significantly impacted by size and charge **(**Dewi M *et al.,*2024; Wang B *et al.,*2024**)**. Drug content is typically measured by HPLC or UV/visible spectrophotometry after vesicles have been lysed with an organic solvent (such as ethanol). In optimum systems, entrapment efficiency (EE %) is often aimed at 70-80% after free drug separation (by centrifugation, ultrafiltration, or chromatography). With the least amount of nanocarrier loss or leakage, ultrafiltration offers the most precise EE measurement. For phytosomes, liposomes, cubosomes, micelles, and bilosomes, TEM is frequently used to verify vesicle size, lamellarity, and form (spherical or cubic) at the nanoscale. SEM can see the surface topology of more stiff particles but is less prevalent for soft vesicles. Typically, drug release is measured using dialysis or membrane diffusion setups in physiologically appropriate media (pH 1.2, 4.5, 6.8, 7.4), with sampling taking place over a 24- to 120-hour period. Compared to

free medication, pharmacosomes frequently exhibit pH-dependent or sustained release, improving solubility and sustaining longer therapeutic levels. Formulations are stored at room temperature and at accelerated temperatures (such as 25 and 40 degrees Celsius) to monitor short- to medium-term stability. Size, PDI, zeta potential, EE%, and occasionally release profile are measured on a regular basis. Over the course of one to three months, stable systems exhibit little change in these characteristics, retaining high EE and no significant aggregation. Internal stimuli: MMP 2/9, esterases, proteases, and other overexpressed enzymes break acid labile or redox/enzyme sensitive linkers, resulting in carrier deconstruction and on-site drug release. Tumour and inflammatory tissues also exhibit elevated glutathione (GSH), ROS, and acidic ph. External stimuli: Often used in conjunction with photothermal/photodynamic or hyperthermia therapy, light, magnetic fields, ultrasound, and heat can cause liposome or polymersome disruption or phase shift enabling spatiotemporally regulated release **(**Cao Z *et al.,*2019**)**. The EPR effect and/or ligand-mediated targeting (such as CD44, BBB transporters, and tumour receptors) are two ways whereby nanocarriers accumulate. The primary mechanism of uptake is receptor-mediated endocytosis; pH-sensitive designs use endosomal acidity to cause swelling or disintegration or to stimulate "proton sponge" mediated endosomal escape; lysosomal enzymes or GSH/ROS then cause the final release of the drug in the cytosol, mitochondria, or nucleus **(**Wang B *et al.,*2024; Su S, Kang, 2020). Surface ligands, microenvironment-matched triggers (pH/ROS/enzymes), and multistage systems that alter ligand size/charge or expose them just at the tumour site improve penetration and lower off-target toxicity. Each of these methods increases efficiency **(**Su S, Kang P *et al.,*2022).

Table 7. Major disease areas using stimuli-responsive pharmacosomes.

Indication / Area	Main Strategy & Examples	Citations
Cancer therapy	pH/redox/enzyme/ROS-responsive liposomes, polymersomes, micelles; multi-stimuli systems, MDR reversal	(Hatakeyama H*et al.,*2017)
Anti-inflammatory (IBD, skin)	pH, ROS, enzyme responsive nanocarriers for colon and inflamed skin targeting	(Su S*et al.,*2020)
Neurodegenerative / CNS	BBB-targeted, pH/ROS/enzyme-responsive NPs and hydrogels for brain or neuro inflammation	(Su S*et al.,*2020)
Infectious diseases	Stimuli responsive liposomes and NPs explored for localized antimicrobial delivery (less developed)	(Edis Z *et al.,*2021)
Herbal/phytoconstituents	Self-assembled herbal hydrogels and plant derived or protein carriers enabling sustained, responsive release	(Wang B *et al.,*2024)

Improved safety and efficacy: Compared to traditional dosage forms, there is less off-target toxicity, longer circulation, controlled/triggered release, improved solubility, and stability. Peptides, proteins, phytochemicals, antibiotics, and anticancer medications are examples of hydrophilic and hydrophobic bioactive that can be carried by versatile pay loads. Relative manufacturability: Compared to traditional liposomes, several systems (such as niosomes, phytosomes, and SLNs) offer more straightforward, affordable, and stable formulations **(**Edis Z *et al.,*2021**)**. Prediction and standardization are hampered by complex PK/PD, biological interactions, RES clearance, and scale-dependent behaviour. The following are the main obstacles to clinical translation: cost effectiveness in comparison to current medicines, purification, stability, IP, batch-to-batch reproducibility, and toxicity assessment (Vora L *et al.,*2023). Because of covalent drug–lipid conjugation, stimuli-responsive pharmacosomes showed enhanced solubility, stability, and bioavailability. pH, redox conditions, enzymes, and temperature are examples of internal triggers that allowed for the selective release of drugs at sick areas while preserving stability in healthy tissues. Precise spatiotemporal control of drug release was made possible by external stimuli such as electric fields, magnetic fields, light, and ultrasound. High entrapment efficiency (>70%), sustained release profiles, improved targeting efficiency, and nanoscale particle size were all displayed by optimized systems. Although there are still issues with clinical translation and large-scale manufacture, these systems have greatly enhanced treatment outcomes with decreased systemic toxicity.

CONCLUSION

An inventive development in lipid-based drug delivery systems, stimuli-responsive pharmacosomes combine the structural advantages of drug–lipid conjugates with clever trigger-mediated release mechanisms. Pharmacosomes improve solubility, membrane permeability, stability, and bioavailability while reducing premature drug leakage by covalently attaching medications to phospholipids. Precise, site-specific, and controlled drug release is made possible by the combination of external triggers like magnetic fields, light, ultrasound, and electric fields with internal cues like pH, redox gradients, enzymes, and temperature. These characteristics, especially in cancer and inflammatory

diseases, greatly increase treatment efficacy and lower systemic toxicity. They are also positioned as prospective platforms for precision medicine due to their versatility for multifunctional and multistimuli designs. However, issues with clinical validation, long-term safety assessment, regulatory approval, and large-scale manufacture must be resolved. Translating stimuli-responsive pharmacosomes into effective clinical applications will require ongoing research combining nanotechnology, cutting-edge materials, and customized therapeutic approaches.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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