INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

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Review Article

Smart Drug Delivery System: An Intelligent Approach Toward Precision Drug Delivery: A Review

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ARTICLE INFO

Published: 2 Nov 2026
Keywords:
Smart drug delivery systems, stimuli-responsive nanoplatforms, targeted drug delivery, controlled drug release, nanocarriers, precision medicine, therapeutic applications
DOI:
10.5281/zenodo.23876242

ABSTRACT

Smart drug delivery systems (SDDS) have attracted growing interest in pharmaceutical research because they offer new ways of carrying drugs to, and releasing them at, the intended site in the body. Unlike conventional dosage forms, these systems can be engineered to respond to conditions inside the body or to externally applied triggers, including changes in pH, redox potential, enzyme activity, temperature, light, magnetic fields, ultrasound, and glucose concentration. This review outlines the principles behind SDDS, the main carrier platforms used to build them, their therapeutic applications, and the obstacles that limit wider clinical use. The platforms covered are liposomes, polymeric nanoparticles, exosomes, hydrogels, dendrimers, microneedles, and polymeric micelles; for each, the key properties and drug-release behavior are discussed. Applications in cancer, infections, diabetes, and inflammatory disease are also considered. Despite their advantages, SDDS still face substantial challenges: biological barriers, toxicity to healthy cells, insufficient accumulation at the target site, unstable formulations, difficulty in reproducible manufacturing, and unresolved regulatory questions. If these obstacles can be overcome, SDDS holds considerable promise for improving how drugs are delivered.

INTRODUCTION:

Drug delivery covers the approaches, formulations, technologies and systems used to carry a therapeutic agent through the body so that it produces its intended effect safely and efficiently [1]. Delivering a drug to prevent or treat disease is, alongside surgery, radiotherapy, physical therapy and psychotherapy, one of the principal modes of medical treatment [2]. A smart drug delivery system (SDDS) is a delivery system that can sense signals, respond to them, release its drug load and stop releasing it again, largely without outside intervention [1]. The signals that regulate such systems may be external, such as light of different wavelengths, magnetic or electric fields and ultrasound [3], or internal, such as redox state, pH, enzyme activity and the

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

concentration of particular molecules [4]. The central aim of an SDDS is to deliver the right dose to the intended site, at the right moment and in a predetermined manner, with high efficiency and specificity, so that patients are also better able to follow their treatment [5]. Nanocarriers used in SDDS include liposomes, nanospheres, quantum dots (QDs), dendrimers, carbon nanotubes (CNTs) and superparamagnetic iron-oxide nanoparticles [6].

NEED FOR SMART DRUG DELIVERY SYSTEMS:

SDDS are intended to deliver medicines in a controlled and safe way. Carriers such as nanoparticles, liposomes, and polymers can protect the drug, time its release, and direct it to a chosen site, which improves outcomes, lowers side effects, and can reduce the overall cost of treatment. Two early milestones are often cited: Tanaka's 1978 study of the phase transition of polyacrylamide gels, which advanced research on the volume-phase change of polymer gels [7], and the first reports from the same period of thermosensitive liposomes for drug delivery [8].

A smart system should place more of the drug in the tissue, cell, or organ that needs it; remain intact in body fluids, improve therapeutic performance without added side effects; and allow the drug to be absorbed properly [9]. Drug delivery systems can also address problems such as poor dissolution, degradation by the environment or by enzymes, rapid clearance, toxicity to healthy cells, and difficulty in crossing the body's barriers [10]. Ideally, the system should not react with the body's own chemistry, should not provoke an immune response, should stay stable both in storage and in the body, should locate the right cells and keep binding to the correct targets, and should release the drug at the appropriate rate. It should also be cost-effective and biodegradable [11].

ADVANTAGES OF SMART DRUG DELIVERY SYSTEMS:

1. Enhanced therapeutic efficacy: Developing drug delivery approaches that can target specific areas of the body or cell types may improve the efficacy of the treatment. These nanoparticles can detect cancer cells, enabling the tumor to be targeted with higher doses of medication and reducing side effect [12].
2. Controlled drug release: Besides targeting, smart drug delivery strategies can guarantee that the drug is released at defined rates or in response to specific signals. That gives you control over when and how the drug is released [13].
3. Improved adherence: Information technology-based smart medicine delivery systems can be designed to enable the physician to remotely monitor a patient's dosage [14].

LIMITATIONS OF SMART DRUG DELIVERY SYSTEMS:

1. Complexity of design: The design of pharmaceutical delivery systems requires in-depth knowledge of the behavior of drugs in the body, the progression of disease, and the interaction of pharmaceutical delivery systems with the body [15].
2. Drug loading capacity: Some of the smart drug delivery networks can only load a small amount of drugs. This limited capacity might impair the effectiveness of treatment. The drug release rate with time may also be affected [16].
3. Biocompatibility and toxicity concerns: The success of pharmaceutical delivery systems depends on their biocompatibility. These systems are made of materials that can be toxic to cells, such as nanoparticles, and can cause side effects [15, 17].

STIMULI-RESPONSIVE MECHANISMS IN SMART DRUG DELIVERY SYSTEMS:

1. pH-Responsive Systems:

pH is among the most widely used triggers for controlling drug release [18]. Conventional pH-sensitive carriers exploit the large pH differences between organs, for example between the stomach (about pH 2) and the intestine (about pH 7). One example is Eudragit S100-coated citrus pectin nanoparticles (E-CPNs), which were developed to deliver 5-fluorouracil (5-FU) to the colon [19]. More advanced carriers can detect smaller pH shifts at disease sites such as inflamed, ischaemic and tumour tissue, and in cellular compartments such as endosomes and lysosomes; pH-

responsive nanocarriers for solid tumours are a well-known case [20].

Blood and healthy tissue normally have an extracellular pH close to 7.4, but because of heightened glycolytic activity the average extracellular pH of many solid tumours is below 7.0 [21]. This acidity can serve as a specific signal for targeted delivery. Inside cells, endosomes and lysosomes are more acidic than other compartments, typically with a pH of 4.5–5.5 [22]. While pH is a widely used stimulus in smart drug delivery systems, it is often combined with other stimuli, such as temperature and redox conditions, to achieve highly accurate and targeted drug release[23].The pH stimulus can be paired with other factors, including redox and temperature, to enable precise drug release at targeted sites, as demonstrated by poly (2-(diisopropylamino) ethyl methacrylate) (PDPAEMA)[24].

2. Redox-Responsive Systems:

Redox-responsive systems have drawn considerable attention for treating disease and are widely applied in intracellular delivery [25]. Redox potential differs from one tissue microenvironment to another, and these differences can be used to design redox-sensitive carriers. Nanoparticles that respond to glutathione (GSH) are a promising route to targeted delivery [26]. GSH reduction is a well-established redox mechanism in cancer cells: its concentration is about 2–20 μM in blood and normal extracellular matrix but 2–10 mM inside cancer cells, an increase of 100- to 500-fold [27]. In addition, levels of mucosal reactive oxygen species (ROS) in inflamed tissue and colon cancer have been reported to be 10- to 100-fold higher than in normal tissue [28, 29], which makes ROS-responsive systems attractive for regulating localised drug release.

3. Enzyme-Responsive Systems:

Enzymes have emerged as triggers for smart delivery systems in recent years because they act with high substrate specificity and selectivity under mild conditions [30]. Since enzymes such as glycosidases, lipases, phospholipases and proteases take part in almost every biological and metabolic process, they can be exploited to trigger release through biocatalytic action in cancerous or inflamed tissue [31]. A drawback is that the onset of the initial response is difficult to regulate [31].

4. Temperature-Responsive Systems:

Temperature is an especially useful trigger for timing drug release [32]. Conditions such as inflammation and cancer are usually warmer than healthy tissue [33], so nanoparticles can be designed to release drug more effectively inside tumours [34]. Alternatively, external heat sources such as ultrasound or magnetic fields can be used to warm the tumour region and improve release there [35]. Temperature-sensitive nanocarriers are generally designed to retain their drug at normal body temperature (37 °C) and to release it rapidly once the temperature rises above roughly 40–45 °C. A key challenge is to ensure safety without losing sensitivity to small temperature changes [34, 35].

5. Light, Magnetic, and Ultrasound- Responsive Systems:

Light-sensitive carriers can switch drug release on and off, because their nanostructure can open or close when exposed to a single or repeated light irradiation [35]. However, owing to the limited wavelengths that can be used in practice, the penetration depth of light currently restricts non-invasive applications in deep tissue [27].

Magnetic stimuli offer a non-invasive way to control carriers in space and time, guiding them to their targets and releasing the drug under a programmable external magnetic field [35]. Core/shell magnetic nanoparticles (MNPs), for instance, have several distinctive magnetic properties [27]. Their large surface-to-volume ratio provides many sites for biomolecule conjugation, so they can be engineered for functions such as long circulation in the bloodstream, selectivity for diseased tissue, and drug delivery under a localized external magnetic field [36]. When MNPs are encapsulated in colloidal carriers such as micelles, liposomes, or solid nanoparticles, the composite structures can respond to a magnetic field [37], giving multifunctional formulations for both diagnosis and therapy [38].

Ultrasound-sensitive nanocarriers make ultrasound a powerful tool for both locating drug carriers and triggering drug release at chosen sites by adjusting the frequency, duty cycle, and duration of the exposure [3]. This allows carriers to circulate for a time, reach the target, and release their drug where it is needed [39]. Because ultrasound is safe and can reach deep into the

body, it is already widely used in hospitals for diagnosis and treatment, and ultrasound-responsive nanocarriers extend its usefulness [3, 39].

6. Other Responsive Systems:

Besides the triggers described above, glucose [40] and electric fields [41] have also been used to control drug release from nanocarriers. Release can be made more precise by combining triggers [42, 43]. The most intensively studied are dual-stimulus systems, such as heat and pH [42, 43], heat and light [44], redox state and pH [45], and ultrasound and magnetic fields [46]. Figure 1 summarises the main mechanisms of stimuli-responsive release from nanocarriers [47].

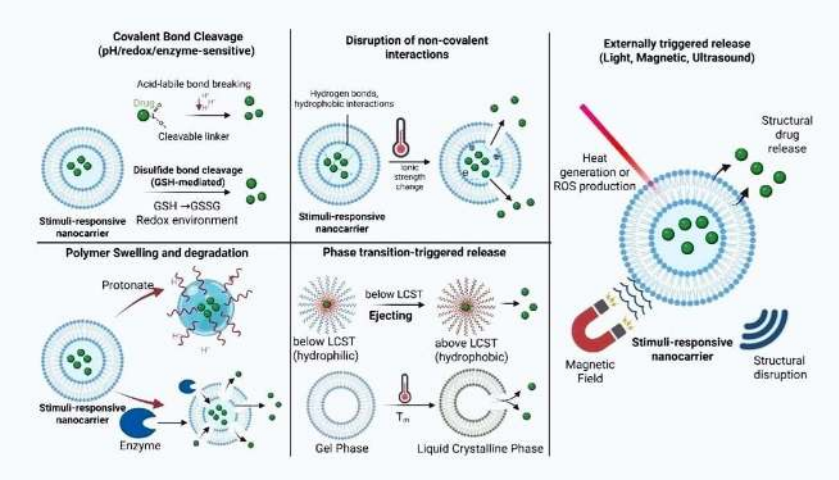


Figure 1: Mechanisms of Stimuli-Responsive Drug Release from Nanocarriers. Source: [47].

NANOCARRIERS USED IN SMART DRUG DELIVERY SYSTEMS:

1. Liposomes:

Phospholipid systems were first described by Alec Bangham and colleagues in 1965 [48], and closed phospholipid bilayer vesicles were subsequently named liposomes [49]. In 1971, Gregoriadis and co-workers became the first to use liposomes as drug carriers [50]. As preparation methods improved, large unilamellar vesicles (LUVs) could be produced by forcing vesicles through polycarbonate filters. Once liposome size was brought down to 100 nm or less, liposomes came into wide use as drug delivery systems in clinical trials of treatments for cancer, inflammation and fungal infections, as well as in gene therapy [51, 52]. Doxil®, the first nanomedicine delivery system approved by the US Food and Drug Administration (FDA), is based on PEGylated liposomes [53]. Alongside the liposomes already on the market, many other lipid-based nanoparticles are moving from concept toward clinical use, which suggests that liposomal carriers will gain further acceptance in clinical practice (Table 1).

Because of this track record, smart liposomes have become a major focus in nanomedicine. They can be triggered by changes in temperature, pH and enzyme levels, and by ultrasound and light [54, 55]. Although many stimuli can control release from liposomes, temperature is one of the most attractive because of its safety and ease of use [56]. The lipid dipalmitoylphosphatidylcholine (DPPC) has a melting temperature of 41.5 °C, which is the property that allows doxorubicin to be released from ThermoDox® at that temperature [57]. The structure of a liposome is shown in Figure 2.

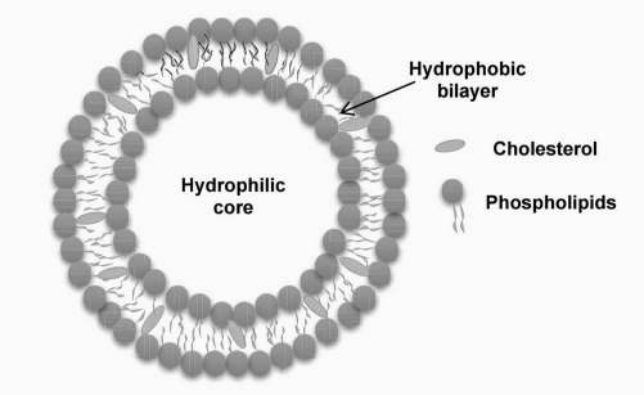


Figure 2: Schematic Representation of Liposomes Showing the Hydrophilic Core, Hydrophobic Bilayer, Phospholipids and Cholesterol. Source: [58].

Table 1: Examples of Liposomal Pharmaceutical Products and Their Active Ingredients.

Sr. No.	Marketed product	Active pharmaceutical ingredient	References
1	Doxil®	Doxorubicin	[53, 59]
2	Arikayce®	Amikacin	[59]
3	Epaxal®	Inactivated hepatitis A virus	[59]
4	DepoDur®	Morphine sulphate	[59]
5	AmBisome®	Amphotericin B	[59, 60]

2. Polymeric Nanoparticles:

Polymers that respond to physical or chemical stimuli are known as smart or stimuli-responsive polymers. Such polymers were used to control the release of active cargo as long as half a century ago, and they have played an important part in the development of nanomedicines. Smart polymeric systems have been reported to respond to a range of stimuli, including ultrasound, pH and magnetic fields [1, 61, 62]. They fall into two groups: single-stimulus responsive polymers and dual- or multi-stimuli-responsive polymers [63].

pH-triggered polymeric delivery systems have advanced considerably in recent years and allow controlled release at tumour sites [64]. A typical example is the pH-sensitive polymeric micelle [65]. In one study, smart micelles were prepared and interfacially crosslinked through hydrazone bonds; these bonds were rapidly cleaved at pH 5.0 and 37 °C [66]. Beyond polyelectrolytes, many self-assembled and other polymeric structures have been developed for controlled delivery, including micelles, polymer gels, polymer nanospheres and dendritic polymers [61]. pH-sensitive polymer systems have also been applied to tumour imaging; for example, the Gao group prepared ultra-pH-sensitive (UPS) fluorescent nanoprobes [67, 68].

Light-responsive polymeric systems can be built by incorporating photosensitive moieties or by triggering a photochemical reaction, and they are useful because their properties change when illuminated [69]. Glucose-responsive polymers, which sense sugar levels, are widely studied for diabetes care and can be used in new medical devices [70]. Some natural polymers can serve as controlled-release biomaterials, and smart release can also be achieved with chitosan blends and cyclodextrin derivatives [71]. Representative marketed nanoparticle-based products are listed in Table 2.

Table 2: Marketed Nanoparticle-Based Drug Delivery Products.

Marketed product	Active pharmaceutical ingredient	Application	References
Doxil®	Doxorubicin	Cancer therapy	[59]
Abraxane®	Paclitaxel	Cancer therapy	[59]

Marketed product	Active pharmaceutical ingredient	Application	References
Onpattro®	siRNA	Hereditary transthyretin amyloidosis	[59]
Comirnaty® / Spikevax®	mRNA	COVID-19 prevention	[59, 72]
DepoCyt®	Cytarabine	Lymphomatous meningitis	[59]
Vyxeos®	Daunorubicin + cytarabine	Acute myeloid leukaemia	[59]

3. Exosomes:

Almost every cell type secretes exosomes, a subset of extracellular vesicles with diameters below about 200 nm [73]. They act as messengers between cells and are involved in many physiological and pathological processes [74]. Exosomes can promote tissue regeneration and repair, largely because of their high biosafety, low immunogenicity and ability to carry a range of bioactive compounds to target cells [75, 76]; this property is useful in cardiovascular applications [77]. In addition, exosomes derived from tumour cells tend to accumulate preferentially in tumour tissue [78, 79]. Attaching tumour-targeting ligands such as proteins, peptides or antibodies to exosomes can further increase the specificity of exosome-based delivery [80, 81].

Although exosomes have entered clinical trials, their use as drug carriers may be limited by how much drug they can be loaded with, how well they retain it while circulating in the body, and whether they deliver it to target cells in a functional form [78, 82].Despite clinical trials with exosomes, the ability to load exosomes with enough drug, the ability of exosomes to hold these drugs while moving through the body, and the ability of exosomes to deliver these drugs to the targeted cells in a functional form may limit exosome use in drug delivery applications. Figure 3 gives an overview of exosome-based delivery, and Table 3 summarises representative cargos, loading approaches and reported outcomes.

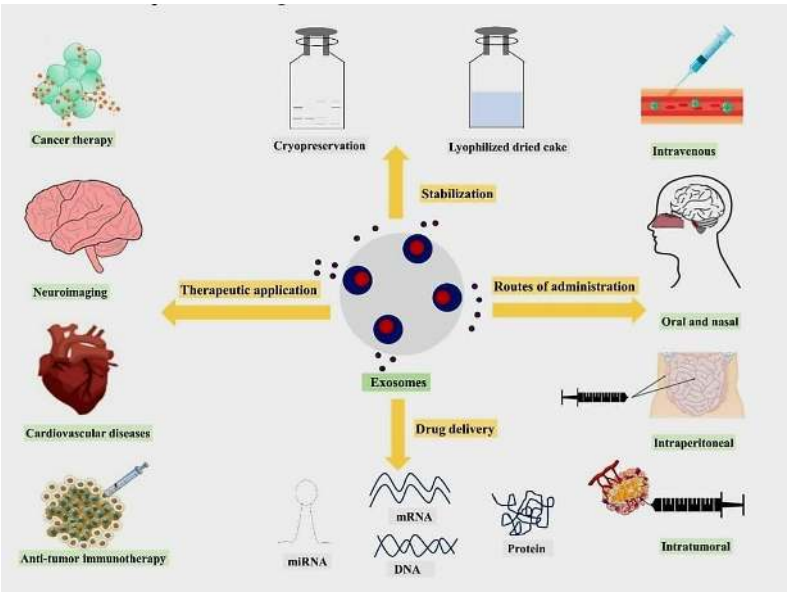


Figure 3: Overview of Exosome-Based Drug Delivery, Including Stabilisation and Storage, Routes of Administration, Therapeutic Applications, and Delivery of Biological Cargo Such as miRNA, DNA and Proteins. Reproduced from Butreddy Et Al. [77].

Table 3: Exosome-based Drug Delivery Systems: Cargo, Cellular Sources, Loading Approaches and Therapeutic Outcomes.

Exosome cargo	Source of exosomes	Therapeutic application	Drug-loading approach	Reported outcome	Reference
Signal regulatory protein α	Human embryonic kidney 293T cells	Cancer	Transfection	Enhanced phagocytosis of tumour cells	[84]
Survivin-T34A	Human embryonic kidney 293T cells	Pancreatic cancer	Transfection	Increased apoptosis	[85]
Anti-epidermal growth factor receptor	Mouse neuroblastoma	Epidermoid carcinoma	—	Target-specific delivery	[81]
miRNA	Glioblastoma cells	Glioblastoma	Transfection	Diagnostic/prognostic potential	[86]
miRNA	Human blood endothelial colony-forming cells	Ischaemic kidney injury	Transfection	Improved kidney function	[87]
Paclitaxel	Prostate cancer cells and LNCaP	Autologous prostate cancer	Co-incubation	Enhanced drug cytotoxicity	[88]
Doxorubicin	Immature mouse dendritic cells	Breast cancer	Electroporation	Improved tumour drug delivery	[89]
Curcumin	Glioblastoma-related cell sources	Brain tumour/autoimmune conditions	Direct mixing	Reduced inflammation	[90]
Dopamine	Kunming mouse brain-derived cells	Parkinson's disease	Co-incubation	Improved therapeutic effect	[91]

4. Hydrogels:

The first hydrogel developed for biological use dates from 1960 [92]. Since then, conventional "dumb" gels have evolved into "smart" gels that respond to specific external stimuli or environmental changes. Smart hydrogels have received considerable attention for drug delivery in recent years because of their responsive behaviour, low invasiveness, ease of administration and ability to release drug in a controlled way over an extended period [93, 94]. Conventional gels may swell or shrink under osmotic pressure, but their responses are generally unpredictable, which leads to inaccurate release and poor control over dose timing [95].

Advances in polymer science and nanotechnology have produced hydrogels that can release drugs at the right time and place [96]. By preventing the drug from accumulating at unwanted sites, smart hydrogels can reduce side effects, lower dosing frequency and maintain stable therapeutic levels after a single injection [97]. They are also easy to prepare and perform well in slow-release devices [95]. The stimuli that can trigger release from smart hydrogels are illustrated in Figure 4, and representative hydrogel types are listed in Table 4.

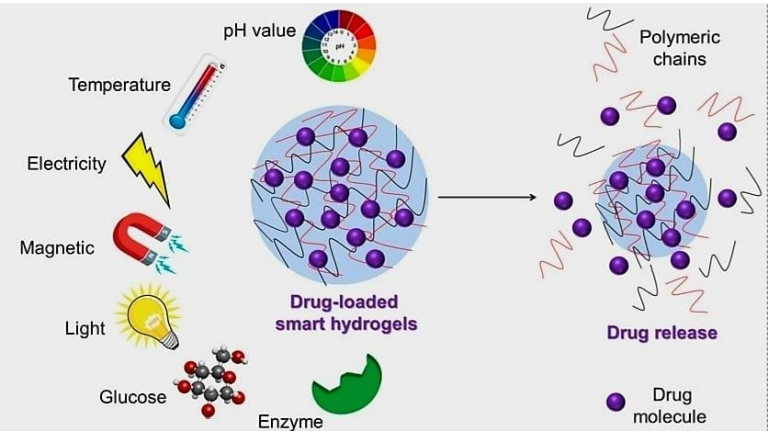


Figure 4: Stimuli-responsive Smart Hydrogels and Their Drug-Release Mechanisms in Response to External Stimuli, Including pH, Temperature, Electricity, Magnetic Fields, Light, Glucose and Enzymes. Reproduced from Bordbar-Khiabani and Gasik [94].

Table 4: Stimuli-responsive Hydrogels: Examples, Materials, Response Mechanisms and Biomedical Applications.

Type of hydrogel	Examples	Response / mechanism	Application	Reference
pH-responsive	Chitosan, κ-carrageenan, PEI, PAA, PMAA	Swelling or shrinking occurs with changes in pH, allowing drug release	Drug delivery, wound healing, sensing	[98]
Temperature-responsive	Poloxamer, Pluronic, PNIPAM, PEG-based polymers	Temperature change causes a polymer phase transition and alters drug release	Drug delivery, tissue engineering	[99]
Electric-field-responsive	PPy nanoparticles, PAA, PEG, chitosan-based hydrogels	Electric stimulation changes hydrogel swelling and drug release	Drug delivery, wound healing, tissue engineering	[100]
Magnetic-field-responsive	Alginate, chitosan, magnetic nanoparticles, Fe_3O_4-containing hydrogels	A magnetic field produces heating or structural changes that trigger drug release	Drug delivery, tissue engineering	[101]
Light-responsive	Photocleavable polymers, azobenzene-containing hydrogels	Light causes structural or chemical changes and enables controlled release	Drug delivery, optical delivery, wound healing	[102]
Biomolecule-responsive	Hyaluronic acid, phenylboronic acid-containing hydrogels	Interaction with biomolecules or enzymes changes hydrogel properties and drug release	Drug delivery, cell culture, tissue engineering	[103]

5. Dendrimers:

The term "dendrimer" was introduced by D.A. Tomalia and originates from the Greek words “dendron” (tree) and “meros” (part), a common suffix for polymers[104]. Dendrimers are described as highly branched, star-shaped three-dimensional macromolecules with nanometer-scale dimensions. Dendrimers are made up of three parts: (i) The multivalent surface with many reactive sites; (ii) the outer layer just below the multivalent surface providing a unique environment; and (iii) the core, the central part of the dendrimer, is safely shielded by the branches of higher generation dendrimers[105]. The surfaces of higher-generation dendrimers can be decorated with many functional groups, enabling effective host–guest interactions [105].

These synthetic macromolecules are built from branched monomer units and combine a defined structure, uniform size, high biocompatibility, a compact globular shape and a modifiable surface bearing functional groups or ligands, which makes them strong candidates for evaluation as drug carriers [105]. The

general architecture is shown in Figure 5, and dendrimer-based products are listed in Table 5.

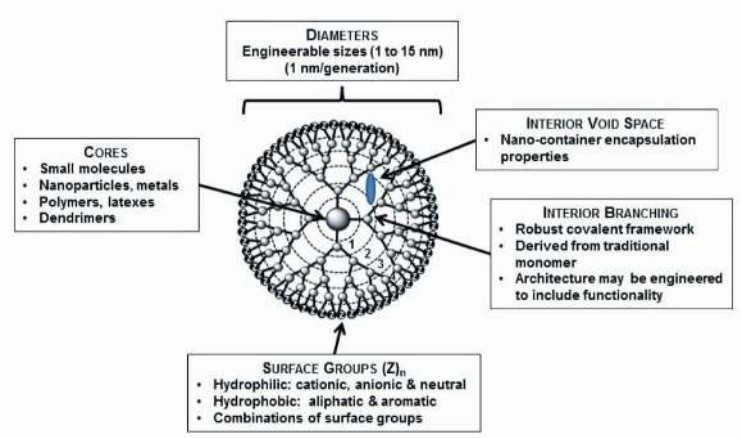


Figure 5: Schematic Representation of Dendrimer Structure Showing the Central Core, Interior Branching Units, Internal Cavities and Surface Functional Groups. Source: [105].

Table 5: Dendrimer-based Products and Applications.

Dendrimer / product	Type of dendrimer	Main application	Development status	References
Priostar®	PEHAM/PEA	Drug delivery	Marketed	[106]
Starburst®	PAMAM	Drug delivery	Marketed	[104]
Astramol®	PPI	Drug delivery	Marketed	[107]
Polylysine	Poly-L-lysine	Drug delivery	Marketed	[108]
VivaGel®	Poly-L-lysine	Prevention of HIV and STDs	Clinical trials	[108]
Stratus CS®	PAMAM	Cardiac assay/diagnostic	Marketed	[109]
SuperFect®	PAMAM	Transfection agent	Marketed	[110]
ProfiTec™	PAMAM	Transfection agent	Marketed	[110]
Alert Ticket™	PAMAM	Anthrax-detection agent	Marketed	[111]

6. Microneedles:

The transdermal route is used in many clinical settings to overcome the main limitations of oral drug delivery [10]. Recent work highlights the effectiveness of microneedle (MN) arrays for the transdermal delivery of compounds that cannot cross the skin by passive diffusion or with other external assistance [112]. Microneedles are an effective means of delivering high-molecular-weight molecules, and they also aim to reduce the pain associated with injection by hypodermic needle [112]. They are too small to be seen without magnification, with heights below one millimetre; reported heights are about 50–900 μm, with a diameter of about 1 μm [112].

Microneedles must be mechanically stable and withstand an insertion force of about 10 N [112]. They are intended to support personalised medication at variable dose levels and self-administration [112]. Durability is one of the most important design considerations in fabrication, because the needles must pierce the epidermis without breaking so that drug is delivered efficiently [112]. Representative microneedle products are listed in Table 6.

Table 6: Microneedle-based Drug Delivery Products [112].

Product	Type	Function	Application
Dermaroller®	Metallic microneedle	Enhances drug absorption	Acne, stretch marks, hair loss
MicroHyala®	Dissolvable microneedle patch	Delivers hyaluronic acid	Wrinkle treatment
VaxMat®	Dissolvable microneedle patch	Delivers macromolecules	Proteins, peptides and vaccines

Product	Type	Function	Application
Micro-Trans®	Microneedle patch	Delivers drugs into the dermis	Transdermal drug delivery
Drugmat®	Dissolvable microneedle patch	Provides rapid drug delivery	Transdermal drug delivery
Nanoject®	Microneedle array-based device	Enables intradermal delivery	Drug delivery and diagnostics
Soluvia®	Hollow microneedle array	Enables accurate intradermal delivery	Vaccines
IDflu® / Intanza®	Intradermal microneedle injection	Delivers vaccine into the skin	Influenza vaccination

7. Polymeric Micelles:

Biocompatible polymers have been widely used in pharmaceutical sciences as excipients in the traditional drug formulations and, more recently, in nanomedicines for enhanced therapeutic efficacy of potent drugs[27]. Approximately thirty years ago, micelles created by amphiphilic block copolymers in water were envisioned as vehicles for poorly soluble therapeutic agents that were either covalently bonded to polymer chains or non-covalently integrated within the micelles [27, 35]. Several novel block copolymers have since been proposed for micelle-based delivery systems as promising nanomedicines for humans [61].

To maximize the delivery of medicinal compounds, numerous important developments in polymeric micelles have been made. Such developments have pushed an increasing number of polymeric micelle medication formulations to enter clinical trials for regulatory approval[59]. The design of block copolymers is aimed at effectively encapsulating medicinal chemicals into polymeric micelles by various molecular interactions, which results in the protection of the cargo from the external environment and improvements of the pharmacokinetic (PK) profile [27]. Representative formulations and their clinical status are listed in Table 7.

Table 7: Representative Polymeric Micelle-Based Drug Delivery Systems and Their Clinical Development Status.

Product	Drug	Polymer	Clinical status	Reference
Genexol® PM	Paclitaxel	mPEG-b-PDLLA	Approved	[59]
Nanoxel® M	Docetaxel	mPEG-b-PDLLA	Approved	[59]
NK105	Paclitaxel	mPEG-b-modified P(Asp)	Phase III completed	[59]
NC-6004	Cisplatin	PEG-b-P(Glu)	Phase III completed	[59]
SP1049C	Doxorubicin	Pluronic® L61/F127	Phase II completed	[59]

APPLICATIONS OF SMART DRUG DELIVERY SYSTEMS:

SDDS are being applied across a wide range of diseases. Table 8 summarises representative applications, the role of the delivery system and examples of products or platforms.

Table 8: Applications of Smart Drug Delivery Systems.

Sr. No.	Application	Role of SDDS	Potential benefit	Examples	Reference
1	Cancer treatment	Delivers anticancer drugs in response to specific stimuli, such as heat or changes in the tumour environment	Improved drug delivery to tumour tissue and reduced exposure of healthy tissue	ThermoDox, Doxil	[29, 53]
2	Brain tumour treatment	Uses magnetic iron-oxide nanoparticles to generate local heat	Localised treatment through magnetic hyperthermia	NanoTherm	[29]

Sr. No.	Application	Role of SDDS	Potential benefit	Examples	Reference
3	Ovarian cancer treatment	Uses polymer-based drug delivery to deliver paclitaxel	May improve drug delivery and modify drug distribution in the body	Opaxio	[29]
4	Fungal infections	Delivers amphotericin B through a liposomal formulation	Improved drug delivery and reduced toxicity compared with conventional amphotericin B	AmBisome	[60]
5	Visceral leishmaniasis	Uses liposomal encapsulation to deliver amphotericin B	Improved delivery of the drug to infected tissues	AmBisome	[60]
6	Colon-targeted drug delivery	Uses pH-responsive nanoparticles to release drugs in response to changes in gastrointestinal pH	More localised drug release and reduced premature release	Eudragit S100-coated citrus pectin nanoparticles	[19, 29]
7	Inflammatory bowel disease	Uses stimuli-responsive nanocarriers to deliver therapeutic agents to affected intestinal regions	Potentially improves local drug delivery and reduces systemic exposure	pH-responsive nanocarriers	[28, 113]
8	Diabetes management	Uses glucose-responsive systems to regulate insulin release according to glucose levels	Potential for glucose-responsive insulin delivery and improved blood glucose control	Glucose-responsive nanocarriers	[40, 70]
9	Intracellular drug delivery	Uses redox-responsive carriers that respond to intracellular reducing conditions, such as elevated glutathione levels	Promotes drug release inside cells and may improve therapeutic effectiveness	Disulfide-bond-containing nanocarriers	[26, 27]
10	Localised cancer therapy	Uses temperature-responsive materials to release drugs following local heating	Provides better control over the location and timing of drug release	Thermosensitive liposomes	[8, 57]

CHALLENGES IN SMART DRUG DELIVERY SYSTEMS:

The human body is a complex and constantly changing system with multiple biological barriers to drug delivery. These include rapid clearance by the reticuloendothelial system, uptake of the drug by healthy cells, enzymatic degradation, dilution in the bloodstream, difficulty in penetrating the dense tissue surrounding tumours [114], and barriers such as the blood–brain barrier and cell membranes, which prevent drugs from entering cells [113]. Polyethylene glycol (PEG) is widely used in drug delivery because it prolongs circulation in the bloodstream and helps carriers avoid immediate recognition by the immune system. However, recent studies show that repeated administration of PEGylated products can induce anti-PEG antibodies, which may lead to faster clearance of the drug, reduced therapeutic effect and tissue damage [115].

SDDS must also address the potential toxicity of nanocarriers, the cost of production, the diversity and complexity of cancer types and the lack of clear regulatory guidelines [116]. For antibody–drug conjugates (ADCs), the main concerns are high production cost, limited penetration into solid tumours and the risk of premature drug release [117]. In addition, inconsistencies in the experimental detail and characterisation reported in published studies have made it harder to advance nanotechnology in medicine [118, 119]. Because the available data are limited and heterogeneous, progress in nanomedicine and its translation to clinical use will depend on more consistent, well-characterised studies that can guide industry. Many researchers hold that nanoparticles can be either beneficial or harmful: their advantages are well established, but information on their safety, their interactions with non-specific proteins and their movement and interactions in non-target organs is limited [120].

Although targeting specific sites can reduce side effects and improve treatment, its benefit depends on whether the drug actually reaches the intended location. This is evident for systemically administered siRNA, which often fails to reach its target cell or organ because enzymes rapidly degrade it and because its negative charge is repelled by cell membranes, leading to poor uptake [121]. Lipid-based nanoparticles such as micelles and liposomes are being studied for targeted delivery, but their effectiveness is reduced by phagocytosis by immune cells and filtration by the liver, which can prevent the drug from reaching its target [122]. These nanoparticles may also have toxic effects [120], and, when given orally, they may interact with food and be broken down by bacteria in the digestive tract [123]. Finally, biocompatibility—how well a system is tolerated by the body without causing immune reactions—remains a major challenge, because the body responds differently to biological materials than to synthetic ones [124].

CONCLUSION:

SDDS is a major step forward for health care. SDDS employs carriers such as liposomes, nanoparticles, dendrimers, hydrogels, exosomes, microneedles, and micelles. These vehicles protect drugs so they can be delivered at the right time and targeted to the tissue or cells that require them. SDDS also reacts to other factors like changes in levels, enzyme activity, temperature, light, magnetic fields, and ultrasound. This makes the delivery more accurate and flexible so the medicine can be released when needed. Advantages of SDDS include their ability to effectively deliver drugs and help patients adhere to their treatment regimens. With these benefits, SDDS could revolutionize the treatment of cancer, heart disease, infections, and many other diseases. There are still issues. SDDS designs can be very complex and may contain certain quantities of drug, and hence there are concerns about their interaction with the body and toxicity issues. If scientists are to get past these problems, they have to keep working on multi-functional and stimuli-responsive systems. They also need nanocarriers to be developed. SDDS is the convergence of nanotechnology, biotechnology, and medicine. I believe SDDS can provide effective therapies that are tailored to each patient. New ideas for SDDS may reduce adverse effects and costs. Make patients feel better. It's a step toward a future of personalized health care."

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HOW TO CITE: Sanjivani Khawashi, Amit Jaiswal, Janhvi Gawande, Rutika Gandhe, Arpit Hadole, Smart Drug Delivery System: An Intelligent Approach Toward Precision Drug Delivery: A Review, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 11, 1-18. https://doi.org/10.5281/zenodo.23876242