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Comprehensive Review on Pulsatile Drug Delivery System: Hybrid Approaches

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Abstract

Pulsatile drug delivery systems (PDDS) represent a groundbreaking approach in pharmaceutical technology, allowing for controlled, targeted, and programmable drug release that aligns with circadian rhythms or caters to time-sensitive therapeutic requirements. Although traditional pulsatile systems have shown considerable clinical promise, their effectiveness is frequently compromised by physiological variations such as gastrointestinal transit times, changes in pH, and enzymatic activity. To tackle these obstacles, hybrid PDDS have been developed by combining two or more release mechanisms – such as time-controlled, stimuli-responsive, or externally triggered within a single framework. These hybrid systems offer improved consistency, flexibility, and accuracy in drug release profiles. This review underlines the basic principles governing PDDS, examines hybridization techniques like time + pH-responsive, enzyme-responsive, multi-stimuli, and device–polymer hybrids, and showcases recent advancements in oral, injectable, transdermal, and wearable systems. Additionally, it addresses the prospects for industrial and clinical application, encompassing areas like oncology, ophthalmology, vaccines, regenerative medicine, and the management of chronic illnesses. Future outlooks highlight the influence of 3D/4D printing, digital therapeutics, and telemedicine in developing personalized hybrid PDDS. Despite facing hurdles in scalability, consistency, and regulatory approval, hybrid PDDS possess transformative potential to enhance precision medicine and next-generation therapeutic approaches.

Keywords: Controlled release, hybrid drug delivery, pulsatile drug delivery systems (PDDS), stimuli-responsive polymers, time-controlled systems

INTRODUCTION

Drug delivery refers to approaches, formulations, technologies, and systems for transporting a pharmaceutical compound within the body as required to safely achieve its desired therapeutic effect [1].

Targeted therapy improves therapeutic potential whilst reducing systemic toxicity by releasing a regulated amount of the drug into the body [2]. Drug delivery systems (DDS) utilize cutting-edge technology. Endogenous physicochemical variables like as enzyme concentration, pH, and redox gradients regulate medication distribution [3]. Researchers are becoming more interested in pulsatile drug delivery systems (PDDS). PDDS are characterized as drug delivery devices that can provide one or more immediate drug release pulses at a predetermined time or location following a programmable lag phase. A single dosage form is intended to deliver an initial dose of medication, followed by a release-free interval, and then a second dose of medication, followed by another release-free interval (Figure 1) [4].

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Pulsatile drug delivery systems (PDDS) represented an innovative and exciting advancement in the field of pharmaceuticals. They

were designed to release medications in a time-controlled pulsatile fashion, reflecting the natural circadian rhythms of the body [5]. The necessity for PDDS emerges in situations that are governed by the body's circadian rhythm or when a drug is broken down in gastric content, making the release delay significant. Moreover, this method is useful for administering drugs that experience considerable first-pass metabolism, for directing drugs to a specific area within the gastrointestinal tract, and for instances where localized drug action is required to reach the intended therapeutic results [6].

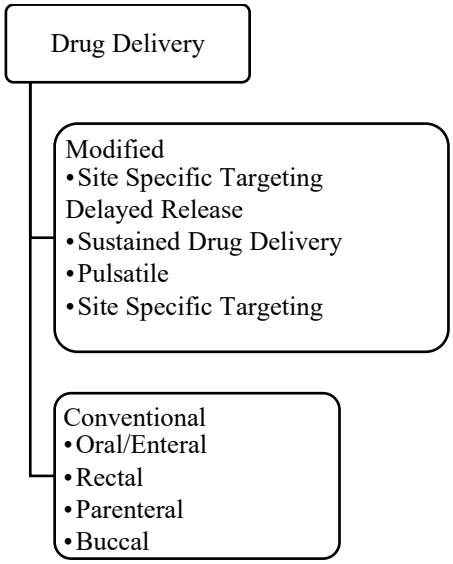

Figure 1. Types of drug delivery system.

Patients with time-dependent conditions such bronchial asthma, myocardial infarction, angina pectoris, hypertension, hypercholesterolemia, arthritis, gastrointestinal ulcers, and cancer, when the drug dosage becomes necessary at a specific moment, benefit greatly from PDDS [7].

Each drug delivery system possesses unique characteristics that influence its rate of release and mechanism. These variations stem from differences in the physical, chemical, and morphological traits, which ultimately affect their interactions with various drug substances [8]. The integration of two different platform technologies provides benefits that surpass those gained from using a single platform. In the realm of biomedical applications, merging two types of drug delivery systems to form hybrid systems (such as hybrid NP–hydrogel) can capitalize on the strengths of both while addressing the weaknesses of either [9].

The functionality of controlled release within a delivery system guarantees the sustained and regulated administration of therapeutic agents. A typical application, as seen in depot systems, involves the gradual release of the active substance over an extended duration, which prolongs the effect, either locally or systemically. This extended duration can help manage prolonged acute conditions or chronic conditions (such as acute and chronic pain respectively). Additional advantages of sustained release can include decreased dosing frequency and enhanced patient compliance [10].

In recent decades, drug delivery systems have been successfully utilized in disease treatment and health enhancement due to improved systemic circulation and control over the pharmacological effects of medications. The progressions in pharmacology and pharmacokinetics have highlighted the significance of drug release in establishing therapeutic effectiveness, leading to the emergence of controlled release concepts [11]. Controlled drug delivery systems release medications at a specified rate over a predetermined period of time. Furthermore, these systems are unaffected by physiological conditions, allowing them to sustain operation for days to years. They also provide spatial control over drug release, featuring either constant or variable rates of release [12].

FUNDAMENTALS OF PULSATILE DRUG DELIVERY SYSTEMS (PDDS)

Specialized drug delivery platforms known as pulsatile drug delivery systems (PDDS) are made to deliver the active pharmaceutical ingredient in a fast and powerful burst after a predetermined lag phase, or time during which no drug is released. The basic idea behind PDDS is to create drug release to resemble biological or circadian cycles by combining a latent lag with an instantaneous pulse phase, in contrast to sustained release formulations that strive for constant plasma concentrations [13, 14].

The standard release pattern follows a sigmoidal shape and includes three separate stages.

- *Lag Phase:* Minimal or no release at all.
- *Pulse Release Phase:* Swift and total drug release occurring within a brief period.
- *Plateau Phase:* No additional significant release after the completion [15].

The consistency of the lag and burst phases is essential, as these factors determine therapeutic dependability and alignment with the intended biological process [16].

Mechanistic Classifications

The principles of PDDS can be understood best by examining the mechanisms that govern both the lag phase and the onset of burst release. These mechanisms can be categorized into three main types (Figure 2).

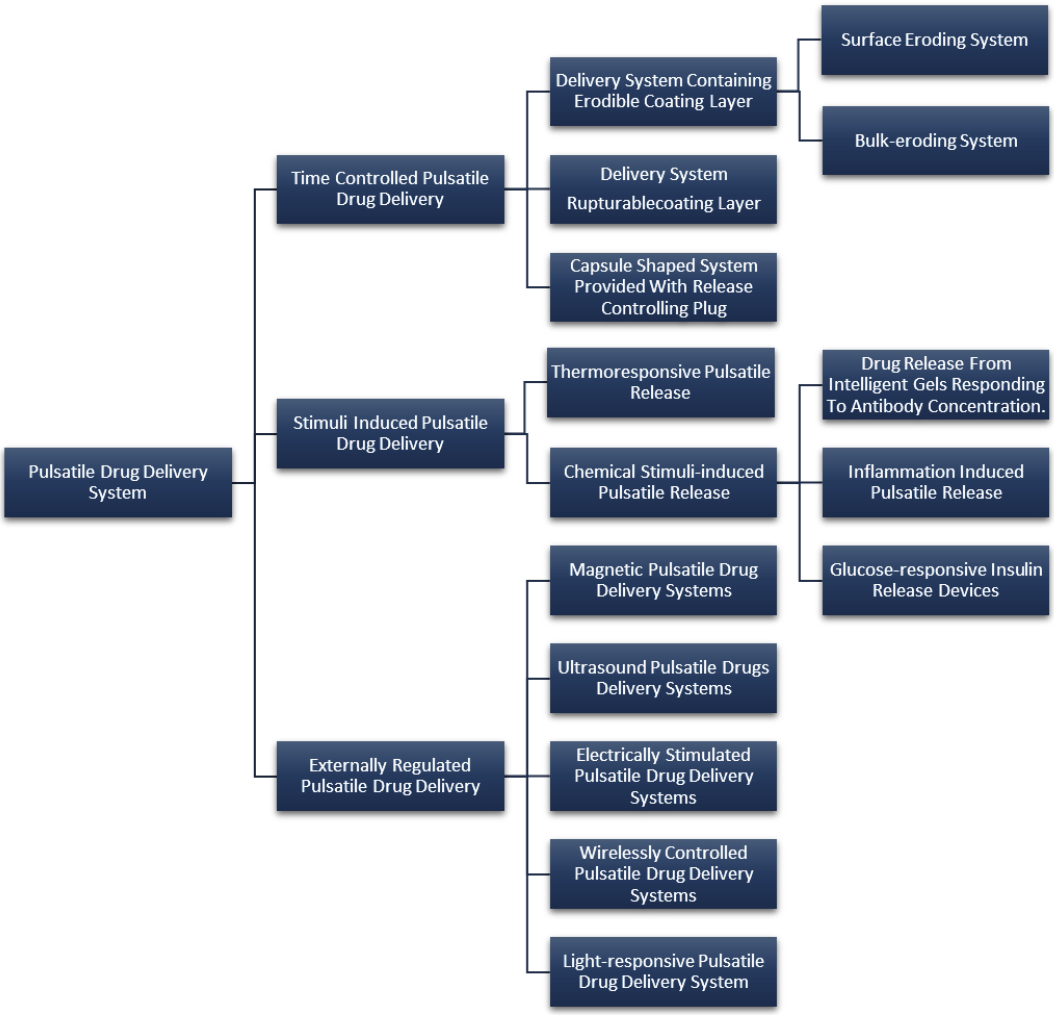

Figure 2. Classification of pulsatile drug delivery system.

Time-Controlled Systems

Time-controlled systems rely on design characteristics to set the delay and burst release pattern. The primary types include:

- *Barrier Erosion/Dissolution Systems:* The drug core is encased in erodible or dissolving polymers (such as HPMC or ethyl cellulose). Drug release happens once the coating dissolves or wears away.
- *Rupturable Systems:* The core formulation includes swelling or effervescent agents that create internal pressure until the surrounding polymer breaks.
- *Plug/Capsular Systems:* Capsules, sealed with polymer or hydrogel plugs (e.g., Pulsincap), remain intact during the lag phase but swell or erode, removing the plug and releasing the drug.
- *Osmotic Systems:* Drug release is initiated when the osmotic pressure inside the device breaches a semi-permeable membrane [17–20].

Stimuli-Induced Systems

These systems respond to physiological stimuli to commence drug release.

- *pH-Responsive Systems:* Coatings made of enteric polymers dissolve in the pH conditions of the intestinal or colonic environment.
- *Enzyme-Responsive Systems:* Natural polysaccharides (like pectin or chitosan) break down under the influence of colonic microbial enzymes, leading to drug release.
- *Thermo-Responsive Hydrogels:* Polymers such as PNIPAAm alter their swelling characteristics at body temperature, resulting in the expulsion of the drug [21–23].

Externally Regulated Systems

Externally triggered systems activate drug release through on-demand signals.

- *Ultrasound-Induced:* Acoustic waves produce cavitation or cause rupture in polymer membranes.
- *Magnetic Field-Responsive:* Magnetic nanoparticles generate heat or deformation when subjected to a magnetic field, resulting in drug release.
- *Light/Electricity-Controlled:* Polymers experience ionization, bond cleavage, or swelling when exposed to light or electrical stimuli [24–26].

Core Design Parameters

The foundations of PDDS necessitate the exact engineering of multiple parameters. The most important factor is lag time (t_{lag}), which is influenced by osmotic accumulation, swelling rate, erosion rate, and polymer thickness.

Kinetics of Burst Release

After latency, release needs to be quick and consistent. Drug solubility, rupture strength, and coating porosity are some of the variables [14, 17].

Selection of Polymers and Materials

Ethyl cellulose, PLGA, and HPMC are erodible polymers.

Methacrylic acid copolymers, PNIPAAm hydrogels, and enzyme-degradable polysaccharides are examples of stimuli-responsive polymers.

Architecture of the Device

Single-unit methods (osmotic tablets, capsules) do accurate lag management, but GI transit can cause unpredictability. Mini-tablets, beads, and pellets are examples of multi-unit systems that offer less variability and more consistent release [8].

Fundamentals of Mathematics and Release Kinetics

The latent lag followed by fast release is represented quantitatively by sigmoidal or logistic functions in the release profile of PDDS [15, 16].

A simplified expression:

$M_t/M_\infty = 1 / (1 + e^{(-k(t - t_{lag}))})$

where

M_t/M_∞ = fraction of drug released at time t,
k = release constant,
t_{lag} = lag time.

The steepness of the curve depends on the swelling/erosion properties of the polymer and formulation design. Weibull distribution models are frequently used to fit experimental release data, while mechanistic models incorporate swelling and diffusion parameters.

CONCEPT OF HYBRID PULSATILE DRUG DELIVERY SYSTEMS (HYBRID-PDDS)

Hybrid pulsatile drug delivery systems (Hybrid-PDDS) are developed by integrating two or more unique release mechanisms within one formulation, resulting in a delivery pattern that is more dependable, controllable, and resilient than traditional single-trigger pulsatile systems. The hybrid approach focuses on the combination of various control elements, where each trigger serves a specific purpose, whether it be extending the lag phase, starting the burst release, or offering alternative support if one mechanism fails [13, 14]. Despite being successful in producing a lag-pulse profile, traditional pulsatile systems struggle with gastrointestinal pH, enzyme levels, and motility fluctuation, which can change the release properties. In order to solve this, hybrid systems integrate two or more processes, such as osmotic pressure plus coating rupture, time-erosion plus pH-responsiveness, or stimuli responsiveness plus external triggering [20, 27]. Essentially, the hybrid technique ensures consistency under complex physiological settings by enabling drug release to occur in a sequential and regulated manner.

Structural Principles of Hybrid-PDDS

The design of Hybrid-PDDS generally includes a layered, multi-unit, or reservoir-type configuration. It comprises of at least two functional layers.

- The primary control element regulates the lag phase through processes like the erosion of coatings, polymer swelling, or the accumulation of osmotic pressure.
- The secondary control element adds a further layer of specificity by incorporating site- or environment-responsive triggers (such as pH-sensitive coatings, enzyme degradation, or redox-sensitive polymers).

This dual-layered structure guarantees that one mechanism initiates or controls the lag time, while the other mechanism activates or enhances drug release at the target site [21, 28].

For instance, a pH-sensitive polymer can be added to a tablet coated with a time-dependent erodible polymer. While the pH sensitivity guarantees the pulse's localization at a particular section of the gastrointestinal system, erosion guarantees the least amount of delay. This hybridization improves control over medication absorption and lowers the likelihood of premature release [29].

Hybridization Strategies in PDDS

Time-Controlled + pH-Responsive Systems

One of the key hybrid strategies involves combining elements that are sensitive to both time and pH levels. The time-controlled barrier, typically a hydrophilic polymer or an erodible coating creates a programmable delay, while the pH-responsive polymer ensures that the release occurs at a specific site. This strategy is especially important in formulations aimed at targeting the colon via oral administration, where time-dependent coatings (such as hydroxypropyl methylcellulose) are utilized alongside

methacrylic acid copolymers. While the time barrier maintains a reliable delay, the pH-responsive layer reacts to the pH of the colon, thereby ensuring spatial precision [22, 30].

Time-Controlled + Enzyme-Responsive Systems

Another commonly used approach includes the integration of time-controlled release layers with polymers that can be degraded by enzymes. Secondary layers of enzyme-sensitive polysaccharides, such as guar gum, pectin, or chitosan, are added. The time-controlled layer guarantees that the drug is released only after a specific delay, while the enzyme-sensitive polymer allows for colonic selectivity by breaking down in the presence of colonic microflora [23, 31]. This dual mechanism is beneficial in cases where intestinal pH may vary. Even if the pH-sensitive trigger is unreliable, enzymatic degradation acts as a backup, ensuring the intended release profile.

Multi-Stimuli Hybrid Systems

Hybrid PDDS can also integrate two or more physiological stimuli simultaneously, creating a multi-stimuli system. Examples include pH combined with enzymatic activity, pH combined with redox potential, or enzymatic activity combined with temperature sensitivity.

These kinds of systems are especially crucial in diseased microenvironments. For instance, tumors usually have significant levels of oxidative stress and an acidic pH. The reproducibility of pulsatile release under heterogeneous conditions is enhanced by a hybrid system that is sensitive to both pH and redox potential, guaranteeing that release takes place precisely in the tumor microenvironment [32].

Device–Polymer Hybrid Systems

Hybridization can also occur through the integration of osmotic and mechanical devices with polymer coatings. Traditional osmotic pump designs, when paired with rupturable polymeric coatings, establish a two-stage control system. The osmotic pressure gradually builds until the external barrier breaks, resulting in a sudden pulse release [19].

In a similar fashion, capsule-based systems like hydrogel-plug devices can be enhanced with rupturable layers. The hydrogel plug enables delayed release by swelling, while the coating bolsters the characteristics of burst release. This combination of devices and polymers exemplifies a hybrid structure that provides improved control over pulsatile kinetics [33].

Externally Triggered + Built-in Mechanism Systems

Hybrid PDDS can also incorporate externally applied stimuli such as ultrasound, light, or magnetic fields in conjunction with internally controlled time barriers. In these instances, the external trigger facilitates the precise initiation of the release pulse, while the built-in barrier provides a backup release mechanism if the external stimulus is not utilized. For example, a capsule could feature a photo-responsive polymer coating paired with an erosion-controlled time layer. Even in the absence of external light exposure, the time-controlled erosion guarantees that release will happen after a specific delay, thereby avoiding therapeutic failure [24, 26].

Mechanistic Fundamentals of Hybrid-PDDS

The following sequential and synergistic actions can be used to understand the core mechanism of Hybrid-PDDS.

- *Sequential Action:* The lag phase is controlled by one mechanism, and the pulse is started by another. For example, a polymeric covering that supplies the pulse ruptures after an osmotic core delays release until enough pressure is built.
- *Synergistic Action:* Two systems work together to increase dependability. For instance, in the colon, enzymatic degradation and pH sensitivity work in tandem to guarantee medication release regardless of pH oscillations or changes in the microbial population [25].

Thus, hybrid PDDS function as dual-guarded systems. By integrating the systems, the release profile becomes more reproducible because neither burst release nor lag time are dependent on a single physiological aspect.

EXAMPLES OF HYBRID PDDS

Oral Hybrid Systems

The oral route continues to be one of the most favorable methods for drug administration due to its convenience for patients; however, creating effective pulsatile oral delivery systems is difficult because of the variability in gastrointestinal (GI) transit times and the harsh physiological environment. To address these issues, hybrid nanoparticles that combine polymers, lipids, and functional coatings have been developed. Polymer-lipid hybrid nanoparticles enhance oral bioavailability and allow for customization of release kinetics through core-shell structures [34, 35]. In particular, PLGA-based hybrids have demonstrated promising outcomes due to their biodegradability and adjustable degradation rates [36]. The addition of pH-sensitive or enzyme-responsive coatings offers an extra layer of control, postponing the release until the formulation arrives at specific areas of the GI tract [37]. Moreover, advanced designs incorporate stimuli-responsive materials, such as thermo- or redox-sensitive polymers, which activate drug pulses under GI conditions [38]. Nevertheless, achieving accurate pulsatile bursts remains a challenge, as most oral hybrids tend to favor sustained or delayed release rather than distinct, multiple pulses [39].

Injectable and Implantable Hybrid Systems

For pulsatile delivery, injectable and implantable hybrids offer a more regulated local environment. The most extensively researched of these are hybrids of nanoparticles and hydrogel. These systems use hydrogels that function as responsive triggers or diffusional barriers to encapsulate drug-loaded nanoparticles [40, 41]. Pulsatile release can be created by adjusting the hydrogel's crosslinking density and responsiveness to pH, temperature, or enzymes [42]. External factors, including magnetic fields or ultrasound, have the potential to improve pulse accuracy by momentarily disrupting the hydrogel structure, allowing for controlled release when needed. Another innovative method includes the use of implantable microchip systems that integrate MEMS technology with biodegradable polymers to enable electronically controlled pulsatile release. Significant challenges involve maintaining long-term biocompatibility, preventing leakage between pulses, and navigating sterilization and regulatory obstacles [43–45].

Transdermal and Microneedle-Based Hybrids

Transdermal administration using microneedles (MNs) has drawn interest for its minimally invasive nature and the possibility of hybrid designs. Hydrogel microneedles (HMNs) merge the mechanical robustness of solid MNs with properties that allow for responsive swelling or degradation, rendering them ideal for pulsatile release [46]. Current developments in multifunctional HMNs use temperature-responsive hydrogels, light-sensitive nanoparticles, or conductive polymers to provide controlled drug release bursts and external activation [47]. For instance, the hydrogel network can be quickly heated and swelled by near-infrared (NIR)-responsive microneedles, resulting in precisely timed release events [48]. Additive manufacturing (3D printing) has made it possible to create intricate, layered microneedle configurations, which facilitate hybrid systems that integrate sensing, drug storage, and external responsiveness [49]. Even with advancements, ensuring both mechanical strength for penetration and effective responsiveness for drug release continues to be a significant challenge [50].

Smart and Wearable Hybrids

Intelligent and wearable hybrid technologies combine biosensors, actuators, and drug storage elements into adaptable platforms, facilitating closed-loop pulsatile drug release. These systems are capable of detecting physiological signals (such as glucose levels, temperature, and pH) and initiating on-demand drug release through built-in actuators like heaters, electrodes, or microvalves [51]. One of the most promising hybrid systems for pulsatile medication delivery and real-time monitoring is wearable microneedle patches with sensors and microelectronics [52]. The potential of these devices

for long-term, programmed drug delivery is further increased by the integration of flexible electronics with conductive nanocomposite hydrogels [53]. Wearable hybrids face several obstacles, including energy management, the downsizing of components, ensuring compatibility with biological systems, and maintaining data security within connected healthcare networks [54].

ADVANTAGES AND CHALLENGES OF HYBRID APPROACHES

PLGA-Lipid Hybrids

PLGA-lipid hybrid formulations combine the biomimetic characteristics of lipids with the structural benefits of PLGA nanoparticles, creating a promising carrier option for various difficult-to-deliver drugs. They enhance the effectiveness of personalized medicine by directing treatment to specific cell receptors, improving drug entrapment and encapsulation efficiency, while also offering a more controlled and sustained release profile due to the presence of lipid components [34]. Current PLGA-lipid hybrid nanoparticles have demonstrated high loading capabilities, exceptional stability in biological environments, and favorable in vivo performance. Their potential for designing co-delivery or multifunctional systems makes them highly researched carriers, paving the way for innovative tools in nanomedicine [55].

The primary limitations of these hybrid nanocarriers involve the challenge of predicting and accurately managing their physical and biological characteristics, in addition to issues with reproducibility, which are crucial factors in evaluating and identifying the best properties for various applications [34]. The development of PLGA-lipid hybrids for effective therapeutics is still in the early stages, and several challenges related to biological, technological, or design/manufacturing aspects remain unresolved in both research and clinical settings [55]. The technological hurdles are linked to issues of reproducibility, given the intricate nature of the engineering process. Certain PLGA-lipid hybrid formulations are generated in limited quantities, and scaling up their production can present challenges. A significant biological challenge is the ability to control and enhance the distribution of hybrid nanocarriers and their passage through biological barriers or targeted cells without compromising their therapeutic efficacy [56].

Smart Microneedles

As a developing technology, microneedles present benefits, such as painless administration, high biocompatibility, and the convenience of self-administration, making them effective for treating various conditions like diabetes, wound healing, and tumor management [57]. Microneedles can deliver active substances efficiently and with minimal invasion, without affecting blood vessels, nerve fibers, or surrounding tissues in the epidermis or dermis, thereby aiding in the healing of wounds [58]. Another promising avenue is the incorporation of microneedles for monitoring functions, leading to the creation of smart microneedles that possess dual functionalities for drug delivery and physiological tracking, allowing for accurate medication delivery [59].

These smart microneedles, which release drugs passively based on internal stimuli, encounter difficulties like decreased drug release rates and inconsistent spatial distribution [58]. The third concern pertains to safety issues. It is essential to standardize the production and regulate smart responsive microneedles. Additional foundational research is needed, encompassing tests for cytotoxicity, systemic toxicity, hemolysis, irritation, biodegradation, and carcinogenicity [59].

INDUSTRIAL AND CLINICAL POTENTIAL OF HYBRID PDDS

Industrial Potential

Factors Driving the Market and Potential Opportunities

The momentum for hybrid drug delivery systems (DDS) is being fueled by the rapid expansion of therapeutic markets, particularly in biologics (including antibodies, peptides, and nucleic acids), oncology treatments, and vaccines. These products often require advanced delivery technologies to address critical challenges such as instability, poor bioavailability, or low patient compliance. Hybrid DDS offers key benefits such as extended half-lives, reduced dosing frequency, and the ability to co-

deliver multiple therapeutic agents, making them highly attractive in high-value drug development pipelines.

For instance, polymer–lipid hybrid nanoparticles (PLHNPs) combine the biocompatibility of lipids with the sustained release properties of polymers, meeting the industry's growing demand for innovative long-acting formulations [35, 60]. Beyond pharmaceuticals, opportunities also extend into tissue engineering and regenerative medicine. Notably, conductive hybrid hydrogels that integrate gold nanostructures are under investigation as bioactive scaffolds for cardiac repair and nerve regeneration – bridging markets across pharmaceuticals, biotechnology, and medical devices [41].

Patent and Intellectual Property Landscape

Patent activity reflects the increasing commercial interest in hybrid DDS. Recent analyses highlight a sharp rise in filings involving hybrid nanoparticles, such as lipid–polymer systems, hybrid microneedle arrays, and nanoparticle–hydrogel depots [61]. These patents protect not only the compositions but also the manufacturing processes and drug–device combinations. This trend demonstrates the transition of hybrid DDS from purely academic research to proprietary innovations, laying the groundwork for licensing, strategic partnerships, and industrial applications.

Importantly, strong intellectual property clusters are forming around co-delivery designs, such as chemotherapy combined with siRNA. This suggests that combination therapies are serving as the initial entry points for commercialization efforts [61–63].

Feasibility of Manufacturing and Scaling Up

A critical factor for industrial translation is the ability to manufacture hybrid DDS at scale. Several well-established pharmaceutical techniques – such as solvent evaporation, nanoprecipitation, emulsification, spray drying, and more recently, microfluidic technologies – are being successfully adapted for this purpose. For example, lipid–polymer hybrids produced through nanoprecipitation have already been scaled to pilot-plant production with reproducible particle sizes below 200 nm [1].

Similarly, PLGA–lipid hybrids benefit from continuous microfluidic approaches, which minimize batch-to-batch variability and improve encapsulation efficiency [35]. In the case of hydrogels, in-situ nucleation methods (where nanoparticle precursors are incorporated during gelation) have proven both simple and scalable [41]. Despite remaining challenges in achieving reproducibility and precise control over hybrid interfaces, advancements in process analytical technologies (PAT) are helping monitor particle size, detect residual solvents, and track drug release, thereby supporting industrial viability [61].

Product Niches and Industrial Applications

Hybrid DDS present strong potential across multiple industrial applications.

- *Depot Injectables:* Hybrid nanoparticle–hydrogel depots extend local retention, making them highly suitable for pain management, ophthalmic disorders, and cancer therapies [41].
- *Transdermal Vaccination:* Microneedle platforms incorporating hybrid nanoparticles enable thermostability, painless delivery, and field-friendly use – attributes particularly valuable for the vaccine sector in the post-COVID-19 era [64].
- *Oral and Mucosal Delivery:* PLHNPs demonstrate improved stability in the digestive tract, creating opportunities for oral delivery of peptides and plant-derived compounds [65].
- *Regenerative Products:* Conductive hybrid hydrogels with embedded nanoparticles are emerging in tissue engineering and bioelectronic interfaces, offering applications that span pharmaceuticals and medical devices [41].

Clinical Potential

Oncology

Cancer therapy represents one of the most advanced applications of hybrid DDS. These nanoparticles enable targeted tumor delivery through both passive mechanisms, such as enhanced permeability and

retention (EPR), and active targeting via ligand modification. Hybrid systems also allow co-delivery of chemotherapeutics alongside siRNA or immunomodulators, resulting in synergistic therapeutic outcomes. Preclinical studies consistently show stronger tumor inhibition compared to single-component carriers [62, 63]. Although still largely in preclinical stages, these approaches align closely with oncology's demand for precision medicine and reduced toxicity.

Ophthalmology and Localized Treatments

Drug delivery to the eye poses significant challenges due to rapid clearance and protective tissue barriers. Hybrid DDS, such as PLGA nanoparticles integrated into hydrogels or lipid–polymer systems incorporated into contact-lens hydrogels, enable sustained intraocular release. In glaucoma models, these depots provided drug release over several weeks, outperforming hydrogels or nanoparticles alone [41]. Clinically, this could reduce injection frequency and improve adherence for chronic eye diseases.

Vaccines and Biologics

Hybrid DDS enhance the stability of fragile antigens and nucleic acids, improving the delivery of vaccines. Microneedle systems loaded with hybrid nanoparticles allow for transdermal administration of mRNA or protein vaccines, offering a painless, self-administered alternative while reducing reliance on cold-chain logistics [64]. Building on the success of lipid nanoparticle-based COVID-19 vaccines, hybrid systems are poised to become the next generation of robust and long-acting vaccine carriers [35].

Regenerative Medicine and Wound Healing

Hybrid hydrogels incorporating conductive nanoparticles are being developed as scaffolds for cardiac patches, nerve guidance conduits, and wound dressings. Their ability to deliver growth factors locally and continuously, while replicating essential mechanical and electrical cues, makes them especially promising. For example, gold nanowire–alginate hydrogels improved electrical connectivity among cardiomyocytes, demonstrating potential for myocardial repair [41]. Likewise, hybrid hydrogels with silver nanoparticles are under investigation for antimicrobial wound care.

Expanded Therapeutic Uses

Emerging research highlights opportunities in diabetes (long-acting insulin formulations), chronic pain (localized anesthetic depots), and infectious diseases (hybrid antimicrobial gels). These applications emphasize the adaptability of hybrid DDS across both acute and chronic health challenges [64].

Regulatory and Safety Considerations

Although detailed regulatory pathways are beyond the scope here, safety assessments are central to both industrial and clinical applications. Regulatory bodies require evaluation of not only individual components but also their interactions. For example, while PLGA particles alone may induce peritoneal adhesions, encapsulation within hydrogels mitigates this effect [41]. Comprehensive toxicological studies covering biodistribution, immunogenicity, and degradation products are essential.

Hybrid DDS also introduce additional complexity in analytical evaluation, making early engagement with regulatory authorities and adherence to standardized testing protocols crucial for successful translation to the clinic [35, 61].

FUTURE PERSPECTIVES FOR HYBRID PDDS

Hybrid drug delivery systems (PDDS) that combine lipids and polymers, utilize nanoparticle-hydrogel depots, and incorporate microneedles with nanoparticles advancing quickly. In the coming decade, these systems will intersect with additive manufacturing, digital health technologies, and translational frameworks, influencing the development of future therapeutic approaches.

Development of Hybrid PDDS through 3D and 4D Printing

3D Printing

Additive manufacturing facilitates customization, precise design, and on-demand creation. Integrating hybrid nanoparticles into printable materials allows for patient-specific implants,

microneedles, and oral delivery devices [66]. Stereolithography enables the manufacturing of high-resolution microneedles, while extrusion-based techniques create nanoparticle–hydrogel scaffolds for localized release [67–68].

Examples

- 3D-printed microneedle patches incorporating lipid–polymer nanoparticles for maintaining vaccine stability.
- Hydrogel reservoirs printed with integrated PLGA–lipid nanoparticles for cancer treatment [41].

4D Printing

4D printing introduces responsive behaviors to stimuli: structures can expand, contract, or reveal channels when exposed to changes in pH, temperature, or electrical fields [21].
This feature allows for,

- Pulsatile release patterns.
- Shape-modifying implants that adapt to fit tissue cavities.
- Gradual release of multiple active ingredients.

In combination, 3D and 4D printing enhances hybrid PDDS to align with personalized and programmable healthcare solutions.

Integration with Digital Therapeutics and Telemedicine

Digital therapeutics (DTx) and telemedicine have the potential to revolutionize hybrid PDDS by creating interconnected drug-delivery systems.

- *Closed-Loop Mechanisms:* A hybrid depot dispenses insulin; wearable devices track glucose levels; DTx algorithms make remote therapy adjustments [69].
- *Telemonitored Microneedles:* Printed microneedles combine biosensors, transmitting data while administering nanoparticles, allowing for distant clinician monitoring [68–69].
- *Chronic Care Frameworks:* Hybrids minimize dosing frequency; DTx enhances adherence and provides lifestyle coaching, offering combined advantages.

This combination of drug, device, and software integration encounters regulatory challenges but aligns with new software as a medical device (SaMD) standards [69].

Pathway to Successful Translation (Academia → Industry → Clinical Application)

Academic Phase

- Identify specific unmet clinical requirements and value propositions.
- Integrate design-for-manufacturability considerations from the beginning (printable inks, scalable nanoprecipitation).
- Utilize sophisticated in vitro models (organ-on-chip, skin models) to confirm release kinetics [41, 67].

Preclinical Phase

- Establish standardized characterization parameters (size, morphology, release, stability).
- Perform preclinical safety and pharmacokinetics/pharmacodynamics studies using various animal models [66].

Industry Phase

- Create scalable Good Manufacturing Practice (GMP) processes (microfluidics, 3D printing).
- Implement process analytical technology (PAT) to ensure consistency and regulatory adherence.
- Involve regulators early for the classification of combination products (drug–device–software) [66, 70].

Clinical and Commercial Phase

- Initiate first-in-human feasibility trials, progressing to adaptive designs suited for real-world environments.
- Utilize telemedicine-enabled monitoring to enhance access and streamline data collection.
- Establish post-market surveillance utilizing digital health platforms to improve safety and efficacy.

Frameworks, such as the DELIVER roadmap for nanomedicine, underscore milestones aimed at reducing translational risk and connecting laboratory innovations to clinical effectiveness [66, 70].

CONCLUSIONS

Hybrid pulsatile drug delivery systems (Hybrid-PDDS) signify an exciting advancement in traditional pulsatile delivery methods, enhancing reliability and therapeutic effectiveness by incorporating various release mechanisms. By utilizing time-, stimulus-, and device-based triggers, hybrid PDDS address the shortcomings of single-mode systems, enabling controlled, site-specific, and consistent drug delivery. Their adaptability has made them strong candidates for tackling intricate clinical challenges, such as conditions that depend on circadian rhythms, localized treatments, and the administration of delicate biologics. In addition to their clinical applications, hybrid systems hold industrial significance due to their suitability for scalable manufacturing processes and the potential for patentable innovations, which aligns with the requirements of high-value therapeutic markets. Nonetheless, challenges such as ensuring material consistency, large-scale production, long-term compatibility with biological systems, and navigating regulatory complexities persist. Advancements in technologies, such as additive manufacturing, nanotechnology, wearable devices, and the integration of digital health, are anticipated to expedite the clinical implementation of hybrid PDDS, shaping the future of personalized, programmable, and interconnected drug delivery.

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