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Advances in gastroretentive drug delivery systems: Formulation strategy and therapeutic applications

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Abstract

Gastroretentive drug delivery systems (GRDDS) have emerged as a promising approach to enhance the bioavailability and therapeutic efficacy of orally administered drugs, especially those with a narrow absorption window or those susceptible to rapid gastrointestinal transit. This systems which may retained in the stomach for a prolonged period of time and thereby improve the bioavailability of drugs and inturn achieve the desired outcome. This review provides a comprehensive overview of the various gastro retentive drug delivery systems, including their formulation strategies, mechanisms of retention, and applications in drug delivery. Their breakthrough into this drug delivering field had played a pivotal role in further developing the new strategies which we were facing problems in passing the clinical trials phases. Mainly we should focus on the Selection of the right technology for the right purpose through the right mechanism of action for attaining the end system with desired therapeutic outcomes. Several examples of recently available GRDDS systems as marketed formulation.

Keywords: Bioavailability; Therapeutic window; Gastric emptying; Residence time; Buoyancy; Bioadhesion; Expansion; High-density formulation

1. Introduction

Gastroretentive Drug Delivery Systems (GRDDS) are innovative formulations designed to prolong the residence time of drugs in the stomach, enhancing bioavailability and therapeutic efficacy. It is an innovative approach in pharmaceutical formulation, aiming to address challenges associated with drug delivery in the gastrointestinal tract. These systems are designed to prolong the residence time of drugs within the stomach, offering controlled release and enhanced bioavailability. These systems find applications across a spectrum of pharmaceuticals, offering tailored solutions for enhanced drug delivery and targeted treatments.[1,2,3] The key differences between conventional drug delivery systems and Gastroretentive Drug Delivery Systems (GRDDS) which lies on the gastric transit time, drug release, absorption, and retention in the gastrointestinal tract are represented in the Table 1 [4,5,6]

1.1. Advantages [7]

- Enhanced Bioavailability: GRDDS prolong the residence time of drugs in the stomach, allowing for controlled and sustained release. This can enhance the absorption of drugs with limited solubility or those requiring specific conditions for optimal uptake.
- Improved Therapeutic Efficacy: The controlled release provided by GRDDS helps maintain therapeutic drug levels in the body over an extended period. This can lead to more consistent pharmacological effects, reducing fluctuations in drug concentration and improving overall therapeutic efficacy.
- Reduced Variability in Plasma Drug Levels: GRDDS minimize fluctuations in drug concentration, providing a

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more predictable and sustained release profile. This is particularly advantageous for drugs with a narrow therapeutic window, where maintaining consistent plasma levels is critical for safety and efficacy.

- Targeted Drug Delivery: GRDDS can be designed to release drugs at specific locations in the gastrointestinal tract. This targeted delivery is beneficial for drugs that are absorbed in particular regions, leading to localized therapeutic effects.
- Patient Compliance: The prolonged release offered by GRDDS often allows for less frequent dosing, improving patient compliance and convenience. Reduced dosing frequency can contribute to better adherence to treatment regimens.
- Treatment of Gastrointestinal Conditions: GRDDS are particularly useful for drugs treating conditions within the gastrointestinal tract, such as peptic ulcers or inflammatory bowel diseases. By ensuring prolonged contact with the affected area, these systems enhance the therapeutic effectiveness of such drugs.
- Minimization of Side Effects: Controlled release can help minimize side effects associated with high peak concentrations of drugs. By maintaining drug levels within the therapeutic range, GRDDS may reduce the likelihood of adverse reactions.

Table 1 Comparison between conventional DDS and gastroretentive DSS

Sl.no	Conventional Drug Delivery Systems	Gastroretentive Drug Delivery Systems (GRDDS)
1	Gastric Transit Time: Conventional systems do not specifically target or control gastric transit time.Rapid transit through the stomach may limit drug absorption, especially for drugs requiring sustained release or those with specific absorption sites.	Gastric Transit Time: GRDDS are designed to prolong gastric residence time, ensuring that the drug remains in the stomach for an extended period.Targeted delivery to the upper gastrointestinal tract allows for optimal drug absorption.
2	Drug Release: Release patterns are typically not tailored to the physiological conditions of the gastrointestinal tract. Drug release may occur in various segments of the gastrointestinal tract, leading to unpredictable absorption profiles.	Drug Release: GRDDS offer controlled and sustained drug release, often tailored to the specific physiological conditions of the stomach.The release profile is optimized for improved bioavailability and therapeutic efficacy.
3	Bioavailability: Variability in drug absorption may occur due to factors such as gastric emptying rate and the presence of food, impacting overall bioavailability. Limited bioavailability may result in the need for higher doses or more frequent administration.	Bioavailability: Enhanced bioavailability is a key advantage of GRDDS due to the controlled release and prolonged residence time in the stomach. The predictability of drug absorption can lead to improved therapeutic outcomes and reduced variability.
4	Retention Mechanisms: Rely on normal gastrointestinal transit for drug delivery. Lack specific mechanisms for prolonged retention in the stomach.	Retention Mechanisms: Utilize various mechanisms such as buoyancy, bio adhesion, expansion, or high-density formulation to achieve prolonged gastric retention. These mechanisms ensure that the dosage form remains in the stomach, facilitating controlled drug release.

- Flexibility in Formulation: GRDDS offer flexibility in formulation design, allowing for the incorporation of various mechanisms such as floating, bioadhesion, or expansion. This adaptability enables the optimization of drug delivery based on the specific characteristics of the drug and the desired therapeutic outcomes.
- Potential for Localized Treatment: GRDDS can be tailored for localized drug delivery, allowing for focused treatment of specific areas within the gastrointestinal tract. This is advantageous for diseases or conditions that primarily affect localized regions.
- Optimization of Drug Therapy for Individual Patients: The customization potential of GRDDS allows for tailoring drug delivery to individual patient needs, promoting personalized medicine approaches and optimizing therapeutic outcomes.

1.2. Disadvantages [8,9,10,11]

- Inter- and Intra-patient Variability: Gastric emptying times can vary significantly among individuals and may

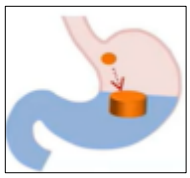
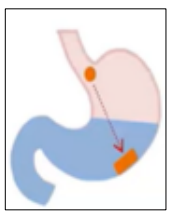
change within the same individual under different conditions. This variability can impact the effectiveness of GRDDS, as their performance relies on predictable gastric residence times.

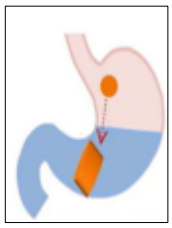
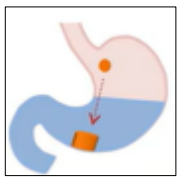
- Influence of Food: The presence of food in the stomach can affect the performance of GRDDS. Food intake may alter gastric emptying rates, potentially leading to inconsistent drug release and absorption.
- Formulation Complexity: Designing effective GRDDS often requires sophisticated formulation techniques, which can increase the complexity and cost of drug development. Achieving the desired balance of buoyancy, bioadhesion, or expansion while maintaining stability and safety is a challenging task.
- Potential for Incomplete Gastric Emptying: In some cases, GRDDS may not completely empty from the stomach, leading to the possibility of accumulation and potential complications. Incomplete gastric emptying could affect subsequent drug doses and may pose a risk of overdose.
- Risk of Gastrointestinal Irritation: Some formulations of GRDDS, particularly those using bioadhesive mechanisms, may pose a risk of irritation to the gastrointestinal mucosa. Prolonged contact with the gastric lining may lead to localized irritation or inflammation.
- Limited Applicability to All Drugs: Not all drugs are suitable candidates for GRDDS. Some drugs may not benefit from prolonged residence in the stomach, and the formulation may not be compatible with the drug's physicochemical properties.
- Potential for Incomplete Drug Release: Factors such as the variability in gastric pH, gastric motility, and the presence of food can influence the release of drugs from GRDDS. This variability may lead to incomplete drug release and affect therapeutic outcomes.
- Patient Acceptance and Compliance: The need for patients is to understand and follow specific administration instructions for GRDDS may pose challenges to acceptance and compliance. Patients may find it challenging to adhere to specific dosing requirements, impacting the effectiveness of treatment.
- Risk of Device Malfunction: Some GRDDS incorporate mechanisms such as floating devices, which may malfunction or lose buoyancy under certain conditions. This could lead to premature drug release or inadequate retention.
- Limited Application to Lower Gastrointestinal Conditions: GRDDS are primarily designed for gastric retention and may not be suitable for conditions in the lower gastrointestinal tract. Targeting drugs to specific regions within the gastrointestinal system may require different delivery strategies.

2. Formulation strategies of GRDDS

GRDDS achieve gastroretention through various mechanisms, which includes buoyancy, bioadhesion, expansion, and high-density formulation. Each mechanism has its unique advantages, allowing for tailored approaches based on the characteristics of the drug and therapeutic requirements. Mechanism of each GRDDS system is explained in the table 2.

Table 2 Summarized mechanisms of the various GRDDS

Sl No	GRDDS Systems	Mechanism
1	 **Floating Systems**	Floating GRDDS rely on the principle of buoyancy to remain afloat on the gastric contents, ensuring prolonged drug release. Formulations often incorporate gas-generating agents or low-density materials, providing the necessary buoyancy.[12,13,14,15]
2	 **Bioadhesive system**	Bioadhesive GRDDS employ mucoadhesive polymers that adhere to the gastric mucosa, promoting retention through adhesive interactions. This strategy is particularly useful for drugs requiring intimate contact with the mucosal surface for enhanced absorption[12,16].

3	 **Expandable Systems**	Expandable Systems increase the size when come in condact with the gastric fluids. This expansion promotes retention through mechanical means, preventing premature transit through the gastrointestinal tract.[12,16]
4	 **High-Density Systems**	There will be a difference in density between the dosage form and gastric contents, high-density GRDDS ensure retention in the stomach. This approach is often employed with metal or dense materials incorporated into the formulation.[12]

3. Floating systems

Floating GRDDS mainly depend up on the principle of buoyancy to remain as a float on the gastric contents, ensuring prolonged drug release. This formulations often incorporate gas-generating agents or low-density materials, providing the necessary buoyancy [17,18]. The fundamental principle behind the floating GRDDS is buoyancy, which enables the dosage form to float on the gastric contents, thereby prolonging its residence time in the stomach. As a result, the dosage form remains a float, ensuring controlled release of the drug over an extended period [19].

3.1. Formulation Strategies of floating GRDDS:

- **Gas-Generating Systems:** Incorporate effervescent agents, such as bicarbonates and carbonates that react with gastric fluids to produce carbon dioxide then creating buoyancy. Gas entrapment systems encapsulate a volatile liquid or gas, generating buoyancy upon contact with gastric contents.[20,21,22]
- **Low-Density Systems:** Utilize hollow microspheres or porous matrices with low-density cores, allowing the dosage form to float on gastric fluids. These systems capitalize on the physical properties of the formulation to achieve buoyancy.
- **Bioadhesive Systems:** Employ mucoadhesive polymers that adhere to the gastric mucosa, preventing premature transit and facilitating sustained buoyancy. In this Bioadhesive microspheres or nanoparticles enhance adhesion to the mucosal surface, prolonging gastric residence time.
- **Expandable Systems:** Swelling systems contain hydrophilic polymers that swell upon contact with gastric fluids, leading to an increase in size and buoyancy. Unfolding systems incorporate dosage forms that expand or unroll in the stomach, promoting buoyancy through increased surface area.

4. Bioadhesive systems

Bioadhesive GRDDS are formulations system designed to adhere to the mucosal surfaces of the gastrointestinal tract, particularly the stomach [13]. These systems employ bioadhesive polymers that have an affinity for the mucin layer present on the gastrointestinal mucosa. The purpose of using bioadhesive materials is to enhance the adherence of the dosage form to the mucosal surface, promoting prolonged contact and retention in the stomach [23, 24]. Theories of mucoadhesion provide insights into the mechanisms underlying the adhesion of polymeric materials to mucosal surfaces in the table 3. [1,25]

Table 3 Mechanisms of bioadhersion/ mucoadhesion

Sl.no	Bioadhesion theory	Meachansim
1	Electronic Theory	According to the Electronic Theory, mucoadhesion is influenced by electronic interactions between charged groups on the mucosal surface and the mucoadhesive polymer. Electrostatic forces, including ion-dipole and dipole-dipole interactions, play a role in the adhesion process [26,27].
2	Adsorption Theory	The Adsorption Theory suggests that mucoadhesion involves the physical adsorption of polymer chains onto the mucosal surface. This theory emphasizes the importance of establishing close contact and intimate association between the polymer and mucin molecules [28].
3	Wetting Theory	The Wetting Theory focuses on the wetting properties of mucoadhesive polymers. Wetting helps in spreading the polymer over the mucosal surface, promoting contact and adhesion. Enhanced wetting is associated with improved mucoadhesion[29,30]
4	Diffusion Theory	According to the Diffusion Theory, the mucoadhesive polymer chains diffuse into the mucus layer and establish interactions with mucin molecules. Due to the diffusion of polymer chains into the mucosal layer contributes to the adhesive strength [31,32].
5	Fracture Theory	The Fracture Theory, also known as the Peel Adhesion Theory, is based on the concept that mucoadhesion involves the formation of numerous micro-bonds between the polymer and mucosal surface. The strength of these micro-bonds determines the adhesive forces[33]

4.1. Formulation Strategies of bioadhesive GRDDS

The goal of the bioadhesive GRDDS is to is to enhance adhesion to the gastric mucosa, prolong residence time in the stomach, and achieve controlled drug release. The key formulation strategies associated with Bio adhesive GRDDS are listed below [12,13]

- **Selection of Bioadhesive Polymers:** In this approach we Choose a bioadhesive polymers which is well known for their mucosal adhesion properties. Examples include hydroxypropyl methylcellulose (HPMC), sodium carboxymethyl cellulose (NaCMC), and chitosan, alginate, and polyacrylic acids. The nature and concentration of the polymer based on the specific requirements of the drug and the targeted gastrointestinal site are the other important factor [34].
- **Combination of Bioadhesive and Gastroretentive Polymers:** In this are mixing the bioadhesive polymers with gastroretentive polymers to create a synergistic effect. Gastro retentive polymers like hydroxypropyl cellulose (HPC), carbomer, or polymethacrylates contribute to buoyancy and retention. It will achieve a balance between adhesion and buoyancy for optimal gastroretentive performance [35].
- **Bioadhesive Hydrogel Formulations:** Develop hydrogel formulations containing bioadhesive polymers. Hydrogels provide a swellable matrix that adheres well to the mucosal surface and helps in controlled drug release.Incorporate hydrophilic polymers for enhanced swelling and bioadhesion.[36,37,38,]
- **Mucoadhesive Microspheres or Nanoparticles:** Formulate microspheres or nanoparticles loaded with bioadhesive polymers. These particles adhere to the gastric mucosa, promoting prolonged drug release. Optimize the size and surface characteristics of particles for effective adhesion [39,40].
- **Bioadhesive Gastro retentive Tablets or Patches:** Develop tablets or patches that combine bioadhesive and gastroretentive properties. These dosage forms adhere to the gastric mucosa and provide sustained drug release. With a patch or tablet design that facilitates adhesion and minimizes the risk of premature detachment [41, 42, 43, 44, 45].
- **Thiolated Polymers:** Incorporation of thiolated polymers into the GRDDS formulation. The Thiolation enhances the bioadhesion by forming disulfide bonds with mucin proteins on the mucosal surface.These Polymers also contribute both mucoadhesion and gastroretentive properties [46,47.]
- **Bioadhesive Gastroretentive Capsules:** Development of capsules that have the combined property of both bioadhesive and gastroretentive features. These capsules adhere to the gastric mucosa and remain buoyant in the stomach, ensuring prolonged drug release.it can be also modified by incorporating gas-generating agents for additional buoyancy.[48,49]
- **Surface Modification Techniques:** Applying the surface modification techniques to enhance the adhesion of dosage forms. Coating tablets or particles with bioadhesive polymers improves their interaction with the

mucosal surface the methods like spray coating or dip coating for uniform surface modification [50,51].

- **Hydrodynamically Balanced Systems:** Design hydrodynamically balanced systems that achieve equilibrium between buoyancy and adhesion. This ensures that the dosage form remains to float and adheres to the gastric mucosa simultaneously. For this we have to optimize the density and geometry of the dosage form for hydrodynamic balance [52,53,54].
- **pH-Sensitive Bioadhesive Systems:** Development of pH-sensitive formulations which having the bioadhesive properties. The pH-sensitive polymers can enhance adhesion at specific pH levels in the gastrointestinal tract. This system can develop using the polymers that respond to the gastric pH for optimal adhesion and drug release [55,56].

5. Expandable GRDDS

Expandable GRDDS represent a sophisticated approach to drug delivery, particularly for medications that require prolonged gastric residence time. These systems are designed to work on the mechanism of expansion or swelling upon contact with gastric fluids, thereby increasing their size and promoting retention in the stomach for an extended period. The prolonged residence time in the stomach enhances the bioavailability of drugs, leading to improved therapeutic outcome [57,58]. This is especially important for drugs with poor solubility or low permeability that require sufficient time for absorption. This systems can be designed to target specific regions of the gastrointestinal tract, providing localized drug delivery as needed which enables the treatment of conditions affecting the stomach or proximal intestine while minimizing systemic exposure and side effects[59,60,61].

5.1. Formulation Strategies of bioadhesive GRDDS

Formulation strategies for Expandable GRDDS involve carefully designing dosage forms that can expand or swell upon contact with gastric fluids to prolong gastric residence time and optimize drug delivery [62,63].

- Selection of Swelling Polymers: Swelling polymers play a crucial role in expandable GRDDS formulations. These polymers absorb water or gastric fluids, leading to an increase in volume and the formation of a gel-like matrix. Common swelling polymers include hydroxypropyl methylcellulose (HPMC), sodium alginate, polyethylene oxide (PEO), and Carbopol®. The choice of polymer depends on factors such as swelling capacity, biocompatibility, and drug release kinetics [64,65].
- Incorporation of Floating Agents: Expandable GRDDS formulations often include floating agents to ensure buoyancy in the stomach and prevent premature gastric emptying. Floating agents such as gas-generating agents (e.g., sodium bicarbonate, citric acid) or low-density materials (e.g., microcrystalline cellulose, calcium silicate) are incorporated into the dosage form to promote floatation on the gastric fluid surface [66,67].

6. High density system

High-density Gastro-Retentive Drug Delivery Systems (GRDDS) are innovative formulations designed to prolong gastric residence time and optimize drug delivery within the gastrointestinal tract which often rely on buoyancy or swelling mechanisms to remain in the stomach [68]. It utilize the materials with higher density to achieve gastric retention. High-density materials such as barium sulfate, bismuth subcarbonate, or heavy metal salts are commonly used in the formulation of high-density GRDDS. These materials have a higher specific gravity compared to gastric fluids, enabling them to sink and remain in the stomach for an extended period [69].

6.1. Formulation Strategies of high density GRDDS[70]

- Material Selection: Choose materials with high density, such as barium sulfate, bismuth subcarbonate, or heavy metal salts. These materials ensure that the dosage form sinks in gastric fluids and remains in the stomach for an extended period, promoting gastric retention.
- Dosage Form Design: Develop dosage forms that maintain structural integrity while incorporating high-density materials. Tablets, capsules, or multiparticulate systems can be formulated to achieve the desired density and drug release characteristics.

6.2. Approaches to the GRDDS

To enhance the gastroretention of the drugs different approaches have been established By employing the various approaches in gastroretentive drug delivery systems development it offer several advantages, including improved drug bioavailability, reduced dosing frequency, and enhanced therapeutic efficacy for drugs with absorption challenges in the upper gastrointestinal tract[71].

Table 4 Recently available marketed formulation of GRDDS systems under different approaches for particular diseases conditions and its mode of action

Sl.no	APPROACHES	Disease condition	Example/Type of system	Mode of action (MOA)
1	**FLOATING GRDDS**	Gastroesophageal Reflux Disease (GERD)	Omeprazole Floating Capsules	GERD often requires sustained acid suppression. Floating omeprazole formulations can provide prolonged release, maintaining therapeutic drug levels to alleviate symptoms and promote healing.
		Peptic Ulcer Treatment	Ranitidine Floating Tablets	Floating ranitidine formulations can enhance the local concentration of the drug in the stomach, ensuring sustained release for the treatment of peptic ulcers and related conditions.
		Anti-Inflammatory Drugs for Gastric Conditions:	Floating Diclofenac Sodium Tablets	GRDDS can be utilized for delivering anti-inflammatory drugs to the stomach, providing targeted relief for gastric conditions without the need for frequent dosing.
2	**BIOADHESIVE GRDDS**	Oral Bioadhesive Tablets:	Metformin Bioadhesive Tablets	Extended-release metformin tablets with bioadhesive properties can adhere to the gastric mucosa, providing controlled release for improved glycemic control in patients with diabetes.
		Nasal Bioadhesive Sprays:	Sumatriptan Nasal Bioadhesive Spray	Bioadhesive nasal sprays of sumatriptan can provide a non-invasive route for migraine treatment. The bioadhesive nature ensures prolonged contact with the nasal mucosa for enhanced drug absorption.
		Ocular Bioadhesive Inserts:	Timolol Ocular Bioadhesive Inserts	Bioadhesive inserts for ocular delivery of timolol can provide sustained release, improving the treatment of glaucoma by reducing intraocular pressure.
3	**EXPANDABLE GRDDS**	Coronary Artery Disease (CAD)	Percutaneous Coronary Intervention (PCI) and Stent Implantation Drug-Eluting Stent (DES)	The expandable DES is a small, mesh-like metal tube mounted on a balloon catheter. During PCI, the deflated balloon catheter with the stent is inserted into the narrowed coronary artery. Once positioned at the target site, the balloon is inflated, expanding the stent and compressing the plaque against the artery walls. The expanded stent remains in place, acting as a scaffold to keep the artery open and allow for improved blood flow.
		Peptic Ulcer	Expandable Hydrogels	Expandable hydrogels loaded with peptic ulcer medication are designed to swell in the stomach upon hydration, forming a gel-like mass. This hydrogel adheres to the gastric mucosa, providing prolonged drug release and enhanced therapeutic efficacy for the treatment of peptic ulcers.
		Allergic Rhinitis	Expandable Nasal Inserts	Expandable nasal inserts containing antihistamines are designed to expand upon insertion into the nasal cavity. The inserts adhere to the nasal mucosa, providing sustained release of the medication to alleviate symptoms of allergic rhinitis, such as sneezing and nasal congestion, over an extended period.

4	**HIGH DENSITY GRDDS**	Peptic ulcers, gastroesophageal reflux disease (GERD)	Carafate (Sucralfate) Suspension	Carafate contains sucralfate, a complex of aluminum hydroxide and sulfated sucrose. Upon oral administration, sucralfate forms a protective barrier over ulcerated mucosa, promoting healing and providing symptomatic relief. Its high viscosity and adherent properties aid in gastric retention, allowing prolonged contact with the gastric mucosa for enhanced efficacy.
		Gastroesophageal reflux disease (GERD), heartburn	Gaviscon (Alginate-Antacid Suspension)	Gaviscon contains alginate, an anionic polysaccharide derived from seaweed, along with antacids. Upon contact with gastric acid, alginate forms a gel-like raft that floats on the stomach contents, acting as a physical barrier to reflux. The high viscosity and density of the raft promote gastric retention, providing sustained relief from acid reflux symptoms.
		Diarrhea, indigestion	Kaopectate (Bismuth Subsalicylate Suspension)	Coats the stomach lining to alleviate symptoms of diarrhea and indigestion. The suspension's high density promotes gastric retention, allowing prolonged contact with the gastrointestinal mucosa for enhanced efficacy.

7. Conclusion

Advancement in gastroretentive drug delivery systems (GRDDS) have significantly contributed to overcoming challenges associated with conventional drug delivery and have opened new avenues for therapeutic applications. Formulation strategies such as floating systems, bioadhesive systems, expandable systems, and mucoadhesive systems have been developed to enhance gastric retention and improve drug release profiles. These strategies offer several advantages, including prolonged residence time in the stomach, controlled drug release, enhanced bioavailability, and targeted delivery to specific regions of the gastrointestinal tract. The therapeutic applications of GRDDS are extensive and diverse, spanning various medical conditions such as gastrointestinal disorders, peptic ulcer disease, central nervous system disorders, and localized treatments. GRDDS have demonstrated promising outcomes in improving patient compliance, reducing side effects, and enhancing therapeutic efficacy. Moreover, the customizable nature of GRDDS allows for tailored formulations based on the unique requirements of different drugs and patient populations.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no conflicts of interest.

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