

Design and Optimization of Floating Pulsatile Drug Delivery System in Nocturnal Acid Secretion

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ABSTRACT

Gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD) are major global health concerns in which nocturnal acid secretion plays a critical role in symptom recurrence and mucosal damage. Conventional therapies such as proton pump inhibitors (PPIs) and H₂ receptor antagonists (H₂RAs) often fail to provide adequate night-time acid suppression due to their inability to align with circadian rhythms of gastric acid secretion. This limitation has led to the development of chronotherapeutic drug delivery systems designed to synchronize drug release with biological rhythms. Floating pulsatile drug delivery systems (FPDDS) combine prolonged gastric retention with time-dependent drug release, ensuring drug availability during peak nocturnal acid secretion. These systems utilize hydrophilic and hydrophobic polymers to control lag time and release kinetics, while buoyancy is achieved through effervescent or swellable mechanisms. Optimization using Design of Experiments (DoE) enhances formulation efficiency, and evaluation through in vitro and in vivo studies confirms their effectiveness. Clinically, FPDDS offer improved nocturnal acid suppression, enhanced mucosal healing, reduced dosing frequency, and better patient compliance. Thus, FPDDS represent a promising chronotherapeutic approach for managing nocturnal acid-related disorders.

Keywords: GERD, PUD, Chronotherapy, Floating systems, Pulsatile release, Nocturnal acid

INTRODUCTION

Gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD) are among the most prevalent acid-related gastrointestinal disorders worldwide, significantly affecting patient quality of life and imposing a considerable burden on healthcare systems [1]. These conditions arise primarily due to an imbalance between aggressive factors such as gastric acid, pepsin, and bile salts, and defensive mechanisms including mucosal barrier integrity, bicarbonate secretion, and prostaglandin-mediated protection [2]. Despite advancements in pharmacotherapy, including the widespread use of proton pump inhibitors (PPIs) and H₂ receptor antagonists (H₂RAs), the effective management of these disorders remains challenging, particularly due to the persistence of nocturnal symptoms [3]. A critical yet often under-recognized contributor to the

pathophysiology of GERD and PUD is nocturnal acid secretion, which refers to the sustained production of gastric acid during the night when physiological defense mechanisms are diminished [4]. During sleep, several protective processes are significantly reduced, including salivary secretion, swallowing frequency and esophageal peristalsis. These changes lead to prolonged exposure of the esophageal and gastric mucosa to acidic contents, thereby increasing the risk of mucosal damage and symptom exacerbation [5]. In patients with GERD, the supine position during sleep further facilitates the backflow of gastric contents into the esophagus, resulting in prolonged acid exposure, epithelial injury, and sleep disturbances [6]. Similarly, in PUD, particularly duodenal ulcers, increased nocturnal acid secretion prolongs mucosal exposure to aggressive factors, delaying healing and contributing to disease recurrence [7].

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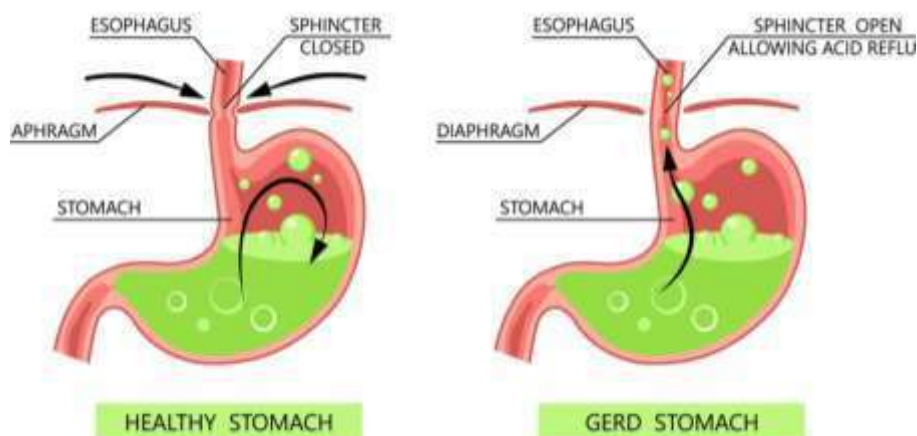


Figure 1: Gastroesophageal Reflux Disease

One of the most significant clinical challenges associated with nocturnal acid secretion is the phenomenon of nocturnal acid breakthrough (NAB), which is defined as a drop in intragastric pH below 4 for at least one hour during the night, even in patients undergoing PPI therapy [8]. This condition highlights the limitations of conventional acid-suppressive therapies, which are primarily designed to control daytime acid secretion but fail to provide adequate night-time coverage. The reduced efficacy of PPIs at night is attributed to their short plasma half-life and their requirement for activation in actively secreting parietal cells, which are less active during nocturnal periods [9]. Consequently, there exists a mismatch between the pharmacokinetic profile of conventional drugs and the circadian rhythm of gastric acid secretion, leading to incomplete symptom control and increased risk of complications such as erosive esophagitis and Barrett's esophagus [10]. The concept of chronotherapy has emerged as a promising approach to address these limitations by aligning drug delivery with the body's biological rhythms [11]. Chronotherapy is based on the understanding that physiological processes, including gastric acid secretion, gastrointestinal motility, and mucosal blood flow, exhibit circadian variations that influence disease activity and drug response [12]. In the context of acid-related disorders, chronotherapeutic strategies aim to deliver drugs at specific times when acid secretion is at its peak, particularly during night-time, thereby enhancing therapeutic efficacy and minimizing adverse effects [13]. However, achieving precise time-dependent drug release through conventional oral dosage forms remains a significant challenge due to factors such as variable gastric

emptying rates, gastrointestinal transit time, and drug degradation in the acidic environment of the stomach [14]. To overcome these challenges, advanced drug delivery systems such as pulsatile drug delivery systems (PDDS) and floating drug delivery systems (FDDS) have been developed. PDDS are designed to release drugs after a predetermined lag time, followed by a rapid release phase, thereby enabling synchronization of drug delivery with circadian rhythms or disease activity cycles [15]. These systems utilize various mechanisms, including rupturable coatings, osmotic pressure, swelling, and erosion-based approaches, to achieve controlled lag time and targeted drug release [16]. On the other hand, FDDS are gastro-retentive systems that remain buoyant in gastric fluids for extended periods, thereby prolonging gastric residence time and enhancing drug absorption in the upper gastrointestinal tract [17]. The floating mechanism is typically achieved through the incorporation of low-density excipients or gas-generating agents, which reduce the density of the dosage form and prevent its premature passage into the intestine [18]. The integration of pulsatile and floating mechanisms has led to the development of floating pulsatile drug delivery systems (FPDDS), which represent a novel and highly effective approach for managing nocturnal acid secretion [19]. These systems combine the advantages of prolonged gastric retention and time-controlled drug release, ensuring that the drug remains in the stomach during the lag phase and is released at the desired time, typically during peak nocturnal acid secretion [20]. By synchronizing drug release with circadian rhythms, FPDDS provide improved therapeutic outcomes, reduced dosing frequency, and enhanced patient compliance compared to conventional dosage forms

[21]. Furthermore, the application of FPDDS is particularly beneficial for drugs that exhibit narrow absorption windows in the upper gastrointestinal tract or are intended for local action in the stomach, such as PPIs, H₂RAs, and certain antibiotics [22]. The ability of these systems to maintain drug concentration in the gastric region and release it in a pulsatile manner enhances bioavailability and therapeutic efficacy while minimizing systemic side effects [23]. Additionally, advancements in polymer science, formulation techniques, and optimization strategies such as Design of Experiments (DoE) have further improved the performance and reproducibility of these systems [24,25].

Chronobiology of Nocturnal Acid Secretion:

Gastric acid secretion is a highly regulated physiological process that follows a distinct circadian rhythm governed by the body's internal biological clock. This rhythm is primarily controlled by the suprachiasmatic nucleus (SCN) located in the hypothalamus, which coordinates peripheral clocks in various organs, including the gastrointestinal tract [25]. The SCN integrates environmental cues such as light–dark cycles and synchronizes neural, hormonal, and molecular pathways that regulate gastric functions, including acid secretion, motility, and mucosal defense. As a result, gastric acid production exhibits predictable diurnal variation, with relatively lower secretion during daytime feeding periods and significantly increased secretion during night-time

fasting [26]. During the nocturnal phase, several physiological mechanisms converge to enhance gastric acid secretion. One of the primary contributors is increased vagal tone, which stimulates the release of acetylcholine, a key neurotransmitter that directly activates parietal cells through muscarinic receptors [27]. This neural stimulation is further amplified by hormonal regulation, particularly through increased secretion of gastrin, a potent stimulator of gastric acid production. Simultaneously, the inhibitory hormone somatostatin, which normally suppresses acid secretion, is reduced during night-time, thereby removing a critical regulatory brake on acid output [28]. The combined effect of enhanced vagal activity, increased gastrin levels, and decreased somatostatin results in a marked elevation of gastric acid secretion during the night. In addition to neural and hormonal influences, circadian variations in endocrine factors such as melatonin and cortisol also play a significant role in modulating gastric physiology. Melatonin levels typically rise during night-time and exert protective effects on the gastric mucosa through antioxidant activity and enhancement of mucosal blood flow [29]. However, despite these protective mechanisms, the concurrent increase in acid secretion often outweighs mucosal defense, particularly in pathological conditions. Cortisol, on the other hand, follows a circadian pattern with peak levels occurring in the early morning hours, which further contributes to acid secretion and may exacerbate early morning symptoms in acid-related disorders [30].



Figure 2: Potential Causes for Acid Reflux

The impact of nocturnal acid secretion is further intensified by the reduction of physiological defense mechanisms during sleep. Salivary secretion, which normally provides bicarbonate ions for neutralizing gastric acid, is significantly decreased at night. Additionally, swallowing frequency and esophageal peristalsis are reduced, leading to prolonged contact of acid with the esophageal mucosa [31]. In patients with gastroesophageal reflux disease (GERD), the supine position during sleep facilitates the backflow of gastric contents into the esophagus, resulting in prolonged acid exposure, mucosal injury, and sleep disturbances [32]. Similarly, in peptic ulcer disease (PUD), increased nocturnal acid secretion interferes with mucosal healing processes, particularly in duodenal ulcers, where prolonged exposure to acid delays tissue repair [33]. A critical clinical manifestation of disrupted chronobiology in acid secretion is nocturnal acid breakthrough (NAB), which is defined as an intragastric pH below 4 for at least one hour during the night, even in patients receiving proton pump inhibitor (PPI) therapy [34]. NAB represents a significant limitation of conventional pharmacotherapy and highlights the mismatch between drug action and circadian physiology. Proton pump inhibitors, although highly effective during daytime, exhibit reduced efficacy at night due to their short plasma half-life and dependence on active proton pumps for activation. Since many parietal cells remain inactive during nocturnal periods, the effectiveness of PPIs is diminished, resulting in inadequate acid suppression [35]. From a molecular perspective, circadian regulation of gastric acid secretion is also influenced by clock genes such as CLOCK, BMAL1, PER, and CRY, which are expressed in gastric tissues and regulate cellular functions in a time-dependent manner [36]. Disruption of these genes, due to factors such as irregular sleep patterns, night-shift work, or lifestyle changes, can alter the timing and magnitude of acid secretion, leading to increased susceptibility to acid-related disorders. This molecular interplay between circadian biology and gastric physiology further emphasizes the importance of maintaining synchronization between biological rhythms and therapeutic interventions [37]. Moreover, the consequences of persistent nocturnal acid secretion extend beyond gastrointestinal symptoms and may involve systemic complications. Chronic exposure to

gastric acid during night-time has been associated with microaspiration into the upper respiratory tract, contributing to respiratory conditions such as chronic cough, laryngopharyngeal reflux, and nocturnal asthma [38]. Additionally, recurrent acid exposure can activate inflammatory pathways involving cytokines and reactive oxygen species, leading to oxidative stress, mucosal damage, and impaired tissue repair [39]. The bidirectional relationship between sleep disturbances and acid reflux further complicates disease management, as disrupted sleep can alter autonomic regulation and exacerbate acid secretion, creating a vicious cycle [40]. Given the complex interplay between circadian rhythms, neural and hormonal regulation, and pathological outcomes, it is evident that effective management of nocturnal acid secretion requires therapeutic strategies that align with the body's biological timing. Chronotherapeutic approaches, particularly those involving modified-release and pulsatile drug delivery systems, offer a promising solution by ensuring drug availability during peak acid secretion periods [41]. By restoring synchronization between pharmacological action and physiological rhythms, these strategies have the potential to significantly improve clinical outcomes, enhance mucosal healing, and reduce the recurrence of symptoms in acid-related disorders [42].

Strategies for Chronotherapy Drug Delivery:

Advancements in pharmaceutical sciences have led to the development of innovative drug delivery strategies aimed at aligning therapeutic outcomes with the body's circadian rhythms. Conventional drug delivery systems, particularly sustained-release and controlled-release formulations, are designed to maintain relatively constant plasma drug concentrations over extended periods. While this approach is beneficial for many chronic conditions, it often fails to address diseases exhibiting circadian variability, such as gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD), where symptom severity and physiological processes fluctuate over a 24-hour cycle [43,44]. As a result, these traditional systems may lead to suboptimal drug levels during periods of peak disease activity, particularly during night-time, while causing unnecessary drug exposure during periods of low activity [45]. To overcome these limitations, chronotherapeutic drug delivery systems have been

developed with the primary objective of synchronizing drug release with biological rhythms. Among these, pulsatile drug delivery systems (PDDS) have gained significant attention due to their ability to release drugs after a predetermined lag time, followed by a rapid and complete release phase. This characteristic allows drug availability to coincide precisely with the time of greatest therapeutic need [46]. Pulsatile systems are particularly advantageous in managing conditions where symptoms follow a predictable temporal pattern, such as nocturnal acid secretion, early morning asthma, and hypertension [47]. Various design approaches have been employed in PDDS, including rupturable coating systems, osmotic pressure-driven systems, swelling-based mechanisms, and erosion-controlled matrices. These systems utilize polymers and excipients that either swell, dissolve, or rupture after a specific time interval, thereby achieving controlled lag time and targeted drug release [48]. In addition to temporal control, spatial control of drug delivery is equally important, particularly for drugs that exhibit site-specific absorption or require prolonged gastric residence. Floating drug delivery systems (FDSS) have been developed to address this requirement by enabling the dosage form to remain buoyant in gastric fluids for extended periods. These systems are typically designed with a density lower than that of gastric fluid, allowing them to float and resist gastric emptying [49]. The buoyancy of FDSS is achieved either through effervescent mechanisms, where gas-generating agents such as sodium bicarbonate produce carbon dioxide, or through non-effervescent systems that rely on swellable polymers to maintain low density [50]. By prolonging gastric residence time, FDSS enhance drug absorption, improve bioavailability, and provide localized drug action in the upper gastrointestinal tract [51]. The integration of pulsatile and floating mechanisms has led to the development of floating pulsatile drug delivery systems (FPDDS), which represent a significant advancement in chronotherapeutic drug delivery. These systems combine the advantages of prolonged gastric retention and time-controlled drug release, ensuring that the drug remains in the stomach during the lag phase and is released at the desired time, typically during peak nocturnal acid secretion [52]. This dual functionality addresses two major challenges associated with conventional oral drug

delivery: rapid gastric emptying and lack of synchronization with circadian rhythms. By maintaining the dosage form in the gastric region and releasing the drug in a pulsatile manner, FPDDS provide improved therapeutic efficacy and reduced variability in drug absorption [53]. From a formulation perspective, floating pulsatile systems are designed using a combination of polymers, gas-generating agents, and coating materials that work synergistically to achieve the desired release profile. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) and polyethylene oxide (PEO) are commonly used to control swelling and gel formation, while hydrophobic polymers such as ethyl cellulose and Eudragit® are employed to regulate drug diffusion and lag time [54]. The thickness and composition of the polymeric coating play a critical role in determining the duration of the lag phase, while the concentration of effervescent agents influences buoyancy and floating duration [55]. Advances in polymer science have also enabled the development of stimuli-responsive materials that respond to pH, temperature, or enzymatic triggers, allowing for more precise control over drug release [56]. When compared to other gastro-retentive drug delivery systems, such as mucoadhesive, expandable, and high-density systems, floating pulsatile systems offer several distinct advantages. Mucoadhesive systems rely on adhesion to the gastric mucosa, which can be inconsistent due to mucus turnover and gastric motility. Expandable systems, although effective in prolonging gastric retention, may face challenges related to mechanical integrity and patient comfort. High-density systems depend on sedimentation and may be affected by gastric motility patterns [57]. In contrast, floating pulsatile systems provide a more reliable and patient-friendly approach by maintaining buoyancy without interfering with normal gastric physiology and ensuring precise timing of drug release [58]. Recent advancements in chronotherapeutic drug delivery have also focused on improving the predictability and reproducibility of these systems through computational modeling and in vitro–in vivo correlation (IVIVC) studies. The application of design of experiments (DoE) and quality-by-design (QbD) approaches has enabled systematic optimization of formulation variables, leading to improved control over drug release kinetics and enhanced product performance [59].

Additionally, the incorporation of advanced manufacturing techniques such as 3D printing and microfluidics has opened new possibilities for the development of personalized drug delivery systems tailored to individual circadian patterns and therapeutic needs [60]. Furthermore, the integration of digital health technologies and wearable devices into drug delivery systems is emerging as a promising approach for real-time monitoring and adjustment of drug release. These technologies can provide valuable insights into patient-specific physiological parameters, enabling the development of adaptive drug delivery systems that respond dynamically to changes in circadian rhythms and disease activity [61,62]. Such innovations are expected to play a crucial role in advancing precision medicine and improving patient outcomes in the management of acid-related disorders.

Design Features of Floating Pulsatile Systems:

Floating pulsatile drug delivery systems (FPDDS) represent an advanced oral controlled drug delivery platform that integrates the principles of gastro-retention and chronotherapy to achieve site-specific and time-dependent drug release. The design of these systems is centered on achieving a programmable lag phase followed by rapid drug release, while simultaneously maintaining buoyancy in the gastric environment. This dual functionality requires careful consideration of structural configuration, polymer selection, buoyancy mechanisms, and dosage form design, all of which collectively determine the therapeutic performance of the system [63].

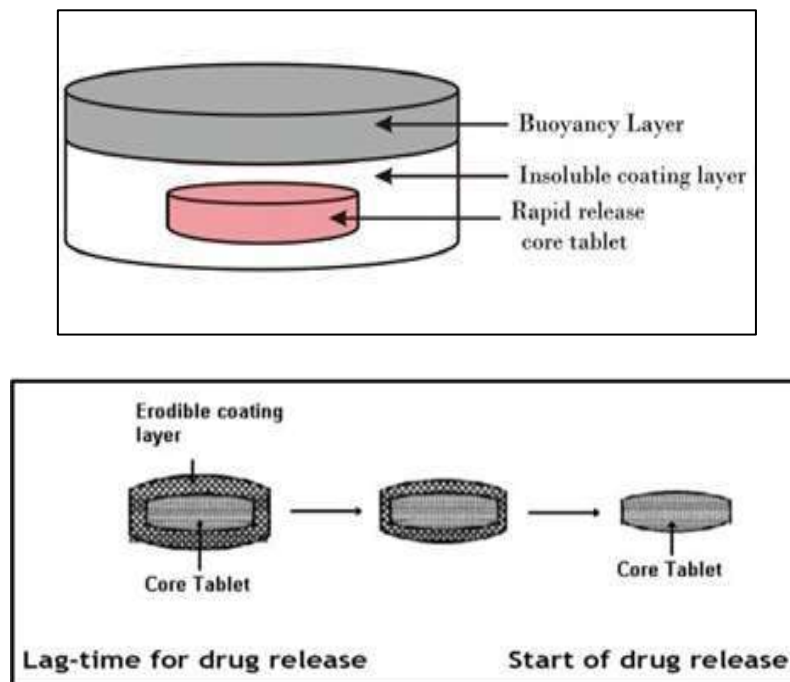


Figure 3: Floating Pulsatile Drug Delivery System and Erodible Coating Layer

A fundamental design component of FPDDS is the core-coat (reservoir-type) structure, which enables precise control over lag time. The core typically contains the active pharmaceutical ingredient (API) along with superdisintegrants or osmotic agents that facilitate rapid drug release once the barrier is compromised. Surrounding this core is a polymeric coating that acts as a barrier to water penetration, thereby delaying drug release for a predetermined period [64]. The lag time is primarily governed by the thickness, composition, and permeability of this

coating layer. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) and polyethylene oxide (PEO) are widely used for their swelling and gel-forming properties, while hydrophobic polymers such as ethyl cellulose and Eudragit® RS/RL are utilized to provide controlled permeability and mechanical strength [65]. By adjusting the ratio and characteristics of these polymers, formulators can finely tune the lag phase to coincide with peak nocturnal acid secretion. The selection of polymers is a critical determinant of the

overall functionality of FPDDS, as they influence not only the lag time but also buoyancy, drug release kinetics, and structural integrity. Hydrophilic polymers facilitate water uptake and swelling, forming a gel barrier that controls drug diffusion, whereas hydrophobic polymers retard water penetration and prolong the lag phase [66]. Natural polymers such as chitosan, guar gum, and xanthan gum have also been explored due to their biodegradability and biocompatibility, although synthetic polymers generally offer better reproducibility and mechanical stability [67]. Additionally, the use of multi-layered or multipolymeric coatings has enabled the development of systems capable of biphasic or multiphasic drug release, which is particularly beneficial for drugs requiring both immediate and delayed therapeutic effects [68]. An essential feature of FPDDS is their buoyancy mechanism, which ensures prolonged gastric residence time by maintaining the dosage form in a floating state within gastric fluids. Buoyancy can be achieved through either effervescent or non-effervescent approaches. In effervescent systems, gas-generating agents such as sodium bicarbonate and citric acid react with gastric acid to produce carbon dioxide, which becomes entrapped within the polymer matrix, thereby reducing the density of the system and enabling flotation [69]. These systems typically exhibit rapid floating onset but may show variability depending on the rate of gas generation and environmental conditions. In contrast, non-effervescent systems rely on swellable polymers that absorb gastric fluid and expand, reducing the overall density of the dosage form and maintaining buoyancy over an extended period [70]. While non-effervescent systems offer more consistent floating behavior, they may exhibit a longer floating lag time compared to effervescent systems. The dosage form design also plays a significant role in determining the performance of floating pulsatile systems. These

systems can be formulated as single-unit dosage forms such as tablets or capsules, or as multiple-unit systems such as pellets, beads, or microspheres. Tablets are widely preferred due to their ease of manufacturing, mechanical strength, and ability to provide consistent lag time and release profiles [71]. Capsules, on the other hand, offer greater flexibility in incorporating multiparticulate systems, which can reduce inter-individual variability and provide more uniform drug distribution [72]. Multiparticulate systems also minimize the risk of dose dumping and are less affected by variations in gastric emptying. Another important design consideration is the hydrodynamic balance of the system, which ensures that the density of the dosage form remains lower than that of gastric fluid (approximately 1.0 g/cm³) to maintain buoyancy [73]. Achieving this balance requires careful optimization of formulation parameters such as polymer concentration, porosity, and gas-generating capacity. At the same time, the system must possess sufficient mechanical strength to withstand gastric motility without disintegration during the lag phase. Parameters such as hardness, friability, and swelling index are therefore critical in evaluating the robustness of the formulation [74]. The mechanism of drug release in FPDDS is typically governed by a combination of diffusion, swelling, erosion, and rupture processes. During the lag phase, the outer polymer layer controls water penetration and prevents premature drug release. Once the coating reaches a critical level of hydration or erosion, it ruptures or dissolves, leading to rapid release of the drug from the core [75]. The release kinetics can be modulated by altering the physicochemical properties of the polymers, such as viscosity, molecular weight, and degree of crosslinking. Advanced systems may also incorporate osmotic pressure or enzyme-triggered mechanisms to achieve more precise control over drug release [76].

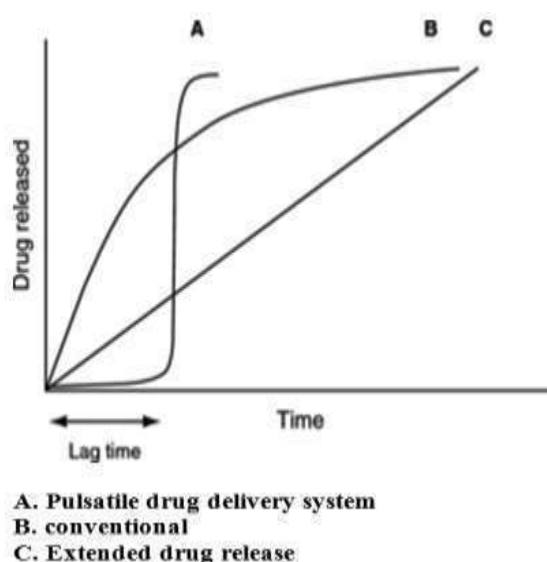


Figure 4: Comparison with conventional and Extended Drug Delivery

Recent advancements in formulation technology have introduced stimuli-responsive and smart polymer systems that respond to environmental triggers such as pH, temperature, or enzymatic activity. These materials enable more sophisticated control over drug release, allowing for site-specific and time-dependent delivery with improved precision [77]. Additionally, the integration of computational modeling and imaging techniques, such as real-time magnetic resonance imaging (MRI) and gamma scintigraphy, has enhanced the understanding of in vivo behavior of floating systems, facilitating better design and optimization [78]. Furthermore, the development of multi-unit floating pulsatile systems, such as floating microspheres and hollow beads, has gained attention due to their ability to provide uniform distribution in the stomach and reduce variability in drug release. These systems offer advantages such as improved gastric retention, reduced risk of dose dumping, and enhanced reproducibility of therapeutic outcomes [79]. The use of advanced manufacturing techniques, including spray drying, extrusion-spheronization, and 3D printing, has further expanded the possibilities for designing complex and patient-specific floating pulsatile formulations [80].

Optimization Parameters of Floating Pulsatile Drug Delivery Systems:

The optimization of floating pulsatile drug delivery systems (FPDDS) is a critical step in formulation development, as it ensures the precise synchronization of lag time, buoyancy, and drug release kinetics with

the circadian rhythm of disease conditions such as nocturnal acid secretion. The primary objective of optimization is to achieve a balance between formulation variables and physicochemical properties so that the system can provide a predictable lag phase followed by rapid and complete drug release at the desired time. This process involves systematic evaluation of formulation components, process parameters, and their interactions, which collectively influence the performance and reliability of the dosage form [82]. Among the various formulation variables, polymer type and concentration play a pivotal role in determining the lag time and release profile of FPDDS. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) and polyethylene oxide (PEO) contribute to swelling and gel formation, which regulate water penetration and drug diffusion, whereas hydrophobic polymers such as ethyl cellulose and Eudragit® act as rate-controlling barriers that delay drug release [83]. The ratio of these polymers significantly affects the thickness and integrity of the coating layer, thereby influencing the duration of the lag phase. Higher concentrations of hydrophobic polymers generally increase lag time by restricting water ingress, while hydrophilic polymers facilitate faster hydration and reduce lag time [84]. Another crucial parameter is the concentration of effervescent agents, such as sodium bicarbonate and citric acid, which are responsible for generating carbon dioxide and imparting buoyancy to the system. The amount and ratio of these agents directly affect the floating lag time and total floating duration. An optimal concentration ensures rapid

buoyancy and prolonged gastric retention, whereas excessive gas generation may compromise the structural integrity of the dosage form, leading to premature drug release [85]. Conversely, insufficient effervescent content may delay flotation or result in incomplete buoyancy, reducing the effectiveness of the gastro-retentive system [86]. The coating thickness and composition are also key determinants of the lag time in pulsatile systems. The polymeric coating acts as a barrier that delays drug release until it undergoes swelling, erosion, or rupture. Increasing the coating thickness generally prolongs the lag phase, while variations in polymer composition can alter the permeability and mechanical strength of the coating layer [87]. The selection of appropriate coating techniques, such as compression coating, pan coating, or fluidized bed coating, further influences the uniformity and reproducibility of the formulation [88]. To achieve precise optimization, Design of Experiments (DoE) has emerged as a powerful statistical tool in pharmaceutical formulation development. DoE allows simultaneous evaluation of multiple formulation and process variables and their interactions, thereby reducing experimental workload and improving efficiency. Common experimental designs used in FPDDS optimization include factorial design, central composite design, and Box–Behnken design [89]. These approaches enable the identification of critical factors affecting key quality attributes such as lag time, floating behavior, and drug release. Statistical analysis methods, including analysis of variance (ANOVA) and regression modeling, are used to establish relationships between independent variables and responses, facilitating the development of an optimized formulation within the desired design space [90]. In vitro evaluation parameters play a vital role in assessing the performance of optimized formulations before in vivo studies. Floating behavior is characterized by measuring floating lag time and total floating duration, which indicate the ability of the dosage form to remain buoyant in gastric fluid. Swelling index studies provide insight into polymer hydration and matrix expansion, while hardness and friability tests evaluate the mechanical strength of the dosage form [91]. Dissolution studies conducted in simulated gastric fluid (pH 1.2) are essential for determining drug release profiles and verifying the presence of a distinct lag phase followed by rapid release. The

release data are often fitted to kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to elucidate the mechanism of drug release [92]. In addition to in vitro studies, analytical characterization techniques such as Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and scanning electron microscopy (SEM) are employed to evaluate drug–excipient compatibility, thermal behavior, and surface morphology of the formulation [93]. These techniques ensure the stability and uniformity of the core–coat structure, which are essential for consistent drug release performance. The translation of in vitro findings to physiological conditions requires in vivo evaluation, which provides critical information regarding gastric retention, drug absorption, and pharmacokinetic behavior. Techniques such as gamma scintigraphy and X-ray imaging using radio-opaque markers are commonly used to visualize the position and movement of the dosage form within the gastrointestinal tract [94]. Pharmacokinetic parameters such as maximum plasma concentration (C_{max}), time to reach maximum concentration (T_{max}), and area under the curve (AUC) are analyzed to assess the bioavailability and therapeutic effectiveness of the formulation [95]. Optimized FPDDS typically demonstrate prolonged gastric residence time, delayed T_{max} corresponding to the programmed lag phase, and improved bioavailability compared to conventional dosage forms. Despite the advancements in optimization techniques, achieving a reliable in vitro–in vivo correlation (IVIVC) remains a significant challenge in FPDDS development. Variability in gastric motility, pH, and fed or fasting conditions can influence the performance of the dosage form in vivo, leading to differences between predicted and actual drug release profiles [96]. To address this issue, advanced computational modeling approaches, including physiologically based pharmacokinetic (PBPK) modelling and simulation, are increasingly being used to predict in vivo behavior and improve formulation design [97].

Applications in Nocturnal Acid Secretion:

Floating pulsatile drug delivery systems (FPDDS) have shown significant potential in the management of nocturnal acid secretion associated with disorders such as gastroesophageal reflux disease (GERD) and peptic ulcer disease (PUD). These conditions are

characterized by increased gastric acid production during night-time, leading to mucosal damage, sleep disturbances, and reduced quality of life. Conventional drug delivery systems often fail to provide adequate acid suppression during this period due to lack of synchronization with circadian rhythms [88]. FPDDS are specifically designed to overcome this limitation by providing a programmed lag time followed by rapid drug release during peak nocturnal acid secretion. This approach ensures optimal therapeutic drug levels when symptoms are most severe, thereby improving efficacy and patient outcomes [89]. Proton pump inhibitors (PPIs) such as omeprazole and lansoprazole, when formulated as floating pulsatile systems, have demonstrated enhanced night-time acid suppression and reduced incidence of nocturnal acid breakthrough compared to conventional formulations [90]. Similarly, H₂ receptor antagonists (H₂RAs) like famotidine have been successfully incorporated into pulsatile systems to provide targeted night-time acid control. These systems improve gastric retention, enhance bioavailability, and reduce dosing frequency, leading to better patient compliance [91,92].

ADVANTAGES AND LIMITATIONS:

Floating pulsatile drug delivery systems (FPDDS) offer several advantages in the management of chronobiological disorders such as nocturnal acid secretion. One of the primary benefits is their ability to provide time-specific drug release, ensuring that peak drug concentration coincides with periods of maximum symptom severity. This improves therapeutic efficacy while minimizing unnecessary drug exposure during inactive phases [93]. Additionally, the floating mechanism prolongs gastric residence time, enhancing drug absorption and bioavailability, particularly for drugs with narrow absorption windows [94]. Another important advantage is improved patient compliance, as FPDDS reduce the need for multiple dosing or night-time administration. These systems also help in protecting acid-sensitive drugs through polymeric coatings, thereby improving drug stability and therapeutic performance [95]. Furthermore, the combination of pulsatile and floating mechanisms reduces fluctuations in plasma drug levels and supports better control of nocturnal acid breakthrough [96].



Figure 5: Advantages of Floating Pulsatile Drug Delivery System

Despite these benefits, FPDDS have certain limitations. The complexity of formulation and manufacturing is a major challenge, requiring precise control over polymer composition, coating thickness, and effervescent components to achieve the desired lag time and buoyancy [97]. Variability in gastric physiology, such as differences in gastric motility and pH among individuals, may also affect system performance and drug release behavior [98]. Additionally, these systems often involve higher production costs and require advanced evaluation techniques, including in vitro–in vivo correlation (IVIVC), to ensure consistent performance.

Regulatory approval can also be challenging due to the complexity of release kinetics and the need for extensive validation studies [99].

FUTURE DIRECTIONS:

The future of floating pulsatile drug delivery systems (FPDDS) lies in the integration of advanced materials, digital technologies, and personalized medicine approaches. The development of smart and stimuli-responsive polymers that can respond to physiological triggers such as pH, temperature, or enzymatic activity is expected to provide more precise control over drug release and improve targeting efficiency

[101]. These innovations can further enhance the reliability of lag time and drug release profiles, especially in chronotherapeutic applications. Emerging technologies such as artificial intelligence (AI) and machine learning are anticipated to play a crucial role in optimizing formulation design by predicting polymer–drug interactions and release kinetics, thereby reducing experimental workload and development time [102]. Additionally, 3D printing technologies offer the potential for fabricating patient-specific dosage forms with customizable lag times and release patterns, supporting the concept of precision medicine [103]. The incorporation of digital health tools, including wearable devices and real-time monitoring systems, may enable dynamic adjustment of drug delivery based on individual circadian rhythms and physiological conditions. However, further research is needed to improve in vitro–in vivo correlation (IVIVC), ensure large-scale manufacturability, and achieve regulatory harmonization for widespread clinical application. Overall, future advancements in FPDDS are expected to transform chronotherapy by enabling more precise, personalized, and effective management of nocturnal acid-related disorders.

CONCLUSION:

Floating pulsatile drug delivery systems represent a significant advancement in the field of chronotherapeutic drug delivery, offering an effective solution for the management of nocturnal acid secretion in conditions such as gastroesophageal reflux disease and peptic ulcer disease. By combining gastric retention with time-controlled drug release, these systems successfully synchronize pharmacological action with circadian rhythms, thereby overcoming the limitations of conventional dosage forms. The ability of FPDDS to provide a programmed lag phase followed by rapid drug release ensures optimal therapeutic drug levels during periods of peak acid secretion, resulting in improved symptom control, enhanced mucosal healing, and better patient compliance. The use of advanced polymers, optimized formulation strategies, and statistical design approaches has further strengthened the development and performance of these systems. Despite their promising advantages, challenges related to formulation complexity, manufacturing scalability, variability in physiological conditions,

and regulatory approval must be addressed to facilitate their successful translation into clinical practice. Continued research focusing on smart materials, predictive modeling and personalized drug delivery approaches is essential for overcoming these limitations. In conclusion, floating pulsatile systems embody the concept of precision chronotherapy by aligning drug delivery with biological timing, thereby improving therapeutic outcomes and quality of life. With ongoing technological advancements and interdisciplinary collaboration, these systems hold great potential for future pharmaceutical innovation and clinical application in time-dependent diseases.

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