REVIEW ARTICLE

Innovations and Applications in Bioadhesive-Based Pulsatile Drug Delivery Systems

Patil SV[1*], Sutar SB[2], Yesare SA,[2] Behera AL[3]

[1]*Dr. Ashok Gujar Institute of Pharmacy, Karad, MS, India.*
[2]*Ashokrao Mane College of Pharmacy, Peth-Vadgaon, MS, India.*
[3]*School of Pharmacy DRIEMS University Tangi Cuttack, Odisha, India.*

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ABSTRACT
Recent technological advancements have significantly increased the demand for Novel Drug Delivery Systems (NDDS) in the pharmaceutical industry. Controlled Drug Delivery Systems (CDDS) are a notable example, maintaining consistent drug levels and enhancing bioavailability. However, oral dosage forms can face challenges with fluctuating plasma levels and bioavailability due to variable gastric emptying rates, particularly affecting drugs absorbed in the upper gastrointestinal tract. To address this, Gastroretentive Formulations (GRDFs) have been created to extend gastric retention and improve drug absorption. These include high-density, floating, swelling, expandable, mucoadhesive, and magnetic systems. Among these, the Bioadhesive Drug Delivery System (BDDS) stands out by adhering to the stomach's mucous membrane, thereby improving retention and bioavailability. Pulsatile Drug Delivery Systems (PDDS), releases drugs quickly after a set lag time aligned with the body's circadian rhythm, can face absorption issues in the small intestine. Combining BDDS with PDDS, resulting in Bioadhesive Pulsatile Drug Delivery Systems (BPDDS), addresses these challenges by ensuring prolonged gastric retention and precise drug release. This approach offers numerous benefits, such as extended drug distribution, enhanced bioavailability, reduction in dosing frequency, minimized side effects, making it particularly effective for drugs that need chrono-pharmacological delivery, nighttime dosing, or have high first-pass metabolism. BPDDS is a promising strategy for improving patient compliance and therapeutic outcomes.
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INTRODUCTION

In recent years, there has been a surge in demand for Novel Drug Delivery Systems (NDDS) within the pharmaceutical industry, driven by advancements in technology. One prominent NDDS approach is Controlled Drug Delivery Systems (CDDS), which ensures a consistent drug concentration in the body, thereby enhancing drug bioavailability. However, in oral dosage forms, fluctuation in peak plasma levels and bioavailability are often occurred, potentially due to variations in gastric emptying rates.[1-4] This issue particularly affects drugs with a narrow absorption range in the upper gastrointestinal tract, such as the stomach and small intestine, rendering Controlled Release Dosage Forms (CRDF) less suitable. To address this challenge, it is essential to develop dosage forms that prolong gastro-retention time to enhance drug absorption. One effective strategy is the use of Gastroretentive Formulations (GRDFs), which can hold the drug within the stomach for an extended period, thereby improving bioavailability.[5-7] GRDFs can be formulated using various approaches, including high-density systems, floating, swelling, mucoadhesive, superporous hydrogels, and magnetic systems. Among these, the Bioadhesive Drug Delivery System (BDDS) has garnered significant interest due to its ability to adhere to the stomach mucous membrane, prolonging gastric retention and enhancing bioavailability.[8,9] Pulsatile Drug Delivery Systems (PDDS) offer another innovative way, designed to release explicit quantities of drugs rapidly after a programmed lag time, aligning with the body's circadian rhythm. However, drawbacks such as poor drug absorption in the small intestine particularly those having maximum absorption in the stomach. Combining PDDS with BDDS can mitigate this limitation.[10-12] The Floating Pulsatile Drug Delivery System (FPDDS) represents a further advancement, aiming to extend gastric emptying time. However, there is a risk of the formulation entering the small intestine post-gastric emptying. This challenge can be addressed by utilizing Bioadhesive Pulsatile Drug Delivery Systems (BPDDS), which adhere to the stomach's mucous membrane, ensuring targeted drug release. BPDDS offers several advantages, including prolonged drug distribution at the target site, improved bioavailability, reduction in dose frequency, lessen side effects. This system is particularly beneficial for drugs requiring chrono-pharmacological delivery, night-time dosing, or exhibiting high first-pass metabolism.[13]

Bioadhesive drug delivery system (BDDS)

**Author for Correspondence: sachinpatil.krd@gmail.com*

BDDS involves polymer adhesion to gastrointestinal mucosa, enhancing gastric retention time and improving absorption and bioavailability. These systems utilize synthetic or natural polymers to form bonds with epithelial cells or mucous layers, facilitating targeted drug delivery and optimizing therapeutic outcomes.[14-16] To understand the development of BDDS, it's essential to delve into the mechanisms underlying the formation of adhesive bonds. These mechanisms can be broken down into three main steps: Wetting and swelling of the polymer, facilitating intimate contact with the living tissue (contact stage) and permeation of bioadhesive polymer groups and enlargement of both polymer and mucin chains.

Formation of weak organic bonds among the entangled chains (consolidation stage).

A) Chemical bonds: Chemical bonds encompass covalent bonds, known for their strength, alongside weaker bonds like ionic bonds, hydrogen bonds, and Van der Waals interactions.

B) Physical Bonds: These bonds arise from physical interactions between surfaces, sometimes involving the expansion of mucin alongside polymer bonds into a polymer substrate.[17-18]

Bioadhesive polymers possess diverse properties dependent on their physical and chemical strengths. They function as both water-soluble and insoluble networks, often interconnected through cross-linking agents. Various types of polymers exhibit bioadhesive characteristics and serve as Drug Delivery Systems (DDS). [19-21]

CURRENT ADVANCEMENTS IN BDDS

BDDS for ocular, topical, rectal, nasal, oral, and vaginal delivery has demonstrated the potential of these systems. The basic principle of bioadhesion can be advantageous for creating BDDS that allow controlled drug delivery. The success of BDDS in pharmaceuticals depends on the physicochemical properties of the bioadhesive polymers. Factors such as mucin flow, the condition of the biological membrane at the site of drug penetration, and variations in mucin rate are also considered in the effective development of BDDS. Recently, the emergence of second-generation bioadhesive polymers has garnered attention for their enhanced control over bioadhesive properties, leading to more effective therapeutic release.[22,23]

PULSATILE DRUG DELIVERY SYSTEM

Oral dosage forms are preferred for due to its high patient compliance. Oral Controlled Drug Delivery Systems (CDDS) maintain a constant drug concentration within the therapeutic window over an extended period, ensuring sustained beneficial effects. However, in cases where a delayed release of medication is needed, CDDS may not be suitable. To address this need, Pulsatile Drug Delivery Systems (PDDS) are designed. PDDS are based on the body's circadian rhythm and are particularly useful for conditions where continuous drug delivery is not ideal but where periodic pulses of medication are required.[24-25] In Pulsatile Drug Delivery Systems (PDDS), drug is released quickly after a predetermined lag time, which is advantageous for various treatments. A PDDS allows for the quick and specified quantity of drug is released shortly after the lag period. The system is premeditated for drug release as per the body's circadian rhythm. In pulsatile systems, medication release occurs in two phases: initially, a small amount of the drug is delivered, followed by the complete release of the remaining medication after the lag time. Most pulsatile systems function as drug reservoirs with a polymeric coating that prevents drug release until the coating dissolves or after a specific lag time, after which the drug released rapidly from the core.[26]

Advantages of PDDS

Medication is delivered in a burst manner at the selected absorption site, leading to improve the bioavailability compared to conventional or sustained-release forms. Reduced drug dosage without compromising therapeutic efficacy. Chronotherapy enables timed release of drugs for optimal disease treatment. Lower daily costs for patients due to reduced dosage requirements. Medication can be tailored to match circadian rhythms in the body. Mucosal protection from irritating medications. Prevention of drug reduction by first-pass metabolism. Elimination of dose dumping risk. Avoidance of biological tolerance. Predictable, reproducible, and short gastric residence time. Enhanced stability.[27]

Marketed technologies of PDDS

In recent years, pharmaceutical companies have focused on developing and commercializing PDDS products to meet the treatment needs of various diseases. For conditions such as bronchial asthma, rheumatic diseases, hypertension, and myocardial infarction, as well as for regulating bodily functions affected by circadian rhythms, delayed or PDDS approaches have become increasingly favoured. Several emerging technologies in this field include:

BIOADHESIVE PULSATILE DRUG DELIVERY SYSTEM

Table 1: Technologies for PDDS.[28-29]

Technology	Mechanism	Brand Name	Drug	Disease
PULSYS™	Rupturable system	Pulsincap™	Dofetilide	Antiarrhythmic
Physicochemical Modifications	Tablet	Pepcid®	Famotidine	Ulcer
3-D Printing	Externally regulated system	Their form	Diclofenac sodium	Inflammation
OROS	Osmotic mechanism	Covera-H5 XL	Verapamil HCL	Hypertension
TIMER$_X$®	Erodible/ER Tablets	OPANA®	Oxymorphone	Pain Management

Table 2: Drug candidates for Bioadhesive Pulsatile Drug Delivery Systems.

S. No.	Dosage Form	Drug	Diseases	Reference
1.	Press coated tablet	Fenofibrate	Hyper-lipidaemia	30
2.	Press coated tablet	Telmisartan	Hyper-tension	31
3.	Press coated tablet	Lisinopril	Hyper-tension	32
4.	Press coated tablet	Losartan	Hyper-tension	33 - 34

The concept of combining bioadhesion with pulsatile drug release offers a promising avenue for achieving site and time specific drug delivery. BPDDS has garnered significant attention in the pharma business due to its potential to enhance therapeutic efficacy. Among the various gastroretentive formulations available for extending gastric residence time, BPDDS stands out for its ability to improve drug absorption and bioavailability.

BDDS aims to extend the gastro retention of drugs by leveraging adhesive properties of polymers, whether synthetic or natural, to adhere to biological membranes for an extended duration. PDDS, on the other hand, involves the rapid and transient release of a specific quantity of drug shortly after a predetermined lag time. Drugs that exhibit maximum absorption in the stomach or encounter intestinal absorption issues are particularly suitable candidates for BDDS. Additionally, bioadhesive systems are well-suited for drugs requiring pulsatile release in the stomach. In the case of hypertension, PDDS is often preferred. However, combining PDDS with BDDS can offer additional advantages by targeting drug delivery to the stomach with time-dependent release. Blood pressure exhibits 24-hour variations in humans, with sharp increases before awakening and the highest values observed in the early morning. Therefore, to maintain blood pressure levels in the morning, BPDDS is beneficial, as drug release occurs after the lag time, which for hypertension is typically around 8 hours. This synchronization with the body's circadian rhythm is crucial for delivering antihypertensive drugs effectively and avoiding gastric emptying, highlighting the importance of utilizing BPDDS. Overall, the bioadhesive pulsatile drug delivery system enhances patient compliance, optimizes drug delivery to the target site, and reduces undesired side effects.

Advantages of BPDDS

Extend the drug residence time at the site of Drug Delivery System (DDS), thereby enhancing the bioavailability of the Active Pharmaceutical Ingredient (API). Facilitates targeted delivery of medication by sites specific release using bioadhesive polymers. Avoids first-pass metabolism, ensuring a higher concentration of the drug reaches systemic circulation. Suitable for drugs with short biological half-lives, poor solubility, poor permeability, and those requiring sustained release. Reduces dose-related side effects by localizing the API at the disease site. Enables site-specific medication targeting, such as the colon. Enhances daytime or nighttime activity by optimizing drug delivery timing. Allows for medication release at sites where continuous drug delivery is unnecessary. Beneficial for drugs with chrono-pharmacological behavior. Minimizes the risk of dose dumping. Improves drug stability during storage.

CONCLUSION

Thus, the progress of NDDS such has significantly advanced due to technological innovations in the pharmaceutical industry. These systems address the limitations of conventional oral dosage forms, particularly the fluctuations in drug absorption caused by variations in gastric emptying rates. The introduction of Gastroretentive Formulations (GRDFs) and Bioadhesive Drug Delivery Systems (BDDS) has further enhanced drug bioavailability by prolonging gastric retention time. BDDS, which utilize the adhesive properties of polymers, have shown promise in maintaining targeted and controlled drug release. Moreover, combining BDDS with Pulsatile Drug Delivery Systems (PDDS), such as in Bioadhesive-Pulsatile Drug Delivery Systems (BPDDS), offers a novel approach to achieve time- and site-specific drug delivery, aligning with the body’s circadian rhythm and improving therapeutic efficacy. This combination is particularly beneficial for drugs requiring timed release, such as antihypertensives, by ensuring synchronized drug delivery and reducing the risk of undesired side effects, thereby enhancing patient compliance and treatment outcomes.

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