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Pulsatile drug delivery system: A review

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Abstract

Pulsatile Drug Delivery Systems (PDDS) are increasingly recognized for their ability to deliver drugs at specific times, tailored to the pathophysiological needs of a disease. This approach enhances therapeutic efficacy and patient compliance. The core concept of PDDS involves a defined lag-time before a rapid drug release, which can be particularly beneficial for treatments requiring synchronization with the body's natural circadian rhythms. By aligning peak plasma concentrations with these biological cycles, PDDS can improve both the safety and effectiveness of drugs over a 24-hour period.

There are various techniques for achieving pulsatile drug release, including pH-dependent and time-dependent systems. These systems are generally classified into multiple-pulse and single-pulse categories. A common example of a single-pulse system is the rupturable dosage form, which releases the drug in one rapid dose after the lag-time. PDDS offer several advantages, including reduced dosing frequency, minimized side effects, and the potential for targeted drug delivery to specific sites such as the colon.

Several innovative PDDS technologies, including Pulsincap and Diffucaps, have been developed and launched by pharmaceutical companies, further expanding the applications of pulsatile release and improving patient outcomes.

Keywords: Pulsatile Drug Delivery System; Circadian Rhythm; Chronopharmacology; Single Unit; Multiple Units; Technologies

1. Introduction

Pulsatile drug delivery systems (PDDS) are gaining attention due to their distinct advantages over traditional dosage forms. They ensure the drug is delivered at the optimal time, to the right site of action, and in the correct amount, offering improved therapeutic benefits and enhancing patient compliance compared to conventional systems[1].

PDDS enhance drug absorption and bioavailability by releasing the drug in a burst at the target site, which improves absorption compared to immediate-release or sustained-release formulations. This allows for a reduction in the total drug dose without compromising therapeutic effects, while also minimizing side effects.These systems also reduce dose frequency, size, and overall cost, which leads to fewer side effects and improved patient adherence. Additionally, PDDS can be designed to align with the body's circadian rhythms or the specific needs of certain diseases[2].

Typically, PDDS are designed as capsules or other dosage forms that release therapeutic agents in a time-controlled or position-controlled manner. They are composed of multiple layers of coated particles (such as beads, pellets, or granules) that release the drug in a pulsatile fashion, depending on the specific formulation requirements and the intended therapeutic application.

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1.1. Advantages of PDDS (polymer-based drug delivery systems):[3,4]

- Prolonged Activity: Enables extended activity during the day or night, depending on the formulation.
- Reduced Side Effects: Minimizes adverse effects due to controlled release.
- Lower Dosing Frequency: Reduces the required dose size and frequency of administration.
- Enhanced Patient Compliance: Fewer doses per day lead to better patient adherence to the treatment regimen.
- Cost Savings: Fewer dosage units are required daily, reducing overall treatment costs.
- Circadian Adaptation: Drug release can be timed to align with the body's natural circadian rhythms or specific disease cycles.
- Targeted Delivery: Can target specific sites, such as the colon, for more precise treatment.
- Protection of Mucosa: Helps protect sensitive mucosal tissues from irritation caused by certain drugs.
- Prevention of Drug Loss: Minimizes drug loss due to extensive first-pass metabolism (e.g., for proteins and peptides).
- Avoidance of Tolerance: Reduces the risk of tolerance build-up, as seen with transdermal systems like Nitroglycerin.

1.2. Disadvantages of PDDS:[5,6]

- Limited Drug Loading Capacity: May have a lower drug loading capacity, which can result in incomplete release of the active ingredient.
- Higher Production Costs: Typically more expensive to manufacture than conventional dosage forms.
- Process Complexity: Involves numerous process variables, making production more complicated.
- Inconsistent Manufacturing: Variability in manufacturing processes can lead to issues with reproducibility and efficacy.
- Batch Production: Often relies on batch manufacturing, which can be less efficient and scalable.
- Unpredictable In Vitro-In Vivo Correlation (IVIVC): Challenges in predicting how the drug will behave in the body based on laboratory testing.

1.3. Chronopharmacology

Chronopharmaceutics is an emerging field that focuses on designing drug delivery systems that release therapeutic agents in a manner synchronized with the body's biological rhythms. This research aims to optimize the timing of drug release to match the biological needs of specific diseases. The term Chronopharmaceutics combines Chronobiology—the study of biological rhythms and their mechanisms—with Pharmaceutics, the science of drug formulation and delivery.

Chronopharmacology is the study of how the effects of drugs vary depending on the biological timing and internal rhythms of the body, such as circadian cycles. This field aims to optimize drug therapy by understanding how the timing of drug administration can influence both the effectiveness (chronoeffectiveness) and the development of tolerance (chronotolerance).

For example, the effectiveness of certain drugs may peak at specific times of day due to natural biological processes like hormone fluctuations, body temperature changes, or sleep-wake cycles. Similarly, the body's ability to metabolize or respond to drugs may vary, influencing how well a drug works or how quickly tolerance develops.

The ultimate goal of chronopharmacology is to tailor medication schedules to an individual's biological clock, improving therapeutic outcomes and reducing side effects or the risk of tolerance over time.[6,7]

1.4. There are four main types of biological rhythms

- Circadian Rhythms: A 24-hour cycle that governs various physiological and behavioral processes, such as sleep-wake patterns.
- Diurnal Rhythms: A type of circadian rhythm that is synchronized with the day-night cycle.
- Ultradian Rhythms: Biological rhythms that occur in cycles shorter than 24 hours, with a higher frequency than circadian rhythms.
- Infradian Rhythms: Biological rhythms that last longer than 24 hours, such as the menstrual cycle.[8,9]

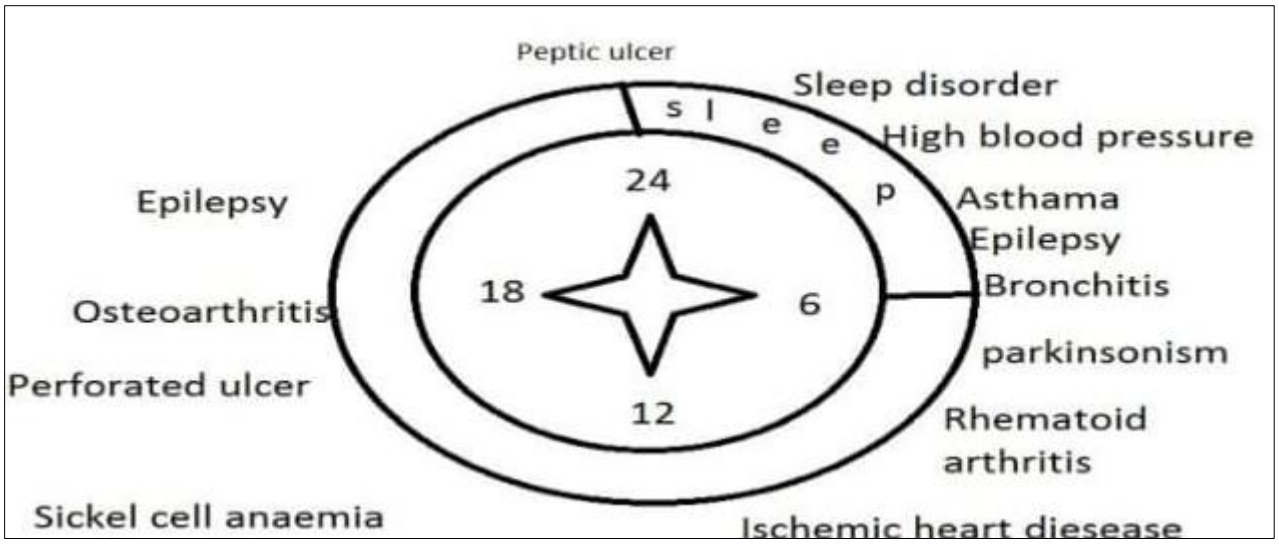

Figure 1 Circadian rhythm

1.5. Diseases requiring pulsatile drug delivery

For widespread chronic conditions with symptoms that primarily occur at night or in the early morning, such as cardiovascular diseases (CVD), bronchial asthma, and rheumatoid arthritis, the use of modified-release medications could offer significant benefits in terms of efficacy, tolerability, and patient compliance. Administering medications at bedtime could allow the therapeutic drug concentrations to align with the time when disease symptoms are most likely to manifest. Pulsatile drug delivery systems (PDDS) are particularly well-suited to achieve these goals.

In addition to their potential use in chronotherapy, pulsatile release mechanisms are also being explored to target both proximal and distal regions of the colon via the oral route. Colon-targeted drug delivery is actively being studied, as it has the potential to improve treatment for certain diseases. Pulsatile technology is particularly useful for conditions that are well-suited to chronopharmaceutical formulations, where there is enough scientific evidence to support the use of time-controlled release systems compared to conventional drug administration methods. Some of the diseases currently targeted by these formulations include:

- Hypercholesterolemia
- Asthma
- Cancer
- Arthritis
- Diabetes

1.6. Diseases

Below is a brief review of the rationale for chronotherapy and pulsatile release for each of these diseases:

1.6.1. Hypercholesterolemia

Circadian rhythms influence lipid metabolism, including the synthesis of cholesterol in the liver. Cholesterol production peaks at night, with maximal synthesis occurring early in the morning, about 12 hours after the last meal. Studies with HMG-CoA reductase inhibitors have shown that evening dosing is more effective than morning dosing in reducing cholesterol levels.[10,11]

1.6.2. Asthma

Asthma symptoms, including airway resistance and bronchoconstriction, exhibit a circadian pattern, worsening at night or in the early morning. The chronopharmacology of asthma suggests that treatment, including oral corticosteroids, theophylline, and β2-agonists, can be optimized through timing to coincide with symptom exacerbation, improving efficacy and reducing side effects.[12,13]

1.6.3. Cancer

Circadian rhythms also play a role in chemotherapy effectiveness. Studies suggest that administering cancer drugs at specific times of the day, aligned with the body's natural rhythms, can enhance tumor targeting and reduce toxicity to normal tissue. Blood flow to tumors is typically higher during active phases of the circadian cycle, offering a therapeutic window for optimized drug delivery.[14,15]

1.6.4. Arthritis

In both rheumatoid arthritis and osteoarthritis, pain and inflammation follow a circadian rhythm. Rheumatoid arthritis patients often experience peak pain in the morning, while osteoarthritis pain intensifies in the evening. Chronotherapy with NSAIDs, such as ibuprofen, can be timed to coincide with peak pain periods, optimizing drug efficacy.[16,17]

1.6.5. Diabetes

Circadian rhythms also affect glucose and insulin metabolism. Insulin therapy aims to mimic the natural circadian secretion of insulin in healthy individuals, with continuous basal secretion and meal-stimulated secretion. Time-dependent insulin administration can better regulate blood sugar levels and align with the body's natural rhythm.[18,19]

1.6.6. Cardiovascular Diseases

Several cardiovascular functions, including blood pressure (BP), heart rate, and cardiac output, exhibit circadian variation. For example, BP is typically lowest during sleep and rises steeply in the early morning, which could be associated with an increased risk of cardiac events. Chronotherapy could help modify these circadian triggers, potentially preventing adverse events in patients with cardiovascular diseases.[20,21]

Table 1 Diseases requiring PDDS

Disease	Chronological behavior	Drugs used
Peptic ulcer	Acid secretion is high in the afternoon and at night	H_2 blockers
Asthma	Precipitation of attacks during night or at early morning hour	B2 agonist Antihistaminic
Cardiovascular disease	BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period	Nitroglycerine, Calcium channel blockers , ACE inhibitors etc.
Arthritis	Pain in the morning and more pain at night	NSAIDs , Glucocorticoids
Diabetes mellitus	Increase in the blood sugar level after meal	Sulfonylurea, Insulin ,Biguanide
Attention	Increase in DOPA levelin afternoon deficit syndrome	Methylphenidate

2. Material and Methods

2.1. Mechanisms of drug release from pulsatile drugdelivery systems (PDDS)

The drug release from Pulsatile Drug Delivery Systems (PDDS) occurs through several mechanisms, each contributing to the controlled and time-dependent release of the active ingredient. The main mechanisms are as follows:

2.1.1. Osmosis

Osmotic pressure can develop within the formulation when water enters the system, interacting with the drug particles inside. This pressure forces the drug from the interior of the system into the external environment. Osmotic agents, such as sodium chloride, are commonly used to generate this osmotic pressure (Jones and Francis, 2000). The controlled influx of water causes the system to release the drug at a predetermined rate.

2.1.2. Diffusion

When water and gastrointestinal fluids diffuse into the formulation, the drug particles dissolve in the aqueous medium, forming a solution. This solution then diffuses through the release barrier or coating of the formulation to the exterior,

allowing the drug to be released. The rate of drug diffusion is typically influenced by the permeability of the coating and the concentration gradient of the drug (Venkataswamy and Nallaguntla, 2021).

2.1.3. Erosion

Over time, certain polymer coatings gradually erode depending on their nature and solubility. This controlled erosion allows for the gradual release of the drug from within the formulation. The rate of erosion depends on factors such as the solubility of the polymer and the environmental conditions, and it ensures that the drug is released in a sustained or pulsatile manner (Valte et al., 2015).

Each of these mechanisms can be tailored to create a specific release profile, making PDDS ideal for drugs that require time-controlled release or need to follow the body's natural rhythms[22].

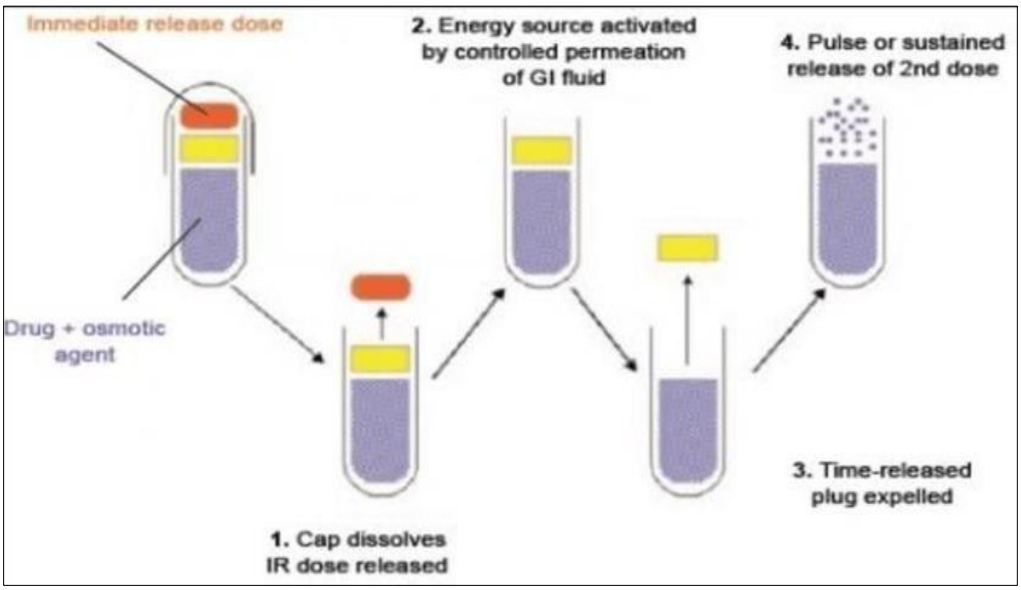

Figure 2 Mechanism of drug release [46]

2.2. Methodologies for the PDDS can be broadly classified into four classes;

- Time controlled pulsatile release
  - Single unit system
  - Multi-particulate system
- Stimuli induced
  - Thermo-Responsive Pulsatile release
  - Chemical stimuli induced Pulsatile systems
- External stimuli pulsatile release
  - Electro responsive pulsatile release
  - Magnetically induced pulsatile release
- Pulsatile release systems for vaccine and hormone products.

3. Single-unit drug delivery systems

3.1. Time Controlled Pulsatile Release

3.1.1. Capsular Systems

Capsular systems release drugs after a controlled time delay. The capsule contains the drug and a plug that swells, erodes, or dissolves after a set period, triggering drug release. The *Pulsincap®* system is an example, where the plug swells in gastrointestinal fluids, pushing out and releasing the drug. Time lag can be adjusted by modifying the plug's size and position, and the system is often enteric-coated to release the drug in the small intestine.[23,24]

3.1.2. Port Systems

Port systems use a gelatin capsule with a semi-permeable membrane and an insoluble plug. Water diffuses through the membrane, increasing pressure inside the capsule and expelling the plug after a time delay. The system can also deliver liquid drugs by osmotic pressure, where moisture from the body causes the capsule to expand, releasing the drug through an orifice at a controlled rate.[25,26]

3.1.3. Delivery by a Series of Stops

This system uses an implantable capsule containing a drug and an osmotic engine with compartments separated by a movable partition. Pulsatile delivery occurs when the partition is obstructed by internal stops, which are overcome as osmotic pressure rises. The number and placement of stops control pulse frequency, while the partition design affects pulse intensity. This method has been used for delivering porcine somatotropin.[27]

3.1.4. Delivery by Solubility Modulation

This system uses a solubility modulator, like sodium chloride (NaCl), to control the pulsed delivery of drugs such as salbutamol sulphate. The modulator affects the drug's solubility, with a concentration low enough to prevent saturation, thus enabling controlled release. The modulator can be an organic acid, inorganic salt, or organic salt.[28]

3.2. Delivery by Reservoir Systems with Erodible or Soluble Coatings

In this pulsatile system, a reservoir device is coated with a barrier layer that dissolves after a predetermined lag period, releasing the drug rapidly. The timing of the release depends on the thickness of the coating material.[29,30]

4. Multiparticulate systems

Multiparticulate drug delivery systems consist of small, independent subunits containing the active drug. These systems offer advantages over single-unit systems, such as reduced variability in gastrointestinal transit time, improved tolerability, no risk of dose dumping, and enhanced stability. However, challenges include manufacturing difficulties, high production costs, and the need for advanced technology.

4.1. Different types of multiparticulate systems include

4.1.1. Pulsatile System Based on Rupturable Coating

This system involves drug-coated sugar seeds, followed by a swellable and an insoluble top layer. When water enters, the swellable layer expands, causing the coating to rupture and releasing the drug. The release is independent of pH and solubility, and the lag time can be adjusted by varying the coating thickness or adding lipophilic plasticizers.[31,32]

4.1.2. Time-Controlled Expulsion System

This system combines osmotic and swelling effects. The drug core contains lipid material and a disintegrant, coated with cellulose acetate. When immersed in water, the lipid material is displaced, increasing internal pressure until the coating ruptures, releasing the drug.[33,34]

4.1.3. Pulsatile Delivery by Change in Membrane Permeability

Acrylic polymers, like Eudragit RS 30D, with quaternary ammonium groups, change their permeability in response to counter-ions in the medium. This allows controlled water uptake and drug release through the polymer membrane.[35,36]

4.1.4. Sigmoidal Release System

In this system, pellet cores containing the drug and succinic acid are coated with a polymer membrane. The time lag is controlled by the rate of water influx, which dissolves the acid and drug, increasing the membrane's permeability and enabling controlled release. Other acids used can include acetic acid, glutaric acid, and tartaric acid.[37]

4.1.5. Low-Density Floating Multiparticulate Pulsatile Systems

Traditional multiparticulate pulsatile systems may experience variability in bioavailability due to differences in gastric emptying rates. Low-density floating multiparticulate systems remain in the stomach, unaffected by pH or gastric

emptying. These systems are ideal for drugs absorbed in the stomach or those requiring localized delivery in the stomach.[38]

4.1.6. Stimuli-Induced Pulsatile Release Systems

Certain polymeric systems release drugs in response to environmental changes such as solvent composition, ionic strength, temperature, electric fields, or light. These systems, including gels and micelles, can undergo phase transitions (swelling/deswelling) or erosion, releasing drugs through mechanisms like diffusion or electrophoresis.

4.2. Chemical Stimuli-Induced Pulsatile Systems

4.2.1. Glucose-Responsive Insulin Release-

For diabetes management, glucose-responsive systems use pH-sensitive hydrogels containing glucose oxidase. As blood glucose rises, glucose oxidase converts glucose into gluconic acid, altering the system's pH and triggering insulin release. When glucose levels drop, the system deswells, reducing insulin release. Examples of pH-sensitive polymers include chitosan and N,N-dimethylaminoethyl methacrylate.[39]

4.2.2. Inflammation-Induced Pulsatile Release

Inflammatory sites produce hydroxyl radicals that trigger the degradation of hyaluronic acid (HA) gels, leading to the release of drugs. This system can be used for treating inflammatory conditions like rheumatoid arthritis using anti-inflammatory drug-loaded HA gels.[40]

5. Drug Release from Intelligent Gels Responding to Antibody Concentration

Novel gels have been developed to release drugs based on the concentration of specific bioactive compounds, such as antibodies. These gels respond to antigen-antibody interactions, changing their swelling/deswelling behavior to release drugs in a controlled manner.

5.1. pH-Sensitive Drug Delivery Systems

pH-sensitive systems release drugs in specific parts of the gastrointestinal tract, utilizing the different pH levels found in the stomach and small intestine. Polymers like cellulose acetate phthalate and sodium carboxymethylcellulose are commonly used for enteric coatings, enabling targeted release in the small intestine.[41]

5.1.1. External Stimuli Pulsatile Release

Electro-Responsive Pulsatile Release

These systems use ionizable polymers (e.g., hyaluronic acid, polyacrylamide) that respond to both pH and electric stimuli. An electric field triggers-controlled drug release from these polymers.[42]

Micro Electro-Mechanical Systems (MEMS)

MEMS devices store and release drugs without moving parts. A microchip with drug reservoirs releases the drug when an electric potential dissolves a gold membrane. This technology allows precise control of release patterns, timing, and rate.

Magnetically-Induced Pulsatile Release: -

Magnetic materials (e.g., magnetite) in drug carriers allow external magnets to control the movement of capsules in the gastrointestinal tract, enabling controlled drug absorption and release timing.[43]

5.2. Pulsatile Release Systems for Vaccines and Hormones

Pulsatile systems can enable single-shot vaccines by controlling the timing of antigen and booster release. For hormones, pulsatile administration (e.g., GnRH in cows) shows higher effectiveness compared to continuous infusions, offering more efficient treatment options.

5.3. Marketed technologies used in PDDS: - [44,45]

Table 2 Marketed technologies used in PDDS

Technology	Mechanism	Proprietary name of dosage form	Api	Disease
PULSINCAP™	Rupturable system	Pulsincap™	Dofetilide	Hypertension
DIFFUCAPS®	Multiparticulate system	Innoprant XL tablets	Verapamil HC, propranolol HCL	Hypertension
OROS®	Osmotic mechanism	Covera- H5 XL tablet	Verapamil HCL	Hypertension
CODAS®	Multiparticular pH dependent system	Verelan® pm xl release capsule	Verapamil HCL	Hypertension
CONTIN®	Extended release tablet	Uniphyl®	Theophylline	Asthma
PULSYS™	Multiparticulate system	Moxatag™ tablet	Amoxicillin	Infection
$TIMER_x$®	Soluble barrier coating ER tablet	OPANA ®	Oxymorphine	Pain relief
CEFORM®	Extended release tablet	Cardiazem® LA	Diltiazem, Verapamil HCL	Hypertension

6. Recent advancements in pulsatile drug delivery systems PDDS)

Have shown considerable potential over traditional immediate-release formulations. These systems allow for less frequent drug administration, which in turn can enhance patient compliance. In recent years, increasing attention has been given to the development of drug delivery technologies that enable the release of active compounds in a pulsatile manner, with a programmable lag phase that begins after administration. Over the past two decades, significant progress has been made in developing time-controlled pulsatile release systems for bioactive compounds. These systems hold particular promise for treating diseases that require non-constant dosing, such as diabetes. Despite these advancements, further research is needed to refine and demonstrate the effectiveness of pulsatile delivery systems, especially for the precise delivery of bioactive compounds like hormones.

7. Conclusion

Sustained and controlled drug delivery systems have achieved considerable success in the field of medication. However, these systems often fail to align with the circadian rhythms of diseases, where pulsatile drug delivery systems offer significant advantages. The development of effective chronotherapeutic dosage forms requires a deep understanding of circadian rhythms, the 24-hour pattern of symptom intensity in chronic conditions, the pathophysiology of diseases, and the principles of chronopharmacology. Notable progress has been made in creating pulsatile drug delivery systems capable of delivering medication in a manner that better matches the fluctuating needs of patients, particularly for conditions requiring non-constant dosing regimens.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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