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Delayed Release Pellets: A Comprehensive Review

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ABSTRACT:

A notable advancement in pharmaceutical formulations, delayed-release pellets provide controlled release and targeted drug delivery for drugs that need to act locally in the gastrointestinal tract or are prone to gastric distress. The various mechanisms and varieties of delayed-release pellets such as enteric-coated, osmotically controlled, enzymatically activated, pH-dependent, time-dependent and diffusion-based systems are examined in detail in this thorough review. Commercially available drugs such as Delzicol, Cymbalta, and Dexilant demonstrate the clinical utility of delayed-release pellets in a range of therapeutic domains. Consideration is given to formulation components and machine variables that may have an impact on delayed release. The review highlights the effectiveness and versatility of delayed-release pellets, which provide more treatment alternatives, better patient compliance, and improved therapeutic results. Progress in this area of study and research has the potential to improve patient care and drug delivery.

Keywords: delayed release, Pellets, drug delivery, enteric coating, enzymatic activation,
pH-dependent release, osmotic pressure-dependent release, osmotically active ingredient,
Time-dependent release, marketed products

Introduction :

Medication known to produce gastric distress, be broken down in the stomach, or have a localized effect at a particular gastrointestinal region is indicated for use with delayed-release dosage forms. They release medication at predetermined time after delivery and target particular GI tract organ or a tissue. The delayed release may be time-sensitive or dependent on the environment (such as the pH of the gastrointestinal tract). [1], [2]. The two types of delayed release systems include:[2]

- Intestinal release systems
- Colonic release systems

1.1 Advantages provided by pellets for pharmaceutical formulation

When compared to single-unit dosage forms, multiparticulate drug delivery systems (MDDS) are innovative pharmaceutical dosage forms that have become more and more popular in recent years. These multi-unit dosage forms (MUDF) are composed of multiple independent subunits, or microparticles, each of which functions as a separate drug reservoir and distributes the drug in a desired manner without relying on the other subunits.
Multiparticulates are particularly well suited for the manufacture of delayed- or sustained-release solid oral dosage forms, which provide advantages including less variable gastrointestinal transit and a reduced risk of dose dumping. Nowadays, coated pellets that are formed into oral dosage forms by either filling them into hard gelatin capsules or by compressing them into tablet form (MUPS, or Multiple Unit Pellet System) are the most widely utilized multiparticulates.[4]
MUDFs, also called pellets, are tiny, free-flowing, spherical particles created through an assembly process that shapes finely ground grains or powders from bulk materials and excipients into spherical units. Their diameters vary from 0.2 to 2.0 mm. They can be easily formed into tablets and capsules. They have a variety of abilities, but one significant benefit is their ability to create a multidrug combination.[3]
Pellets offer advantages in pharmaceutical formulation, including a better understanding of pharmacokinetics, improved stability, and the ability to address physicochemical interactions. They provide consistent, predictable absorption and efficacy, increase stability and shelf life for unstable medications, and offer flexibility in formulating active chemicals into oral dose forms, including sustained release, gastro-resistant, and controlled release.
They offer several benefits for pharmaceutical formulation, including site-specific drug delivery, capacity for multiple drug strengths, low hygroscopicity, uniform shape and particle size distribution, and advancements in coating methods. They minimize systemic side effects, enhance therapeutic efficacy, and simplify manufacturing. Their low hygroscopicity ensures stability and extends shelf life. Polymer coatings can be tailored to achieve targeted release rates, improving therapeutic outcomes.[3]

1.2 Delayed Release Pellets

Small, spherical, or granular particles having a medication or active component, usually encased within a polymer covering or matrix, are referred to as delayed-release pellets. These pellets are made to release the medication into the gastrointestinal tract at a specific rate and location, which allows for controlled or sustained release of the drug over an extended period. Instead of being released right away after consumption, the delayed release feature makes sure the medication is delivered at a particular location in the digestive system, like the small intestine.[5]
Manufacturers can adjust the release profile to ensure controlled drug release over a predetermined length of time by adjusting the coating's thickness and composition.[6].

2. MECHANISMS OF DELAYED DRUG RELEASE

Drug release from these layered and coated pellets is typically controlled by a number of mechanisms, including diffusion, osmosis, or polymer erosion. A number of factors, including the characteristics of the coat (polymer types, coating level), the conditions of the coating process, and—perhaps most importantly—the core's properties, also have an impact.

Enteric coatings are made to withstand dissolution in the stomach's acidic environment but dissolve in the intestine's higher pH, enabling the release of medication there.

Enteric coating controlled delayed release

- Enteric coating polymers are primarily employed to prevent the release of the active pharmaceutical ingredient (API) in the stomach's acidic gastric fluid while still permitting release above pH 5.0.
- At low pH, they continue to be unionized and insoluble.
- Enteric polymer's functional acidic groups can ionize the intestinal fluid when the pH rises in the GI tract, causing the polymer to become soluble and swell in the small intestine.
- The swollen polymer still serves as a barrier, though, holding back the drug's release until it reaches the intended location in the GI tract.[7]
- Enteric polymers ionize and degrade to release medication from the underlying core when they reach more neutral to alkaline conditions typical of the intestinal milieu.[8]
- The drug granule surface substrates, coating solution, and polymer have to be compatible with one another.
- In order to ensure that the continuous film experiences as little deterioration as possible over time, Enteric polymer stability should be controlled and maintained both alone and in coating solutions.[7]

Ex:1**.** Hydroxypropyl Methylcellulose Phthalate (HPMCP): HPMCP is a pH-dependent polymer that is widely used for enteric coating.

2. Eudragit L, Eudragit S

3.Eudragit L 30D, Eudragit L 100-55[7]

Osmotic pressure controlled delayed release

osmotic effects might contribute to the control of drug release from coated pellets, a well as known process for devices containing an osmotically active core material (for instance sugar cores) surrounded by a semipermeable polymer wall. In these cases, an osmotic gradient is created across the polymer wall.[6]

- In this technique, a concentration gradient is created across the semipermeable membrane coating by the osmotically active substance included in the pellet cores. (for instance, sugar cores).
- Water permeates the pellet's membrane when they come into contact with an aqueous environment, including the gastrointestinal tract, dissolving the soluble components inside the core. As a result, there is an osmotic pressure difference between the inside and outside the pellets, resulting in a high solute concentration inside the core.[9]
- Water from the surrounding environment is sucked into the core through the semipermeable membrane as a result of this osmotic pressure gradient. The fast enlargement of the core due to this water inflow leads the membrane to expand, which in turn causes pores or channels to form in the coating. [9]

- Both the API and the osmotically active component can be released from the pellets into the surrounding media through these pores.

  The regulated release of the API is made possible by the addition of an osmotically active component to the pellet core, which improves the osmotic pressure gradient. The lag time and drug dissolution rate can be adjusted to obtain the appropriate delayed release profile by modifying the semipermeable membrane coating's characteristics and the core's composition.[9]

- The properties and composition of the polymeric barrier determine the water influx, which is measured as follows.

$$\frac{dv}{dt} = \frac{A\theta\Delta\pi}{l}$$

- Where dV/dt denotes the water flow,
- A is the membrane surface area, *l* the membrane thickness,
- θ the permeability of the polymeric membrane, and
- Δπ the difference in osmotic pressure (neglecting the counteracting hydrostatic pressure) [6]

Ex: **cellulose acetate** and other cellulose derivatives like **ethyl cellulose and hydroxypropyl methylcellulose** are examples of polymers that can be used to create

semipermeable membranes. These polymers have the necessary properties to allow controlled permeability of both water and solutes. [9]
The osmotically active ingredient's creation of an osmotic pressure gradient may also help postpone the drug's release until the pellets arrive in the intended region of the gastrointestinal system.

Enzymatically controlled delayed drug delivery [10]

The term "enzymatically delayed drug release" describes a process in which certain enzymes found in the biological environment act to either delay or modify a medication's release from a pharmaceutical formulation. In this case, the medication is formulated to withstand or delay drug release until it reaches a particular bodily location where these enzymes are active.

The procedure usually entails adding materials or components to the formulation that are sensitive to enzymes. These constituents may be engineered to experience enzymatic breakdown, resulting in modifications to the formulation's physical characteristics, including dissolution, swelling, or erosion, which in turn initiates the drug's release.

Ex: Pectin-based systems for colon-specific drug delivery via oral route**.** Pectin is a structural polysaccharide found in plants that remains as macromolecule aggregates in acidic environments. Pectin aggregates have a tendency to dissociate and expand in neutral solutions. Additionally, while a lot of the colon's microflora break down pectin, it is resistant to the active proteases and amylases in the upper GI tract. Owing to these characteristics, there's a good chance pectin will serve as a means of transporting protein and polypeptide medications from the mouth to the colon.
Pectin is completely broken down by the pectinolytic enzymes of the colonic microflora, but the enzymes of the upper GIT do not break them down.
This microflora's makeup is largely constant among a wide range of human populations. Pectin-derived drug carriers therefore provide encouraging possibilities for colon-specific medication administration.

PH dependent release.[13].

Tartaric acid pellets are widely employed in formulations requiring pH-dependent release. The acidic property of tartaric acid enables drug release in the lower gastrointestinal system, where the pH is higher and drug absorption is best. They function as carrier systems and a pH modifier in weakly basic drug formulations. In higher pH environments, like the lower intestine, these medications generally exhibit poor solubility, which can be improved by using TAP as a starting core.
Ex: The solubility of Dabigatran Etexilate is pH sensitive and decreases at more neutral pH ranges ; therefore, tartaric acid pellets were used as a core pellet in the formulation of Dabigatran Etexilate mesylate pellets, which create an acidic environment that helps the drug dissolve.

Diffusion[11]

Rate release in diffusion systems is dependent on how quickly the drug dissolves through a barrier, often a polymer. [12]
Release from multiparticulate dosage forms coated with water-insoluble polymers may happen via a number of different processes.
2.5.1. Diffusion through the continuous plasticized polymer phase: According to this mechanism, the plasticizer and other additives are uniformly distributed throughout the polymer, which is assumed to be a continuous phase. The cross-linked polymer chains in the polymer film have molecular-sized openings. The drug molecules most likely diffuse through these openings via a process called hindered molecular diffusion. The plasticizer and other additives work together to wet the openings, which is necessary for the drug molecules to diffuse.
Diffusion through plasticizer channels: In cases where the plasticizer content is high and the plasticizer is not evenly distributed throughout the film, the plasticizer may conceptually manifest as a continuous phase in the form of patched channels. It is feasible that the drug would be preferentially transported through such plasticizer channels if its solubility in the plasticizer is greater than its solubility in water.
Diffusion through aqueous pores: The coating in this model is dotted with pores rather than being uniform and continuous. When the dosage form comes into contact with an aqueous medium, these pores fill with solution, which helps with the diffusion of the drug.

3.TYPES OF DELAYED RELEASE PELLETS

3.1 INTESTINAL RELEASE

Enteric-coated pellets: [14]

1. Duloxetine-containing enteric-coated pellets, which are an inhibitor of serotonin-norepinephrine reuptake (SNRI).

The product being marketed is Cymbalta® Delayed-Release Capsules, which contain duloxetine hydrochloride. Enteric-coated pellets containing duloxetine hydrochloride are used in Cymbalta to treat major depressive disorder, generalized anxiety disorder, and other medical conditions. The enteric coating protects the drug from degrading in the stomach's acidic environment, ensuring that it is delivered into the higher pH of the intestines for optimal absorption.

In order to prevent drug degradation in the stomach and to release the medication when the enteric-coated pellets are delivered to the small intestine, duloxetine hydrochloride, which is commercialized, is manufactured into enteric-coated pellets using fluidized bed coating technology.

2. Pancrelipase, an extract from pig pancreatic glands, is the main ingredient in **CREON**, a pancreatic enzyme preparation. Lipases, proteases, and amylases are among the several enzyme classes found in pancrelipase. [15]

Combining porcine-derived lipases, proteases, and amylases, CREON® (pancrelipase) Delayed-Release Capsules is a pancrelipase that is prescribed to treat exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other ailments. [15]

- Enteric-coated spheres (0.71–1.60 mm in diameter) are present in every delayed-release capsule intended for oral use.[16]
- Marketed product: Creon® (pancrelipase)

3. pH-dependent release (dual delayed-release formulation). [17]

EX: DEXILANT (dexlansoprazole) delayed-release capsules for oral use.

For oral use, DEXILANT is provided in capsule form as a dual delayed-release formulation. Dexlansoprazole is included in the capsules as a combination of two kinds of enteric-coated granules with varying pH-dependent dissolving characteristics.

The dual delayed-release approach combines two independent sets of enteric-coated granules to deliver two distinct, pH-dependent drug releases. (4)

- The first set of granules are released into the proximal duodenum (pH 5.5), which holds around 25% of the drug dosage, when the granule-containing gelatin capsule dissolves in the stomach after ingestion.
- This also raises the plasma concentration early (1-2 hours), similar to other PPIs.
- A second concentration peak occurs four to five hours after consumption because the remaining 75% of granules are intended to be released in the distal small intestine (pH 6.75). With this delivery mechanism, acid suppression lasts longer, and there may be less need for several daily doses.

COLONIC RELEASE

1.Using a pH-dependent polymer for coating

The pH-dependent release of mesalazine from SALOFALK granules is facilitated by their Eudragit-L coating. Eudragit□ L is an anionic polymer, which dissolves above pH 6.0[19]. It ensures gastric resistance to enable the active ingredient, mesalazine, to be released in a pH-dependent manner and allow a reliable distribution at the targeted site of action, which is the ileocoecal area. In addition, the granules' particle core has a matrix system that releases mesalazine independently of pH. **[18]**

2. Time-dependent delayed release pellets [19]

Mechanism of time-dependent release:

After oral administration, the pellets are protected by an external gastroresistant polymer coating and are anticipated to stay intact in the stomach, where the residence duration varies. It would "know" that it has left the stomach upon entering the small intestine because of the pH shift, or the triggering phase. After the enteric coating dissolves in the duodenum, the delay phase—during which no release should occur—can begin and last for at least four hours (the amount of time needed to reach the colon). A solvent-activated mechanism, such as the dissolution, erosion, dispersion, or swelling of various polymeric or non-polymeric components, is what drives the delay phase.

Following the delay phase, the drug release would occur in accordance with the characteristics and design of the drug-containing core of the pellets. Depending on the requirements of the formulation and the intended therapeutic outcome, this release can be either immediate or prolonged.

Ex: Budesonide's colon delivery formulation was created using a pH- and time-dependent method, compressing film-coated pellets into multiparticulate tablets. Budesonide is one of the standard drugs used for the localized treatment of inflammatory bowel diseases and is a potent glucocorticoid. [28]

MICROBIALLY-CONTROLLED (OR MICROBIALLY-DEPENDENT) SYSTEMS [19]

These systems operate by taking advantage of the unique enzymatic activity of the colon's enterobacteria, or microflora. The majority of colonic bacteria are anaerobic, and they release digestive enzymes that may break down substrates like proteins and carbohydrates that escape digestion in the upper GI tract.

Biodegradable polymers appear to be a more site-specific method for colon-specific drug delivery because biodegradable enzymes are only found in the colon. In addition to transporting the medication to the colon, these polymers protect it from the environment found in the stomach and small intestine. As they reach the colon, they are either broken down by an enzyme, assimilated by microorganisms, or the polymer backbone breaks down, releasing the drug.[31].

The most prevalent methods of microbial activation in the colon are glycosidic-bond hydrolysis and azo-reduction.
Ex: olsalazine sodium or azodisal sodium (Dipentum capsules), balsalazide disodium (Colazal capsules)

4. Factors Influencing Delayed Release

Numerous factors, particularly those related to machine performance and formulation, might affect the delayed release of drugs from pellets.

Formulation elements:

- **Composition of enteric coating**: A key factor in postponing drug release is the selection and makeup of the enteric coating material. Enteric coatings delay the release of the medication until the pellets reach the intended site of action by resisting gastric acidity and dissolving in the higher pH environment of the intestines.[21]

- **Coating thickness**: The most crucial component of coated pellets is the coating thickness; if it was not properly controlled, the finished product would not have the expected functionality. In the case of immediate release dosage forms with protective coating, coatings that are too thick may cause a delay in the disintegration or dissolution, while coatings that are too thin may not guarantee the desired functionality in the case of delayed release dosage forms. Therefore, to guarantee the quality of solid dosage form products, coating thickness needs to be carefully regulated.[29]

- **Core formulation:** The drug release kinetics can be greatly influenced by the nature of the starter core material. For example, a highly hygroscopic core material like sugar can increase the amount of water influx into the coated system. The continuous penetration of water into the pellets is likely to cause a hydrostatic pressure within the pellets to increase monotonically. On the other hand, inert core materials, like microcrystalline cellulose, are thought to be osmotically neutral and do not cause the pellets to absorb a significant amount of water when they come into contact with aqueous environments. [6]

- **Type of drug:** The physicochemical characteristics of the drug in the formulation may significantly affect the release of the drug. Since only the dissolved medicine can diffuse through the intact polymeric layer or through water-filled pores, the drug's water solubility is crucial. Because of this, drugs that are highly soluble in water are typically released at a faster rate than those that are not. However, the drug's solubility in the polymeric film coating may also be crucial for the release behaviour, in addition to its solubility in the release media. [6]

- **Subcoating:** Sub coating is mostly used to protect the drug coated pellets from environmental factors and enteric coating. Water-soluble drug migration and drug-polymer interaction are inhibited by the polymeric subcoats' ability to seal the substrate from the aqueous enteric film coating. [22] [2].

Factors pertaining to machines: [20] [23] [24]

- **Coating equipment**: The choice and configuration of coating equipment have a major impact on coating quality during the delayed release pellet preparation process. In particular, devices like the Wurster apparatus allow for precise and continuous coating, ensuring consistency as well as efficiency in the formation of layers. Fluidized bed coater column with a Wurster insert is one of the systems that works best for coating particles . Its ability to prevent dead zones is one of its primary benefits. The thickness and homogeneity of the coating are largely dependent on variables such as pump RPM, blower speed, inlet air temperature, and spray rate and drying conditions. Understanding and optimizing these variables is crucial in achieving consistent and high quality enteric coatings within the pharmaceutical production process.

- **Process variables**: A number of variables such as
- Process variables (inlet air temperature, air velocity, spray rate, and atomization pressure)

- Ambient variables (ambient air temperature and ambient air relative humidity)

- Thermodynamic variables (outlet air temperature and outlet air relative humidity)

- can have an impact on the coating procedure and the characteristics of the final pellets. The thickness and homogeneity of the coating are largely dependent on variables such as pump RPM, blower speed, inlet air temperature, and spray rate and drying conditions. Understanding and optimizing these variables is crucial in achieving consistent and high quality enteric coatings within the pharmaceutical production process.

- **Equipment Maintenance**: To guarantee uniform coating application and consistent drug release properties, coating equipment must undergo routine maintenance and calibration. Variability in drug release from batch to batch may be caused by equipment failures or deviations from ideal operating conditions.

- **Training and experience of the operator**: Ensuring the quality and uniformity of delayed-release pellet formulations depends in large part on the operator's proficiency using coating equipment and supervising the coating process.

5. Applications of delayed release pellets

There are several uses for delayed medication release pellets in the pharmaceutical industry, such as:

Gastroesophageal reflux disease (GERD), peptic ulcers, and dyspepsia are among the conditions linked to stomach acid that are frequently treated using delayed-release pellets. These formulations guarantee targeted delivery to the site of action in the intestines and protect the medication from breakdown by stomach acid by delaying drug release until the pellets reach the small intestine, where pH values are higher.[25]

Chronotherapy: In order to maximize therapeutic results and reduce adverse effects, chronotherapy entails giving drugs at particular intervals. In order to facilitate scheduled drug administration and compliance with circadian rhythms, delayed-release pellets can be engineered to release the medication within the gastrointestinal system at a certain time or location. This method works especially well for disorders like asthma, arthritis, and cardiovascular issues that have symptoms that change throughout the day. [26]

Long-lasting medication action: It is possible to create delayed-release pellets to have a long-lasting medication effect. These formulations can reduce the frequency of dosage and increase patient compliance by extending the duration of therapeutic drug concentrations in the body by regulating the rate of drug release from the pellets.[3]

Targeted medication delivery: Certain gastrointestinal tract segments can be the target of a medicine administered using delayed-release pellets. Depending on the intended site of action, formulations can be created to release the medication in the duodenum, or other areas of the intestine by choosing enteric coatings that dissolve or disintegrate at particular pH levels. [14][16][19]
Coated pellet-based colon delivery systems can take advantage of the natural pH fluctuations that occur in the small and large intestine, be broken down enzymatically by the colonic microbiota, or delay release until the dosage forms have had time to reach the colon. [30]

Combination therapy: Multiple medications with distinct release patterns can be combined in combination products made with delayed-release pellets. Drugs having immediate-release, delayed-release, Extended delayed-release or sustained-release properties can all be included in one formulation to maximize combination therapy's benefits, decrease adverse effects, and increase efficacy.[27]

6.MARKETED PRODUCTS OF DELAYED RELEASE PELLETS

MARKETED NAME	**API**	**RATIONALE**
Dexilant	Dexlansoprozole	Acid reflux and other stomach and oesophageal issues are treated with Dexlansoprazole. It functions by reducing the amount of acid production in the stomach. It relieves the symptoms of heartburn, difficulty swallowing, and coughing. This drug helps in the healing of acid damage to the stomach and oesophagus, protects against ulcers, and can protect against oesophageal cancer. Dexlansoprazole is a member of the proton pump inhibitor (PPI) drug class.
Cymbalta	Duloxetine	The following conditions are approved for treatment with Cymbalta in adults: major depressive disorder (MDD) • Anxiety disorders in general (GAD) • discomfort brought on by diabetic neuropathy (damage to the nerves) • fibromyalgia • long-term musculoskeletal pain, which includes discomfort in the tendons, ligaments, muscles, and nerves

Pradaxa	Dabigatran	It aids in preventing blood clots from forming in the veins following surgery. It is used to reduce the risk of stroke in patients suffering from atrial fibrillation. Additionally, blood clots in the veins or lungs can be treated or prevented using it.
Delzicol	Mesalamine	used as a treatment for ulcerative colitis. It helps in reducing stomach pain, rectal bleeding, and diarrhoea associated with ulcerative colitis. Mesalamine is a member of the Aminosalicylate drug class. It functions by reducing swelling in colon.
Prevacid	Lansoprazole	Used to treat disorders involving excessive production of stomach acid, such as gastroesophageal reflux disease (GERD) and also in • NSAID-Associated Gastric Ulcer • Treatment Of Active Benign Gastric Ulcer • Maintenance Of Healed Duodenal Ulcers
Nexium.	Esomeprazole	Used to treat symptoms of gastroesophageal reflux disease (GERD). The following conditions are the most typical ones for which Nexium is used: Indigestion, or dyspepsia: Heartburn, nausea, and discomfort and fullness in the upper abdomen are among the symptoms.
Entocort EC	Budesonide	ENTOCORT EC is used as therapy for mild to moderate active Crohn's disease affecting the ileum and/or ascending colon.

7. CONCLUSION

In conclusion, delayed-release pellets are a viable method for the manufacture of pharmaceuticals, offering several benefits such as enhanced stability, targeted drug administration, and pharmacokinetics. For medications that induce gastric discomfort, are broken down in the stomach, or need to be delivered to a specific spot, these pellets are indispensable. They release medication at a specified time and location in the gastrointestinal system. Drug release patterns can be customized to meet individual therapeutic demands by a variety of mechanisms, including enteric coating, osmotic pressure control, enzymatic activation, time dependent and pH-dependent release. Prior to adding polymers, API, and other excipients to the formulation, it is important to completely comprehend their physiochemical and physiological constitution. To guarantee reliable and efficient drug delivery, factors affecting delayed release that are connected to the formulation (coating composition and core formulation, type of drug) as well as the process (coating equipment and operator experience) must be carefully taken into account.

Delayed-release pellets are used in several therapeutic domains, such as combination treatment, chronotherapy, long-acting medications, targeted delivery, and gastrointestinal diseases. Dexilant, Nexium, Pradaxa, Cymbalta, and Delzicol are examples of commercially available medications that use delayed-release pellets and show the clinical and financial feasibility of this formulation strategy.

Overall, the thorough analysis shows how delayed-release pellets may help the pharmaceutical sector by increasing treatment options, increasing patient compliance, and boosting therapeutic efficacy. New avenues for improved drug delivery and therapeutic results will continue to be opened up by more research and development in this area.

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