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Strategies and Approaches for Designing of Press-Coated Tablets for Chrono drug Delivery System

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Abstract: *Chronotherapeutic drug delivery system (CDDS) are innovative approaches designed to optimize the timing of drug release to align with the body's natural circadian rhythms. The physiological and biological states of the human body fluctuate significantly throughout the day, leading to variations in both the condition of diseases and the levels of drugs in the plasma. In the development of CDDS, press-coating technology-an inventive method of controlled drug release - has gained concern. By applying a coating around a drug core, this technique gives exact control over the drug's release profile. One special benefit of the press-coating process is that it guarantees the release of the active pharmaceutical ingredient (API) at specific times that correspond with the body's biological rhythms, particularly in conditions where symptoms vary over time (e.g., hypertension, asthma, arthritis).The press-coating method is a perfect match for chronotherapy because it uses compressive pressures to encapsulate the medicine in a multi-layer structure that can be made to react to different stimuli like pH, enzymes, or pressure. The coating's thickness and composition can be altered to create systems that can delay release, shield the medication from deterioration, and ensure targeted delivery. Better results will come from medications and treatments that are administered in alignment with the body's circadian rhythms. The methods of press-coating drug delivery and its production in chronotherapeutic drug delivery are the primary focus of this review. It analyses the different coating materials, the variables influencing press- coated delivery systems' performance and drug release. The possible advantages of these systems are also covered, including increased therapeutic efficacy, decreased side effects, and better patient compliance. In order to prepare the way for next-generation chronotherapeutic systems, the paper ends with future perspectives on combining press-coating technology with other modern drug delivery techniques.*

Keywords- *Chronotherapy, Circardian rhythm, Press-coating technology, CDDS.*

INTRODUCTION

In general, "chrono" refers to the knowledge that every metabolic activity undergoes periodic variations across time (1). The fields of chronobiology and pharmaceutics are combined to form chronopharmaceutics (2). Pharmaceutics concentrates on the creation of dosage forms (4), whereas chronobiology investigates biological rhythms and the mechanisms that underlie them (3). The study of chronopharmacology looks at how various medications' pharmacological effects change over the course of the day (5). Over a day, the physiological and biological parameters associated with human structure can change dramatically, leading to alteration in disease states and level of drug in the plasma. Based on the sleep-wake cycle, the human circadian rhythm is impacted by hereditary variables and impacts daytime and nighttime body activities. There is strong evidence that some illnesses are caused by biological timing. For example, certain hormones are secreted as you sleep, while others are released in the morning. As a result, diseases like gastric ulcers, arthritis, asthma, hypertension, and allergic rhinitis coincide with the body's circadian cycle (1,6).

By definition, targeted drug administration into the lower gastrointestinal tract—which mostly takes place in the large intestine, or colon—is referred to as Colon-specific delivery. For the localized therapy

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of a number of colonic disorders, primarily IBD conditions (such as irritable bowel syndrome, Crohn's disease, colon cancer, ulcerative colitis site-specific medication administration to the lower GI tract is beneficial (7–10).Colonic administration may also be used chronotherapy (11) and in the treatment of nicotine addiction (12).

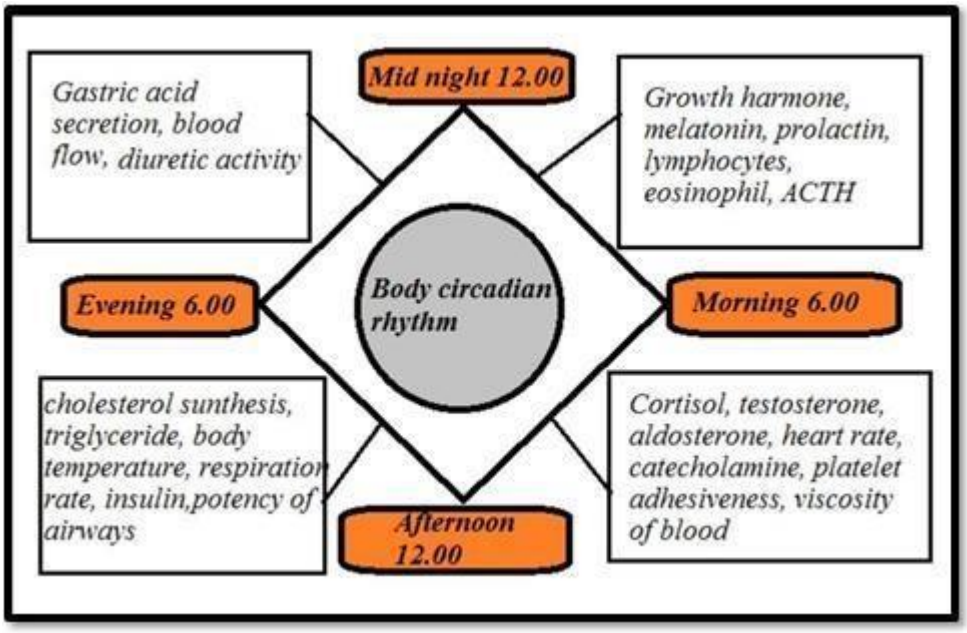

Figure 1: Structure of circadian rhythm of body.

❖ Chronotropic systems, a unique medication delivery method, have been designed for these specific reasons:

i. Chronopharmacotherapy for illnesses when the pathophysiology is significantly influenced by circadian rhythms.

ii. To prevent medication degradation (proteins and peptides) in the proximal gastrointestinal tract.

iii. For hormone transport that is programmed, controlled release dose forms may cause disruptions to the body's normal feedback mechanism and may also result in the development of resistance.

iv. For medications that target a particular location in the gastrointestinal system, such as the colon, and that undergo considerable first pass metabolism, such as nitroglycerines, which acquire biological tolerance (2).

Local environmental stimuli are another way that medicine can be released (13). The presence of a biological substance is necessary for this kind of medication release. An illustration of this technique necessitates the release of insulin when glucose is present. Other delivery systems have been created that use temperature, ultrasound, electricity, inflammation, antibodies, and other triggers to release drug.

Another chronotherapeutic condition is cancer. High intravenous drug dosages are necessary for cancer treatment in order to eradicate a significant number of malignant cells; normal cells are also eliminated, but this results in unpleasant side effects (14,15). The degree of cytotoxicity in different cancer drugs can be linked to the time of drug delivery (14,15). According to this review, chronotherapy can strongly influence on cancer patients' quality of life and survival rate.

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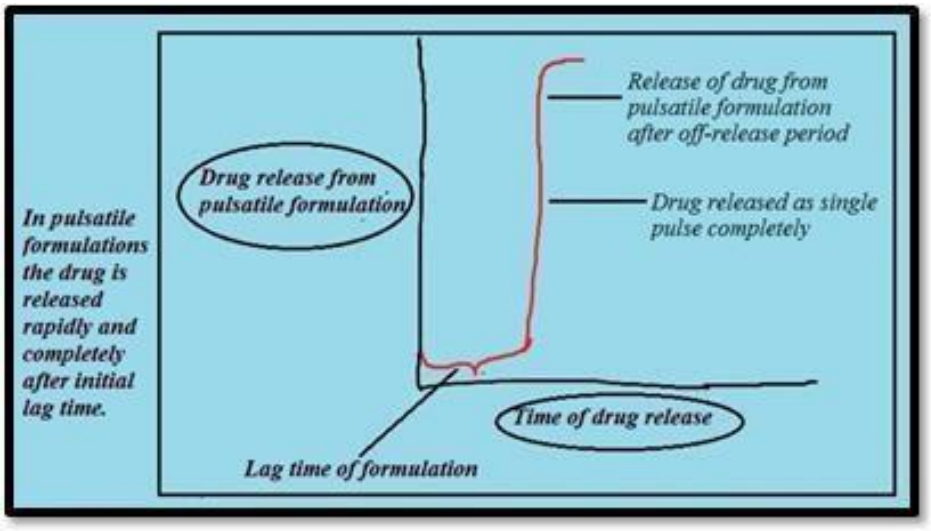

Figure 2: Drug release profiles of pulsatile systems.

Circadian Rhythms:

Most living organisms, including animals, flora and microorganism , exhibit circadian rhythms, which are 24-hour cycle changes that are thought to be a normal course of action in relation to light and dark effects (16). Typically, circadian rhythms are aligned with the interensic biological rhythms associated with the sleep-wake pattern, and they regulate many bodily functions, including metabolism, hormone production, sleep patterns, gastric acid production, and physiology (17).

Chronotherapeutics

Drug distribution that corresponds with the natural course of a disease over a predetermined amount of time is the focus of chronotherapeutics (18).

Chronotherapy:

Chronotherapy is the coordination of medicinal therapies with biological rhythms.

Chronobiology

Chronobiology examines the biological causes of illnesses using a temporal framework (19). Chrono denotes time, whereas biology is the study of life, or the science of it.

Chronopharmacology [20]

The analysis of pharmacological impact of various medication alter during the day is known as chronopharmacology.

Chronopharmacokinetics [20,21]

Many physiological systems that exhibit circadian rhythm change the pharmacokinetic properties that are generally assumed to be constant over time. The study of how drug distribution, metabolism and excretion evolve over time is known as chronopharmacokinetics.

CHRONOPHARMACEUTUICS

Definition and concept

The terms "chronobiology" and "pharmaceutics" make up chronopharmaceutics. The study of biological rhythms and their mechanisms is known as chronobiology. Our bodies have three different kinds of mechanical rhythms:

a. **Circadian rhythms:** The Latin words "circa," which means "about," and "dies," which means "day," were used by Franz Halberg to create the term "circadian." Our bodies oscillate during the course of a 24-hour period, which is known as a circadian rhythm.

b. Ultradian rhythms: Oscillations that occur more than once in a 24-hour period are referred to as ultradian rhythms.

c. Infradian rhythms: Infradian rhythms are cycles that extend beyond twenty-four hours (less than 1 cycle each day).

Positive points of chronotherapeutic drug delivery system:

1. Enhanced efficacy, repeatability, tolerability, and bioavailability.
2. There is an improvement in patient compliance (22).
3. For medications displaying chronopharmacological characteristics.
4. Prevents peak-valley fluctuations by maintaining consistent drug levels at the activity site.
5. Improves tolerance and lessens negative effects.
6. There is a decreased chance of local discomfort and less dose dumping (22).
7. It is possible to lower the medication's dosage without compromising its therapeutic efficacy.
8. Increase patient comfort and stability.
9. Medication and drug administration adapt to human circadian cycles.
10. It enables the transportation of weakly bioavailable drugs, such as proteins and peptides, that are unstable in the GIT environment (23,24).
11. Less cytochrome P450 isoenzymes result in fewer medication interactions.
12. Different dosages are possible with pulse delivery in a solitary dosage form.

Negative Points of Chronotherapeutic Drug Delivery System:

1. After the treatment, a non-24-hour sleep-wake syndrome develops because the patient sleeps for more than 24 hours. Although it's not very prevalent, it's unknown how risky it is.
2. A person may occasionally experience sleep deprivation.
3. During chronotherapy, a person becomes less productive, and it will be a little uncomfortable to stay up till the other timetable.
4. Because therapy takes time, you will need to take a break from your hectic daily routine.
5. This therapy requires medical supervision. Additionally, it is advised to see sleep specialists on a regular basis.
6. Until the following sleep schedule, one must keep himself awake. In order to keep oneself up till the other schedule, he must occupy himself.
7. The person receiving therapy may occasionally feel abnormally hot or cold.
8. To prevent side effects, you must see your doctor frequently (25).

SITUATIONS ENCOURAGING FORMULATION OF PDDS:

Table 1 lists the following circumstances that call for pulsatile formulations that are beneficial for patients with enhanced therapeutic efficacy. Figure 3 illustrates the circadian pattern of a number of illnesses when symptoms are heightened.

Bronchial Asthma

In individuals with asthma, airway resistance gradually rises during the night, indicating the importance of sleep-wake cycle in both the pathophysiology and for management of asthma. Asthma is regarded as a common disease that exhibits circadian rhythms in its pathophysiology. Early mornings are when

histamine, a bronchoconstictor, is released (26). Cortisol, an anti- inflammatory drug released in the morning, also causes more asthma attacks during the morning hours, necessitating the release of a bronchodilator at a time when symptoms are at their worst, resulting in therapeutic action (27).

Peptic Ulcers

It is clear from observations and research that the gastrointestinal tract is highly susceptible to circadian rhythms. This could be explained by the fact that during the night, the stomach secretes a lot of acid and its motility, including its emptying, is slow. As a result, Drug absorption, solubility, and disintegration may be hindered (28). Patients with peptic and duodenal ulcers are treated by suppressing their nocturnal acid secretion, which is thought to be higher at night. Since maximum acid secretion, ulcer-related suffering and gastric ulcer and duodenal ulcer perforation are more likely at night, these histamine blockers are best used before bed rather than throughout the day for an efficient course of treatment (29). In order to achieve the anticipated therapeutic efficacy, these medications must be administered as PDDS at bedtime, which would release the medication at night after a predetermined lag time (30).

Cardiovascular Disease

Numerous cardiovascular conditions, including those affecting heart rate, stroke volume, blood pressure (BP), cardiovascular system blood stream and cardiac output exhibit the circadian rhythm pattern. For example, vascular reactivity and capillary resistance are higher in the morning and fall later in the day (26). It has been noted that aggregation of platelet rises and thrombolytic activity falls in the morning, resulting in hypercoagulability of the blood. In the morning, blood pressure and heart rate rise. The blood pressure drops in the middle of the day, reaching its lowest point at midnight. The morning surge is the term for the apparent spike in blood pressure that occurs after one awakens (31,32). A large number of myocardial infarctions occur between 6 a.m. and noon, and they are seen to occur more frequently in the morning. According to reports, the causes include an increase in platelet aggregation, vascular tone, catecholamine release, and cortisol. In these circumstances, chronotherapy is recommended to administer the medication at the proper concentration at a moment of acute need. Angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, and nitroglycerine are among the treatments.

Table no.1 Conditions benefitted by chronotherapy.

Disease	**Circadian rhythm of disease**	**Category of drugs used**	**Examples**	**References**
Cardiovascular diseases	BP is low during the sleep cycle and rises steeply during the early morning awakening period	a. Calcium channel blockers b. ACE inhibitors c. Nitroglycerine	a. Dilitiazem, Amlopdipine b. Lisinopril, Enalapril c. Nitroglycerine	(33)
Attention deficit Hyperactivity Disorder	Elevation in DOPA levels in the afternoon	a. Stimulants	a. Methylphenidate, amphetamine	(34)
Arthritis	Morning pain followed by greater pain at night	a. Glucocorticoids b. NSAIDs	a. Ibuprofen, Diclofenac b. Exogenous glucocorticoidslike prednisone in low dose	(2)
Asthma	Onset of attacks during the night or early morning hours	a. β2 agonist, b. Anti- histamines	a. Albuterol, Terbutaline b. Fexofenadine, cetirizine	(35)

			c. Loratidine	
Peptic Ulcer	There is a higher acid secretion in the afternoon and evening	a. H2 Blockers	a. Cimetidine, famotidine	(36)
Hyper cholesterolemia	Cholesterol production is typically greater during the night compared to the daytime	a. HMG CoA reductase inhibitors	a. Lovastatin, Simvastatin	(24)
Diabetes mellitus	Increase in the blood sugar level after meal	a. Sulfonylurea b. Insulin c. Biguanids	Omeprazole, Lansaprazole	(35)
Neurological Disorder	The central pathophysiology of epilepsy and the behavior of convulsive events	MAO-B inhibitors	a. Selegiine b. Rasagiline	(38)
Cancer	Tumor blood flow is three times higher during each active phase of the circadian cycle compared to the rest phase.	a) Alkalyting agents b)Antimetabolites c)Antimicrotubular agents	a. Nitrosoureas, platinum analogs like cisplatin b. Folate antagonists like methotrexate c. Vinca alkaloids like vincristine	(38)
Duodenal Ulcer	Gastric acid secreation is highest at night, while gastric and small bowel mobility and gastric emptying are all slower at night.	a. Proton pump inhibitors	a. Omeprazol, Lansaprazole	(37)

Arthritis

Patients with osteoarthritis tend to have greater pain at night and less in the morning, whereas those with rheumatoid arthritis typically have significant pain that increases in the morning and decreases as the day goes on. The presence of a circadian pattern in the plasma concentrations of C-reactive protein and interleukin-6 in individuals with rheumatoid arthritis is explained by chronotherapeutics and the chronobiology of pain (35). In these conditions, chronotherapy offers a planned release of medications, such as NSAIDS (non-steroidal anti-inflammatory drugs) like Ibuprofen, ketoprofen, and glucocorticoids for all forms of arthritis in order to ensure that the drug is available at high blood levels at the site of activity when pain is high (39).

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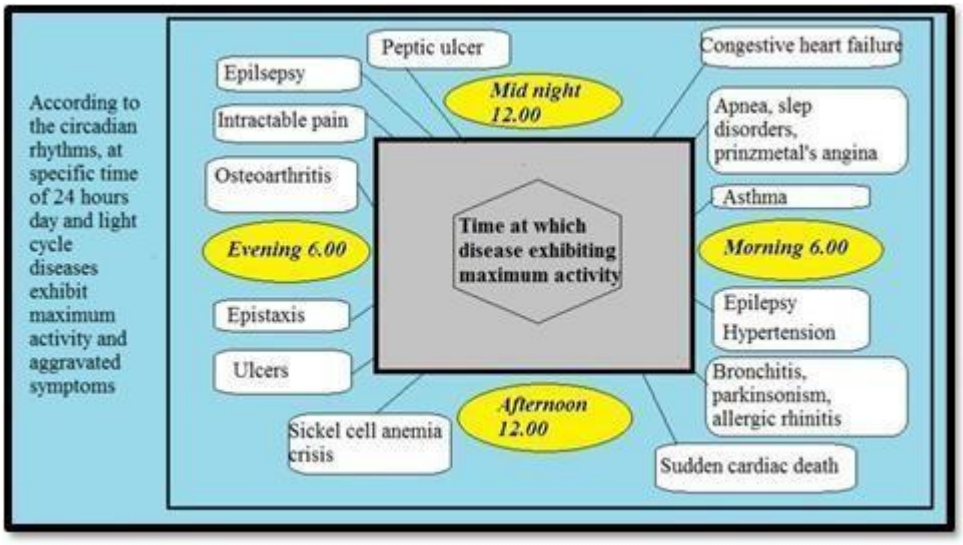

Figure 3. Circadian rhythm of various diseases when symptoms are exaggerated.

Asthma

Hyper responsiveness to a range of stimuli is a characteristic of asthma, a chronic inflammatory illness of the airways. Conditions such as asthma cause the lungs' functions to deteriorate and the airways to become more sensitive. The importance of circadian rhythms in the pathophysiology and management of asthma has been established and concluded by research scholars based on extensive studies. These studies show that airflow resistance gradually rises during the night in patients with asthma, then drops to its lowest level in the early morning. These indications usually appear during midnight and, more specifically, about 4 am (40,41). For the treatment of asthma, Padmaxi et al. developed the One-Pulse Drug Delivery System using a press-coated tablet form of montelukast sodium. In accordance with the requirements of chronotherapeutic drug delivery, a press-coated tablet's preprogrammable time-controlled release was obtained over a preplanned time lag of five hrs, and sudden release was attained after an interval (42).

Cerebrovascular accidents

Cerebrovascular accidents are more often in the morning (43) between 10:00 am and 12:00 pm, and they are less common in the afternoon and evening.

Pain

Not every tissue will exhibit the same systematic pattern in terms of the level of pain a patient experiences or the threshold of pain (43). When it comes to acute pain, it has been found that circadian cycles influence the pain pattern. In instances like dental surgery, where a high morning peak pain is noted on the first day following the procedure, it is documented (44).

Sleep disorders

Although there is diversity among individuals, the amount of time and duration of sleep required for each person will be largely constant (45). Sleep involves a circadian rhythm combination of changes in numerous systems including but not only limited to physiological, biochemical, and psychological activities.

Cancer

Chemotherapy may be more effective and less harmful if cancer medications are given to patients carefully at specific times, taking advantage of tumor cell cycles, resulting in fewer side effects and less toxicity to healthy tissue (46). This is supported by research on both humans and animals. Blood flow to the tumors exhibits circadian cycles, usually three times higher during the daily rest phase when engaging in daily activities.

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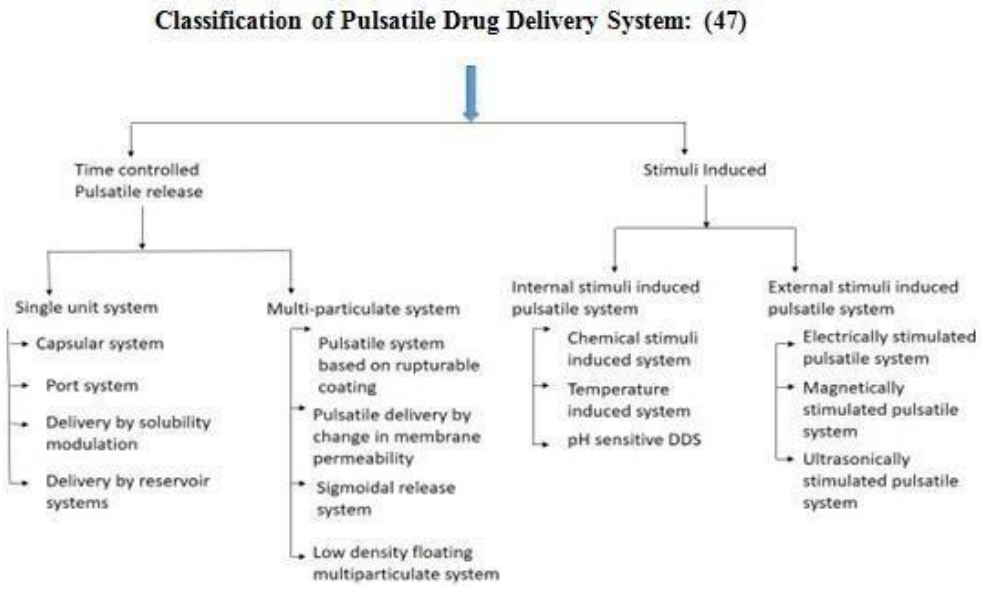

❖ **Single unit system**

i) **Pulsicap system/Capsular System**: It is made consisting of a cross-linked hydrogel plug that expands when it comes into contact with the medication's dissolving media or gastrointestinal fluids, forcing the drug out of the water-insoluble capsule body (48, 49). The medicine is released instantly after the plug expands and pushes itself out of the capsule after a period of time after coming into touch with the dissolving media or gastrointestinal fluids. One example is the Pulsincap system, which features a water-insoluble capsule that contains a medication formulation. The time lag can be modified by adjusting the dimension and the position of the plug. Effervescent agents or disintegrants can be added to water-insoluble medications to guarantee a rapid release. The plug material is made up of glycerylmonoole, and enzymatically controlled erodible polymers, like pectin), erodible compressed polymers (like hydroxyl propyl methyl cellulose, polyvinyl alcohol, and polyethylene oxide), and insoluble but permeable and swellable polymers (like polymethacrylates).

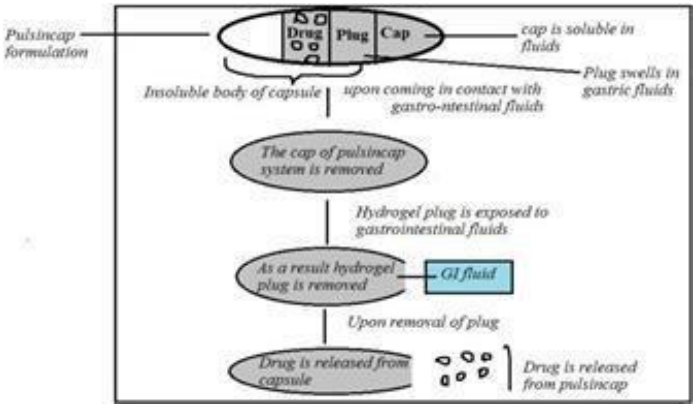

Figure 4: Drug release from pulsincap system.

ii) **Port systems**: Inside a gelatin capsule that is surrounded by a cellulose acetate membrane which is semi-permeable are the medication, an osmotic active agent, and an indissoluble barrier. After a lag period, the plug is expelled due to elevated internal pressure caused by the imbibing of stomach contents. Fluid enters the system through a semi-permeable layer upon interaction with the dissolution medium, dissolving the osmotic agent and producing osmotic pressure, which causes the solid blockage to be removed after a designated period of delay (50,51).

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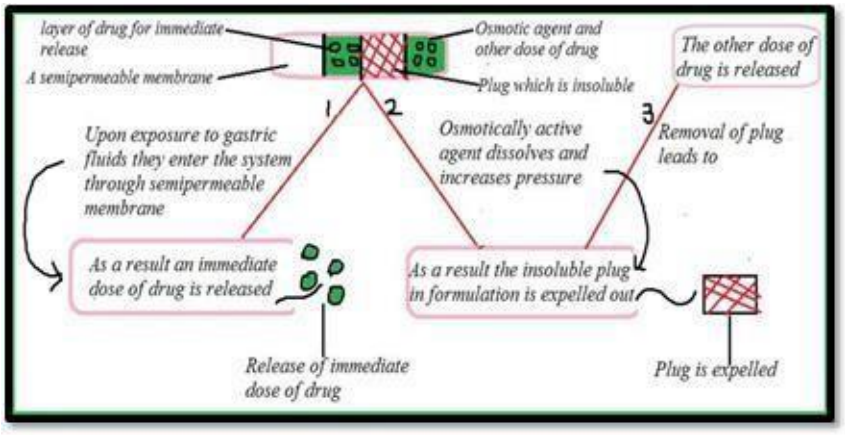

Figure 5: Schematic representation of PORT system.

iii) Delivery by solubility modulation:
A chronotherapeutic system is required for the pulsatile delivery of pharmaceuticals provided by the solubility modulation of formulation design. These formulation types were specifically developed in order to deliver medications such as salbutamol sulfate, it makes use of a material similar to sodium chloride (NaCl) as a modulating agent (52). The amount of NaCl needed to reach the saturation in the fluid during entering the device was less than what was desired. The total solubility of the medicine determines whether it can be delivered in a pulsatile manner.

In contrast to sodium chloride, which is soluble in a range of 321 mg/ml with water as a solvent and 320 mg/ml in saturated solution, salbutamol is dissolve in a range of 275 mg/ml in the presence of H_2O and 16 mg/ml in the presence of the sodium chloride saturated solution. Although the solubility of the modulator is independent of the drug concentration, the aforementioned values suggest that drug solubility would be the primary function influencing the concentration of the modulator that should be used in the formulation (53). An organic salt, an inorganic salt, and an organic acid (solid) could all be used as solubility modifying agents in formulation. It may be possible to alter the proportion of medicine combined with the modulator to create pulsatile delivery of medications.

iv) Delivery by reservoir systems:
Super-disintegrants are employed as agents that cause swelling to help release particles in a burst when water enters. A swelling membrane was added, along with an impermeable top coating after the medication was initially applied to the non-peril seeds (54,55). According to IVIVC (in vitro in vivo correlation) investigations, time-controlled explosion systems with a 3-hour lag time for the drug's blood appearance and a 5-hour maximum release were seen (56). Erosion and the disintegration of the barrier coating after a defined time lag that control the pharmaceutical discharge from the device. The thickness of the coating layer can be changed to help manage the necessary lag time.

- The Chronotropic Formulation System: As the drug-containing core in these formulations serves as a reservoir onto which the layer of swellable hydrophilic hydroxypropylmethylcellulose (HPMC) polymer is applied. By changing the viscosity gradients of HPMC and the thickness of the polymer film, it creates the necessary lag time (57). Coating the device with enteric polymeric film allows for colon targeting and reduces variability in the gastrointestinal tract's emptying time (58).
- **TIME CLOCK system:** This pulsatile drug delivery system was created using the idea that an aqueous dispersion should be coated on a solid dose formulation (59). A hydrophobic surfactant layer will be aqueously dispersed at 75°C using materials such as beeswax, carnubawax, etc. to coat the solid dose formulation or core material. To improve adherence to the core coating layer, an outside water-soluble coating is applied. Redispersion of the formulation results from rehydration of the dispersion, which is evident when the device interacts with gastrointestinal fluids or dissolving fluid (60).

International Journal of Environmental Sciences
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https://www.theaspd.com/ijes.php

- **Compressed tablets:** The direct compression technique is part of the compression coating process. In order to avoid using coating solutions, the core components and coating layers are compressed. The first dose is administered by the external, press-coated tablet, which dissolves immediately in the gastric portion. The innermost layer is made up of ingredients that are insoluble in the gastric media's pH but will be release into the intestinal area (61).

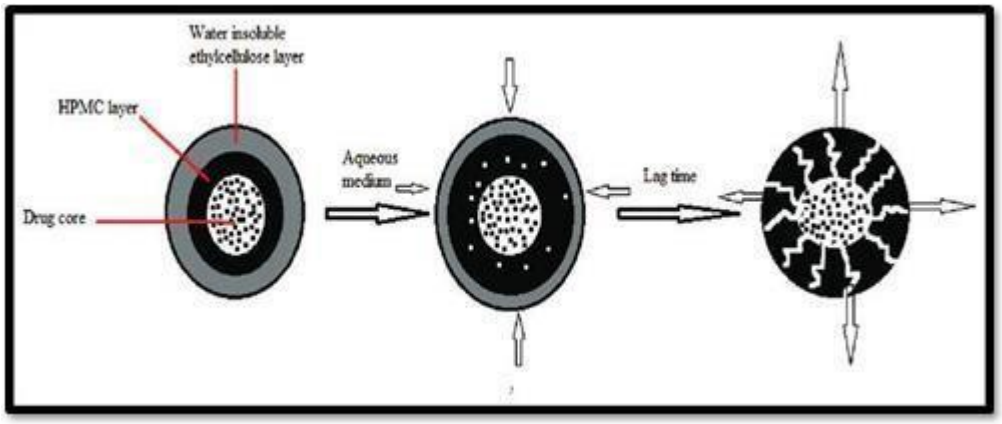

Figure 6: Time controlled explosion system

❖ **Multiparticulate Systems**

Compared to single-unit systems, multiparticualte systems (like pellets) provide a number of benefits. These include repeatable and short stomach residence time, flexibility in combining units with varying release patterns, and no chance of dose dumping. However, because there are more excipients present, multiparticulate systems have a decreased drug-carrying capacity. These systems are always reservoirs with a covering of altered permeability or rupturable material. (62,63)

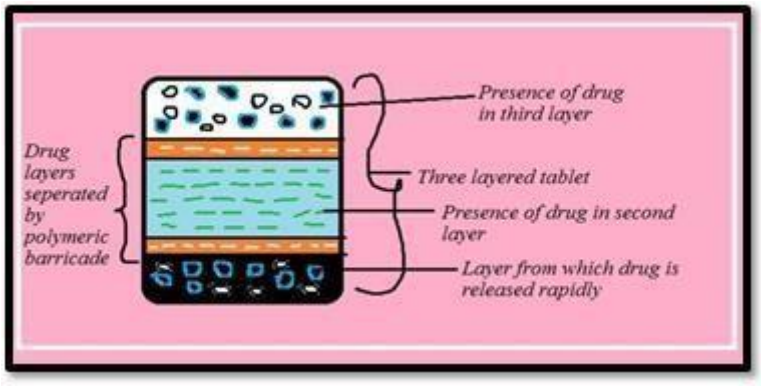

Figure 7. Design of multilayered tablets.

i) A reservoir with a time-controlled explosion mechanism or a rupturable polymeric coating:

The medicine, mineral oil, disintegrant, and low bulk density diluent are all included in the formulation. An enteric polymer, such as cellulose acetate, is added on top [64,65]. Water begins to seep into the core of the medication type as it is submerged in a liquid medium, pushing out the lipid substance. Pressure within the dosage formulation increases sufficiently as the lipid material exits the delivery system entirely to cause stress, which breaks the coating material and causes the medicine to leak out of the system [64,65,66].

ii) Modification of membrane permeability for pulsatile delivery: (67,68)

The penetrability and water absorption properties of quaternary ammonium functionalized acrylic polymers can be affected due to the presence of various counter-ions within the medium. This ion exchange has led to the development of several delivery systems. Reports indicate that Eudragit RS 30D is the polymer of choice for such applications. Typically, this polymer features a positively charged

quaternary ammonium group in its side chain, which is generally paired with negatively charged HCl counter-ions. The hydrophilic nature of the ammonium group facilitates the polymer's interaction with water, thereby modifying its permeability and allowing for controlled water penetration into the active core (69).

iii) Sigmoidal release systems:
Ammonia methacrylate copolymer USP/NF type B coats pellets of various acids, such as citric, malic, glutamic, succinic, and acetic acids. Water ingress transforms the drug core into an acidic solution, improving the penetration of the hydrated polymer layer (70).

iv) Time-regulated, low-density floating system with pulsatile system:
These mechanism, are made up of low-density floating pulsatile system that simply exist in the gastric area and are unaffected by changes in the local environment, pH and gastric emptying time. Both single units (floating dosage form) and multiparticulates (pellets, micrspheres, beads and granules) capabilities are possible for these dosage forms. These are especially beneficial for medications that must be locally delivered in the stomach or that are absorbed from there. Due to their broad regulatory approval, non-solubility of cross-linked spheres in the stomach area, and ease of control over cross-linking, polysaccharides are frequently utilized in oral administration system to acquire appropriate drug release kinetics and therapeutic delivery system. For the purpose of chronotherapy, Badave et al. developed hollow calcium pectinate beads that enable a floating, that enable a pulsatile release of diclofenac sodium (71). Particularly for those medications with a window for absorption in the gastric area, low-density floating microparticle with a time-controlled dose forms keep the medication in the stomach for longer and are unaffected by changes in pH or gastric emptying (72).

Stimuli Induced

- **Internal stimuli induced pulsatile system**

These systems are essentially site-specific medication delivery systems that were created in accordance with the body's physiochemical processes. Drug release from this system is influenced by a number of stimuli, including chemical stimuli and temperature, including pH, insulin, enzyme release, glucose and hormone secretion(73,74). These systems were created based on the body's physiochemical functions. To put it another way, these systems are innovative drug delivery techniques designed to deliver drugs precisely to a specific location by inducing certain physiochemical stimuli there. These drug delivery system facilitate the medication in reaction to biological triggers such as the concentration of biomolecules (glucose, neurotransmitters, inflammatory mediators), pH, temperature, presence of particular cells, release of particular enzymes, hormones, and antibodies, etc. Two subcategories can be used to further classify these systems:

1. Chemically release induced by stimuli pulsatile drug delivery system.
2. Pulsatile drug delivery systems triggered by temperature changes.
3. Ph-triggered pulsatile drug delivery system.

1. Further types of chemically release induced by stimuli pulsatile drug delivery system:(75)

- **Glucose-Responsive Insulin Release Devices**

There are a number of known methods that can adapt to changes in the concentration of glucose. The pH-sensitive hydrogel with the glucose oxidase enzyme fixed in it is the greatest example

(76). The enzyme i.e glucose oxidase transform glucose into gluconic acid as blood glucose level rises, resulting in a change in the Ph of the formulation. This alteration in pH encourages the swelling of polymers, initiating the process of insulin release.The concentration of gluconic acid will drop as blood glucose levels drop, and the system will release less insulin (77).

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- **Inflammation Induced Pulsatile Formulations**

Inflammation is seen at the aforementioned locations after an injury, fracture, or chemical or physical stress. The cells that react to inflammation generate hydroxyl radicals. Yui and her team concentrated their research on the free hydroxyl radicals produced by inflammation and subsequently created drug delivery systems based on this approach. Hyaluronic acid was used, which is degraded by hyaluronidase or in the presence of free radicals in this formulation.(78).

- **Ph Sensitive Pulsatile Drug Delivery Formulations**

The formulation is made up of 2 parts i.e an immediate release and a pulsed chamber and a pulsed chamber that reacts to pH changes to deliver the drug (78). Choosing pH-dependent polymeric materials will aid in designing formulations so that drug release will be observed at the targeted site or at the specified site of activity, taking into account the fact that different parts of the gastrointestinal tract have different pH environments. Examples of these polymers include sodium carboxymethyl cellulose, cellulose acetate phthalate, eudragits, polyacrylates, etc. (79). The medication is released in the small intestine through the use of the aforementioned polymers.

2. Temperature

One of the most common triggering signals in many stimuli-induced systems is temperature. Numerous temperature-responsive medication delivery systems have been created by different formulators or research experts.It is designed to modify the characterstics of the polymers within the system by using temperature as the activating trigger. Comparable to thermally reversible coil/globule transition, polymer swelling or de-swelling mechanisms, and crystalline melting, it can alter the characteristics of polymers (80).

3. pH Sensitive Drug Delivery Systems:

Eudragit, pthallates, carboxymethyl cellulose, and methacryllic are examples of pH-dependent polymers that allowed the release of drug within the appropriate pH range; in particular, polymers like Eudragit L and S which preferred colon-specific delivery (81,82). Two parts make up a pH- sensitive system: a pulsed-release component and an immediate release component that release the medication in reaction to a pH shift. The variation in pH levels across different sections of the gastrointestinal tract has been utilized in a pH-sensitive system. By selecting pH-sensitive polymers, it is feasible to trigger the release of medication at a targeted site. These polymers are applied as enteric coatings to enable drug release in the small intestine. (83)

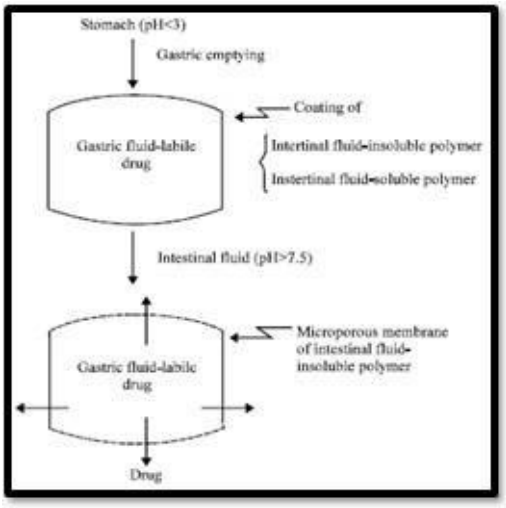

Figure 8: Schematic representation of pH-triggered drug delivery system.

- **Externally stimuli induced pulsatile system**

These devices need external means to induce the drug deliverance in a pulsatile fashion and they include the following.

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Vol. 11 No. 8S, 2025
https://www.theaspd.com/ijes.php

- **Electro Responsive Pulsatile Release:**

The application of an electric field to a membrane containing polyelectrolytes that controls rate facilitates drug release [84–86].

- **Magnetically Induced Pulsatile System:**

Figure 9 illustrates how magnetic minerals including magnetite, iron, nickel, and cobalt are incorporated into tablets or capsules under the external influence of a magnetic field. The timing or degree of drug absorption into the stomach or intestine can be altered by positioning the drug in a particular location or preventing it from reaching undesirable locations (87–89).

- **Ultrasonically Stimulated Pulsatile Drug Delivery Formulations:**

In ultrasonically modulated systems, the polymeric matrix is eroded by ultrasonic waves, which modifies the release of the medication. In their evaluation of the influence of ultrasonic waves (1 megahertz) on the rate of bovine insulin release from reservoir-based drug delivery system and ethylene-vinyl alcohol copolymer matrices, as examined by Miyazaki et al. discovered a significant decrease in blood sugar levels following the utilization of high-frequency sound waves(90).

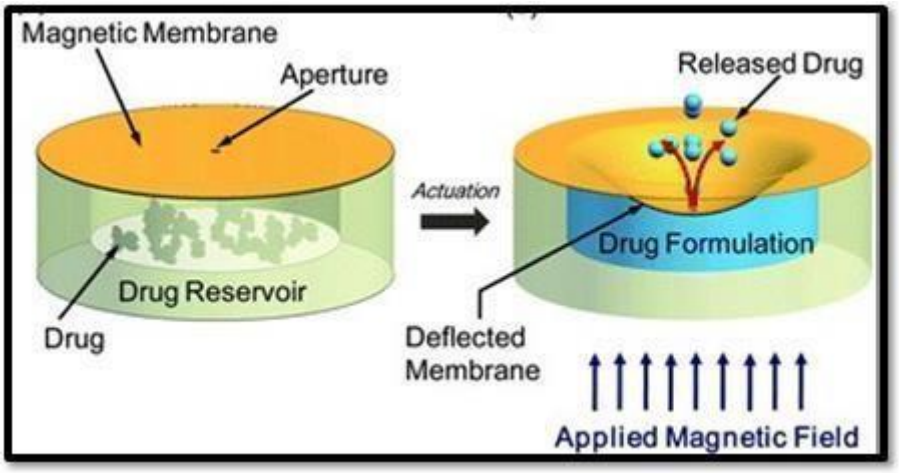

Figure 9: Drug release from magnetically induced pulsatile systems.

Compression-coated Delivery System Approaches:

1. Coating for Pharmaceutical Product:

It is a crucial method for creating different types of solid dosage form, and the pharmaceutical industry is certain to see future advancements in this approach (91,92). The primary method used to create coated solid dosage forms involves depositing various ingredients from powders, suspensions, or solutions. When it comes to coating pharmaceutical solid dosage forms, there are four main coating techniques: Press coating, microencapsulation, film coating, and sugar coating are the first four methods. The initial three elements used for coating solid dosage forms fall under the category of liquid coating technology, specifically in solutions or suspensions. Aqueous and organic coating are the most widely used liquid coating methods in the pharmaceutical business; nonetheless, they have several drawbacks, including time consumption, medication stability issues due to hydrolysis and heat lability, and environmental contamination. In order to avoid the limitations related to the pharmaceutical coating of several medications, non- soluble solvent or solvent-free coating techniques, such as compression- coating, are used as substitute methods for applying coatings.

2. Solventless Coating Technology:

Issues with solvent exposure, solvent disposal, and product residue can be avoided with solvent less coating technique (93,94). By doing away with the time-consuming and costly solvent treatment procedures, solvent less processing makes cost reduction possible. Furthermore, because the method eliminates the need for drying and evaporation, processing times can be greatly shortened. Specifically,

the solvent less coating method, which typically doesn't require a heating source, can offer a different way to coat medications that are sensitive to temperature changes. Using modified tableting machines, press coating allows for the creation of a dense and arid layer created around a tablet core manufactured by similar equipment.

3. Compression film-coating Technology:

It is an ancient method that was initially put forth by Noyes in a patent in 1896 (95). It is also known as dry coating, compression coating, and double compression coating. In order to enable the formulation of incompatible medications, an industrial application of this technology was created between 1950 and 1960 (96). In the past twenty years, the technique of press coating has become more popular because it does not use solvents, allows for a quicker manufacturing process, and is more effective in increasing the bulk of the core tablet compared to methods that rely on solvents (97). Press coating tablets represents a modern approach to developing new drug delivery systems, while being an ancient idea (98–100). The method necessitates a certain tablet press that can apply compression coating. In addition to protecting hygroscopic, light-sensitive, oxygen- labile, and acid-labile medications, the press coating technique also isolates incompatible medications from one another and offers a way to modify the drug release profile and achieve sustained drug release (97,101,102). A press- coated tablet generally includes a coating shell on the outside and a core tablet on the inside. Because the outer layer envelops the inner core, the choice of materials for the outer layer greatly impacts the tablet's stability, drug release characteristics, and mechanical strength of the coating.

In the same dosage form, incompatible drugs can be physically segregated within the core and the coating through the process of press-coting. The need for an additional coating procedure may be eliminated by directly compressing the coated shell and the core. The shell of the coating can be composed of any type of material that possesses appropriate compaction properties. The compression-coating approach have been utilized to safeguard volatile substances and modify the release of various medications, and cover up the bitter taste of medications. The method has a number of distinct advantages, including quick manufacturing times and no need for specialized coating solvents or equipment.

The use of this technology has recently been studied in the creation of delayed-release tablets, time clock systems, and timed-release dosage forms (101–103).

A rigid blockade, usually composed of a diluent (acting as release modifier), a polymeric material and the medication (for either faster or extended release), can be compressed onto a quick disintegration or modified release core to create a press-coated tablet (104,105). The distribution method of the drug, along with the types of polymers utilized in both the tablet's core and its outer coating, can be modified to achieve various release profiles. The changes in drug release might be influenced by elements such as time, pH levels, or the presence of microbes, allowing for targeting of specific areas in the gastrointestinal tract. Press-coating enables a dosage form for delivering medication in a pulsatile manner, as opposed to a controlled release, at specific times and places following oral administration. This feature qualifies it as a chronopharmaceutical technology. (102,105,106).

Production of Press Coating Tablets:

Compression-coating production involves a number of procedures. After formulation, the inner core tablet is squeezed under the right circumstances. The tablet made by compressing the innermost core which is situated at the center of the powder bed, which has been prepared by filling the die of the tableting machine with shell-coating materials in advance, & leftover of exterior coating layer contents are then added. Lastly, the inner core tablet is squeezed around the outer covering shell (107).

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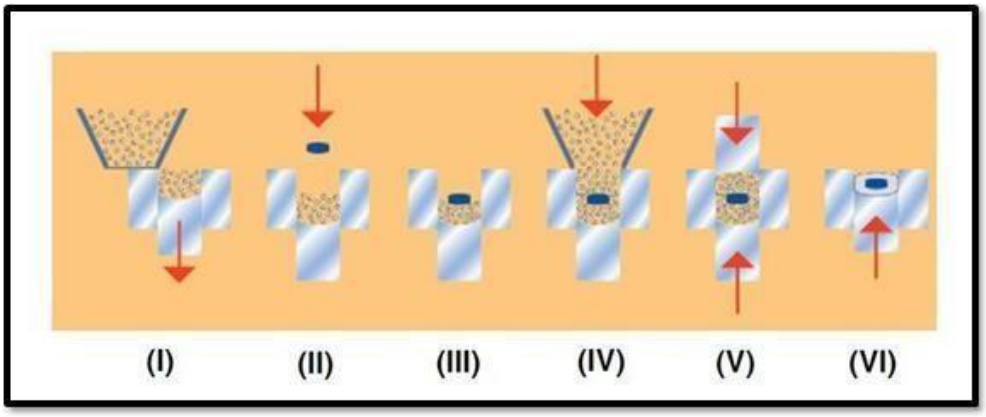

Figure 10: Production processes of compression coating

I. Pre-filling the die with half of the components for the external coating.

II. Placing the inner core onto the powder layer of the external coating material

III. Aligning.

IV. Adding the remaining half of the external coating components.

V. Compression

VI. Prepared press-coated tablet are ejected from the die.

Factors influencing the effectiveness of the rates at which drug are released from press- coated delivery systems:

The effectiveness of compression-coated tablets and their drug release patterns are affected by several factors, which we go into depth about below. Two layers make up press-coated tablets: an exterior shell and an interior core that has been compacted into a tiny tablet. Additionally, rate- controlling substances such fillers and controlled release polymers may be dry-coated onto the core tablet (108,109). The core-shell press-coating assembly may be able to regulate medication release both in terms of rate and time. The size and shape of the excipient particles, the type of component that was utilized to compact the interior core and external coating, the quantity of the density and permeability of the outer layer, the amount of compression applied to compress the various layers, and the inner core's site inside the tablet are some of the factors that influence the drug release rate.

Inner Core Tablet:

Granules, microspheres, beads, drug-excipient blends and pure drug crystals can all be found in the inner core of a press-coated tablet. Incorporating elements within the core tablet to aid in disintegration or altering the drug release in other ways is another option. By adding various polymers added into inner core formulations, several drug release mechanism can be achieved.

Drug Solubility:

Since a drug's solubility and permeability are the primary characteristics that affect its absorption, formulators have always been concerned with a drug's solubility. It has been demonstrated that poor solubility is the reason for many unsuccessful medication development attempts. Therefore, in addition to the drug's dissolution behavior, another important factor to keep an eye on is the dissolution rate of a medication located within the compression-coated tablet. Lin et al. investigated how the different kinds of medications found in the inner core have an impact on how press-coated tablets release their drugs (110). Four medications with different solubility's- carbamazepine, acetaminophen, propranolol HCl, and chlorpheniramine maleate-were created by Rujivipat and Bodmeier and then press-coated into distinct core tablets using hydroxypropyl methylcellulose (HPMC) with different molecular weights
(111). The findings showed that release patterns, which are primarily influenced by drug solubility, exhibit a clear lag time followed by multiple stages of release.

International Journal of Environmental Sciences
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Vol. 11 No. 8S, 2025
https://www.theaspd.com/ijes.php

- **Core Composition Variables:**

Osmotic agent incorporated. The presence of sodium chloride significantly affects the drug dissolution profile, even when EC is utilized as an outer coating shell, since it acts as an osmotic agent when incorporated into the inner core tablet. When compared to 16.4 hours for the medication alone, Lin discovered that the time delay for the tablet coated with sodium chloride is considerably reduced(110). As the amount of sodium chloride increased, the lag time decreased. Osmotic pressure is believed to be crucial in regulating drug dissolution; in this case, the higher rate of dissolution of powdered sodium chloride created a significant internal osmotic pressure inside the tablet's core, leading to a rapid separation of the compression-coated tablet outer layer from the loosely packed lateral surface. However, Nuntanid et al used HPMC compression coated tablet and spray-dried chitosan acetate to demonstrate the effect of different core compositions with respect to therapeutic release(112).

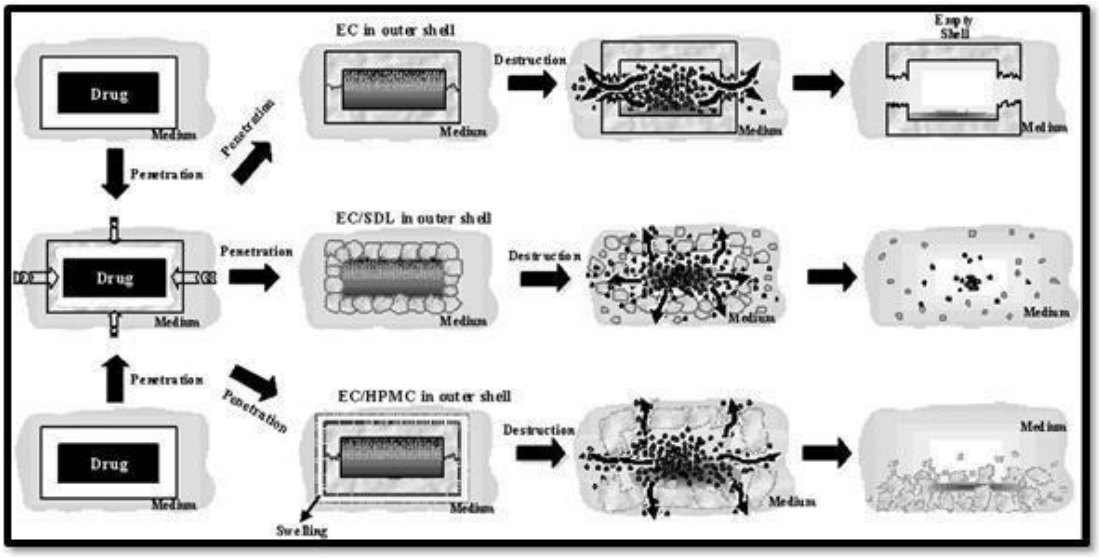

Figure 11: A potential method for the drug liberation from press-coated dosage form (tablet) that disintegrates or ruptures in a time-controlled manner.

- **Polymers and Excipients present surround the core:**

Lin et al. showed how the type of ingredients in the core influences the press-coated tablets' lag time and release characteristics (110). Inner core formulations were enhanced with a binding agent (HPMC) along with several excipients that can be directly compressed (sodium starch glycolate, microcrystalline cellulose, or spray-dried lactose). A noticeable time lag was succeeded by fast drug release in the release behavior of the drug in press-coated tablets, which feature an outside layer made up of (EC) ethyl cellulose, has been investigated. The formulations of the inner core have been enhanced with a binding agent (HPMC) along with various excipients that can be directly compressed.

Amounts of Inner Core:

Rujivipat and Bodmeier et al. examined the effect of various inside core:outer shell ratios in order to optimize possible drug loading (113). Three proportions utilized: 3:1 (9mm core in a 10mm press-coated tablet), 2:1 (9mm core in an 11mm press-coated tablet), and 1:1 (6mm core in an 8mm press-coated tablet), along with 1:2 (6mm core in a 9mm press-coated tablet). Following a significant delay at pH 7.4, a pulsed release was observed; however, no formulations released any substance at pH 1.0 over a span of 20 hours. The drug release rate improved due to the thin layer coating and quicker erosion, as the delay in release time increased as the compressive force and the ratio of the internal core to the external layer decreased.

Compression Pressure:

In the process of making tablets, the compression force is crucial, especially during the process of developing press-coated, time-controlled tablets, Lin examined how varying the pressure applied to the

internal core during compression, varying between 50-200kg/cm^2, affected the release profile of sodium diclofenac, while the compression force on the outer coating shell remained constant at 300kg/cm^2 (114). The core tablet releasing profiles made with compressive forces ranging from 50 to 150 kg/cm2 were similar, and the line slopes for the three products looked the same, with lag durations of about 12.5 hours. The lag time extended from 12.5 to 16.3 hours for internal core compressive pressures higher than 200kg/cm^2, suggesting that the inner core tablet's compression force had less of an impact the release of the drug occurs after applying a consistent compression force for formation of outer layer.

Position of the Inner Core:

A major source of complications and failures for the press coating process is the precise consolidation of the press-coated tablet core, which is crucial for the proper centering of the inner core. Since issues and errors might result from uneven coating, off-center core positioning, or both, and the repeatability of medication release from the tablets with a press-coated layer is not satisfactory. However, a special OSDRC-method and non-invasive x-ray CT imaging compression tool have lately solved this issue (115,116).

External Coating Shell:

The outer shell of a press-coated tablet is crucial to its design because it guarantees that the drug will consistently reach the designated location after oral delivery. Press coating eliminates the need for coating solutions or separate coating procedures by directly compressing the outer coating shell and inner core. In order to create the medication form, a tablet is compressed inside another tablet, forming a coating layer on the outside. An outer layer that is either designed to rupture, swell, or erode, or a permeation coating made from a combination of hydrophobic and hydrophilic polymers, can influence the rate at which H2O infiltrates the outside coating, thereby regulating the release of the drug.

Polymer Particle Size:

EC powder in a variety of particle sizes was used in the direct compression method to create the external coating layer of press-coated tablets. The EC particle size determined the first lag period in the release of drug from these tablets, which was followed by fast drug release. Different EC particle sizes produced a range of lag periods, from one to twenty hours; larger lag times were achieved for smaller particle sizes (117). Because the polymer powder consolidates more effectively at finer particle sizes, there will be less residual porosity in the coated layer.

Formulation Variables:

A range of pharmaceutical polymers is commonly employed in the press coating process, including cellulose such as ethyl cellulose (EC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), hydroxypropyl methylcellulose acetate succinate (HPMCAS) hydroxyl propyl methylcellulose (HPMC). Other polymers utilized include pectin and polysaccharides like guar gum, sodium aliginate; hydrophilic polymers such as polyethylene glycol (PEG); waxes like behenic acid; and methacrylate co-polymers are utilized in the press-coating process, either individually or together.

The characteristics of above polymers can be applied in many ways to control medication release. Conte et al. demonstrated that the drug release from press-coated tablets may be both controlled and modified by altering the type of polymer and its molecular weight utilized for the outer coating (118). For instance, a polymer with a low molecular weight like HPMC, releases more after the lag period than one with a higher molecular weight. The release rate from a gel- forming coat rises as its molecular weight decreases (119). For a range of physiochemical characteristics, various release patterns of drugs were observed from press-coated tablets that contained different hydrophilic excipients. Because the latter is more water soluble, Lin et al. found that the time lag associated with a compressed tablet layer made from HPMC/EC was greater than that associated with a shell comprised of EC and spray-dried lactose (120). Fukui et al. studied the impact of HPMC as on the plastic distortion of the outer layer coating using soluble in water and insoluble in water plasticizers (121). According to their findings, Due to the correlation between water-soluble plasticizers and HPMCAS, the shell displayed plastic distortion; Fukui proposed that this might be beneficial for colon-directed delivery.

Another study examined the impact of water-insoluble agents found that a proper ratio of calcium stearate, magnesium stearate, and HPMCAS can lengthen the lag time (122,123). Matsuo et al. outlined the application of hydroxyethyl cellulose (HEC) in tablets with press-coated layer for developing a delayed-release method (124). The dissolution apparatus's paddle speed determined the lag time, which was regulated by the HEC viscosity. A non-cellulose outer coat composed of a lactose-containing alginate/chitosan combination allowed for a time-controlled release, according to Takeuchi et al. (125). An induction period and a sustained release were the characteristics of the drug release profiles; this kind of release pattern was said to be helpful for a medication intended for the lower intestine. The delay time and delivery of medication from compressed tablets were examined with respect to the outer layer pore size of the excipients (calcium tartrate, sucrose, mannitol, sodium chloride and instantly anhydrous dextrose) (126,127). A quicker release of the medication could result from the creation of conducting channels. When applied to the HPMCAS coat, poor wettability additives like calcium and magnesium stearate stop solution media from passing through the pores (122,123).

Quantities of the External Layer:

The quantity of components in external coating layer is a crucial factor in ensuring a consistent compression coating for tablets. The external layer should be approximately two times the weight of internal core, or even greater, with the amount needing to exceed that of internal core. If the internal core is primarily composed of less-dense substances like fatty substances and waxes, a thicker coating is required to ensure an even layer over the internal core and to give sufficient bonding between internal core and external coating layer.

During Compression Stability of Drugs or Enzymes:

Careful attention must be paid to the stability of enzymes or medications when compression force is applied through press or compression techniques. Enzymes are globular proteins, and it has been documented that pressure can decrease the activity of some enzymes (128–130). Some enzymes, on the other hand, are not as susceptible to the forces applied during tableting. the tableting process, the nattokinase enzyme was effectively stabilized and did not exhibit any discernible decrease in activity (131). It has also been shown that press coating is a unique encapsulating technique that increases probiotic bacteria cells' ability to survive in acidic environments. After hydration, sodium alginate's hydrogel barrier forms as a coating shell, which may prevent acidic fluid from penetrating the cells (132). To show that E. Coli, Lactobacillus rhamnosus, and pancreatic enzymes provide gastroprotection for the delivery of probiotics to the colon, a new formulation with ionic self-stabilization was recently developed utilizing press-coating technique. It consists of amino (chitosan) additives and carboxylated (carboxymethyl high amylose starch, CM-HAS) (133–135).

Table No. 2: Commercially available Technologies of Chronotherapeutic Drug Delivery System. [136, 137, 138, 139]

Technology	Propritory Name: Dosage	API	Disease
1. CODAS	Verelan, ER Tablet	Verapamil HCl	Hypertension
2. Pulsincap	Pulsincap	Dofetilide	Hypertension
3. Pulsys	Moxatag, Tablet	Amoxicillin	Pharyngitis/Tonsillitis
4. DIFFUCAPS	Innopran-XL	Propranolol, Verapamil HCl	Hypertension
5. CONTIN	Uniphyl, ER Tablet	Theophylline	Asthma/ Increased Bronchocontriction
6. Covera HS	Covera HS, ER Tablet	Verapamil HCl	Hypertension
7. OROS	Covera, ER Tablet	Verapamil HCl	Increased BP in early morning.
8. CEFORM	Cardizem, ER Tablet	Diltiazem HCl, Verapamil HCl	Hypertension

Current issues with Press Coating Technology:

A pre-formed inner core tablet is enclosed in an outer coat using the compression process known as press coating (100–104). The inner core is first compressed before being moved to a bigger die that has half of the necessary coating material in it (97). On a laboratory scale, the compression process is straightforward, but large-scale manufacturing requires specialized equipment. However, centering the inner core tablet under fast processing events is the biggest challenge in press-coated tablet manufacturing (140). Drug bioavailability may change as a result of eccentric localization's alteration of time lag and release behavior. Press-coated tablets lose their reproducibility of drug release when the core tablet is positioned off-center. Recent advancements have tackled the issue of deviation from the center position and the lack of an inner core in press- coated tablets by employing the novel ENCORETM method for single-stage dry-coated tablets like x-ray computed tomography (CT), OSDRC, and alongside pulse-echo ultrasonic technology.

Conclusion and Future Prospective:

Numerous scientific findings from different phases of clinical or chronological research clearly demonstrate that the clinical relevance of chronotherapy based drug delivery systems isgrounded in its theoretical and investigative foundations, and their marketing process's approval is dependent on this idea(27).We present press-coated dose forms, which are chronopharmaceutical products designed to satisfy patients' physiological requirements. We provide a revised collection of all research papers, methods for press-coated release, and factors that affect the efficacy and release of drugs in press-coated delivery systems. As a novel way to administer a medicine pulsatilely at specified times after oral administration, the press-coated tablet has received more focus nowadays. In order to maximize a drug's intended effects and avoid undesirable ones, the emerging field of medical therapy known as chronotherapeutics takes into account the patient's biological cycles when deciding when and how much to take. By giving the proper quantity of medication towards the ideal target organ at the correct time, chronotherapeutics aims to deliver the best possible therapy (80,141).

Various physiological processes and functions in humans are closely correlated with circadian rhythms, especially when it comes to patients' day-night variations. The significance of circadian rhythms to medication therapy has been shown by chronopharmacology research, which has led to a new trend in DDS design. In order to deliver effective pharmacological therapies, the timing of drug administration is crucial because the symptoms and development of some diseases are more prevalent during specific times of the day. Simple modifications like changing the dosage schedule, reformulating a medication, or using programmable pumps can have an enormous effect. In addition to improving the risk to benefit profile for prolonged use, the results of altering the drug's administration schedule along with chrono-drug delivery system or novel preparation could also provide patients with minimal-dose therapy to reduce drug negative effects. Since the timing of dosage in illness therapy greatly affects the effectiveness of treatment, chronotherapeutics will be a crucial therapeutic technique for medications in the future. Nowadays, there are numerous novel Chronopharmaceutics that administer medication in alignment with the circadian rhythm; these dosage forms enhance patient compliance in addition to treatment results (142).

A specialized compression press is used to create the outermost layer that envelops the center core of the compression -coated tablet. By shielding the medicine from moisture, the compression approach increases drug stability and does away with laborious and complex coating or granulation procedures. Future compression-coated tablet design strategies include different materials may be integrated into the formulations of the core and external layer to create distinct chronopharmaceuticals with enhanced

release control, site-specific targeting and dosage management capabilities. Recent years have seen the discovery of numerous colon diseases and disorders, such as Chron's disease, ulcerative colitis, irritable bowel syndrome, carcinomas, and various infections. Targeted drug delivery to the colon and lower GI tract is the most significant problem of the future (143–145). Given that many medications have low absorption because of their instability in the GI system, press-coated tablets are an appealing dosing form. Targeted release of press-coated dosage forms is a promising research issue that should be investigated further employing multiple formulations strategies for treating multiple of colon disorders.

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