REVIEW ON RECENT TRENDS IN PRESS-COATED PULSE DRUG DELIVERY SYSTEM

*SATANI R. R.¹, CHOTALIYA M.B.², RAVAL M. K.³, SHETH N. R.⁴

SUMMARY

The past several decades have seen the development of many controlled-release preparations featuring constant release rates to maintain drug concentrations in the human body, regardless of the patient's physiological condition. Oral pulsatile/Time-controlled drug delivery systems are designed to elicit programmable lag phases preceding a prompt and quantitative, repeated or prolonged release of drugs. Accordingly, they draw increasing interest because of the inherent suitability for accomplishing chronotherapeutic goals, which have recently been highlighted in connection with a number of widespread chronic diseases with typical night or early morning recurrence of symptoms (e.g. bronchial asthma, cardiovascular disease, rheumatoid arthritis, early-morning awakening). However, long-term constant drug concentrations in the blood and tissue can cause problems such as resistance, tolerability, and drug side effects. People vary considerably in their physiological and biochemical conditions during any 24 h period, due to the circadian rhythm, and thus, the constant delivery of a drug into the body seems both unnecessary and undesirable. The press coating technique is a simple and unique technology used to provide tablets with a programmable lag phase, followed by a fast, or rate-controlled, drug release after administration. The technique offers many advantages, and no special coating solvent or coating equipment is required for manufacturing this type of tablet. The present review article introduces chronopharmaceutical press-coated products from a patient physiological needs perspective. The contents of this article include biological rhythms and pulsatile hormone secretion in humans, the reasons for using pulsatile drug delivery for disease treatment, recent chronopharmaceutical preparations appearing on the market, updated compilation of all research articles and press-coated delivery techniques, factors affecting the performance and drug release characteristics of press-coated delivery systems, and recent challenges for the press coating technique. We also provide a brief overview of press-coating approaches intended for chronotherapy.

KEYWORDS

Lag time, Press-coated tablet, Time-controlled Pulsatile DDS, Chronodelivery

AFFILIATION

1,2,3&4. Department of pharmaceutics, Saurashtra University, Rajkot-360 005

*Author for Correspondence: Email: raj.satani52@gmail.com
INTRODUCTION

Since many diseases exhibit predictable cyclic rhythms, the timing of medication regimens can be used to improve the outcome of the chronic conditions for patients [1-5, 39, 40].

Thus, after understanding the disease physiology an advanced DDS with pulsatile hormone secretion function may be applied as a part of the treatment.

The pulsatile drug delivery system (PDDS) is intended to deliver a rapid, or transient, and quantified medication release after a predetermined off-release period (lag time) [16,17,41,42].

PDDS can deliver the correct amount of medication at the desired location at the optimal time for maximum effect against disease, thereby enhancing therapeutic efficacy and improving patient compliance.

PDDS avoids problems with degradation of drugs in the stomach or first-pass metabolism, enables the simultaneous administration of two different drugs, allows the release drugs at different sites within the gastro-intestinal tract, and can deliver a drug release burst at one or more predetermined time intervals, according to patient requirements.

The advantages of PDDS extend to drugs with chronopharmacologicalbehaviours, where nighttime dosing is required, and for various diseases that are influenced by circadian rhythms [42-46].

Since PDDS has a unique mechanism of delivery, whereby a drug releases rapidly after a lag time, various PDDSs have appeared on the markets that replace modified-release dosage forms. Various release patterns are illustrated in Fig. 2. [46-48]

The PDDS is formulated to release a drug after a predetermined lag time in a specific region of the gastrointestinal tract, or as a chronotherapeutic time-dependent release. Pulsatile drug release should occur independently of the environment (e.g. pH, enzymatic activity, intestinalmotility) or other stimuli, lag timeprior to the release of the drug is primarily determined by the formulation's design [41,49].

PDDS is a type of time-controlled DDS, it may be classified as a single- unit or multiple-unit system by application of different coating systems [42,50], as shown in Fig. 1[16, 42, 45, 50].

Fig.1: Schematic presentation of time-controlled release technologies according to relevant formulation strategies.
The single-unit PDDS is applied for rapid dissolution after a designated lag time, and it is possible to avoid deviation in dissolution lag time for each unit.

The single-unit PDDS can be further sub-divided into capsule based or tablet-based systems. The single-unit PDDS is fabricated by coating the system with an eroding or soluble polymer, or a polymer coating that may be ruptured. Multiple-unit PDDS can provide precise time-control over drug release, though it requires more complex and expensive manufacturing techniques. Multiple-unit PDDS units can be fabricated by coating multi-particulates with a pH-dependent barrier membrane, then, by blending variously coated multi-particulates, the desired release profile is obtained.

Moreover, pulsatile release may be monitored by altering membrane permeability, or by coating the unit with a soluble, erodible, or rupturable membrane.

![Diagram of different release patterns for various pharmaceutical dosage forms.](image)

**Fig.2: Different release patterns for various pharmaceutical dosage form.**

**Advantages of PDDS**

1. Nearly constant drug levels at the site of action.
2. Avoidance of undesirable side effects.
3. Reduced dose.
4. Improved patience compliance.
5. Used for drugs with chronopharmacological behaviour.
6. No risk of dose dumping.
7. Improved bioavailability, tolerability and reduces side effects.

**Limitations of PDDS**

1. Lack of manufacturing reproducibility and efficacy.
2. Large number of process variables.

3. Multiple formulation steps.
5. Need of advanced technology.

1.1 Chronopharmaceutics

It is evident that drug delivery and therapy should be modified to achieve an efficient drug level at an optimum time, rather than merely maintaining constant drug concentrations.

Thus, the time-controlled function of third-generation DDSs currently under development is finding application in new and improved disease therapeutics.

Biological rhythms may be applied to pharmacotherapy by adopting a dosage form that synchronizes drug concentrations to rhythms in disease activity [5–8].

During the past two decades, diseases that follow rhythmic patterns have given rise to the creation of new drug delivery dosage forms, called chronopharmaceuticals [9, 10].

Chronopharmaceutics includes the fundamentals and research into various aspects of chronobiology, chronopathology, chronogenetics, chronopharmacology, chronopharmacokinetics, chronopharmacodynamics, chronotherapeutics, and chronotoxicology. Broadly, chronopharmaceutics bring together chronobiology and pharmaceutics [11, 12].

Chronobiology is the study of biological rhythms and mechanisms in living systems. It assumes that the bioprocesses and functions of all living organisms exhibit predictable variability over time [14].

Pharmaceutics is one of the most diverse subject areas in all of pharmaceutical science and deals with both the scientific and technological aspects of the design and manufacture of dosage forms for medicines to assure their safety, effectiveness, quality, and reliability [15].

Thus, chronopharmaceutics is defined as a branch of pharmaceutics devoted to the design and evaluation of DDSs, that release a drug at a rhythm to match the biological requirement for a given disease therapy.

It has been found out that circadian rhythm is useful for the treatment of various pathophysiological conditions of human body, but such chronopharmacological phenomena are markedly influenced by not only the pharmacodynamics but also the pharmacokinetics of drugs. Thus, the application of circadian rhythm to pharmacotherapy may be accomplished by the optimal timing of the special formulation or DDS designed to synchronize drug concentrations to rhythms in disease activity [9, 10].

The new chronotropic DDS technology for delivering drugs precisely in a time-controlled fashion in accordance with circadian rhythms may be developed as a chronopharmaceuticals product to treat different human diseases, as proposed by Fig. 3.
Fig. 3. Design and development of new chronotropic DDSs in accordance with circadian rhythm of human body.

Rationale behind designing these chronotropic DDSs is to release the drug at desired time based on pathophysiological need of disease, which results in the improvement of therapeutic efficacy and patient-compliance. These systems are meant for treatment of those diseases that are caused due to circadian changes in body but the zero-order drug released products seem to have no desire.

1.2.1 Biological rhythms and pulsatile hormone secretion

1.2.1.1 Circadian rhythm

Biological rhythms exist in all living organisms, and may be necessary for survival under changing environmental conditions \(^{[2-4]}\). The interval of biological rhythms can vary considerably according to the type of living organism. Some biological rhythms are very fast while others can be very slow, and many normal human biological functions exhibit predictable cyclic rhythms.

A biological clock exists in the brains of all mammals, and provides circadian information to all cells in the body, thereby allowing animals to adjust their physiology according to the time of day \(^{[18,19]}\).

Circadian rhythms can change the sleep-wake cycles, hormone release, body temperature, and other important bodily functions driving the alteration of various physiological, biochemical, and behavioural processes (Fig. 4) \(^{[8,23]}\).
1.2.1.2 Pulsatile hormone secretion

Many hormones in the human body are secreted in a cyclical or pulsatile manner, rather than continuously.

Secretions of the anterior and posterior pituitary hormones, adrenal glucocorticoids, mineralocorticoids and catecholamine’s, gonadal sex steroids, parathormone, insulin, and glucagon are pulsatile [24].

During hormone secretion, a baseline release is combined with the pulsed release. Insulin is one good example of a pulsatile hormone release.

Pulsatile release of gastrointestinal hormones, stimulated by presence of food in the gastrointestinal tract, generally causes the release of digestive enzymes from the pancreas and stomach. Many hormones including follicle stimulating hormone (FSH), leutinizing hormone (LH), leutinizing hormone releasing hormone (LHRH), estrogen, and progesterone are also regulated in the body in pulsatile manner. Numerous biological functions in the body are thus regulated by the temporal and pulsatile release of hormones [25].

If the hormones were continuously secreted, a hormonal imbalance may arise, which would not only induce down regulation of hormone receptors on the target cellular membranes, but might also produce undesired side-effects [26].

1.2.1.3 Circadian variation

Circadian rhythm regulates several body functions such as metabolism, physiology, behavior, sleep patterns, hormone production, and so on.

The circadian rhythm not only affects most physiological functions but also influences the absorption, distribution, metabolism, and elimination (ADME) of drugs, leading to changes in drug availability and target cell responsiveness [1,27–29].
Thus, the time-dependent dynamic bioprocesses in human body are significantly dependent on circadian variations, and so constant delivery of a drug into the human body seems both unnecessary and undesirable.

Timing the administration of some medications in accordance with the body's circadian rhythm may significantly affect the drug's pharmacokinetics and pharmacodynamics (Fig. 5) [30].

Fig. 5: Effect of circadian rhythms on the ADME of drugs.

Many common diseases also display a marked circadian variation during onset or exacerbation of symptoms, as shown in Fig. 6.

Fig. 6: The circadian pattern of disease.
Since the circadian rhythm influences normal biological processes, the occurrence or intensity of symptoms of these diseases is not constant throughout the day.

Several diseases, including arthritis, asthma, allergies, peptic ulcer disease, dyslipidaemia, and cancer exhibit predictable circadian variation. Medications and treatments given at the appropriate time according to the body's circadian rhythms will result in more favourable outcomes \[31,32\].

1.2.2 Disease treatments requiring pulsatile drug delivery

1.2.2.1 Normal physiological condition

The body varies greatly in physiological and biochemical status over a 24-hour period due to circadian rhythm. Variation may be expressed as sleep-wakefulness, changes in body temperature, cell division, heart rate, and other factors (Fig. 3 and Table 1).

Normal lung function undergoes circadian changes that reach a low level during the early morning hours. Endocrine substances, such as growth hormones, gonadotropins, and insulin are secreted from glands and organs in a pulsatile fashion, according to circadian rhythms, which maintain the normal condition of human life \[20–22\]. The secretion of growth hormone reaches peak rates during sleep, but the plasma levels of both testosterone and cortisol are typically greatest in the early morning \[33\].

1.2.2.2 Disease status

Variation in the severity of many diseases over a 24-hour period is well known \[34–36\].

Diseases such as bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcers, diabetes, attention deficit syndrome, hypercholesterolemia and hypertension show symptomatic changes due to circadian rhythmicity.

Aggravation of asthmatic attacks occur after midnight or in the early morning due to limited lung function promoted by circadian changes at that time.

Also cardiovascular diseases like angina, hypertension, myocardial infraction, and stroke are more common in the early morning \[36\].

Circadian changes also contribute in lipid metabolism in patients, leading to complications in cholesterol synthesis in patients \[37,38\].

Administrating anticancer medication according to circadian rhythm can increase chemotherapy effectiveness and decrease drug toxicity. Disease may alter either the drug's pharmacokinetics and pharmacodynamics, or both, resulting in failure of constant delivery within 24 hours.

Thus, understanding the biological basis of these changes over the day and during the night can help to enhance drug therapy, by identifying appropriate times for drug administration.
1.2.3 Chronopharmaceuticals dosage forms on the market

The use of chronopharmaceuticals DDSs, which control drug release in accordance with patient needs and the timing of symptoms, has increased during recent years.

Variations in the disease state and drug concentration in plasma should be considered in the design of chronopharmaceuticals DDSs intended for the treatment of diseases by optimal dosage at an appropriate time. Ideally, chronopharmaceuticals deliver drugs in a rhythmic pattern that matches the occurrence of symptoms.

To reduce the risk of side effects, conventional therapies aim to deliver medication at greater than optimal concentrations during times of greatest need, and at lower concentrations when the need is reduced.

In the development of chronopharmaceutical pulsatile-release products, the challenge is to provide the right drug in the right place at the right time.

Among emerging chronotherapeutic approaches, PDDS has attracted increasing interest among academic and industrial researchers for its ability to liberate medication following a programmed lag phase [16,17,41–48].

PDDS provides an optimal chronopharmaceutical dosage form, which is based on physiological needs, because of its time-controlled and site-specific drug delivery functions.

Pharmaceutical companies have focused on developing and commercializing chronopharmaceutical drug products that fulfil unmet medical needs in the treatment of various diseases. In this review, examples of currently marketed chronopharmaceutical dosage forms, the manufacturing techniques applied, drug release mechanisms, and the timing of drug administration are collected and compiled in Table 2.

Table 2

<table>
<thead>
<tr>
<th>Registered trademark®</th>
<th>Drug</th>
<th>Chronopharmaceutical technology®</th>
<th>Drug release mechanism</th>
<th>Timing of drug administration</th>
<th>Indications for chronotherapy</th>
<th>References</th>
</tr>
</thead>
</table>

List of the chronopharmaceutical dosage forms marketed and the pulsatile drug delivery technologies used
<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Active Ingredient</th>
<th>Technology</th>
<th>Dosage Form</th>
<th>Time of Administration</th>
<th>Indications</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEXILANT</td>
<td>Dextansoprazole</td>
<td>DDR technology</td>
<td>Dual drug release</td>
<td>Fasting state before breakfast</td>
<td>Healing of erosive esophagitis</td>
<td>Expert Opin Pharmacother. 10: 2329–2336 (2009)</td>
</tr>
<tr>
<td>Glumetza</td>
<td>Metformin HCl</td>
<td>AcuForm technology</td>
<td>Gastric retention delivery systems - swelling/erosion</td>
<td>Evening with food</td>
<td>Type II diabetes</td>
<td>Expert Opin Pharmacother. 7: 803–809 (2006)</td>
</tr>
<tr>
<td>Oleptro ER</td>
<td>Trazodone HCl</td>
<td>CONTRAMID technology</td>
<td>Diffusion/rupture</td>
<td>Bedtime</td>
<td>Major depressive disorder</td>
<td>Psychiatry. 6: 20–33 (2009)</td>
</tr>
<tr>
<td>Opana ER</td>
<td>Oxymorphine HCl</td>
<td>TIMERx technology</td>
<td>Swelling, gelling, erosion</td>
<td>Bedtime</td>
<td>Pain</td>
<td>Expert Opin Pharmacother. 8: 1515–1527 (2007)</td>
</tr>
<tr>
<td>Ritalin LA</td>
<td>Methylphenidate HCl</td>
<td>SODAS technology</td>
<td>Bimodal release</td>
<td>Morning</td>
<td>Attention deficit hyperactivity disorder (ADHD)</td>
<td>Paediatric Drugs. 5: 833–841 (2003)</td>
</tr>
<tr>
<td>Sanctura XR</td>
<td>Tropium chloride</td>
<td>Pellet coating technology</td>
<td>Controlled release</td>
<td>Morning</td>
<td>Overactive bladder (OAB) symptoms</td>
<td>NeurouroUrolodyn. 29: 551–554 (2010)</td>
</tr>
<tr>
<td>Seroquel XR</td>
<td>Quetiapine fumarate</td>
<td>Hydrophilic matrix technology</td>
<td>Diffusion, erosion</td>
<td>Evening</td>
<td>Major Depressive Disorder</td>
<td>CNS Spectr. 14: 299–313 (2009)</td>
</tr>
</tbody>
</table>

METHODS

Techniques of press-coated delivery systems

2.1.1 Pharmaceutical coating

Pharmaceutical coating is an important technique for the preparation of solid dosage forms, and it is assured that this technique will develop further within the pharmaceutical industry [51,52].

The main technique employed in the preparation of coated solid dosage forms is based on the deposition of different materials from solution, suspensions, or powders. There are four major coating techniques for applying coatings to pharmaceutical solid dosage forms: (1) sugar coating, (2) film coating, (3) microencapsulation, and (4) press coating.

The first three items for the coating of solid dosage forms are classified under liquid coating technology by solution or suspension. Liquid coating techniques most commonly used by the pharmaceutical industry are aqueous or organic coating, however, these present some disadvantages: they are time consuming, drug stability for heat labile and hydrolysis, and environmental pollution becomes a problem.

Therefore, non-solvent or solventless coating methods, such as press coating, are used as alternative coating techniques, to avoid disadvantages in the pharmaceutical coating of many drugs.

2.1.2 Solventless coating technology

Solventless coating technology can avoid problems of solvent exposure, solvent disposal, and residual solvent in the product [53,54].

Solventless processing enables a reduction in costs, by eliminating the slow and expensive processes associated with solvent treatment. Moreover, the technology can significantly reduce processing times because there are no drying and evaporation steps.

In particular, the solventless coating process without any heating source in most cases can provide an alternative method to coat the temperature-sensitive drugs.

Among these techniques, press coating has recently been adopted as a means of special coating for specific drug delivery applications. Press coating involves the use of modified tableting machines, which allow the compaction of a dry-coat around a tablet core produced on the same machine.

2.1.3 Press coating technology

Press-coating, also referred to as double compression coating, compression coating, or dry coating, is an old technique first proposed by Noyes in an 1896 patent [55].

An industrial application of this technique was introduced during the period 1950–1960 to allow the formulation of incompatible drugs [56].

Press coating found increasing application during the past two decades; the process does not require solvents, has a relatively short manufacturing process, and achieves a greater increase
in mass of the core tablet than solvent-based methods do [57]. Although it is an old concept, presscoating is a novel technology for the formulation of new DDS systems [58–60].

The technique requires a specific tablet press, with compression coating capability. The press coating technique offers many advantages, such as protection of hygroscopic, light sensitive, oxygen labile, and acid-labile drugs, isolation of incompatible drugs from each other, and provides a method for both sustained drug release and modification of the drug release profile [57,61,62].

In general, a press-coated tablet consists of an inner core tablet and an outer coating shell. The outer layer surrounds the inner core, and so selection of outer layer materials has a significant impact on the performance of the tablet, including the coating's mechanical strength, drug release characteristics, and tablet stability. It is also possible to produce combination dosage forms, in which two active substances target different areas of the gastrointestinal tract.

Press coating allows the physical separation of incompatible drugs in the core and coat within the same dosage form. Direct compression of both the core and the coating shell can remove the necessity for a separate coating process.

Any type of material with adequate compaction properties can be used for the coating shell. More recently, DDSs based on press-coated functional layers have been proposed for delayed, pulsatile, and programmable release of different drugs in a single tablet. The press-coating technique has been used to modify the drug release of many drugs, mask a medication's bitter taste, and protect volatile substances. The technique offers several unique features, such as no requirement for special coating solvents or coating equipment and short manufacture times. Recently, the application of this technology was investigated in the development of timed release dosage forms, time clock systems, and delayed-release tablets [61–63].

The press-coated tablet may consist of a fast disintegration or modified release core, coated by compression with a solid barrier, commonly made of polymeric material, a diluent (as a release modifier) and drug (for both rapid or extended release) [64,65].

Press-coated tablets may be modified to provide different release patterns, by varying the drug distribution and type of polymers used in the core and outer coating shell. The resulting modified drug release may be dependent on the time, pH, or microbial control to target a specific region in gastrointestinal tract. Thus, press-coating may be classified as a chronopharmaceutical technology [62,65,66], in that it provides a solid dosage form for drug delivery in a pulsatile fashion rather than continuously, and at predetermined times and sites following oral administration.

### 2.1.4 Manufacturing process of press coating

There are extensive reports of the use of the press-coating technique for managing drug delivery from the tablets in the literature; these are represented as far as possible in Table 3.
### Table 3: Oral pulsatile drug delivery tablets prepared by press coating techniques.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage form (named from each reference)</th>
<th>Formulation of inner core</th>
<th>Formulation of outer layer</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Fluorouracil</td>
<td>Compression-coated tablet</td>
<td>Drug+MCC/PVP K30, MgSt</td>
<td>HPMC, lactose, MgSt</td>
<td>Pharm Devel Technol. 12: 203–210 (2007)</td>
</tr>
<tr>
<td>Diltiazem HCl</td>
<td>Press-coated tablet</td>
<td>Drug+cornstarch/PVP P, calcium citrate, Ca-CMC, MgSt</td>
<td>HPMCAS+hydrophobic agents</td>
<td>J Control Rel. 70: 97–107 (2001)</td>
</tr>
<tr>
<td>Cevimeline HCl</td>
<td>Press-coated tablet</td>
<td>Drug+HPMC, stearic acid, MgSt</td>
<td>Drug+HPMC, stearic acid, MgSt</td>
<td>Int J Pharm. 383: 99–105 (2010)</td>
</tr>
<tr>
<td>Drug</td>
<td>Coating Type</td>
<td>Compositions</td>
<td>Coating Type</td>
<td>Reference</td>
</tr>
<tr>
<td>-----------</td>
<td>-------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-------------------------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Tinidazole</td>
<td>Compression-coated tablet</td>
<td>Drug+spray-dried lactose, sodium starch glycolate, talc, MgSt</td>
<td>Guar gum, HPMC, starch, talc, MgSt</td>
<td>Drug Delivery, 10: 263–268 (2003)</td>
</tr>
</tbody>
</table>

Note: MgSt: magnesium stearate; HPMC: hydroxypropylmethylcellulose; EC: ethylcellulose; PEO: polyethylene oxide; NaCMC: sodium carboxymethylcellulose; MCC: microcrystalline cellulose; PVP: polyvinylpyrrolidone; CaSt: calcium stearate; Ac-Di-Sol: sodium croscarmelllose; HPC: hydroxypropylcellulose; Ca CMC: calcium carboxymethylcellulose; DCP: dicalcium phosphate dihydrate; PEG: polyethylene glycol; HPMCAS: hydroxypropylmethylcellulose acetate succinate; PNIPAAm: poly(N-isopropylacrylamide); PNIPAAm-co-NVA: poly(N-isopropylacrylamide) co-N-vinylacetamide; HEC: hydroxyethylcellulose.

The press-coating manufacturing processes employ several steps (Fig. 7) [67].
Fig. 7: Manufacturing processes of press coating.

The inner core tablet is formulated, and then compressed under appropriate conditions. The tabletting machine die is pre-filled with shell-coating materials to form a powder bed, the compressed inner core tablet is placed at the center of the bed, and any remaining outer coating shell materials added. Finally, the outer coating shell is compressed around the inner core tablet. The possibility of schematic designs for preparing various types of press-coated tablets is shown in Fig. 8.

Fig. 8: Different possible schematic designs for preparing various types of press-coated tablets.
3. Factors Affecting Performance and Drug Release of Press-Coated Delivery Systems

Press-coated tablets have two layers, an inner core compressed as a small tablet and an outer shell. The core tablet may additionally be dry-coated with rate controlling materials such as controlled release polymers and fillers.[57,62,67]

The press-coated assemblage comprising core and shell may provide both rate-control and time-control to drug release. The drug release rate is influenced by various factors including the thickness and porosity of the outer shell, type of material used to compress the inner core and outer shell, excipient particle size, force used to compress each layer, and position of the inner core within the tablet.

The manufacturing procedures described above(Section 5) include several factors that affect performance and drug.

3.1 Inner core tablet

The inner core of the press-coated tablet may comprise pure drug crystals, drug-excipient blends, granules, microspheres and beads. It is also possible to incorporate materials into the core tablet to facilitate disintegration, or otherwise modify the drug release.

Various drug-release mechanisms may be obtained by incorporation of different polymers into the inner core compositions.

3.1.1. Drug solubility

The solubility of drugs has always been a concern for formulators, since the solubility and permeability of drug are the major factors that influence the drug's absorption. Poor solubility has been shown to be the cause of numerous drug development failures.

Thus, the solubility of a drug embedded within the inner core of a press-coated tablet is also a major parameter to monitor along with the dissolution behavior of the drug. Lin et al. investigated the effect of types of drugs present in the inner core, on the drug release behavior of press-coated tablets[68].

The results indicated that release profiles show a distinct lag time followed by various release phases that are chiefly determined by drug solubility.

Carbamazepine, a water-insoluble drug, was released in pulsatile fashion after a lag produced by erosion of the HPMC outer shell, while more soluble drugs exhibited a sigmoidal release profile by diffusion through the gel prior to erosion.

By increasing HPMC's molecular weight, carbamazepine's lag time increases significantly because of the erosion-based release mechanism. However, increasing HPMC molecular weight did not affect the release of more soluble drugs. Good control over lag time and release rate is possible by varying the HPMC thickness in the press-coating layer.
3.1.2. Core composition variables

3.1.2.1. Osmotic agent incorporated.

When incorporated in the inner core tablet, sodium chloride performs as an osmotic agent, and the drug dissolution profile is heavily influenced by the amount of sodium chloride present, even when using EC as an outer coating shell.

Lin reported that the lag time for the sodium chloride loaded press-coated tablet shortens markedly to b1 h, as compared with 16.4 h for the drug alone [68].

The lag period shortened with increasing amounts of sodium chloride. Osmotic pressure is thought to play a key role in controlling the drug dissolution, in which the greater dissolution rate of pulverized sodium chloride generated high internal osmotic pressure within the inner core tablet, to quickly rupture the outer coating layer of the press-coated tablet away from the loose packing of the lateral surface. The osmotic function appears more appropriate than super disintegration for press-coated tablets with time-controlled disintegration.

3.1.2.2. Excipients and polymers contained within the core.

Lin et al. demonstrated that press-coated tablet release behavior and lag time are dependent on the type of excipient present in the core [68].

Several direct-compressible excipients (spray-dried lactose, microcrystalline cellulose, or sodium starch glycolate) and a binding powder (HPMC) had been added to inner core formulations. The drug release behavior of such press-coated tablets using EC as an outer outing shell was characterized by a distinctive lag time, followed by a fast drug release [69].

3.1.3. Amounts of inner core

To maximize potential drug loading, Rujivipat and Bodmeier investigated the effect of different inner core:outer shell ratios [70].

Three ratios were used, 3:1 (9mm core in 10 mm press-coated tablet), 2:1 (9mm core in 11 mm press-coated tablet), 1:1 (6mm core in 8 mm press-coated tablet) and 1:2 (6 mm core in 9 mm press-coated tablet).

None of the formulations released at pH 1.0 for 20 h, but a pulsatile release occurred after a distinct lag time at pH 7.4. The rate of drug release was increased with an increase in the inner core:outer shell ratio, due to faster erosion and the thinner press coating, while increasing the compression force and decreasing the inner core:outer shell ratio caused the lag time to increase.

3.1.4. Compression pressure

The compression force plays an important role in the tablet manufacturing process, particularly in the fabrication of time controlled press-coated tablets [71].

Inner core tablets prepared using a compressive force between 50 and 150 kg/cm2 all exhibited similar release profiles, and the slopes of the lines for all three products appeared identical, with lag times of around 12.5 h. However, at inner core compression forces greater
than 200 kg/cm², the lag time increased from 12.5 to 16.3 h, implying that the compression force applied to the inner core tablet has less influence on drug release after application of a constant compression force to form the outer shell.

3.1.5. Location of inner core

Correct centering of the inner core within the press-coated tablet is essential, and the exact centralization of the press-coated tablet core is a common cause of complication and failure for the press coating process.

The press-coated tablet drug-release reproducibility is always poor, since problems and mistakes can arise from unequal coating or off-center positioning of the core, or both. However, a novel compression tool of the OSDRC-system and a non-invasive X-ray computed tomography have recently overcome this problem [72,73].

Other validated techniques have also been explored, and we discuss these in detail in the following section.

3.2 Outer coating shell

To design a press-coated tablet, the outer shell is key in ensuring that medication will reliably reach the predetermined site following oral administration. Press coating involves direct compression of both the inner core and the outer coating shell, without separate coating processes or the use of coating solutions. The drug form is manufactured by compressing a tablet within a tablet, so that the outer shell becomes a coating layer. Various drug release mechanisms become available by incorporating different polymers or other materials into the outer shell formulation, or by increasing the layer's thickness. An outer shell made of a rupturable, swellable, or erodible coating, or a permeation coating using combinations of hydrophilic and hydrophobic polymers, can modulate the speed of water penetration into the outer layer to control drug release (Fig. 9). The outer coating shell of the press-coated tablet may also provide the initial dose of drug.

Fig.9. Possible scheme for drug release from the time-controlled disintegrating or rupturing press-coated tablet.
3.2.1. Polymer particle size

The drug release from these tablets exhibited an initial lag period, dependent on the EC particle size, followed by rapid drug release. Various lag times, ranging from one to 20 h, were obtained for different EC particle sizes, with smaller particle sizes providing greater lag times\textsuperscript{[74]}.

The finer the particle size, the less residual porosity will remain in the coating shell due to more efficient consolidation of the polymer powder. Smaller EC particle sizes in the shell provide the fabrication of time-controlled press-coated tablets with less porosity and a more tortuous path for medium infiltration, and so greater lag times of drug release are obtained. This suggests that the EC powder particle size could be used to modulate the timing of drug release from such a press-coated tablet.

Providing compressive force from the sides of the tablet structure during the press-coating process, rather than to the upper and lower surfaces, produces less dense packing characteristics.

The lower density was responsible for the formation of the lateral breach in the EC shell \textsuperscript{[75]}. Duration of the silent phase turned out was greatly affected by the EC particle size. Indeed, larger particle sizes produced greater coating layer porosity in the fabrication of time-controlled press-coated tablets. Accordingly, the longest delays were attained using micronized polymer powders. Longer tablet lag times were achieved by applying higher compression forces, in addition to thicker micronized EC layers. These results suggest that press-coated tablets prepared with an outer coating shell containing particular EC powder particle sizes might offer a programmable release profile for drug delivery at predetermined times and sites.

3.2.2. Formulation variables

Many pharmaceutical polymers, including cellulose derivatives EC, HPMC, hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), and hydroxypropylmethylcellulose acetate succinate (HPMCAS); polysaccharides guar gum, sodium alginate, and pectin; water soluble polymers (polyethylene oxide, PEO), wax (behenic acid), and methacrylate copolymers are commonly used in the press coating process, whether alone or in combination. By classifying these polymers by function, the outer coating shell containing these polymers can be classified into various groups, such as water insoluble/rupturable (EC), erodible (low molecular weight HPMC, HPC, PEO), gellable or swellable (high molecular weight HPMC, gums), pH-dependent soluble (HPMCAS, Eudragit copolymers), waxy and bacterial digestible. These polymers’ properties can be used to modulate drug release in different ways (Table 3).

Conte et al. showed both controlled and modulated drug release behavior from press-coated tablets by varying the type and molecular weight of the polymer used to form the outer coating shell \textsuperscript{[75]}.

Drug release starts when the shell is completely eroded, swollen, or dissolved. A purely erodible coating prevents drug release from the inner core until it is removed by the dissolution medium. An erodible shell coating does not modify the release behavior of the inner core; however, a gellable coat can delay and alter the presscoated tablet release performance.
Release rate from a gellable coat increases with decreasing molecular weight, for example a low molecular weight polymer, such as HPMC 2208, provides a greater release rate following the lag time than a higher molecular weight does [76].

Hydrophilic excipients incorporated into an insoluble outer shell possibly act as pore-forming agent to aid water penetration; lag time decreases as water soluble excipient content in the coating shell is increased.

Different drug release behaviors from press-coated tablets containing various hydrophilic excipients were observed for various physiochemical properties. Lin et al. showed that lag time from a press-coated tablet shell containing EC/HPMC was longer than that for an EC/spray-dried lactose (SDL) shell, due to the greater water solubility of the latter [77]. Viscous HPMC gel deposited within and on the surface of press-coated tablets increased the lag time.

3.2.3. Compression pressure

The compression force used in the fabrication of the press-coated tablet is a critical parameter influencing the dosage form design performance. Lin et al. investigated the influence of the compression force applied to the outer coating shell on drug release [71].

Fig. 10. Effect of compression forces on release profile

Fig. 11: Relationship between lag time and compression force.
Turkoglu and Ugurlu found that the compression pressure is not a reliable release modifying factor for press-coated tablets with pectin-HPMC as the outer coating shell. A compression force applied to the pectin-HPMC K100M shell had small effect on the erosion rate of the shell, resulting in no observed difference in the drug release of 5-amino salicylic acid from the inner core.

The swelling and hydration of a hydrophilic pectin-HPMC mixture, to form a hydrogel layer provided a more predictable release than that of compression pressure, in an aqueous medium.

3.2.4. Amounts of outer shell

The amount of material in the outer coating shell is a key parameter in achieving a uniform coating for press-coated tablets. The tablet requires an outer coat, which is about twice the mass of the inner core tablet or more, however, the volume must be greater than that of the inner core itself. If the inner core mainly consists of low-density materials, such as fats and waxes, the mass of the coating shell must be greater to assure a uniform covering for the inner core, and provide adequate adhesion between the inner core and outer coating shell.

The outer coating layer controls the swelling, erosion, disintegration, and dissolution behavior of the press-coated tablet, and so the amount of material in this layer plays a unique role in the performance of these dosage forms. Lin investigated the effect of the amount of coating material on the release profile of press-coated tablets.

Greater quantities of outer coating were found to prolong the lag time before drug release. Press-coated tablets prepared using 160 mg of EC as the outer coating shell had a shorter time lag, and exhibited a different initial release profile compared to tablets prepared using greater than 200 mg of EC.

The initial stage of drug release from the press-coated tablet prepared using 160 mg of EC as the outer coating shell showed a linear release rate and quick dissolution of the drug, up to 50% completion.

This linear release behaviour might due to the thinner EC layer, which as with the porous EC film, may control drug penetration by obeying Fick's law. Drug permeability plays a dominant role during the initial dissolution stage, and fast disintegration of the tablet results in quick dissolution of the drug.

Increasing the EC amount to greater than 200 mg increases the time lag, although rapid disintegration and dissolution are again observed.

This suggests that the amount of material present in the outer coating shell plays a key role in determining the time controlled disintegration behaviour.

3.2.5. Double layered outer shell

In the design of a novel press-coated tablet, the outer coating shell is critical in ensuring reliability to reach the target site.

Lin et al. formulated different weight ratios of coarse and fine EC powders, or coarse EC powders with different excipients in the upper layer of the outer coating shell of press-coated tablets.
Drug release from all press-coated tablets exhibited an initial lag period, followed by a stage of rapid drug release.

When the mixture of the coarse and fine EC particles was incorporated into the entire layer, the lag time was almost the same, because fine EC powder filled inter- and intra-particulate gaps of the coarse EC powder.

The outer shell broke into two halves to provide a rapid drug release after the lag period, an example of the time-controlled disruption release mechanism.

When the lower layer of the outer shell was composed of coarse EC powder and the upper layer was formulated of different mass ratios of coarse and fine EC powders, the drug release also exhibited time-controlled disruption behaviour.

The lag time might be freely modulated, depending on the amount of fine EC powder added. Incorporating different excipients into the upper layer of the outer shell, different release mechanisms were observed as follows: time-controlled explosion for Explotab, disruption for microcrystalline cellulose and spray-dried lactose, erosion for dibasic calcium phosphate anhydrate, and a sigmoidal profile for HPMC.

Different possible schematic designs for preparing various types of press-coated tablets have also been proposed in Fig. 10.

### 3.2.6. Compressibility and layer-binding

The compressibility of press-coated tablets mainly focuses on the outer shell coating material, in which cohesiveness and plasticity of the outer coat are required to provide adequate mechanical strength.

To ensure adhesion between the inner core and outer coating shell, the final compression force applied to prepare the tablets needs to be greater than the compression force that was applied to the inner core. A common problem to occur is tablet lamination between the two layers; layer binding is one of the most common problems in the press coating process. If firm layer binding is not achieved, then lamination of the final tablet may cause the two layers to separate from one another after ejection.

Waterman and Fergione developed a novel adhesive coating to allow even small quantities of immediate-release powders to be press-coated onto controlled-release dosage forms without damaging the controlled-release coating [82].

### 3.2.7. Stability of enzymes or drugs under compression

The stability of enzymes or drugs after application of compression force by press coating or compression should be carefully considered. Enzymes are globular proteins, and pressure-induced reduction in the activities of a number of enzymes has been reported [83-85]. However, inactivation of α-amylase was prevented by using k-carrageenan as excipient for tableting [86].

The enzyme protection provided by k-carrageenan might be attributed to its ability to expand and so release mechanical stresses present in the tablet. However, some enzymes are less sensitive to the forces involved in tableting. The enzyme nattokinase was successfully stabilized and showed non-significant reduction in activity after tableting [87].
Press coating has also been demonstrated to be a novel encapsulation method for improving the survival of probiotic bacteria cells when exposed to acidic media.

4. Recent challenges for press coating technology

The press coating technique is a compression process that forms an outer coat around a pre-formed inner core tablet \(^{60-64}\).

The process involves an initial compression of the inner core, which is then transferred to a larger die containing half of the required coating material \(^{57}\).

The compression process is simple on a laboratory scale, but specialist equipment is needed for large-scale manufacture. However, the main difficulty in the manufacture of press-coated tablets is how to center the inner core tablet under rapid processing conditions \(^{88}\). Eccentric localization may alter lag time and release profile, leading to the changes in drug bioavailability. Reproducibility of drug release from press-coated tablets becomes uncertain with off center placement of the core tablet.

Recently, the novel ENCORE™, one-step dry-coated tablet (OSDRC) method, pulse-echo ultrasonic approach, and x-ray computed tomography (CT) technique has been applied to solve manufacturing problems with central position deviation and absence of a core in the press-coated tablet.

4.1. ENCORE™

Press-coated tablets prepared by ENCORE™ are produced on a modified rotary tablet machine using hollow punches; first an inner tablet is formed, then the outer shell is compressed using the same die (“tablet-within-a-tablet”). This method is applied in the fabrication of press-coated tablets with an outer coating shell comprising 35% polyethylene oxide (PEO) and 65% lactose, to provide time controlled delivery of theophylline \(^{89,90}\).

4.2. OSDRC system

Ozeki, using a uniquely designed rotary tableting machine, developed OSDRC \(^{72, 91, 92}\). The machine has a variable double punch configuration for single-step production of press-coated tablets. The rotary-type tableting machine uses only a single set of punches and dies.

All punch assemblies have a double structure, consisting of center and outer punches. The inner core tablet position is precisely controlled, and the outer coating layer is very flexible for control over geometry and thickness.

The novel OSDRC compression tool is capable of producing press-coated tablets in a single process, without prior core tablet preparation. The OSDRC manufacturing process involves three compressions. At the first compression, the lower-outter layer is formed by pre-compression by the upper-centre punch. Then, the lower-center punch is lowered and the upper-center punch is raised.

Ando et al. applied OSDRC-technology to the preparation of capsule-like tablets containing pellets of greater than 50 wt% medication content \(^{93}\). In addition, in terms of crushing strength, the tablets compressed by OSDRC method were also found to be superior to those obtained by the conventional compression method \(^{94}\).
This technology now forms the basis of a new business platform within the global pharmaceutical market. Ozeki also developed a double core press-coated tablet using a dividable OSDRC system with double punches [95].

The dividable-OSDRC controls doses more precisely, by dividing them even when they are press-coated or enteric-coated.

Furthermore, the dividable-OSDRC can reduce the number of tablets required by patients, by producing tablets containing different drug contents, and is expected to bring about a medical economical advantage. The dividable-OSDRC tablet seems likely to become a new platform for the controlled release of drugs in future.

4.3. X-ray computed tomography

Tokudome et al. introduced X-ray computed tomography (CT) as a fast and non-invasive tablet observation method for the online process control of press-coated tablets [73, 96]. The internal structure of press-coated tablets is very rapidly observed, without pre-treatment or destruction.

X-ray CT provides cross-sectional images, which are combined to build a three-dimensional image of the tablet interior. X-ray transmittance varies with tablet density, and so can reveal the interior geometrical structure of tablets. This helps in quality control of the press-coated tablets and also identifies any cracks within the tablet. The other In-vitro tomography and non-destructive imaging will also be useful as a tool of process analytical technology (PAT) to provide quality control of the in-vitro characterization of dosage forms [96].

4.4. Pulse-echo ultrasonic approach

The accuracy of the geometry (the outer layer wall and core thicknesses), mechanical properties (Young's moduli and mass densities of associated materials), and integrity (core eccentricity, compaction state of layers, and bonding state of interfaces) of a press-coated tablet are crucial to its structural function and therapeutic effectiveness.

Thus, a pulse-echo ultrasonic technique had been developed for the real-time quality monitoring of press-coated tablets in the tablet press during compaction [97, 98].

This real-time in-die compaction monitoring may be conducted directly to determine tablet hardness (affecting bonding and mechanical strength), porosity for its effect on dissolution profiles, and product quality (e.g. mechanical integrity), and conforms with key objectives of quality monitoring and regulatory initiatives such as the U.S. Food and Drug Administration's (FDA) Quality by Design (QbD), and PAT programs.

CONCLUSIONS AND FUTURE PERSPECTIVES

In this review article, we introduce press-coated dosage forms, developed as chronopharmaceutical products to meet the physiological conditions and needs of patients. The review considers biological rhythms and pulsatile hormone secretion in humans, and describes the benefits of pulsatile drug delivery for disease treatments, recent chronopharmaceutical preparations on the market. We provide an updated compilation of all research articles and press-coated delivery techniques, factors affecting performance and drug
release of press-coated delivery systems, and recent challenges for the press coating technique.

Chronotherapeutics is the new discipline of medical treatment of drugs by considering patient's biological rhythms in determining the timing (sometimes the amount) of medication to optimize a drug's desired effects and minimize any adverse drug effects.

Circadian rhythms correlate well to many human physiological processes and functions, and particularly so for day-night variation in patients. The press-coated tablet has recently received renewed attention, as a novel system to deliver a drug in a pulsatile manner at predetermined times following oral administration. These novel systems are both rate and time controlled. A variety of press-coating approaches are also reviewed.

Chronopharmacology research has demonstrated the significance of biological rhythms to drug therapy, and this has sparked a new trend in the design of DDSs.

This new chrono-DDS whether including new medicines or old ones can vary the timing of drug administration to coincide better with the function of circadian rhythms, leading to the improvement of drug therapy for different diseases. The adjustment of dosing schedule, reformulation of a drug or usage of programmable pumps, is some of the simple changes that may bring in great benefits. The effects of optimizing the timing of drug administration with this chrono-DDS or new formulation not only can improve the risk-benefit ratio of long-term use, but also can give the low-dose drug treatment for patients to decrease the side effect of drug. Thus, the dosing timing in disease therapy has a significant impact on treatment success, chronotherapeutics will become an important therapeutic tool for future medication.

Many unique chronopharmaceutics that provide medication at times associated with the circadian clock now exist; these dosage forms not only improve the treatment outcome but also improve patient compliance.

This because of an increasing awareness of the importance of circadian rhythms with respect to physiology, the disease state and drug action, which has given rise to the related fields of chronotherapeutics and chronopharmacology. The press-coated tablet, prepared by a unique compression press, consists of an inner core and an outer shell. The compression method eliminates time-consuming and complicated coating or granulation processes, and improves drug stability by protecting it from moisture.

Future design strategies for press-coated tablets may incorporate different materials into core and outer shell formulations to develop unique chronopharmaceutics with improved rate-control, site control and quantity-control functions.

Recently, many colon disorders and diseases, such as ulcerative colitis, diverticulitis, irritable bowel syndrome, Crohn's disease, carcinomas and other infections have been diagnosed. Future greatest challenge is the targeted delivery of drugs to the lower GI tract and colon.

The press-coated tablet is an attractive dosage forms, particularly because many drugs offer poor bioavailability due to their instability in the GI tract. The targeted liberation of press-coated dosage forms should be further developed through a variety of formulation approaches for treatment of different colon conditions, and is a worthy challenge for future investigation.
REFERENCES


72. Y. Ozeki, Y. Watanabe, S. Inoue, K. Danjo, Comparison of the compression characteristics between new one-step dry-coated tablets (OSDRC) and dry-coated tablets (DC), Int. J. Pharm. 259 (2003) 69–77.


