

Review Article

Pulsatile drug delivery system using core-in-cup approach: a review

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ABSTRACT

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. Pulsatile drug delivery system (PDDS) can be defined as a system where drug is released suddenly after a well-defined lag time according to the circadian rhythm of the disease. PDDS can be classified according to the pulse-regulation of drug release into three main classes; time-controlled pulsatile release (single or multiple unit system), internal stimuli- induced release and external stimuli-induced pulsatile release systems. Pulsatile delivery is generally intended as a release of the active ingredient that is delayed for a programmable period of time to meet particular chronotherapeutic needs and, in the case of oral administration, also target distal intestinal regions, such as the colon. Most oral pulsatile delivery platforms consist in coated formulations wherein the applied polymer serves as the release-controlling agent. When exposed to aqueous media, the coating initially performs as a protective barrier and, subsequently, undergoes a timely failure based on diverse mechanisms depending on its physico-chemical and formulation characteristics.

Keywords: Pulsatile drug delivery system, Core-in-cup approach, Inlay tablets

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Introduction

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance.^{1,2} The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired. The release of the drug as a pulse after a lag time (an interval of no drug release) has to be designed in such a way that a complete and rapid drug release follows the lag time. Pulsatile release is also useful for the targeting of the drug irritating the stomach or degradable therein, as well for drugs developing biological tolerance or with an extensive first-pass metabolism. Conventional controlled release drug delivery systems are based on single or multiple-unit reservoir or matrix systems, which are designed to provide constant or nearly constant drug levels over an extended period of time.¹⁻⁴

The temporal rhythms of body functions have been shown to affect not only the severity of a number of diseases but also the pharmacokinetics and pharmacodynamics of most bioactive compounds in use. Accordingly, chronotherapeutic treatments, tailored to supply the patient with the appropriate dose of the required drug at the perfect time, are gaining an increasing interest. Many diseases follow a well-defined circadian pattern such as hypertension, allergic rhinitis, osteoarthritis, rheumatoid arthritis, nocturnal asthma, angina pectoris and peptic ulcer.^{1,7}

Pulsatile drug delivery system (PDDS) can be defined as a system where drug is released suddenly after a well-defined lag time according to the circadian rhythm of the disease. PDDS can be classified according to the pulse-regulation of drug release into three main classes; time-controlled pulsatile release (single or multiple unit system), internal stimuli- induced release and external stimuli-induced pulsatile release systems. PDDS can also be classified according to the dosage form into three main types; capsules, pellets and tablets among which the 'core-in-cup' tablet system. The core-in-cup tablet system consists of three different parts: a core tablet, containing the active ingredient, an impermeable outer shell and a top cover plug layer of a soluble polymer.^{7,9}

In the field of oral delivery, besides a widespread use of pro-longed-release dosage forms increasing interest has been focused on the development of formulations able to release active pharmaceutical ingredients after programmed lag times or to specific regions of the gastrointestinal (GI) tract. The time-dependent approach, in particular, is based on the relatively constant small intestinal transit time (SITT; 3 ± 1 h standard error) of dosage forms.¹⁰⁻¹²

On the contrary, the duration of gastric residence of solid dosage forms, which depends on their size and density as well as fasted or fed conditions of subjects, is unpredictable; hence, by the application of an outer gastro resistant layer, which dissolves only after the dosage form is emptied from the stomach, the influence of variable gastric emptying can be overcome. Subsequently, a lag phase imparted to the drug-containing core allows the system to reach delay duration comparable to SITT.

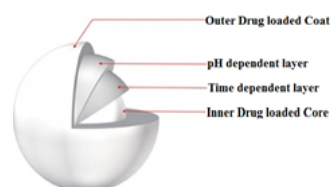


Figure 1: Pulsatile core-in-cup tablet.

Among time-based devices, a platform for delayed and site-specific release of drugs in the form of a reservoir system, named Chronotopic™, has already been developed. Such device is based on single- or multiple-unit drug cores (tablets, capsules, pellets) coated with a functional layer composed of swellable/erodible polymers (namely, hydroxypropyl methylcellulose, HPMC) of few hundred microns of thickness applied by different techniques (press-coating, spray-coating and powder layering). When intended for time-based drug delivery, an outer enteric film is subsequently applied. Once the device is emptied from the stomach, the enteric coating dissolves and the HPMC-based layer delays the contact of the biological fluids with the core, allowing the release of the drug only after a programmed period of time. The effectiveness of the Chronotopic™ system, its flexibility in terms of duration of the lag phase, both *in vitro* and *in vivo*, as well as the possibility of scaling up the manufacturing process has been demonstrated. A step forward in the development of the Chronotopic™ system was represented by a capsular device (Chronocap™) that combined the release functionality of the polymeric coating with the ability to convey a variety of drug preparations (solid, semi-solid, liquid), thus bringing about both technical and regulatory advantages.¹¹⁻¹⁵

Pulsatile delivery is generally intended as a release of the active ingredient that is delayed for a programmable period of time to meet particular chronotherapeutic needs and, in the case of oral administration, also target distal intestinal regions, such as the colon. Most oral pulsatile delivery platforms consist in coated formulations wherein the applied polymer serves as the release-controlling agent. When exposed to aqueous media, the coating initially performs as a protective

barrier and, subsequently, undergoes a timely failure based on diverse mechanisms depending on its physico-chemical and formulation characteristics. Indeed, it may be ruptured because of the gradual expansion of the core, swell and/or erode due to the glassy-rubbery polymer transition or become permeable thus allowing the drug molecules to diffuse outwards. Otherwise, when the coating is a semi permeable membrane provided with one or more orifices, the drug is released through the latter as a result of an osmotic water influx. The vast majority of pulsatile delivery systems described so far have been prepared by spray-coating, which offers important versatility and feasibility advantages over other techniques such as press- and dip-coating.¹⁶⁻¹⁸

Pulsatile delivery systems are non-conventional dosage forms designed to release the active ingredient after a lag phase of programmable duration thereby allowing a chronotherapeutic effect to be attained. Most current pulsatile delivery systems are typically time-controlled in that the onset of release is prompted by inherent mechanisms irrespective of the differing conditions they may encounter in the outer environment. Among them, formulations intended for the oral route are of particular interest in the case of chronic pathologies with circadian symptoms that have a high likelihood of recurring in the night or early morning hours, such as cardiovascular disease, bronchial asthma, rheumatoid arthritis and sleep disorders. Indeed, medications able to provide an appropriate delay phase prior to drug release, administered at bedtime, could selectively cover the especially critical period during which the disease state tends to worsen with no need for waking up the patient for drug intake. In addition, oral pulsatile delivery devices, particularly when able to yield multiple release profiles, may serve in place of prolonged-release systems with drugs that are subject to a strong first-pass metabolism or develop pharmacological tolerance and, in the specific case of antibiotics, would limit the growth of resistant bacterial strains by circumventing defensive dormancy and affecting a larger number of micro-organisms in the division phase. Moreover, it has recently been suggested that the use of pulsatile release dosage forms could prevent detrimental interactions between co-administered drugs from occurring within the gastrointestinal (GI) tract. Although the earliest pulsatile delivery formulations were devised as multi-layer tablets partially enclosed in an impermeable shell, a timed liberation of orally-administered bioactive compounds is currently achieved mainly by the application of a functional polymeric coating to a drug-containing core. The core may either be a single- or a multiple-unit dosage form, the latter enabling improved reproducibility in the GI transit and absorption consistency. The performance of the coating strictly depends on the relevant physico-chemical nature and is started on exposure to the aqueous biological fluids (solvent activation).¹³⁻¹⁷

Chronobiology and chronopharma-cotherapy of disease

Chronotherapy is co-ordination of biological rhythms and medical treatment. Chrono-therapeutic is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. It is becoming increasingly more evident that the specific time that patients take their medication may be even more significant than was recognized in the past. In chrono-pharmacotherapy drug administration is synchronized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient.

Chronotherapy coordinates drug delivery with human biological rhythms and holds huge promise in areas of pain management and treatment of asthma, heart disease and cancer. The coordination of medical treatment and drug delivery with such biological clocks and rhythms is termed chronotherapy.

Chronotherapeutics, or delivery of medication in concentrations that vary according to physiological need at different times during the dosing period, is a relatively new practice in clinical medicine and thus many physicians are unfamiliar with this intriguing area of medicine. It is important that physicians understand the advantages of chronotherapy so that they can make well-informed decisions on which therapeutic strategies are best for their patients-traditional ones or chronotherapies.^{10,13,17}

The goal of chronotherapeutics is to synchronize the timing of treatment with the intrinsic timing of illness. Theoretically, optimum therapy is more likely to result when the right amount of drug is delivered to the correct target organ at the most appropriate time. In contrast, many side effects can be minimized if a drug is not given when it is not needed. Unlike homeostatic formulations, which provide relatively constant plasma drug levels over 24 hours, chronotherapeutic formulations may use various release mechanisms. e.g., time-delay coatings (Covera-HSTM), osmotic pump mechanisms (COER-24TM), and matrix systems (GeminoxTM), that provide for varying levels throughout the major objective of chronotherapy in the treatment of several diseases is to deliver the drug in higher concentrations during the time of greatest need according to the circadian onset of the disease or syndrome. The chronotherapy of a medication may be accomplished by the judicious timing of conventionally formulated tablets and capsules. In most cases, however, special drug delivery technology must be relied upon to synchronize drug concentrations to rhythms in disease activity.¹⁵⁻¹⁹

Ideal pulsatile drug delivery system

Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of drug molecules within a short time period immediately after a predetermined off-release period, i.e., lag time. Pulsatile drug delivery aims to release drug on programmed pattern i.e. at appropriate time and at appropriate site of action. A single dosage form provides an initial dose of drug followed by one release-free interval, after which second dose of drug is released, which is followed by additional release-free interval and pulse of drug release. The pulsatile effect, i.e., the release of drug as a "pulse" after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time may not always be desirable. Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount.²⁰⁻²²

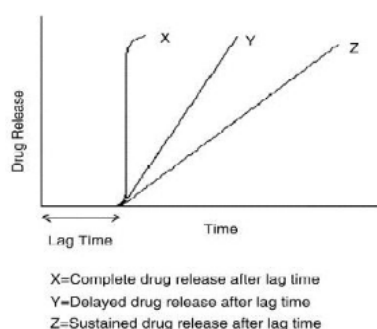


Figure 2: Drug release profile of pulsatile drug delivery system.

Pulsatile system: a tool to increase therapeutic efficacy of drug

In recent years considerable attention has been focused on the development of pulsatile drug delivery system. Delivery system with pulsatile release pattern has gained most popular form of controlled drug delivery system because conventional systems with a continuous release are not ideal. Oral controlled drug delivery systems are generally used due to convenient dosage form & it also releases drug in constant or variable rates^{8,9,10}. In these system drug release generally occurs within therapeutic window for prolong period of time. Hence these systems show sustained release of drug from dosage form.

Advantages of pulsatile delivery

- Extended daytime or night time activity.
- Reduced side effects
- Dosage frequency.
- Reduction in dose size.
- Improved patient compliance.
- Lower daily cost to patient due to fewer dosage units are required
- Drug adapts to suit circadian rhythms of body functions or diseases.
- Drug targeting to specific sites like colon.

- Protection of mucosa from irritating drugs.
- Drug loss is prevented by extensive first pass metabolism.

Drawbacks of pulsatile delivery

- Lack of manufacturing reproducibility and efficacy
- Large number of process variables.
- Multiple formulation steps.
- Higher cost of production.
- Need of advanced technology.
- Trained/skilled personal needed for manufacturing.²⁰⁻²³

Classification of pulsatile systems

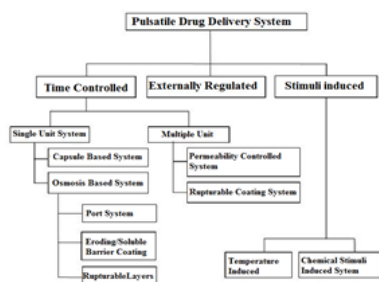


Figure 3: Classification of pulsatile drug delivery system.

Single unit pulsatile system

These are sub-classified as capsule-based systems, osmotic systems, delivery systems with soluble or erodible membranes, and delivery systems with rupturable coating.

Capsular systems

Single-unit systems are mostly developed in capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion, and the drug is released as a "Pulse" from the insoluble capsule body. System that comprises of a water-insoluble capsule enclosing the drug reservoir which is describe later in advances.

Osmosis based system

This system contains a drug and a water-absorptive osmotic agent that are placed in compartments separated by a movable partition. The pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops obstruct the movement of the partition but are overcome in succession as the osmotic pressure rises above a threshold level. Osmotic delivery capsules ("osmotic pumps") function by virtue of walls which selectively pass water into the capsule reservoir. Absorption of water by the capsule through these walls is driven by a water-attracting agent in the capsule interior which creates osmotic pressure across the capsule wall.

Drug delivery system with eroding or soluble barrier coating

These systems are based upon a drug reservoir surrounded with a soluble barrier layer that dissolves with time, and the drug releases at once after this lag time. Chronotropic® system consists of a core containing drug reservoir coated by a hydrophilic polymer HPMC. An additional enteric-coated film is given outside this layer to overcome intra-subject variability in gastric emptying rates. The lag time and the onset of action are controlled by the thickness and the viscosity grade of HPMC.

Drug delivery system with rupturable layers or membranes

These systems are based upon a reservoir system coated with a rupturable membrane. The outer membrane ruptures due to the pressure developed by effervescent agents or swelling agents. A pulsatile system with rupturable coating on drug present in hard gelatin capsules. These capsules were first coated with a swelling layer and then with an insoluble but water-permeable outer coating. These coated capsules when immersed in the release media could take up the media at a constant rate up to a point when the outer coating would rupture because of the pressure caused by the swelling layer.²²⁻²⁶

Based on solubility modification

These systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was especially developed for delivery of salbutamol sulphate. The compositions contain the drug (Salbutamol sulphate) and a modulating agent, sodium chloride (NaCl). The pulsed delivery is based on drug solubility.

Reservoir systems

These systems are based up on a drug reservoir surrounded with a soluble or erodible barrier layer that dissolves with time and the drug releases at once after the lag time. These systems are of two types;

Time clock systems

The time clock system consists of a solid dosage form coated with lipid barriers containing carnauba wax and bees wax along with surfactants, such as polyoxyethylene sorbitan monooleate. This coat erodes or emulsifies in the aqueous environment in a time proportional to the thickness of the film, and the core is then available for dispersion.

Chronotropic systems

The chronotropic system consists of a drug containing core coated by hydrophilic swellable hydroxyl propyl methyl cellulose (HPMC), which is responsible for a lag phase in the onset of drug release. Time lag is controlled by the thickness and the viscosity grades of HPMC used in coating the drug core. The system is suitable for both tablets and capsule formulations.^{22,23}

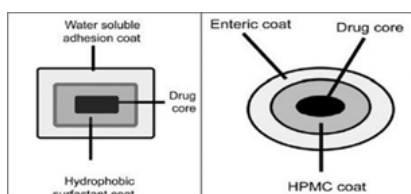


Figure 4: Time clock system and chronotropic system.

Multi-particulate system

Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiplicity of small discrete units, in which the active substance is present as number of small independent subunits. More reliable gastric emptying patterns are observed for multiparticulate formulations as compared to single-unit formulations, which suffer from 'all or none' concept. Multiparticulate systems are further classified as systems based upon change in membrane permeability and systems based upon rupturable coating.

These systems show various advantages over single unit systems, which includes:

- Short gastric residence time
- Reproducible gastric residence time
- No risk of dose dumping

- Flexible to blend pellets with different composition or release pattern
- Lowest transit time variability
- Unique profiles
- Capable of pulsatile release

Disadvantages:

- Multiple manufacturing steps
- Low drug load
- Incomplete release
- High cost of production

Pulsatile system based on change in membrane permeability:

Pulsatile system based on change in membrane permeability based on Change in Membrane Permeability Numerous pharmaceutical forms with delayed release for oral administration are available. As already mentioned the release of the drug must be controlled according to therapeutically purpose and the pharmacological properties of the active ingredient. In consequence, it is not always desirable the blood levels to be constant. On the contrary, in order to avoid any habituation and in order to limit the side effects provoked by the active ingredient, it would be absolutely advantageous for the plasmatic rate to follow the metabolic rhythm and the specific needs of the patient during certain periods.

Pulsatile systems with rupturable coating

This is a multiparticulate system in which drug is coated on non-pareil sugar seeds followed by a swell able layer and an insoluble top layer. The swelling agents' used include super disintegrants like sodium carboxy methyl cellulose, sodium starch glycolate, L-hydroxypropyl cellulose, etc. Upon absorption of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer.

Time controlled explosion systems

This system is based on a combination of osmotic and swelling effects. The core contains the drug, a low bulk density solid and/or liquid lipid material and a disintegrant. The core is further coated with cellulose acetate. Upon contact with aqueous medium, water penetrates the core displacing the lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of the coating material.

Floating delivery based systems

The low density floating multiparticulate pulsatile dosage forms reside only in stomach and not affected by variability of pH, local environment or gastric emptying rate. These dosage forms are also specifically advantageous for drugs either absorbed from the stomach or requiring local delivery in stomach.

Methodologies for pulsatile drug delivery

Methodologies for the pulsatile drug delivery system can be broadly classified into three classes;

- Time controlled pulsatile release system
- Stimuli induced pulsatile systems
- Externally regulated system

Time controlled pulsatile release system

In time controlled drug delivery systems pulsatile release is obtained after a specific time interval in order to mimic the circadian rhythm. Such type of pulsatile drug delivery system contains two components: one is of immediate release type and other one is a pulsed release type. Various methodology that can be used for time controlled Disease Chronological behavior Drugs used like

- Release using pH of target site
- Oral pulsatile drug delivery
- Enzymes present in the intestinal tract
- Transit time or pressure of various part of the intestine
- Delivery systems with rupturable coating layer
- Delivery systems provided with erodible coating layers
- Capsule shaped system provided with release controlling plug
- Miscellaneous pulsatile systems

Stimuli induced pulsatile systems

In these systems there is release of the drug after stimulation by any biological factor like temperature, or any other chemical stimuli. These systems are further classified as following.

- Temperature induced systems
- Chemical stimuli induced pulsatile systems
- Glucose responsive insulin release devices
- Inflammation induced pulsatile release
- Drug release from intelligent gels responding to antibody concentration
- pH sensitive drug delivery system

Externally regulated systems

For releasing the drug in a pulsatile manner, another way can be the externally regulated systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. It is generally classified in two categories;

- Electro responsive pulsatile release
- Magnetically induced pulsatile release

Magnetically regulated system contains magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads. There is different formulation for *in vitro* magnetically triggered delivery of insulin based on alginate spheres. In case of ultra sonically modulated systems, ultrasonic waves cause the erosion of the polymeric matrix thereby modulating drug release. Evaluations the effect of ultrasound (1 MHz) on the release rates of bovine insulin from ethylene vinyl alcohol copolymer matrices and reservoir-type drug delivery systems in which they found sharp drop in blood glucose levels after application of ultrasonic waves.²⁵⁻³⁰

Multilayered tablets for controlled drug delivery

Multilayered systems are becoming increasingly recognized as controlled-release drug delivery systems. Namdeo expressed that multilayered tablets have demonstrated promise, possessing various benefits, namely the ability to prevent interactions between drugs and excipient; and by providing an array of release profiles in one delivery system of either the same or different drugs, treatment for conditions that require a regimen of more than one drug, immediate drug release using a disintegrating monolithic matrix in order to achieve an initial peak in plasma drug level, delayed drug release using an eroding monolithic matrix which may deliver another active drug to a different part of the gastrointestinal tract, providing controlled drug release instituting as well able monolithic matrix and better control and regulation of release profiles by retarding initial burst release and achieving zero-order kinetics.¹⁷ It would be beneficial if research focused on further modification of these systems for improved and comprehensive drug release capabilities that enable a larger scope of application in drug delivery.

Controlled-release multilayered tablets typically involve a drug core layer that is surrounded by barrier layers that may be made up of hydrophilic swellable polymers such as Hydroxypropyl-methyl cellulose (HPMC) and poly (ethylene oxide) (PEO) or hydrophobic polymers such as ethyl-cellulose (EC). The barrier layers minimize and therefore delay the interaction of the gastrointestinal environment with the active core, by decreasing the surface area available for drug release or by controlling the rate at which the solvent penetrates the layers. This allows the initial burst release to be minimized and therefore the drug release can be controlled at a near constant level while the barrier layers undergo erosion or swelling. The swollen barrier layers undergo erosion as time goes on, thus increasing the surface area which ultimately

allows more drug to be released. Following the same principle, it is possible to obtain a constant release profile as well as other types of dissolution patterns such as pulsatile or delayed delivery as well as extended drug delivery depending on the characteristics of the polymers employed. In either case the system should ideally erode completely (i.e., leaving no residue in the gastrointestinal tract after the entire amount of drug is released).²⁵⁻²⁷

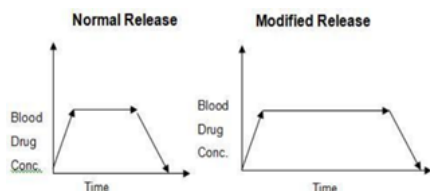


Figure 5: Comparison of concentration of drug with different release study.

Tooling

To demonstrate proof-of-concept of the compression-coated tablet process, 9/16-in. tooling from a single punch press was modified to simulate the special hollow tooling with the core rod. Three punches were machined, to simulate the shape of the punch tip presented to the powder bed in the die when the core rod is in the extended position. These three punches were machined to various dimensions to produce cups with a thick wall (4.8 mm), intermediate wall (4.1 mm), or a thin wall (3.2 mm). Another punch was machined as shown in Figure 1b to mimic the shape of the punch tip in the retracted position of the tooling with the core rod. The lower punch was an unmodified flat-faced punch.

Inlay tablets

- A type of layered tablet in which instead the core tablet being completely surrounded by coating, top surface is completely exposed.
- Tablet compressing was done with core rod tooling in which only one surface of core is exposed to outside and other drug is incorporated in cup portion.
- While preparation, only the bottom of the die cavity is filled with coating material and core is placed upon it.
- The main body portion may consist of an uncoated granulation which is compressed around the enteric coated inlay portion. In this modification the main body portion of the tablet is first released and assimilated in the gastrointestinal tract while the enteric coating protects the inlay portion for a predetermined period of time so as to provide time delayed or sustained medication.
- A to z is offering inlay tablets with combinations like Metformin 500 mg sustained release (Outer coat) and Pioglitazone 15 mg (core tablet) which has a very unique advantage.
- Ursinos is the marketed inlay tablets containing aspirin.

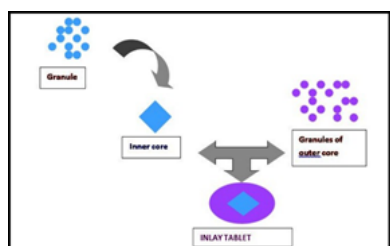


Figure 6: Preparation of inlay tablets.

Advantages of inlay tablets

- Dosage form comprising of an active ingredient as modified release and an active ingredient as immediate release can be prepared.
- Plasma level can be maintained constant and within the therapeutic window throughout the period of treatment.
- Adverse effects due to sub therapeutic plasma concentration can be avoided.
- The burst effect, namely, large release within a short period of time, is common in highly soluble drugs, and shall be avoided, as it may lead to high concentration of active ingredients in the blood stream.
- Has the ability to release soluble and insoluble drugs at a zero-order rate of release in dissolution media.
- Dosage frequency of highly water soluble drugs can be reduced providing same efficacy.
- Tablets of different shape such as triangular, rectangular, or capsule shaped tablets can be manufactured.

Advantages of inlay tablets over other compressed tablets

- Less coating material is required.
- Core is visible, so coreless tablets can be easily detected.
- Reduction in coating forms a thinner tablet and thus freedom from capping of top coating.
- The layered tablet is preferred over compression coated tablet as the surface contact is less and the production is simple and more rapid.

Preparation of the compression-coated tablets

A carefully weighed amount of powder blend (hereinafter referred to as the coating blend) was placed in the die and compressed on a Carver Press (Wabash, IN) at a known force with the tooling to produce a cup-shaped tablet (cup). The cup was left within the die, and a known amount of either a model drug or a blend containing the drug was placed inside the cup and tamped lightly with the punch in an extended position. A weighed amount of the coating blend was placed on top of the die contents, and the cup was compressed for a second time with the punch in a retracted position at a known force to produce the final compression-coated tablets.

1. Triple-layered tablets

Triple-layered tablets are comprised of an inner drug core layer which is sandwiched between two surrounding barrier layers. These barrier layers may also contain drug and serve as matrices to release drug in various release patterns. The general mechanisms of action of triple-layered tablets include erosion of matrix layers, creation of a drug concentration gradient, limiting surface area of release of the swellable matrix by the barrier layers, erosion and swelling of the barrier layers to achieve a constant area for uniform drug release, as well as varying of the layers dissolution to achieve pulsatile or alternating release profiles. Triple-layered systems have some rewards in contrast to typical systems due to the varying release pattern capability, simplicity of manufacturing, reduced dosing frequency that leads to enhanced patient compliance, enhanced safety profile of drug levels and reduced cost.

2. Core-in-cup devices

Danckwerts developed a core-in-cup tablet system that was able to provide zero order drug release of aqueous-soluble and aqueous-insoluble drugs. The system consisted of a disc-shaped matrix core that was compression-coated on one surface as well as at the circumference in order to form a cup around the core. Drug was released in a sustained manner from one stable surface that had a constant surface area. By manipulating the grade, quantity and exposed surface area of any hydrophilic polymer or mixture of polymers that erode constantly over time, the core-in-cup compressed tablet is able to deliver a constant amount of drug over time. Results showed that the system was able to provide zero-order drug release for time intervals between 8 and 23 hours, the time of linear release was approximately 8 hours when 5% w/w HPMC K4M with caffeine core-in-cup tablets were produced and approximately 23 hours when 15% w/w HPMC K15M in ibuprofen core-in-cup tablets were produced. The research that has been conducted on core-in-cup devices showed several interesting and useful techniques as well as beneficial application in terms of the solubility of drugs, the flexibility of

delivering both aqueous soluble and aqueous insoluble drugs pose an advantage. Danckwerts also studied the effectiveness of cup tablets of different depths for use in core-in-cup tablets and the optimal formulation in terms of drug release behavior. He developed a specific punch that is able to change the depth of the cup tablet, thus allowing it to carry various cores in terms of hardness and mass. The efficiency of cup tablets with varying depths and the optimal formulation in terms of drug release were investigated in the study. The cup tablets were composed of 15% w/w carnauba wax in EC while the core tablets were composed of 5% w/w HPMC K4M in ibuprofen. The results indicated that Ibuprofen was released at a near zero-order rate for 18 hours for the cup tablets that had a final depth of 4 mm.²²

Divided core tablets

There also possible to make divided tablets with separate cores in one step operation, which is not possible with current technology. For example divided enteric coated tablets are the world's first dividable enteric coated tablets. Dividable core tablets so called because the core fully encased in the coating even when the tablet is divide, even though the release profile is remain unaffected by dividing.

Cored tablets with poorly compressible cores

By using this technology there is no need of separate manufacturing of core tablet even using of powders with poor compressibility as the core matrix. As it possible to directly encase core pharmaceutical ingredients with the outer covering, these ingredients can be used in oral rapid disintegration tablets. Pellets can also be used instead of powder as core material, drugs normally formulated as capsule dosage form can be formulated as tablet dosage form.

Procise® technology (geometrically altered drug delivery system)

The Procise® device has a specific geometric configuration that controls drug release behavior. It is composed of a core which contains uniformly dispersed drug with a core hole in the middle. It has been made known that, altering the geometry of the core can change the drug release kinetics into zero-order or even first order if desired the core's entire surface besides the surface of the cylindrical face is surrounded by a permeable inactive coat so that drug release occurs solely from the cylindrical area. The device is also able to deliver up to two drugs simultaneously with varying release profiles. This technology further adds to the varied geometrical systems for flexible and simplified drug delivery.

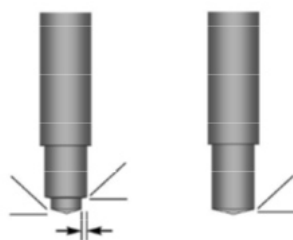


Figure 7: Upper punches for producing prototype compression-coated tablets on a Carver press: (a) construction of the punch used to make a cup and (b) construction of a used for the final compression.

Evaluation of inlay tablets

The following standards or quality control tests should be carried out on compressed tablets:

- General appearance
- Content uniformity
- Mechanical strength of tablets
- Disintegration
- Dissolution
- Swelling and erosion test

Others are content uniformity, friability, weight variation, organoleptic properties etc.

Applications of inlay tablets

1. Formulation and development of modified release in layered tablet of glimpiride & Metformin

The object of the present invention is to provide a dosage form comprising of an active ingredient as modified release and an active ingredient as immediate release.

Biguanides, particularly Metformin, improve glucose tolerance but do not stimulate insulin secretion. Sulfonylurea lower blood glucose levels acutely by stimulating the release of insulin from the pancreas, an effect that is dependent upon properly functioning beta cells in the pancreatic islets.

A combination therapy of a biguanide and sulfonylurea has a synergistic effect on glucose control, since both agents act by different, but complementary, mechanisms.

The so-called burst effect, namely, large release within a short period of time, is common in highly soluble drugs, and shall be avoided, as it may lead to high concentration of active ingredients in the blood stream.

A new core-in-cup oral drug delivery system that has the ability to release soluble and insoluble drugs at a zero-order rate of release in dissolution media has been developed.

The core-in-cup tablets were manufactured with the aid of a novel adjustable punch that has the ability to produce cup-shaped tablets of various depths.

2. Novel controlled release formulation for highly water soluble drug Tramadol HCl

Tramadol, a synthetic opioid, is a dual action analgesic agent. Despite a good oral bioavailability (75%) and moderate elimination half life (5.5 hrs), Tramadol needs frequent oral dosing throughout the day (50 mg/4-6 hrs).

High aqueous solubility causes the rapid diffusion of drug from sustained release formulations. A novel and robust controlled release formulation of Tramadol HCl to reduce the dosing frequency can be prepared.

Developed formulation of Tramadol HCl showed controlled release in-vitro behavior with a release profile of less than 15% for initial two hours (retarding initial burst) followed by a controlled complete release in controlled manner.

Developed formulation could be novel alternative to traditional immediate release formulations of tramadol is stable, convenient to manufacture and cost effective for commercial use.



Figure 8: Samples of inlay tablets.

3. Preparation of compound pseudoephedrine hydrochloride sustained-release inlay tablets:

Compound pseudoephedrine hydrochloride sustained-release inlay tablets were prepared by twice-compressing technology using HPMC as the matrix of sustained-release part.

Compound pseudoephedrine hydrochloride sustained-release inlay tablets exhibit prominent sustained-release and rapid release characteristics *in vitro*.

Naproxen sodium released more than 75% in 0.5 hr, while pseudoephedrine hydrochloride released 7%±3.6% in 0.5 hrs,

15.8%±2.3% in 1 hr, 49.5%±3.9% in 4 hr and more than 85% in 8 hr.

4. A hypnotic tablet with Pentobarbital and Mephesisin

The outer layer with uncoated granulations is promptly disintegratable for immediate hypnotic effect and the inlay portion with an enteric coating or envelope around begins to disintegrate after three to four hours to maintain or continue the desired effect.

5. An appetite depressant tablet with Amphetamine sulfate and Amobarbital:

In the outer layer the particles of the granulation are enteric coated to provide slow release over a period of ten to twelve hours. The inlay portion is formed from an uncoated readily disintegratable granulation for immediate therapeutic effectiveness.

6. Inlay Tablets Containing Sumatriptan Succinate and Naproxen Sodium.

7. Rosiglitazone IR + Metformin SR Tablet.

8. An oral decongestant tablet containing Phenylpropanolamine hydrochloride, Pyrilamine maleate and Pheniramine maleate.¹⁵

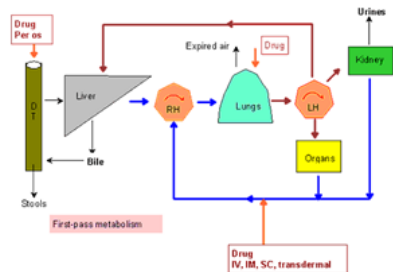


Figure 9: Phases of oral administration.

Introduction to coating

Tablet coating can be described as a process of applying an edible paint on the surface of a pharmaceutical dosage form to achieve specific benefits. This is an additional process in tablet which causes an increase in the cost of tablet production. Coating can be applied to several kinds of solid dosage forms like tablets, pellets, pills, drug crystals, etc. When a coating solution is applied to a batch of tablets in a coating pan, the surfaces of the tablets get covered with a tacky polymeric film. The tablets are then allowed to dry and the film eventually forms a non-sticky dry surface. The coating technique involves parameters such as the spray pattern, drop size, and nozzle spacing (in addition to multiple other non-spray related parameters) which must all be precisely controlled in order to ensure uniform distribution of the coating material.

Coating process

It is most desirable that the coating should be uniform and should not crack under stress. Hence, various techniques were designed for the application of the coating on the tablet surface. Generally, the coating solutions are sprayed onto the uncoated tablets as the tablets are being agitated in a pan, fluid bed, etc. As the solution is being applied, a thin film is formed which sticks to each tablet. The liquid portion of the coating solution is then evaporated by passing air over the surface of the tumbling pans. The coating may be formed either by a single application or may be developed in layers through the use of multiple spraying cycles. Rotating coating pans are often used in the pharmaceutical industry.

Sugar coating

Tablet coating developed originally from the use of sugar to mask the taste and provide an attractive appearance to the core. The process of tablet coating consists of several steps, which are described below:

Sub coating

This step is done to round the edges and increase the tablet weight.

Syrup coating

The imperfections in tablet surface are covered up and the predetermined size is achieved. This step requires the maximum skill.

Coloring

Gives the tablet its final color.

Polishing

Powdered wax (beeswax or carnauba) is applied to provide a desired luster.

Film coating

As the sugar coating process is very time consuming and is dependent on the skills of the coating operator, this technique has been replaced by film coating technology. The process involves spraying of a solution of polymer, pigments and plasticizer onto a rotating tablet bed to form a thin, uniform film on the tablet surface. The choice of polymer mainly depends on the desired site of drug release (stomach/ intestine), or on the desired release rate. Some of the non-enteric coating polymers are Hydroxypropyl methyl cellulose (HPMC), Methyl hydroxyethyl cellulose, Ethyl cellulose, Povidone, etc, while the commonly used enteric coating polymers are Cellulose acetate phthalate, Acrylate polymers (Eudragit L & Eudragit S), HPMC phthalate, etc. An ideal film coating material should possess the following characteristics:

- It should be soluble in a solvent of choice.
- It must produce an elegant coat.
- It should be stable in presence of heat, light or moisture.
- It should not possess disagreeable color, taste or odor.
- It should be non-toxic and pharmacologically inert.
- It should be compatible with coating additives.

Organic film coating

Currently, the most common technology for coating solid dosage forms is the liquid coating technology (aqueous based organic based polymer solutions). In liquid coating, a mixture of polymers, pigments and excipient is dissolved in an organic solvent (for water insoluble polymers) or water (for water soluble polymers) to form a solution, or dispersed in water to form a dispersion, and then sprayed onto the dosage forms in a pan coater (for tablets) and dried by continuously providing heat, typically using hot air, until a dry coating film is formed. Organic solvent based coating provides a variety of useful polymer alternatives, as most of the polymers are soluble in the wide range of organic solvents. However, there are certain disadvantages like they are flammable, toxic, and costly and possess environmental issues. ICH guidelines also prefer the avoidance of organic solvents in pharmaceutical dosage formulations considering products safety profile. So, Pharmaceutical industries are now paying much attention in developing formulations with aqueous film coating.

Aqueous film coating

All above problems with organic solvents resulted in shift to use of water as the preferred coating solvent. Aqueous-based coatings have been increasingly used compared with organic-based coatings. The conversion from organic solvent based coating to aqueous based coating makes the coating process more economical, though initially it may need a little investment to upgrade the coating facility.

The need of this up-gradation arises due to the need of higher drying capacity (the latent heat of water is 2200 kJ as compared to 550 kJ for methylene chloride). This implies that one would require 4 times more energy as compared to

organic solvent.

Recent technologies in tablet coating

Electrostatic coating

It is an effective way of applying a coat on conductive substances. A strong electrostatic charge is applied to the substrate. The coating material consisting of conductive ionic species of opposite charge is sprayed on the charged substrate. A complete and uniform coating of corners on the substrate is achieved.

There are two kinds of spraying units, based on the charging mechanism a) corona charging and b) tribo charging.

Corona charging

This is done by the electrical breakdown and then ionization of air by imposing high voltage on a sharp pointed needle like electrode (i.e. charging pin) at the outlet of the gun. The powder particles pick up the negative ions on their way from the gun to the substrate. The movement of particles between the charging gun and the substrate is mainly governed by the combination of electrical and mechanical forces. The mechanical forces produced by the air blows the powder towards the substrate from the spray gun. For the corona charging, the electrical forces are derived from the electrical field between the charging tip of the spray gun and the earthen substance, and from the repulsive forces between the charged particles. The electrical field can be adjusted to alter the powder's flow, control pattern size, shape, and powder density as it is released from the gun.

Tribo charging

Unlike corona charging guns, the tribo charging makes the use of the principle of friction charging associated with the dielectric properties of solid materials and therefore no free ions and electrical field will be present between the spray gun and the grounded substance. For tribo charging guns, the electrical forces are only regarded to the repulsive forces between the charged particles. After spraying when charged particles move into the space adjacent to the substrate, the attraction forces between the charged particles and the grounded substrate makes the particle to deposit on the substrate. Charged particles are uniformly sprayed onto the earthen substrate in virtue of mechanical forces and electrostatic attraction. Particles accumulate on the substrate before the repulsion force of the deposited particles against the coming particles increase and exceed the electrostatic attraction. Finally once the said repulsion becomes equivalent to the said attraction, particles cannot adhere to the substrate any more, and the coating thickness does not increase any more.

Magnetically assisted impaction coating (MAIC)

Many dry coating methods have been developed such as compression coating, plasticizer dry coating, heat dry coating and electrostatic dry coating. These methods generally allow for the application of high hearing stresses or high impaction forces or exposure to higher temperature to achieve coating. The strong mechanical forces and the accompanying heat generated can cause layering and even embedding of the guest particles onto the surface of the host particles. Many food and pharmaceutical ingredients, being organic and relatively soft, are very sensitive to heat and can quite easily be deformed by severe mechanical forces. Hence, soft coating methods that can attach the guest (coating material) particles onto the host (material to be coated) particles with a minimum degradation of particle size, shape and composition caused by the buildup of heat are the better candidates for such applications. The MAIC devices can coat soft organic host and guest particles without causing major changes in the material shape and size.

Although there is some heat generated on a micro scale due to the collisions of particles during MAIC, it is negligible. This is an added advantage when dealing with temperature sensitive powders such as pharmaceuticals.

Vacuum film coating

It is new coating technique that employs specially designed baffled pan. The pan is hot and water jacketed and it can be sealed to achieve a vacuum system. The tablets are placed in pan and the air in the pan is displaced by nitrogen before the desired vacuum level is obtained. The coating solution is applied by airless spray system. The vapors of the evaporated solvents are removed by vacuum system. Organic solvents can be effectively used with this coating techniques and high environment safety is also there.

Compression coating

Compression coating is not widely used, but it has advantages in some cases in which the tablet core cannot tolerate organic solvents or water and yet needs to be coated for taste masking, or to provide delayed or enteric properties to the product. In addition incompatible ingredients can be conveniently separated by process. This type of coating requires a specialized tablet machine.

Dip coating

Coating is applied by dipping them into coating liquid the wet tablets are dried in conventional coating pans. Alternate dipping and drying steps may be repeated several times to achieve the coating of desired one. The process lacks the speed, versatility, and the reliability of spray coating techniques.²⁵⁻³⁰

Defects and solutions of coated tablets

Picking and sticking

This is when the coating removes a piece of the tablet from the core. It is caused by over-wetting the tablets, by under-drying, or by poor tablet quality.

Bridging

This occurs when the coating fills in the lettering or logo on the tablet and is typically caused by excess application of the solution, poor design of the tablet embossing, high coating viscosity, high percentage of solids in the solution, or improper atomization pressure.

Erosion

This can be the result of soft tablets, an over-wetted tablet surface, inadequate drying, or lack of tablet surface strength.

Twinning

This is the term for two tablets which stick together, and it's a common issue with capsule shaped tablets. Suppose you don't want to change the tablet shape, you can solve this problem by changing the pan speed and spray rate. Try lowering the spray rate or increasing the pan speed. In some cases, it is necessary to alter the design of the tooling by very slightly changing the radius. The change is almost impossible to see, but it solves the twinning problem.

Peeling and frosting

This is a defect where the coating peels away from the tablet surface in a sheet. Peeling indicates that the coating solution did not lock into the tablet surface. This could be due to a defect in the coating solution, over-wetting, or high moisture content in the tablet core.

Blistering

Too rapid evaporation of solvent from the coated tablets and the effect of high temperature on the strength and elasticity of the film may cause blistering. Milder conditions are required in this case.

Mottled color

This can happen when the coating solution is improperly prepared, the actual spray rate differs from the target rate, the tablet cores are cold, or the drying rate is out of spec.

Orange peel

This refers to a coating texture that resembles the surface of an orange. It is usually the result of high atomization pressure in combination with spray rates that are too high.

Coated tablet evaluation

Determination of the quality of a tablet coat involves studying of the film and the film-tablet interactions. The following test methods can be employed.

- Adhesion test with tensile strength testers are used to measure the force needed to peel the film from the tablet surface.

• Diametric crushing strength of the coated tablets is determined using a tablet hardness tester. The rate of coated tablet disintegration and dissolution should also be studied. Stability studies can be conducted on coated tablets to verify whether temperature and humidity changes would result in film defects.

• Exposure to elevated humidity and measurement of tablet weight gain provide relative information on the protection provided by the film.²⁷⁻³⁰

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