Abstract

Modified release product can be defined as a system where “The drug release characteristic of time. Course and/or location are chosen to accomplish therapeutic or convenience objective not offered by conventional dosage forms”. Delayed release and extended release these are title under the modified release In modified release a two layer press coated tablet consisted of polymers with different dissolution rates. the preparation of chronotherapy-focused press-coated tablets, have an active drug inside an outer tablet layer consisting of a mixture of hydrophobic wax and brittle material in order to obtain a pH-independent lag time prior to core drug delivery at a predetermined release rate. During the dissolution test, the shell is progressively eroded and removed from the system in a well-defined period of time and, only when the active core is cleared of its coating, does the drug release start [1].

Keywords: Modified release oral tablet; Single pulsatile drug; pH independent drug delivery; Sustain action; Challenges; Approaches; Market status.

Introduction

Modified release denoting a formulation of a medicinal drug taken orally that releases the active ingredients over several hours, in order to maintain a relatively constant plasma concentration of the drug. Also called sustained-release, continuous-release. The European pharmacopoeia defines Modified Release in terms of the rate or site at which the active ingredient is released. This guideline concerns the puality aspects of products, which are designed to modify the rate of release or to control the timing of release of the active ingredient (s)
rather than those formulations affecting the site of release. A single-pulse delayed-release (“SPDR”) low-dose prednisone tablet, was recommended for European regulatory approval for the treatment of rheumatoid arthritis (“RA”) and associated morning stiffness in January 2009. Germany lead the decentralised procedure is now also considered approvable by the regulatory agencies of 14 other countries (the “euro15”) is expected to launched in Germany within the next few weeks. \(^2\) Pulsatile drug delivery aims to release drugs on a programmed pattern i.e.: at appropriate time and/or at appropriate site of action. Currently, it is gaining increasing attention as it offers a more sophisticated approach to the traditional sustained drug delivery i.e.: a constant amount of drug released per unit time or constant blood levels. Technically, pulsatile drug delivery systems administered via the oral route could be divided into two distinct types, the time controlled delivery systems and the site-specific delivery systems. The simplest pulsatile formulation is a two layer press coated tablet consisted of polymers with different dissolution rates. Homogeneity of the coated barrier is mandatory in order to assure the predictability of the lag time. The disadvantage of such formulation is that the rupture time cannot be always adequately manipulated as it is strongly correlated with the physicochemical properties of the polymer. Gastric retentive systems, systems where the drug is released following a programmed lag phase, chromo pharmaceutical drug delivery systems matching human circadian rhythms, multiunit or multilayer systems with various combinations of immediate and sustained-release preparation are all classified under pulsatile drug delivery systems. On the other hand, site-controlled release is usually controlled by factors such as the pH of the target site, the enzymes present in the intestinal tract and the transit time/pressure of various parts of the intestine. In this review, recent patents on pulsatile drug delivery of oral dosage forms are summarized and discussed. Several disease states have been proven to follow biological rhythms, expressed by short-, intermediate-, and long-period oscillations. Circadian (24-h) time structure is the most studied and rather the most common oscillation met in a number of pathological cases such as asthma where the crisis are mostly happening late at night, osteoarthritis where the pain is more intense again during night, rheumatoid arthritis where the pain peaks at the morning, duodenal ulcer where the highest gastric secretion is happening in the nighttimes, neurological disorders such as epilepsy where the oscillations are following melatonin secretion, hypercholesterolemia where the cholesterol synthesis is higher during the night and several cardiovascular
diseases such as cardiac and/or platelet aggregation. Diseases with time structures other than circadian rhythm are also possible, for example, diabetes is following the secretion of insulin stimulated by meal, or tumour growth in cancer states that follows body changes in blood flow. Menstrual cycle and the corresponding hormonal flux are also following cyclic patterns. Pulsatile delivery systems aim to deliver a drug via the oral route at a rate different than constant, (i.e. zero order.)

Ideally such systems aim to match drug release rate to a biological requirement of a given disease therapy and thus to manage the disease while minimizing treatment’s side effects. Pulsatile drug delivery systems (PDDS) are characterized by at least two distinctive drug release phases following a predetermined lag time. Drug’s release may be controlled by time, by site or a combination of the two parameters. Different rate of release of drug is depend up on the geometric structure of the tablet is most important in formulation of press coated tablet. Use of shape is round, capsule, oval, mod. capsule, square, rectangular, FFBE, concave, bevel con, double radius, flat, etc.

**MISCELLANEOUS PULSATILE SYSTEMS**[^3].

Some really novel systems of pulsatile release has also been proposed. For example, Weinbach and coworkers described a delayed release oral formulation (a capsule, tablet, compression coated tablet or bilayer tablet) comprising at least two populations of carrier particles where the first population comprises a biologically active substance and a penetration enhancer (absorption enhancer), and the second population comprises a penetration enhancer and a delayed release coating or matrix.[^3]
Modified release' means (4).

'Modified release' means that the escape of the drug from the tablet has been modified in some way. Usually this is to slow the release of the drug so that the medicine doesn't have to be taken too often and therefore improves compliance. The other benefit from modifying release is that the drug release is controlled and there are smaller peaks and troughs in blood levels therefore reducing the chance of peak effects and increasing the likelihood of therapeutic effectiveness for longer periods of time. Tablets and capsules which are designed to provide modified release often have the letters MR, LA, XL, CR or SR in their names e.g. Diffundox MR, Elantan LA, Dilzem 1XL Calcicard CR, Dilcardia S,. Sometimes the words 'slow' or 'retard' can be used to denote modified release e.g. Diclomax retard, Voltarol retard & Slow K. There are a number of ways in which a medicine can have its release modified. Perhaps the most famous is that used in Contac 400 capsules. The pellets inside are of different thicknesses and therefore the thinnest release the drug first and the thickest last(4).

**Significance:**

1. It maintains constant plasma concentration.
2. It is pH independent lag time prior to core drug delivery at a predetermined release rate.
3. It reduces dose frequency.
4. It gets targeted action.

Fig. press coated, pulsatile drug delivery system tablet., double layer tablet (inner core is active ingredient and outer shell is inactive)
5. Dose requires very less quantity.

**Principle of modified release system**[^1].

The modified release systems should be described in terms of:

- The manner in which release is intended to be achieved (membrane type, matrix, etc);
- Single non-disintegrating unit, multi-unit pelletised preparation, single eroding unit etc;
- Release mechanism and kinetics (diffusion, erosion, osmosis, etc. or combination of these).

**Classification:**

Modified Release dosage form may be classified as

A. Delayed release

B. Extended release

B.1: Sustained release

B.2: Controlled release

**MRDF SYSTEMS CAN BE SPLIT:**

- DISSOLUTION
- ERODIBLE
- MATRIX
- HYDRODYNAMICALLY BALANCE SYSTEM
- Ion exchange resins

**Advantages of modified release dosage form:**

1) Improved therapy:

a) Sustained plasma drug concentration level.

   The dosage form provides uniform drug availability unlike peak and valley pattern obtained by intermittent administration.

b) Attenuation of adverse effects.

The incidence and intensity of undesirable side effects caused by excessively high peak drug concentration resulting from the administration of conventional dosage forms is reduced.
c) It is seldom that a dose is missed because of non-compliance by the patient.

2) Patient Convenience/improved patient compliance:

Frequency of administration is reduced and thus disturbance to the patient is less particularly at night (resting time).

3) Economy:

Economy may also be affected due to decreased cost of nursing time for administration of drug.

4) Reduce amount of drug administration.

5) Maximizing availability with a minimum dose.

6) Control of drug absorption; high peak level peaks that may be observed after administration of high availability drug can be reduced.

7) Safety margin of high potency drugs can be increased.

8) Increased reliability of therapy.

Disadvantages:

However, sustained release products are not altogether free from disadvantages some of which are as follows:

1) Dose Dumping:-

Dose dumping is a phenomenon where by relatively large doge in a controlled release formulation is rapidly release, introducing potential toxic quantities of the drug into the systemic circulation. Dose dumping can lead to facilities in case of potent drug, which have a narrow therapeutic index. e.g. Phenobarbital.

2) Less flexibility in acute dose adjustment:-

In convenient dosage form, dose adjustments are much simpler e.g. tablet can be divided into two fractions. In case of controlled / sustained release dosage forms, this appears to be much more complicated. Controlled release property may get lost, if dosage form is fractured.

3) Poor in vitro – in vivo correlation:

In controlled release dosage form, the rate of drug release is deliberately reduced to achieve drug release possibly over a large region of gastrointestinal tract. Here the so called “Absorption Window” become important and may give rise to unsatisfactory drug absorption in vivo despite excellent in vitro release characteristics.
4) Patient variation:-

The time period require for absorption of drug release from the dosage form may vary among individuals. Co-
administration of other drugs, presence or absence of food and residence time in GIT is different among patients.
This also gives rise to variation in clinical response among the patient.

5) In case of accidental failure of the product effective antidote may be difficult to employ.

6) Sustained Release dosage forms are some time costlier because of the technology involved in producing the
formulation.

7) Sustained Release medication should not be used with person known to have impaired or erratic
gastrointestinal absorption or kidney troubles.

8) Drugs having long biological half life are not suitable for presentation in Sustained Release form, eg.
digitoxin.

9) There is little control in hands of the physician so far as dose variation is concerned.

10) Problem in case of elderly people.

Type of Modified release dosage formulation:

- **Dissolution granules**
- **Diffusion granules**.
- **Enteric coated granules**
- **Reservoir**
- **Matrix**
  - a. Inert
  - b. Erodible
  - c. Swellable
  - d. Hydrophilic
- **Osmotic pump**
- **repeat action**
- **altered density**
Hydro dynamically balanced

SODAS

The details require in application for marketing authorisation[^5].

- The nature of the active substances.
- The rationale of the formulation and/or design principle of the devices.
- The target species.
- The route of administration.
- The therapeutic intention, for example to achieve sustained drug levels, eliminating peak and trough etc.

**Marketed Pulsatile Delivery Technologies:**

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Marketed preparation</th>
<th>Mechanism of action</th>
<th>Principal Dose daily (mg)</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Prednisone</td>
<td>Rheumatoied arthritis (“RA”)</td>
<td>Geoclock</td>
<td>5</td>
</tr>
<tr>
<td>2.</td>
<td>Zaleplon</td>
<td>Hypnotic</td>
<td>SyncroDose® Penwest</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Verapamil</td>
<td>Calcium channel blocker (anti hypertensive)</td>
<td>Geomatrix™ SkeyPharma</td>
<td>20</td>
</tr>
<tr>
<td>4.</td>
<td>Metronidazole</td>
<td>Anthelmintics</td>
<td>Pulsincap® Scherer DDS, Ltd</td>
<td>20,30,40mg</td>
</tr>
<tr>
<td>5.</td>
<td>Food Nutrition</td>
<td>Supplement of diet</td>
<td>Port® Port Systems, LLC</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Morphine ER</td>
<td>Narcotic drugs for pain management</td>
<td>EGALET® TIME RELEASE Egalet</td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Drug Name</td>
<td>Category</td>
<td>Formulation</td>
<td>Strength</td>
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<tr>
<td>8.</td>
<td>Amoxicillin</td>
<td>Antibiotic</td>
<td>PULSYS™ MiddleBrook</td>
<td>500mg</td>
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<td></td>
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<td></td>
<td>Pharmaceuticals™</td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>Entacapone</td>
<td>Calcium Channel Blocker</td>
<td>Calcium Channel Blocker</td>
<td>5mg</td>
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<tr>
<td>10</td>
<td></td>
<td>Diffucaps®</td>
<td>Diffucaps® Eurand</td>
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<tr>
<td>11</td>
<td>Paliperidone</td>
<td>Antipsychotic</td>
<td>OROS®</td>
<td>5mg</td>
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<tr>
<td></td>
<td>Nifedipine</td>
<td>Antihypertensive</td>
<td>OROS® Push Pull™ Alza</td>
<td></td>
</tr>
</tbody>
</table>

A Typical Modified Release Forum Agenda Covers[^6].

- Strategies driving the selection of modified release formulations
- Review of current and emerging technologies
- New developments in both controlled/extended and delayed drug release
- Discussion of experimental design criteria
- Theoretical treatment of release kinetics

Category of modified release dosage forms (modified release oral dosage forms)[^5].

2. Delivery systems (intrauminal devices).
3. Intravaginal dosage forms (e.g., vaginal sponges).
5. Insecticidal collars, ear tags, strips.
6. Ophthalmic preparation (ocular inserts).
7. Prantal product.
8. Injection.
8. Other (include novel formulation)

**What is modified-release?**

The term modified-release defines preparations that have been designed in such a way that the rate or place at which the active ingredients are released has been modified.\(^\text{19}\)

This is an all encompassing term that the BNF now uses to cover preparations such as Sustained-release, Controlled-release and delayed release. Although theoretically covered by M/R, the BNF has retained the separate term enteric coated. The sole use of the term modified-release is helpful to simplify the confusing terminology. However, its use conceals the differences between the drug delivery systems, which may be defined as:

- **Sustained-release** - the drug is released slowly at a rate governed by the delivery system.

- **Controlled-release** - the drug is released at a constant rate and plasma concentrations after administration do not vary with time.\(^\text{20}\)

- **Delayed-release** - the drug is released at a time other than immediately after administration\(^\text{3}\) i.e. the site of release is controlled. There are many mechanisms by which drug release from a preparation can be modified. Controlling the site of delivery M/R preparations can be developed to deliver a drug to a specific site in the GI tract. For example, enteric coated preparations direct delivery to the small intestine, preventing drug release in the stomach. This aims to either protect the stomach from the drug, or protect the drug from the degrading environment of the stomach. Other preparations, such as those containing amino salicylates for inflammatory bowel disease, are formulated to allow site specific delivery to the colon or small intestine to exert local effects.

**Which drugs are suitable as M/R preparations?**

Apart from formulations that control the site of drug delivery, most m/r preparations slow the rate of drug release. To ensure maximum absorption from these preparations, it is essential that the drug is well absorbed throughout the entire GI tract. Drugs which are absorbed only at specific sites, such as iron\(^\text{16}\), folic acid and vitamin B12, are not suitable as m/r preparations.\(^\text{9}\) Drugs with a narrow therapeutic index, those which are rapidly absorbed, and those with a short duration of action are often formulated into m/r preparations. Drugs
with a long duration of action, such as amitriptyline, do not need to be given frequently and an m/r preparation is unnecessary. It is also important to consider whether the therapeutic area lends itself to the use of m/r preparations. For example, m/r analgesic preparations with a slow onset of action are of little value when immediate pain relief is required. For some drugs, an M/R preparation can offer clinical advantages. If theophylline is prescribed for nocturnal asthma and early morning wheezing, an m/r preparation given as a single dose at night is advisable.\cite{7} The slow release of theophylline decreases side-effects seen with rapid absorption and ensures therapeutic levels are maintained throughout the night, provided a suitable dose is prescribed. If nifedipine is prescribed for angina or hypertension, an m/r preparation is recommended. Short-acting preparations have been associated with large variations in blood pressure and reflex tachycardia.\cite{7} They have also been controversially linked to an increase in the risk of cardiovascular events. A recent, randomised double-blind trial in 6321 patients with hypertension found Adalat LA (a once daily m/r nifedipine preparation) to be as effective as co-amiloizde (amiloride/hydrochlorothiazide) in preventing overall cardiovascular or cerebrovascular complications. PRODIGY guidance for prescribing nifedipine in angina and hypertension only offers the drug as an m/r preparation prescribed by brand name.\cite{29} Conventional-release carbamazepine is often prescribed three or four times a day for epilepsy. M/R preparations allow twice daily dosing and may also reduce the incidence of dose-related side-effects.\cite{7,8}

**What are the problems with M/R preparations?**

The release of a drug from an m/r preparation is dependent on changes in GI transit time. In patients with ‘GI hurry’ some of the dose may be lost if the preparation passes through the body before drug release is complete. Conversely, if the transit time is delayed, excessive release of the drug or ‘dose dumping’ can occur. This may cause local GI damage (e.g. with NSAIDs), or acute systemic toxicity. Breaking, chewing or crushing an m/r preparation can result in the immediate release of possibly toxic amounts of drug. Therefore, patients should be told to swallow most m/r preparations whole. To avoid undue concern, patients should also be informed if there is a possibility of the tablet shell passing through the GI tract unchanged, as with Slow-K. By slowing the rate of drug release and prolonging its action, m/r preparations can cause problems if taken in overdose or if a severe adverse reaction occurs.
Prescribing issues
Prescribers should always consider whether an m/r preparation is clinically justified.

This decision should be based on both good quality clinical evidence and the individual requirements of the patient. For those limited situations where an m/r preparation is appropriate, it is important that the correct preparation, i.e. that intended by the prescriber, is dispensed. As confusion can arise if such prescriptions are written generically, it seems sensible to recommend brand name prescribing for m/r preparations. Of more importance is the problem that different m/r preparation of the same drug have different release characteristics. Therefore, bioequivalence cannot be assumed and all m/r preparations are licensed by brand name. Switching between m/r preparations of drugs with a narrow therapeutic index may have serious clinical consequences. Therefore, both the Royal Pharmaceutical Society and the BNF recommend brand name prescribing for m/r theophylline (or aminophylline) preparations. This is also advisable for all formulations of lithium. Brand name prescribing is also recommended for m/r preparations of nifedipine and longer-acting diltiazem\cite{7,8} where numerous formulations exist. These preparations are available in different strengths and have different licensed dosage regimens. They are not interchangeable and, due to different release characteristics, even formulations containing the same strength of drug may not be bioequivalent. If a prescription for an m/r preparation of theophylline, nifedipine or diltiazem is written generically, the pharmacist should contact the prescriber to agree the brand before dispensing.\cite{27} When local formularies are put in place it would be useful, if an m/r preparation is considered appropriate, to select just one or two brands for inclusion. This ensures familiarity for prescribers and pharmacists, while preventing the need for pharmacies to stock many different brands of one drug. The decision to include a particular brand should be based on licensed indications, supporting clinical evidence, cost and availability. Close collaboration between primary and secondary care is also necessary to ensure treatment continuity for patients. Familiarity for prescribers and pharmacists, while preventing the need for pharmacies to stock many different brands of one drug. The decision to include a particular brand should be based on licensed indications, supporting clinical evidence, cost and availability. Close collaboration between primary and secondary care is also necessary to ensure treatment continuity for patients.
Pharmaceutical modification\textsuperscript{[10,11]}. The rate of drug release is reduced by increasing particle size or forming insoluble crystals e.g. Tegretol Retard or Adalat Retard.

- **Coated pellets**
  
  Drug pellets are coated with a slowly dissolving polymer of varying thickness for varied release. The pellets can either be compressed into a tablet or put in a gelatin capsule e.g. Fenbid, Slo-Phyllin or Inderal-LA.

- **Insoluble matrix**
  
  The drug is dispersed within an insoluble porous matrix. As fluid enters the matrix, the drug is dissolved and diffuses out slowly e.g. Slow-K, Imdur or Betaloc-SA.

- **Eroding matrix**
  
  The drug is dispersed within a soluble matrix. As the matrix is eroded, the drug is slowly released e.g. MST Continus or Phyllocontin Continus.

- **Osmotic pump**
  
  The drug and an osmotic agent are enclosed by a semipermeable membrane. As water is drawn into the tablet, dissolved drug is released in a controlled way through a laser-drilled hole e.g. Volmax, Adalat LA.

- **pH sensitive coating**
  
  The formulation is coated with a polymer of pH dependent solubility for site specific delivery. This can either avoid drug release in the stomach (enteric coating) e.g. Nu-Seals Aspirin, or specifically deliver drug to the colon e.g. Asacol.

**Modified release dosage form and drug delivery**

Advance in technology have resulted in novel modified release dosage form. In contrast to conventional (immediate release) forms, modified release products provide either delayed release or extended release of drug. Extended release products are designed to release their medication in a controlled manner, at a predetermined rate, duration, and location to achieve and maintain optimum therapeutic blood levels of drug\textsuperscript{[10,11]}. 
Terminology:

Drug products that provide extended release first appeared as a major new class of dosage form in the late 1940’s and early 1950s. Over the years, many terms (and abbreviations), such as sustained release (SR), sustained action (SA), prolonged action (PA), controlled release (CD), extended release (ER), timed release (TR), and long acting (LA), have been used by manufacturers to describe product types and features. Although these terms often have been used interchangeably, individual products bearing these descriptions may differ in design and performance and may differ in design and performance and must be examined individually to ascertain their respective feature.

Modified release dosage form and drug delivery

Sustained release In case of sustained release (SR) dosage forms the release of the active agent, although, is lower than in the conventional formulations, however, it is still substantially affected by the external environments into which it is going to be released. Controlled release Controlled release (CR) systems provide drug release in an amount sufficient to maintain the therapeutic drug level over extended period of time, with the release profiles of predominantly controlled by the special technological construction and design of the system itself. The release of the active constituent is therefore, ideally independent of exterior factors. Extended release Extended release formulation is a controlled release formulation designed to produce even and consistent release of active ingredient. Extended release (ER) dosage forms are those which due to special technology of preparation provided, soon after a single dose administration, therapeutic drug levels maintained for 8-12 hours. Prolong action Prolong or long action products are dosage forms containing chemically modified therapeutic substances in order to prolong biological half live (Lee and Robinson, 1987).[10,12,13,14,15]

Modified Release tablets[16].

The main aim behind formulation of this dosage form is to release the medicament slowly for long time duration after administration of a single tablet.
A widespread use of this type of tablet is seen in present scenario, as well as many researchers have concentrated their attention in this direction. This is mainly because of improvement in patient’s compliance as the dosage frequency is reduced, patient can take an undisturbed sleep at night, it’s also beneficial for psychiatric patients who forget to take their tablets regularly and the dose related side effects and toxicities are reduced. Any adjuvant that can alter water uptake rate, swelling and gelling characteristics of Matrixing agents can alter the release rate of API e.g., electrolytes in HPMC matrix tablet. It’s also possible to achieve pulsed drug release. Weakly basic drugs exhibit good solubility at low pH while less soluble at high pH conditions, which can result in incomplete drug release for sustained release formulations. The drug release can be modified by providing suitable micro environmental pH in the tablet e.g., acidic polymer, succinic acid, etc. Similarly, inclusion of alkaline polymers results in desirable drug release of acidic drugs. On the other hand, formulation of this type of dosage form presents challenge for the formulator: increases the cost of manufacturing, chances of burst drug release and drop in drug release rate in terminal phase and thus incomplete release on API. In case of accidental poisoning, the doctor has to deal with special treatment problems. Due to large size, patient may feel difficulties in swallowing as the matrixing agent to drug ratio is high. Classic approaches are usually based on adaptation of either film coated or multiparticulate technologies or those involving slow release matrices.

Immediate-Release Prednisone[17].

They conclude: “Our results have confirmed that the new modified-release formulation is clinically and statistically better than the conventional immediate-release preparation with regard to morning stiffness of the joints. Furthermore, the effects of the new tablet taken at night were achieved in addition to the established clinical control of the disease resulting from previous treatment with conventional immediate-release prednisone.
Ion Exchange Resins In Extended Release:-

The rate at which a drug is released from a resinate is dependent on many factors but in its simplest form can be considered as an exponential curve. In many cases the rate is sufficiently slow that the resulting effect is an extended or sustained release over many hours albeit at an ever-changing concentration. By some practitioners, this exponential decline of release was considered as a limitation to the usefulness of ion exchange resins in extended release pharmaceutical formulations.

However, novel recent work has demonstrated that the release rate of the drug from a formulation based on functional polymers can be accurately controlled with the potential for zero order release over prolonged periods. This was demonstrated on a number of Diclofenac formulations developed a novel GI dissolution system to demonstrate the performance of the improved formulations\(^3\).

**Press-coated devices**\(^{18}\).

Such a time-dependent barrier is obtained using HPMC of low viscosity. The behaviour and efficiency of this type of coating were tested on active cores coated by compression on the whole surface (press-coated devices): during the dissolution test, the shell is progressively eroded and removed from the system in a well-defined period of time and, only when the active core is cleared of its coating, does the drug release start.

![Swelling behaviour of the Geomatrix three-layer systems with the different types of barrier coatings](image)

**Fig. 2:** Swelling behaviour of the Geomatrix three-layer systems with the different types of barrier coatings: erodible or gellable.
The ability of the erodible barrier to control drug release from the Geomatrix systems is investigated on different core compositions, using drugs characterized by a different water solubility and their release profiles are compared. Moreover, to investigate which is the prevailing action mechanism of the different types of coatings in the modulation of drug release, tablets coated by compression on the whole surface were prepared and their dissolution profiles were analysed.

Also the morphological modification of the devices during dissolution and particularly of the barrier layers is examined and the extension of the gelled and glassy phases was measured using a penetrometer and a video-microscope equipped with an image-analyser. Both types of polymeric barrier are able to modulate drug release from the multi-layer devices. Their time-dependent coating effect modulates water penetration and drug release from the protected surfaces for a programmable period of time, until the coating is eroded or swollen. When the erodible barrier is completely dissolved, the release process depends only on the formulation characteristics of the active core. The swellable coating, instead, shows a double effect: as long as a portion of the coating remains in a solid state, it protects the underlying surfaces from hydration and drug diffusion, but even when completely gelled, still acts as a modulating device: prevents the core erosion process, provides a further diffusion path-length to drug release and acts as a diffusion barrier. The swellable barrier that shows a stronger protective effect is more suitable to control the release of soluble drugs while the erodible barrier provides a more accurate modulation of the dissolution profile of sparingly soluble drugs.

**Geometry technology**[19].

1. Diffucaps® Eurand

The active drug is layered onto a neutral core (such as cellulose spheres) and then one or more rate-controlling, functional membranes are applied.

2. Orbexa® Eurand

This technology produces beads that are of controlled size and density using granulation, spheronization and extrusion techniques.

Alza
A bilayer / trilayer tablet core consisting of one or more drug layers, surrounded by a semi-permeable membrane with a drilled orifice.

3. CODAS™ Elan

Drug delivery system enables a delayed onset of drug release, resulting in a drug release profile that more accurately compliments circadian patterns. This delay in release is introduced by the level of release controlling polymer applied to the drug loaded beads. The release controlling polymer is a combination of water soluble and water insoluble polymers. As water from the gastrointestinal tract comes in contact with the polymer coat beads, the water soluble polymer slowly dissolves and the drug diffuses through the resulting pores in the coating.

4. SODAS® Elan

Based on the production of uniform spherical beads of 1-2 mm in diameter containing drug plus excipients and coated with product specific controlled release polymers.

**Oral Pulsatile Drug Delivery Recent Patents on Drug Delivery & Formulation,**

5. SyncroDose®

Penwest

Allow drugs to be delivered after predetermined lag times to coincide with the body's circadian rhythm pattern or to allow drugs to be delivered to different sites within the gastrointestinal tract. A SyncroDose tablet consists of an inner core of drug and a surrounding compression coating containing TIMERx-based materials. Lag time is controlled by variations in the two polysaccharides, xanthan gum and locust bean gum.

6. Geoclock® SkeyPharma

Allows the preparation of chronotherapy-focused press-coated tablets, have an active drug inside an outer tablet layer consisting of a mixture of hydrophobic wax and brittle material in order to obtain a pH-independent lag time prior to core drug delivery at a predetermined release rate.

7. Geomatrix™ SkeyPharma

The controlled release is achieved by constructing a multilayered tablet made of two basic key components: 1) hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) and 2) surface controlling barrier layers.
Active loaded core surface that is available for drug release when exposed to the fluid is controlled by barrier layers.

8. Pulsincap®, Scherer DDS, Ltd

A water impermeable capsule body with hydro gel plug. Plug length and insertion depth controls lag time.

9. Port®, Port Systems, LLC

A water permeable coated gelatin capsule with n osmotic core that swells and is sealed with an insoluble wax plug. The contents swells to remove the plug. The wall thickness and composition, concentration of the osmotic contents and the length of the hydrogel plug control lag time.

10. EGALET® TIME RELEASE Egalet The Egalet®

Time Release consists of three compartments: a coat, a drug release matrix and a lag component. The drug is contained in the inner (middle) layer of the matrix, with the outer layers providing a predetermined delay in release of the drug.

11. OSDrC®, OSDrC

Technology allows placement of any number of cores of any shape into the tablet just where they need to be positioned for optimum delivery of active pharmaceutical ingredients (API). Precise OSDrC® positioning technology enables product development scientists to control the release of the API by altering the thickness of the outer coating. The ability to precisely position multiple cores allows the creation of tablet products with a variety of pulsatile drug release profiles.

12. PULSYS™ Pharmaceuticals™

The typical PULSYS drug delivery format is a tablet containing multiple pellets with different release profiles.

13. COLAL®, Alizyme Therapeutics Limited.

COLAL® involves a coating for drug pellets, tablets or capsules which is composed of ethylcellulose and a form of starch called 'glassy amylose'. The glassy amylose is not digested by human enzymes as the preparation moves down the GI tract, but is digested by bacterial enzymes that are found only in the colon. When the coated product reaches the colon, the coating is degraded, allowing the drug to be released.
Evaluation Process of Modified Release Tablet:

1. **TD-BD. (tapped density and bulk density):**
   - Bulk density: Mass / Volume
   - Tapped density: Mass / Tapped Volume
   - Compressibility Index:
     \[
     \% \text{ Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100
     \]
   - Hausner Ratio: Tapped density / Bulk density

2. **Sieve analysis (particle size determination).**

3. **DT (disintegration time).**
   Disintegration time means time required to disintegrate the tablet the sieve size 10 micron.

4. **Dissolution of tablet.**
   In dissolution two factors are defined that is one is dependent (hexane model, first order, second order etc. and independent \( F_1 \) and \( F_2 \)) and other is independent factor.

5. **UV (percentage of absorption).**

6. **Check the thickness.**
   In which tablet thickness and tablet diameter is tested.

7. **Hardness test.**
   In which tablet breaking strength is measured in newton and kg.

8. **Polymorphism study.**

9. **Friability.**
   \[
   \% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100
   \]
10. Weight variation test are carried out in the process of tablet:

11. LOD:

LOD (Loss on Drying):

\[
\% \text{ LOD} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \times 100
\]

References:


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