



Pulsatile Drug Delivery System

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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. However, there are certain conditions for which such a release pattern is not suitable like cardiovascular diseases, Diabetes mellitus, Asthma, Arthritis, Peptic ulcer etc. In such cases pulsatile drug delivery system is used in which release drug on programmed pattern i.e. at appropriate time & at appropriate site of action. Pulsatile Drug Delivery systems are basically time controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastro-intestinal motility, etc. 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. In chronopharmacotherapy drug administration is synchronized with biological rhythms to produce maximal therapeutic effect & minimum harm for the patient. 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, thus providing special and temporal delivery. In recent pharmaceutical applications involving pulsatile delivery; multiparticulate dosage forms (e.g. pellets) are gaining much favor over single-unit dosage forms. Designing of proper pulsatile drug delivery will enhance the patient compliance, optimum drug delivery to the target side & minimizing the undesired effects.

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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. However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release. 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. In chronopharmacotherapy (timed drug therapy) drug administration is synchronized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient. By basing drug delivery on circadian patterns of Diseases, drug effect can be optimized and side effects can be reduced. If symptoms occur at daytime a conventional dosage form can be administered just prior the symptoms are worsening. If symptoms of a disease became

worse during the night or in the early morning the timing of drug administration and nature of the drug delivery system need careful consideration. 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. [1, 2, 3, 4]

Chronobiology and chronopharmacotherapy of disease:

Chronotherapy is co-ordination of biological rhythms and medical treatment. Chronotherapeutic 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. The tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24-hour period, may be changing as researcher's report that some medications may work better if their administration is coordinated with day night patterns and biological rhythms.

Many of circadian dependent diseases display symptoms in early morning hours or in the morning at awakening. It is well known that patients with asthma experience symptoms at night. Dyspnoea and peak of expiratory flow (PEF) values have been found to become worse during the night. Most asthma attacks occur at 04:00 to 06:00 hours. Nocturnal asthma is a complex interaction of several coincident circadian rhythms e.g. hydrocortisone and adrenalin secretion. Symptoms of allergy,

e.g. runny nose, stuffy nose, wheezing and sneezing are also most frequent in the morning before breakfast. Ischemic heart diseases, such as angina, myocardial infarction and stroke manifest itself several times more frequent from 09:00 to 11:00 hours than any other time of the day of night. Rapid increase in blood pressure is largely responsible for these attacks. In both hypertensive and normotensive individuals blood pressure arises notably before awakening. In most patients with essential hypertension blood pressure generally declines from mid-afternoon and reaches a minimum between midnight and 03:00 hours. Morning stiffness in observed rheumatoid arthritis is one of the diagnostic criteria of the disease. Joint size and stiffness and pain are greatest on awakening and in the early morning hours when grip strength is lowest. Circadian rhythm of levels of interleukin- 6 might correspond to the rhythm of symptoms of rheumatoid arthritis. [5, 6, 7]

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. [8, 9]

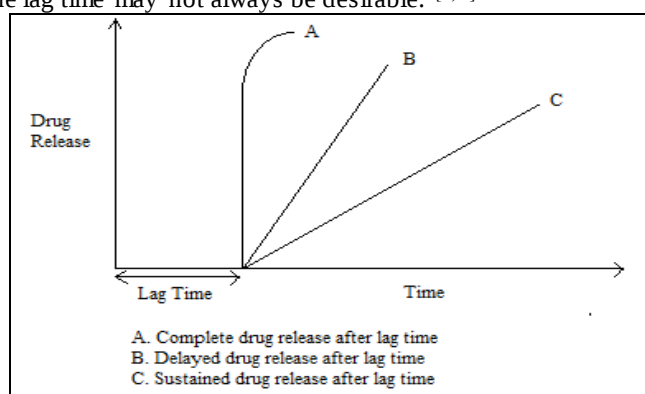


Fig.2: Drug release profile of pulsatile drug delivery system

Table 1. Diseases Requiring Pulsatile Delivery [10]

Disease	Chronological behavior	Drug used
Cardiovascular diseases	BP is at its lowest during night or at early morning awakening period	Nitroglycerin, Calcium channel blocker, ACE Inhibitors etc.
Diabetes mellitus	Increase in the blood sugar level after meal	Sulfonyl urea, Insulin, Biguanide
Asthma	Precipitation of attacks during night or at early morning hour.	B2 agonist, Antihistaminics
Arthritis	Pain in the morning and more pain at night	NSAIDS, Glucocorticoids
Peptic ulcer	Acid secretion	H2 blockers
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during day time	HMG CoA reductase Inhibitors
Arthritis	Pain in the morning and more pain at night	NSAIDS, Glucocorticoids

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. [11, 12, 13]

Advantages Of Pulsatile Delivery [14]:

- 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 by the patient in therapy.
- 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 [15]:

- 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.

Classification Of Pulsatile Systems [16]

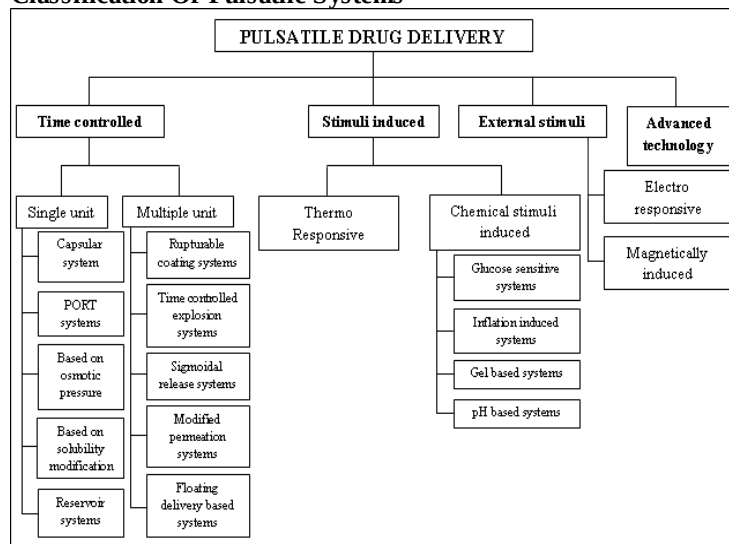


Fig.3: Currently reported classification of pulsatile drug delivery

Time Controlled Pulsatile Release

The principle of time controlled drug delivery systems is that the release of the drug happens according to a predetermined rate so to achieve maximum therapeutic and minimum toxic effect. Systems having a lag phase [delayed release systems] and systems where the release is following a biological/circadian rhythm are the most commonly used controlled release systems. As already mentioned the delayed drug release for meeting chronotherapeutical needs provides

optimum drug delivery for a number of widespread chronic pathologies.

Most delayed release delivery systems are reservoir devices covered with a barrier coating, which dissolves, erodes or ruptures after a lag phase. Well known coating techniques are applied to pellets and tablets to delay drug's release. Conventional coatings dissolve slowly to release drugs into the intestine. Another well-known coating technique employs a water-permeable but insoluble film which encloses the active ingredient and an osmotic agent. As water from the gut slowly diffuses through the film into the core, the core swells until the film bursts, releasing the drug. The film coating may be adjusted for selecting suitable rates of water permeation, and thereby, release time. Alternatively, the tablet coating may be impermeable, and water enters through a controlled aperture in the coating until the core bursts releasing the drug. The film coating may be adjusted for selecting suitable rates of water permeation, and thereby, release time. Alternatively, the tablet coating may be impermeable, and water enters through a controlled aperture in the coating until the core bursts. [17, 18, 19]

1. 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.

1.1 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.

Pulsincap[®] was developed by R. P. Scherer International Corporation, Michigan, US, and is one such system that comprises of a water-insoluble capsule enclosing the drug reservoir. A Swellable hydrogel plug was used to seal the drug contents into the capsule body. When this capsule came in contact with the dissolution fluid, it swelled; and after a lag time, the plug pushed itself outside the capsule and rapidly released the drug. Polymers used for designing of the hydro gel plug were various viscosity grades of hydroxyl propyl methyl cellulose, poly methyl methacrylate, poly vinyl acetate and poly ethylene oxide. The length of the plug and its point of insertion into the capsule controlled the lag time. Pulsincap[®] was studied in human volunteers and was reported to be well tolerated. A low-volume diagnostic test kit was marketed in 1997 under the trade name of 'Sprint salmonella' by Oxoid Ltd., Basingstoke, U.K. developed Pulsincap[®] system with erodible compressed tablet. [20, 21, 22]

1.2 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. This system was used to deliver porcine somatotropin.

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. The water-attracting agent may be the beneficial agent itself whose controlled release is sought, but in most cases, it is a separate agent specifically selected for its ability to draw water, and this

separate agent is being isolated from the beneficial agent at one end of the capsule.

In either case, the structure of the capsule wall does not permit the capsule to expand, and as a result, the water uptake causes discharge of the beneficial agent through an orifice in the capsule at the same rate that water enters by osmosis. Examining the patent literature of pulsatile osmotic pumps several systems were described during time. In one case, the pulsatile effect of a drug is achieved by combining the drug with a modulating agent. The modulating agent is selected on the basis of its solubility in the delivery medium relative to the beneficial agent and the pulsatile effect results from one of the two agents falling below its saturation point, causing more of the other to go into solution and to thereby be released. [23, 24]

1.2.1 Port[®] System

The Port[®] system was developed by Therapeutic system research laboratory Ann Arbor, Michigan, USA. The Port System consists of a gelatin capsule coated with a semi permeable membrane (e.g: cellulose acetate) housed in an insoluble plug lipophilic in nature and an osmotically active agent along with the drug. When it comes in contact with the aqueous medium, water diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a time lag. The time lag is controlled by the thickness of semi permeable membrane. In order to deliver drug in liquid form, an osmotically driven capsular system was developed. In this system, liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semi permeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved.

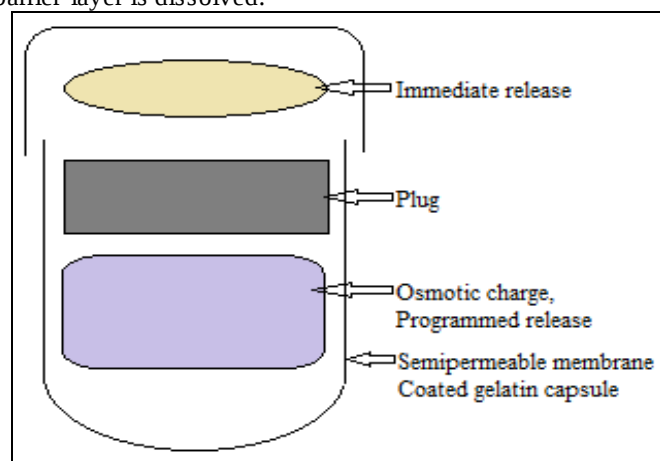


Fig.9: Port System

Such a system was utilized to deliver methylphenidate used in the treatment of attention deficit hyperactivity disorder as the pulsatile port system. This system avoided second time dosing, which was beneficial for school children during daytime.

An osmotic drug (single-unit) delivery capsule from which the delivery of the drug was driven by the osmotic infusion of the moisture by the capsule from a physiological environment. It was provided with a delivery orifice that opened intermittently to achieve a pulsatile delivery effect. The technology involves a movable position that divides the capsule interior into two compartments – one for the beneficial agent and the other for the osmotically active agent. The orifice is located on the capsule wall surrounding the beneficial agent side. The whole capsule is surrounded by an elastic wall in the osmotically active compartment due to inward diffusion of water, which is transmitted through the partition. [25]

1.2.2 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. The time clock system is a delivery device based on solid dosage form that is coated by an aqueous dispersion. This coating is a hydrophobic-surfactant layer to which a water-soluble polymer is added to improve adhesion to the core. Once in contact with the dissolution fluid, the dispersion rehydrates and redisperses. The lag time could be controlled by varying the thickness of the film. After the lag time, i.e., the time required for rehydration, the core immediately releases the drug. This system has shown reproducible results *in vitro* and *in vivo*. The effect of low calorie and high calorie meal on the lag time was studied using gamma scintigraphy. The mean lag time of drug release was 345 and 333 min, respectively.

A drug delivery device with readily adjustable intervals between drug delivery pulses. This could be accomplished by providing for a constant driving force against multiple layers contained in an impervious compartment having an opening away from the constant driving force. The design of the multiple layers was such that the drug layer was adjacent to an expansion layer with an inert and impervious spacer layer alternating with the adjacent drug layer and so on. Two factors affected the duration between pulses, viz., the rate of constant driving force and the thickness of the spacer layer and the multiple layers (drug or combined drug/expansion layer). A thicker layer exhibited a longer duration between pulses of drug since it took a long time for thicker spacer layer to completely traverse the opening. [26, 27, 28]

1.2.3 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 drug delivery system where the tablets of buflomedil HCl prepared by direct compression with varying amounts of spray-dried lactose and microcrystalline cellulose were coated with an inner swelling layer using croscarmellose sodium and an outer rupturable layer using ethyl cellulose. It was observed that by increasing the amount of ethyl cellulose coating, the lag time could be prolonged. Ethyl cellulose, being water insoluble, retarded the water uptake. Similar results were obtained with croscarmellose sodium. Increasing the amount of microcrystalline cellulose decreased the lag time substantially.

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. It could be concluded that by increasing the swelling layer, the lag time could be shortened. However, by increasing the outer coating, the lag time could be prolonged. It was also observed that addition of HPMC to the outer coating shortens the lag time. [29, 30, 31]

1.3 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. [32]

1.4 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;

1.4.1 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. [33]

1.4.2 Chronotropic systems

The chronotropic system consists of a drug containing core coated by hydrophilic swellable hydroxypropylmethyl 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. [34, 35, 36, 37]

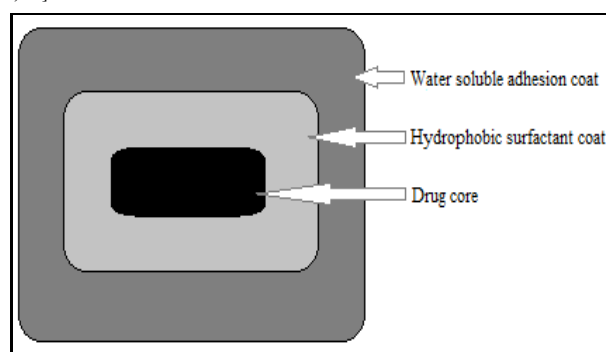


Fig.10: Time clock system

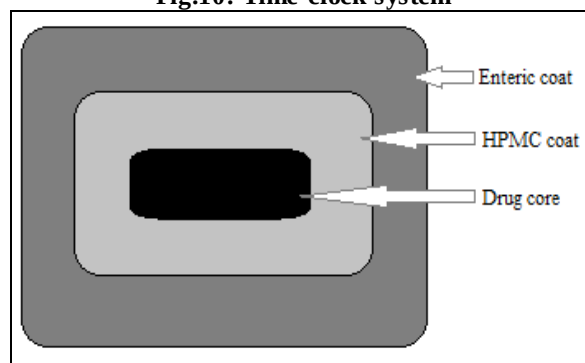


Fig.11: Chronotropic system

2. 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 a 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. As the units of multiparticulate systems are distributed freely throughout the gastrointestinal tract, their transport is affected to a lesser extent than single-unit formulations by the transit time of food. Multiparticulate systems are further

classified as systems based upon change in membrane permeability and systems based upon rupturable coating.^[38,39] 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
- Amenable to capsule & tablets
- Capable of pulsatile release

Disadvantages:

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

2.1 Pulsatile System Based On Change In Membrane Permeability:

A Sigmoidal release system (SRS) is reported which is based upon the interaction of acrylic polymers with quaternary ammonium groups in the presence of different counter ions. SRS system consists of pellet cores having drug and succinic acid coated with ammonio-methacrylate copolymer USP/NF type (B). The water in the medium dissolves succinic acid. The drug inside and the acid solution increase the permeability of the polymer film. This system was used to design an acid-containing core. The system was tested in beagle dogs. Good *in vitro/in vivo* correlation of lag time was observed.

Systems 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.

A formulation of a multiparticulate pharmaceutical form of a delayed and/or pulsed release, enabling to obtain the onset of the availability of the active ingredient within 4 to 8 hours after the ingestion of the pharmaceutical form, and then a progressive release of the totality of the active ingredient within the 8 to 20 following hours. The formulations is in the form of spheroids consisting of a neutral spherical core comprising a first coating based on a mixture of at least one hydro soluble polymer and of at least one non hydro soluble polymer throughout which the constitutive particles of an active ingredient are uniformly distributed. A second coating based on at least two pH independent polymers presenting rates of permeability different from one another with respect to the gastric and intestinal mediums, was also used. A system composed of a large number of pellets made up of two or more populations of pellets or particles. Each pellet contains a drug containing core, and a water soluble osmotic agent enclosed in a water-permeable, water-insoluble polymer film. Incorporated into the polymer film is a hydrophobic, water insoluble agent which alters the permeability of the polymer film. The film coating of each

population of pellets differs from the coating of every other population of pellets in the dosage form in the rate at which water passes through to the core and the rate at which drug diffuses out of the core. The osmotic agent dissolves in the water, causing the pellet to swell and regulating the rate of diffusion of drug into the environment of use. As each population of pellets releases drug into the environment sequentially, a series of pulsatile administrations of the drug from a single dosage form is achieved.^[34,35,36,37]

2.2 Pulsatile Systems With Rupturable Coating:

This is a multiparticulate system in which drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer. The swelling agents used include superdisintegrants like sodium carboxymethyl 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.

Similar to single-unit system, the rupturing effect is achieved by coating the individual units with effervescent or swelling agents. A pulsatile drug delivery system comprising of a plurality of particles that are divided into several individual delivery units, each has its own distinct composition. Drug delivery was controlled by the rupture of the membrane. The timing of release was controlled by the thickness of coating and the amount of water-soluble polymer to achieve the pulsed release. The individual particles had the same composition of internal core, but the thickness of the external coating layer varied.^[40-44]

2.3 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.^[45,46]

2.4 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.

Advanced Technology

Currently pharmaceutical company focused on developing and commercializing pulsatile drug products that fulfil unmet medical needs in the treatment of various diseases. For several diseases (e.g. bronchial asthma, hypertension, rheumatic disease and myocardial infarction) as well for control of body functions (blood pressure, levels of many hormones e.g. aldosterone, rennin, and cortisol) influenced by circadian rhythms, delayed or pulsatile drug release could be an optimal approach. Recently develop various technologies are ACCU-BREAK™, AQUALON, CODAS®, PRODAS®, SODAS®, MINITABS®, DIFFUCAPS®, OROS® etc.^[47]

Commercial Products^[47-50]

A lot of work is being done to achieve pulsatile release so that the drug release can be delivered according to circadian rhythms of our body. Advancis Pharmaceutical Corp., German

town, Maryland, USA has developed once-a-day pulsatile delivery system called Pulsys[®], which enables the delivery of antibiotic amoxicillin in regular concomitant pulses. The rationale behind designing such a system is that it has been reported that antibiotics are more effective against fast-growing bacteria. When an immediate release antibiotic is administered, bacteria respond to it by going into a dormant stage, while the administration of a pulsatile system in such a case is more effective because the regular release of increased pulses of antibiotic does not let defence system of the bacteria to go into a dormant stage.

The preclinical studies have shown that pulsatile approach of delivering antibiotic is more effective. Advancis is developing Pulsys versions of three of the top five most prescribed antibiotics in the United States. Asthmatic patients suffer from lung discomfort more in early morning due to circadian changes. Therefore, it is desirable to get maximum broncho dilating effect in the morning hours. One such example is of a bronchodilator "Uniphyll" (theophylline), which was developed by Purdue Pharmaceuticals Products L. P., Stamford, USA, and approved by FDA in 1989. It's a once-a-day formulation. When taken in the evening, it reaches to peak blood levels in the morning hours, resulting in improved lung functioning and relief to the patient.

There are examples where varying plasma levels are required during the day time. Elan applied this technology to a product of Novartis, Ritalin, containing methylphenidate to get a pulsatile once-daily dosage form that replaces the twice-a-day regimen.

Current Situation And Future Scope

Now a day's pulsatile drug delivery is gaining popularity. The prime advantage in this drug delivery is that drug is released when necessity comes. As a result chance of development of drug resistance which is seen in conventional and sustained release formulations can be reduced. Furthermore, some anticancer drugs are very toxic. These drugs give hazardous problems in conventional and sustained release therapies. Now many FDA approved chronotherapeutics drugs are available in the market. This therapy is mainly applicable where sustained action is not required and drugs are toxic. Key point of development of this formulation is to find out circadian rhythm i.e. suitable indicator which will trigger the release of drug from the device. Another point is absence of suitable rhythmic biomaterial which should be biodegradable, biocompatible and reversibly responsive to specific biomarkers in rhythmic manner. Regulatory is another big question. In preapproval phase it is sometimes difficult to show chronotherapeutics advantage in clinical settings. In post-approval phase causal recreational drug abuse along with on a much larger scale, by the criminal diversion of these modified formulations for profit have arisen problems. The FDA has now heavily relied on the development and implementation of risk management programs as a strategy to allow an approval of a drug to go forward while exercising some restrictions. Many researches are going on the pulsatile drug delivery to discover circadian rhythm with suitable device in the world. In future this delivery will be a leading way to deliver therapeutic agents due to its some unique characters like low chance of dose dumping, patient compliance and the above factors. The future of chronotherapeutics and more specifically the future of delivering drugs in a pulsatile manner seem to be quite promising as in certain disease states pulsatile release exhibit several advantages over the traditional

zero or first order drug delivery mechanisms. Pulsatile drug delivery systems can be either time controlled or site-specific, single or multiple units. At the moment pulsatile release (site or time specific) most often is achieved by using different polymers in coating layers or by changing the coating thickness. From technological point of view, multiparticulate systems seem to be more efficient than single-unit dosage forms in achieving pulsatile drug delivery and it can become even more sophisticated when coating technologies are incorporated. The authors of this paper believe that an increasing number of multiparticulate coated systems would become commercially available in the years to come.

Conclusion

Oral drug delivery is the largest, oldest, and most preferred route of drug delivery. Universally sustained and controlled-release products provide a desired therapeutic effect, but fall for diseases following biological rhythms. Circadian disorders such as asthma, osteoarthritis, RA, cholesterol synthesis, etc., require chronopharmacotherapy. Pulsatile drug delivery can effectively crack this problem as it is modulated according to body's circadian clock giving release of drug after a specified lag time. Pulsatile drug delivery systems are gaining a lot of interest now days. These systems are designed according to the circadian rhythm of the body. These systems deliver the drug at specific time as per the pathophysiological need of the disease, resulting in improved patient compliance and therapeutic efficacy. Pulsatile delivery, which is meant as the liberation of drugs following programmed lag phases, has drawn increasing interest, especially in view of emerging chronotherapeutic approaches. Various pulsatile technologies have been developed on the basis of methodologies as discussed previously. These includes OROS[®] technology, CODAS[®] technology, CEFORM[®] technology, DIFFUCAPS[®] technology, Three-dimensional printing[®], timerx[®] etc. The large variety of oral pulsatile delivery systems described in the literature highlights the current interest in this particular area of pharmaceuticals. Indeed, the assessment of temporal rhythms in an increasing number of disease states, the consolidation of chronotherapeutic approaches and a growing awareness of the impact of patient compliance are likely to strengthen the research efforts towards the design, preparation and evaluation of such devices. Innovation, scalability, lack of severe regulatory constraints and availability of human proof-of-concept results, however, are expected to play a key role for a successful development of the delivery technologies proposed. Thus, designing of proper pulsatile drug delivery will enhance the patient compliance, optimum drug delivery to the target side & minimizing the undesired effects.

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