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Research Article

AN OVERVIEW ON STUDY OF PULSATILE DRUG DELIVERY SYSTEM

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ABSTRACT

Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. These systems are designed according to the circadian rhythm of the body. 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 has to be designed in such a way that a complete and rapid drug release follows the lag time. Various systems like capsular systems, osmotic systems, single and multiple-unit systems based on the use of soluble or erodible polymer coating and use of rupturable membranes have been dealt with in the article. These systems are beneficial for the drugs having chronopharmacological behavior where night time dosing is required and for the drugs having high first-pass effect and having specific site of absorption in GIT.

INTRODUCTION

Tablets are solid dosage forms each containing a unit dose of one or more medicament. They are intended for oral administration. Some tablets are swallowed whole or after being chewed, some are dissolved or dispersion in water before administration and some are retained in mouth where the active ingredient is liberated. Tablets are tamperproof solid unit dosage forms containing medicament or mixture of flat or convex surfaces. Tablets are solid unit dosage forms of medicament or medicaments with suitable diluents and prepared either by molding or compression[1]. The oral route of drug administration is the most important and convenient method of administering drug. It is probable that at least 90% of all the drugs used to produce systemic effect are administered by oral route.

Novel Drug Delivery System

Novel drug delivery system (NDDS) is a novel approach to drug delivery system that attempts to eliminate all the disadvantages associated with the conventional drug delivery system which include the following[2].

a. Poor patient compliance leading to discontinuation of therapy or missed doses in case of frequently administered drug.
b. Fluctuation of drug concentrations which may result in under medication.
c. Changes of occurrence of toxicity are high especially upon usage of drug with small therapeutic index.

Gastroretentive Drug Delivery System (Grdds)[3]

Majority of the drugs are well absorbed from all the regions of the G.I tract while some are absorbed only from specific areas, due to low permeability in the intestinal tract, Floating drug delivery system (FDDS) and bio adhesive drug delivery are widely used techniques for gastro retention. Low density porous multiparticulate systems have been used by researchers for formulation of FDDS.

Circadian Rhythms

The symptom intensity of many medical conditions and the occurrence of life-threatening medical emergencies exhibit rather precise timings. Gout, gallbladder, and peptic ulcer attacks are most frequent at night. Acute pulmonary edema, congestive heart failure, and asthma worsen nocturnally. Sudden infant death and the symptoms of allergic rhinitis and rheumatoid arthritis are either most intense overnight or in the morning upon wakening[4]. Migraine headache typically is triggered during rapid eyeball movement (REM) episodes during night time sleep or in the early morning hours after

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awakening. Depression is most severe in the morning. Some seizure disorders are triggered during specific sleep stages and/or by transitions between sleep and wakefulness

Chronotherapy

The knowledge of 24 hr rhythm in the risk of disease plus evidence of 24 hr rhythm dependencies of drug pharmacokinetics, effects, and safety constitutes the rationale for pharma-cotherapy (chronotherapy)[5]. One approach to increasing the efficiency of pharmacotherapy is the administration of drugs at times at which they are most effective and/or best tolerated Pulsatile drug delivery system (PDDS) is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after a predetermined off-release period, i.e., lag time. Pulsatile release pattern is receiving increasing interest for the development of drugs for which conventional controlled drug-release systems with a continuous release are not ideal.6 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.

Methodologies for Pulsatile Drug Delivery

Various techniques are available for the pulsatile delivery, broadly classified as single-unit and multiple-unit systems. System based on change in membrane permeability. General methodologies for the pulsatile drug delivery system can be broadly classified into three classes, viz. time controlled, stimuli induced and externally regulated.

Floating Pulsatile Drug Delivery Systems[6]

Site and time specific oral drug delivery have recently been of great interest in pharmaceutical field to achieve improved therapeutic efficacy. Various diseases like asthma, hypertension, and arthritis show circadian variation that demand time-scheduled drug release for effective drug action. Based on these considerations novel approach termed "floating pulsatile drug delivery system" was developed. The basic features of this delivery system comprise of following.

a. Combination of gastro retentive and pulsatile principles,
b. An idealistic drug release profile delivering higher amounts of drug at morning time,
c. Increased gastric residence time useful for drugs having absorption window in upper GIT,
d. Low drug release in stomach (due to lag time) suited for NSAID class of drug (ibuprofen)-gastric irritant.

Classification of Pulsatile Systems[7]

Pulsatile systems can be classified into single- and multiple-unit systems. Single-unit systems are formulated either as capsule-based or osmosis-based systems. Single-unit systems are designed by coating the system either with eroding/soluble or rupturable coating. In multiple-unit systems, however, the pulsatile release is induced by changing membrane permeability or by coating with a rupturable membrane.

Single Unit Pulsatile Systems

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

Capsule Based 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 methacrylates, polyvinyl 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 'Sprintsalmonella' by Oxoid Ltd., Basingstoke, U.K. Steven *et al.* developed a Pulsincap system with erodible compressed tablet. As the swelling hydrogel polymer plug replaced the erodible tablet, the dependence of the dimensional accuracy between the plug and the capsule for the pulling mechanism of the plug from the capsule was also overcome Ross *et al.* used low substituted hydroxypropylcellulose for the expulsion system for the release of propranolol over a time period of 2-10 h. This could be controlled using compressed erodible tablets made of lactose and HPMC.

Krogel and Bodmeier studied the release of chlorpheniramine utilizing the erodible plugs fitted in the capsules. Altering the composition and the weight of the erodible plug could control release of drug. Stevens *et al.* designed a hydrophilic sandwich capsule that was based on a system where a capsule was enclosed within a capsule and the space in between was a gel barrier layer composed of HPMC. When the outer capsule dissolved, the delay in the second pulse was provided by the barrier gel layer. Soutar *et al.* studied the delivery of 500 mg paracetamol with a gastroresistant hydrophilic sandwich capsule targeted to ileocaecal junction / proximal colon. Analysis of salivary samples gave a mean T_{max} of 7.9 h (SD±0.96)

Systems Based on Osmosis

The Port system was developed by Therapeutic system research laboratory Ann Arbor, Michigan, USA, and consists of a capsule coated with a semipermeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug formulation[8]. When this capsule came in contact with the dissolution fluid, the semipermeable membrane allowed the entry of water, which caused the pressure to develop and the insoluble plug expelled after a lag time. 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.The pulsatile delivery provided by the aforementioned devices in this invention may be for therapeutic purpose, nutritional purpose, preventive purpose, and a wide variety of situations in general.

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[9]. 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/ 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. Sungthongjeen *et al.* designed 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.

Multiple unit Pulsatile Systems

More reliable gastric emptying patterns are observed for multi particulate formulations as compared to single-unit formulations, which suffer from 'all or none' concept. As the units of multi particulate 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[10]. Multi particulate systems are further classified as systems based upon change in membrane permeability and systems based upon rupturable coating.

Advantages of Pulsatile Drug Delivery System[11]

- Extended daytime or night time activity
- Reduced side effects
- Reduced 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 site like colon
- Protection of mucosa from irritating drugs
- Drug loss is prevented by extensive first pass metabolism
- Patient comfort and compliance: Oral drug delivery is the most common and convenient for patients, and a reduction in dosing frequency enhances compliance

Limitations of Pulsatile Drug Delivery System[12]

Pulsatile drug delivery system has certain limitations, so in many cases it fails.

- Multiple manufacturing steps in case of multiparticulate pulsatile drug delivery system
- Only less quantity of the drug can be loaded
- Incomplete release from the system
- There is variability in *in-vivo* drug release in single unit pulsatile drug delivery system

Commercial Products

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 amoxycillin 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 Pulsysâ 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 bronchodilating effect in the morning hours. One such example is of a bronchodilator "Uniphyl" (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, Ritalinâ, 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 chronotherapeutic drugs are available in the market. This therapy is mainly applicable where sustained action is not required and drugs are toxic[13]. 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 chronotherapeutic advantage in clinical setting. 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.

CONCLUSION

There is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients. Pulsatile drug delivery is one such system that, by delivering drug at the right time, right place, and in right amounts, holds good promises of benefit to the patients suffering from chronic problems like asthma, hypertension, etc. and also for drugs like antibiotics.

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