INTERNATIONAL JOURNAL OF APPLIED BIOLOGY AND PHARMACEUTICAL TECHNOLOGY

Volume: 2: Issue-4: Oct - Dec -2011 IJABPT *ISSN 0976-4550*

CHRONOTHERAPEUTICS: A RANGE OF NEWER DRUG DELIVERY APPROACHES FOR BETTER PATIENT COMPLIANCE

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ABSTRACT : A major objective of chronotherapy in the treatment of several diseases is to deliver the drug in higher concentration during the time of greatest need according to the circadian onset of the disease or syndrome. The physiology and biochemistry of a human being is not constant during the 24 hours, but it shows some variability in a predictable manner as defined by the timing of peak and trough of each of the body circadian processes and functions in relation to the time. There are quite a few approaches are in progress to control the drug to the desired degree to the clinical physiology of diseases with the aid of single unit and multiparticulate systems. The chronotherapy of a medication may be accomplished by the judicious timing of conventionally formulated tablets and capsules are of current interest.

Keywords: Chronotherapeutics, circadian rhythm, Controlled drug, delivery systems, dosage forms.

INTRODUCTION

Variation of physiological and pathophysiological functions in time has brought a new approach to the development of drug delivery systems. The foremost goal is to develop formulations to meet therapeutic needs relating to particular pathological conditions. Research in chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy. Some of the rhythm that affect our body include, ultraradian, which are cycles shorter than a day; circadian, which last about 24 hours; infradian, referring to cycles longer than 24 hours which causes depression in susceptible people during the short days of winter.[1] Optimal clinical outcome cannot be achieved if drug plasma concentrations are constant. If symptoms of a disease display circadian variation, drug release should also vary over time. Utilization of different technologies in development of time-controlled, pulsed, triggered and programmed drug delivery devices has been undergoing recent years. Thus explored recent technologies and devices are duly conversed in this article.

CHRONOBIOLOGY AND CIRCADIAN RHYTHMS

Chronobiology[2] is the scientific study of biological rhythms and their underlying mechanism. Up to now design of drug delivery systems has been governed by the homeo-static theory. This theory is based on the assumption of biological functions that display constancy over time. However, chronobiological studies have established circadian rhythm for almost all body functions, e.g. heart rate, blood pressure, body temperature, plasma concentration of various hormones, gastric pH and renal function. It has become apparent that rhythmic processes are indispensable for treatment of human diseases. As well as physiological functions vary over time pathological state of disease has circadian rhythms. Epidemiological[3] studies document the elevated risk of disease symptoms during 24-hour cycle (Fig No. 1)

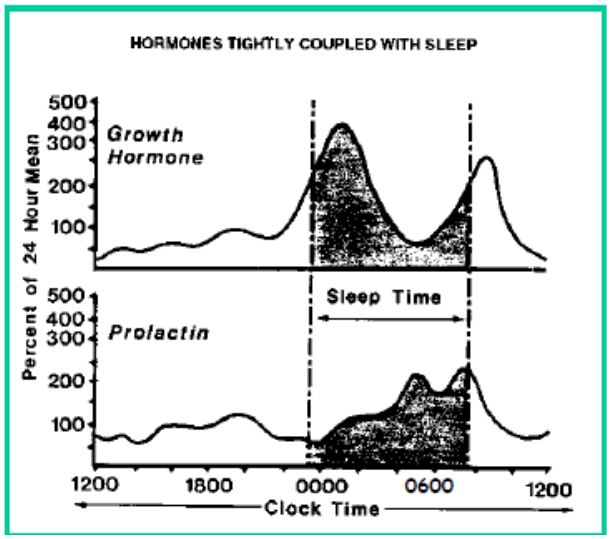


Fig No. 1 Circadian rhythm of Hormone release

Circadian rhythms[4] are self sustaining, endogenous oscillations, and exhibiting periodicities of about one day or 24 hours. Normally, circadian rhythms are synchronized according to the body pacemaker clock, located in the suprachiasmic nucleus of the hypothalamus. Through a number of clinical trials and epidemological studies, it has become evident the levels of disease activity of a number of clinical disorders have a pattern associated with the body's inherent clock set according to circadian rhythms. Examples of some diseases are shown in table 1.

Table No. 1 The Diseases in relation to Circadian rhythm

Sl.No	Syndrome	Circadian rhythmicity
1	Allergic Rhinitis	Worse in the morning/ upon rising
2	Asthma	Exacerbation more common during the sleep period
3	Rheumatoid Arthritis	Symptoms are more intense upon awakening
4	Osteoarthritis	Symptoms worse in the middle/ latter portion of the day
5	Angina Pectoris	Chest pain and ECG changes more common in early morning
6	Myocardial infraction	Incidence greatest in the early morning
7	Stroke	Incidence higher in the morning
8	Sudden Cardiac death	Incidence higher in the morning after awakening
9	Peptic Ulcer disease	Worse in late evening and early morning hour

Predictable circadian variation can be useful in diagnosis of certain diseases. The disease with the greatest intrinsic circadian variation is probably asthma, which has a 300 fold difference in incidence between the peak at 2 am to 4 am and the trough at 10 am to 12 pm.

CHRONOTHERAPEUTICS

Chronotherapeutics[5] refers to a treatment method in which in vivo drug availability is timed in relation to repetitive rhythms of drug related biological phenomena to produce the maximum health benefit and minimum harm to the patient. Chronotherapy decisions are based on the observation that there is an interdependent relationship between the peak-to-trough rhythmic activity in disease symptoms and the risk factors, pharmacologic sensitivity and pharmacokinetics of many drugs.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 the 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. Chronotherapeutic formulations may use various release mechanisms eg., time-delay coatings (Covera-HS), osmotic pump mechanisms (COER-24), matrix systems (Geminex), that provide for varying levels throughout the day.[6,7]

Table No. 2 Various group of drugs and its Chronotherapies

CLASS	EXAMPLES
Cardiovascular drugs	Verapamil, Propanolol, Diltiazem, Nifidipine, Enalapril
Antiasthmatic drugs	Methylpredisolone, Predisolone, Albuterol, Terbutaline, Theophylline
Anticancer drugs	Cisplatin, Oxaliplatin, Doxorubicin, 5-Fluorouracil, Folinic acid, Methotrexate, Mercaptopurine
Non-steroidal anti-inflammatory agents	Ibuprofen, Ketoprofen, Indomethacin, Tenoxicam. Acetylsalicylic acid
Anti-ulcer agents	Cimetidine, Ranitidine, Famotidine, Pirenzipine,Omeprazole
Anticholesterolemic agents	Simvastatin, Lovastatin
Others	Vitamin D3, Diazepam, Haloperidol

Bronchial asthma

Research has proven that normal lung function under goes circadian changes. Airway resistance, bronchoconstriction and exacerbation of symptoms increase progressively at night in asthmatic patients. Risk of asthma attack is 100–fold greater during night time sleep than during daytime activity. Chronotherapy for asthma is aimed at getting maximal effect from bronchodilator medications during early morning hours. Several chronotherapies have been proposed. Daily or alternate day, morning dose of glucocorticoid medications such as methylpredisolone (Medrol) significantly moderates side effects and enhance therapeutic benefits. Oral predisolone administered at 3 pm rather than at 8 am has been shown to be highly effective in the treatment of nocturnal asthma. Findings demonstrate that conventional β2 agonist aerosol medications administered at 3 pm rather than at 8 am results in further optimization of asthma chronotherapy. In one study, use of a timed release formulation of theophylline (Theo-24) administered at 3 pm achieved an elevated theophylline level overnight, thereby reducing the risk of acute episode of asthma. Evening once daily dosing of controlled release theophylline tablets (Uniphyl 400 mg tablets) showed chronotherapeutical potential in the treatment of nocturnal and early-morning asthma.

Arthritis

Symptoms of rheumatoid arthritis are most intense when awaking from night time sleep, while those of osteoarthritis are worse in the evening or at night. Chronopharmacological studies of once daily sustained release indomethacin preparation for the treatment of osteoarthritis have indicated that time of dosing influences tolerances and effectiveness.

Hypercholesterolemia

Diurnal variation in the human cholesterol synthesis has been studied. It has been observed that cholesterol synthesis increases during the night. Free cholesterol levels are reported to be lowest at 2 pm to 6 pm and peak at 6 am. Chronotherapy can be achieved by timing the medication in accordance with circadian rhythm for hypercholesterolemia. Morning versus evening administration of HMG-CoA-reductase antagonists (Lescol, Mevacor, Pravachol and Zocor) showed that evening dosing of these medications is more effective than morning dosing.

Myocardial Infarction

Onset of myocardial infarction has been shown to be more frequent in the morning with 34% events occurring between 6 am and noon. Acute cardiac arrest and transient myocardial ischemia shows an increased frequency in morning. The causes for these findings have been suggested to be release of catecholamines, cortisol, increase in the platelet aggregation and vascular tone.

Cerebrovascular accidents

The cerebrovascular accidents have been shown to occur on the first hours of morning between 10 am and 12 noons, and the incidence declines steadily during the evening and the midnight. A major objective of chronotherapy for cardiovascular disease is to deliver the drug in higher concentration during time of greatest need and in lesser concentrations when the need is less. ACE inhibitors are more effective when administered during night. Atenolol, Nifedipine and Amolodipine are more effective when administered at night. The first chronotherapeutic therapy for hypertension and angina pectoris has recently been developed which matches drug delivery to the circadian pattern of blood pressure and rhythm of myocardial ischemia. Verapamil has been employed in this system where release is observed after 4-5 hours and continues for 18hours. Taken at bedtime, this provides optimal blood concentration between 4a.m. and 12 noons. Data from recent studies demonstrate that antihypertensive and antianginal therapy can be designed to mimic the circadian rhythms.

Peptic ulcer

In peptic ulcer patients, pain, gastric distress and acute exacerbation of the disease are most likely in the late evening and early morning hours. This is attributed to high gastric acid secretion and slows gastric motility and emptying at night. Suppression of nocturnal acid is an important factor in duodenal ulcer healing. Once daily nocturnal administration of H2 antagonist tablet medications not only reduce acid secretion more effectively but also promote ulcer healing and reduce ulcer reoccurrence.

TIME CONTROLLED RELEASE SYSTEMS

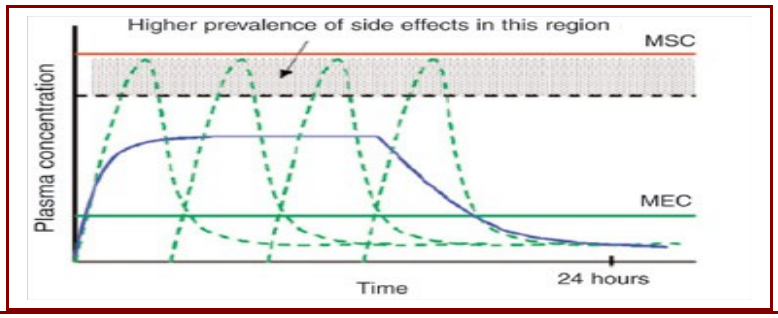
Controlled-release formulations have many advantages over immediate-release formulations. With these formulations a less frequent drug administration is possible, lower plasma peak concentrations can be obtained to avoid adverse effects, and patient compliance can correspondingly be improved. The category of controlled release formulations can be divided into subgroups of rate-controlled release, delayed-release and pulsed-release formulations. Delayed-release formulations include time-controlled release and site-specific dosage forms. When constant drug plasma levels need to be avoided, as in chronopharmacotherapy, time controlled or pulsed release formulations are preferable, especially in the treatment of early morning symptoms. By timing the drug administration, plasma peak is obtained at an optimal time. Number of doses per day can be reduced. When there are no symptoms there is no need for drug. Saturable first pass metabolism and tolerance development can also be avoided (Vyas et al. 1997). Recent studies in the area of oral controlled drug delivery includes novel approaches, which prolong the gastrointestinal residence time (Deshpande et al., 1996) and delivery systems, which release the drug in a pulsatile fashion (Gurny et al., 1993). Pulsatile drug delivery systems are characterized by two release phases. First phase with no (or) little drug being released, followed by a second phase, during which the drug is released completely within a short period of time after the lag time (Hurny et al., 1993). The release can be either time (or) site-controlled.[9]

PULSATILE DRUG DELIVERY [10]

Controlled drug delivery systems have acquired a center stage in the arena of pharmaceutical R&D business. Such systems offer temporal and/or spatial control over the release of drug and grant a new lease on life to a drug molecule in terms of patentability. 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

- 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.

The oral controlled-release system shows a typical pattern of drug release (Figure 2) in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action. Thus, the release commences as soon as the dosage form is administered as in the case of conventional dosage forms.



Plasma Drug Concentration Profiles for Conventional Tablet or Capsule Formulation (-------) and a Zero-Order Controlled-Release Formulation (————).
MEC = Minimum Effective Concentration
MSC = Maximun Safe Concentration.

Fig No. 02 Plasma concentration profile for Tablet and capsules

NEED OF A PULSATILE DELIVERY SYSTEM

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 conditions that demand such release include:

- Many body functions that follow circadian rhythm, i.e., their activity waxes and wanes with time. A number of hormones like rennin, aldosterone, and cortisol show daily fluctuations in their blood levels. Circadian effects are also observed in case of pH and acid secretion in stomach, gastric emptying, and gastro-intestinal blood transfusion.
- Diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension display time dependence. Dethlefsan and Repges reported sharp increase in asthmatic attacks during early morning hours. Such a condition demands considerations of diurnal progress of the disease rather than maintaining constant plasma drug level. A drug delivery system administered at bedtime, but releasing drug well after the time of administration (during morning hours), would be ideal in this case. Same is true for preventing heart attacks in the middle of the night and the morning stiffness typical of people suffering from arthritis.
- Drugs that produce biological tolerance demand for a system that will prevent their continuous presence at the biophase as this tends to reduce their therapeutic effect.
- The lag time is essential for the drugs that undergo degradation in gastric acidic medium (eg, peptide drugs) irritate the gastric mucosa or induce nausea and vomiting. These conditions can be satisfactorily handled by enteric coating, and in this sense, enteric coating can be considered as a pulsatile drug delivery systemTargeting a drug to distal organs of gastro-intestinal tract like the colon requires that the drug release is prevented in the upper two-third portion of the gastrointestinal tract

- The drugs that undergo extensive first-pass metabolism (β blockers) and those that are characterized by idiosyncratic pharmacokinetics or pharmacodynamics resulting in reduced bioavailability, altered drug/metabolite ratios, altered steady state levels of drug and metabolite, and potential food-drug interactions require delayed release of the drug to the extent possible.

All of these conditions demand for a time-programmed therapeutic scheme releasing the right amount of drug at the right time. This requirement is fulfilled by Pulsatile Drug Delivery Systems. A pulsatile drug delivery system is characterized by a lag time that is an interval of no drug release followed by rapid drug release. The ideal drug-release profile of pulsatile drug delivery systems is depicted in Figure 2. The first pulsed delivery formulation that released the active substance at a precisely defined time point was developed in the early 1990s. In this context, the aim of the research was to achieve a so-called sigmoidal release pattern (pattern A in Figure 3). The characteristic feature of the formulation was a defined lag time followed by a drug pulse with the enclosed active quantity being released at once.
Thus, the major challenge in the development of pulsatile drug delivery system is to achieve a rapid drug release after the lag time. Often, the drug is released over an extended period of time (patterns B & C in Figure 3).

CURRENTLY REPORTED SYSTEMS

Pulsatile 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.

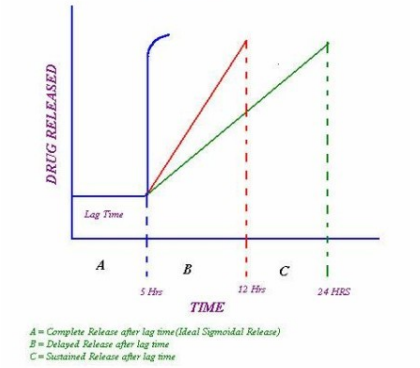


Fig No. 03 Drug Release Profile of Pulsatile Delivery System

These time-controlled systems can be classified as single unit (eg, tablet or capsule) or multiple unit (eg, pellets) systems.

SINGLE-UNIT SYSTEMS

Capsular Systems

Different single-unit capsular pulsatile drug delivery systems have been developed. A general architecture of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined lag time owing to swelling, erosion, or dissolution. The Pulsincap® system (Scherer DDS, Ltd) is an example of such a system that is made up of a water-insoluble capsule body filled with drug formulation. The body is closed at the open end with a swellable hydrogel plug. Upon contact with dissolution medium or gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a lag time. This is followed by a rapid drug release. The lag time can be controlled by manipulating the dimension and the position of the plug.

Capsular System Based on Osmosis

The Port® System (Port Systems, LLC) consists of a gelatin capsule coated with a semipermeable membrane (eg, cellulose acetate) housing an insoluble plug (eg, lipidic) and an osmotically active agent along with the drug formulation (Fig 4). When in contact with the aqueous medium, water diffuses across the semipermeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. The lag time is controlled by coating thickness.

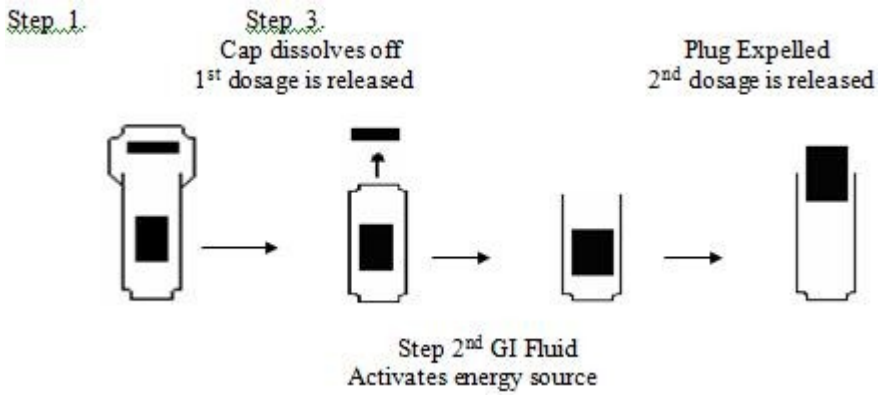


Fig. 04 Drug Release mechanism from Port System

Pulsatile Delivery by Solubility Modulation

Such systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was especially developed for delivery of salbutamol sulphate. The composition contains the drug (salbutamol sulphate) and a modulating agent (sodium chloride, NaCl). The amount of NaCl was such that it was less than the amount needed to maintain saturation in a fluid that enters the osmotic device. The pulsed delivery is based on drug solubility. After the period of zero-order release, the drug is delivered as one large pulse. A similar system is described for delivery of terbutaline and oxprenolol. However, in general, the large-scale manufacturing of these systems is complicated and calls for special equipments and several manufacturing steps.

Pulsatile System with Erodible or Soluble Barrier Coatings

Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly. The lag time depends on the thickness of the coating layer. The Time Clock® system (West Pharmaceutical Services Drug Delivery & Clinical Research Centre) consists of a solid dosage form coated with lipidic barriers containing carnauba wax and bees wax along with surfactants, such as polyoxyethylene sorbitan monooleate. The lag time increased with increasing coating thickness. Such systems are better suited for water-soluble drugs. The major advantage of this system is its ease of manufacturing without any need of special equipment. 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 release. In addition, through the application of an outer gastric-resistant enteric film, the variability in gastric emptying time can be overcome, and a colon-specific release can be obtained, relying on the relative reproducibility of small intestinal transit time. The lag time is controlled by the thickness and the viscosity grades of HPMC. The cores containing Antipyrine as the model drug were prepared by tabletting and retarding, and enteric coats were applied in a fluidized bed coater.

Multilayered Tablet

A release pattern with two pulses was obtained from a three-layered tablet containing two drug containing layers separated by a drug-free gellable polymeric barrier layer.

This three-layered tablet was coated on three sides with in impermeable ethyl cellulose, and the top portion was left uncoated. Upon contact with dissolution medium, the initial dose incorporated into the top layer was released rapidly from the non-coated surface. The second pulse was obtained from the bottom layer after the gelling barrier layer of HPMC was eroded and dissolved. The rate of gelling and/or dissolution of the barrier layer controls the appearance of the second pulse. The gelling polymers reported include cellulose derivatives like HPMC, methylcellulose, or polyvinyl alcohols of various molecular weights and the coating materials include ethyl cellulose, cellulose-acetate-propionate, methacrylic polymers, acrylic and methacrylic co-polymers, and polyalcohols.

Pulsatile System with Rupturable Coatings

In contrast to the swellable or erodible coating systems, these systems depend on the disintegration of the coating for the release of drug. The pressure necessary for the rupture of the coating can be achieved by the effervescent excipients, swelling agents, or osmotic pressure. An effervescent mixture of citric acid and sodium bicarbonate was incorporated in a tablet core coated with ethyl cellulose. The carbon dioxide developed after penetration of water into the core resulted in a pulsatile release of drug after rupture of the coating. A reservoir system with a semipermeable coating was designed for delivery of drugs that exhibit extensive first-pass metabolism. The release pattern was similar to that obtained after administration of several immediate-release doses.

MULTIPARTICULATE SYSTEMS

Multiparticualte systems (eg, pellets) offer various advantages over single-unit systems. These include no risk of dose dumping, flexibility of blending units with different release patterns, and reproducible and short gastric residence time. But the drug-carrying capacity of multiparticulate systems is lower due to presence of higher quantity of excipients. Such systems are invariably a reservoir type with either rupturable or altered permeability coating.

Pulsatile System Based on Rupturable Coating

Time-Controlled Explosion System (Fujisawa Pharmaceutical Co., Ltd.):

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. Alternatively, an effervescent system comprising a mixture of tartaric acid and sodium bicarbonate may also be used. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer.

Osmotic-Based Rupturable Coating Systems

Permeability Controlled System

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

Pulsatile Delivery by Change in Membrane Permeability

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter-ions in the medium. Several delivery systems based on this ion exchange have been developed. Eudragit RS 30D is reported to be a polymer of choice for this purpose. The cores were prepared using theophylline as model drug and sodium acetate. These pellets were coated using Eudragit RS30D (10% to 40% weight gain) in four different layer thicknesses.

Sigmoidal Release System

This consists of pellet cores comprising drug and succinic acid coated with ammonio-methacrylate copolymer USP/NF type B. The lag time is controlled by the rate of water influx through the polymer membrane.

The water dissolves succinic acid, and the drug in the core and the acid solution in turn increases permeability of the hydrated polymer film. In addition to succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, or citric acid can be used. The increased permeability can be explained by improved hydration of film, which increases free volume. These findings were used to design a coated delivery system with an acid-containing core. The *in-vitro* lag time correlated well with *in-vivo* data when tested in beagle dogs.

EXPERTISE TO DEVELOP TIME CONTROLLED DRUG DELIVERY SYSTEM

Various technologies to develop time-controlled peroral drug delivery systems have been extensively studied recent decades. Some of these systems are discussed below.

Enteric-coated systems

Enteric coatings have traditionally been used to prevent the release of a drug in the stomach. Enteric coatings are pH sensitive. Drug is released when the pH is raised above 5 in the intestinal fluid. Although enteric-coated formulations are used mainly in connection with site-specific delivery such formulations can be utilized in time-controlled drug administration, when a lag time is needed. Because of the unpredictability of gastric residence, such systems cannot be the first choice when a time controlled release is wanted. In the treatment of nocturnal asthma a salbutamol formulation containing a barrier coating, which is dissolved in intestinal pH level above about 6, has successfully been used (Bogin and Ballard 1992). Enteropolymers in time-controlled drug delivery has been used e.g. in the Chronotopic® drug delivery system (Gazzanigaet al. 1994, 1995; Sangalli et al 1999). The system contains a core which is film coated with two polymers, first with HPMC and then with a gastroresistant polymer (Eudragit® L30D).

Layered systems

To allow biphasic drug release a three-layer tablet system has been developed (Conte et al. 1989). Two layers both contain a drug dose. An outer drug layer contains the immediately available dose of drug. An intermediate layer, made of swellable polymers, separates the drug layers. A film of an impermeable polymer coats the layer containing the other dose of drug. The first layer can also involve a drug-free hydrophilic polymer barrier providing delayed (5 h) drug absorption (Conte et al. 1992a). The Conte et al. group has also studied a multi-layer tablet system (Geomatrix®). It consists of a hydrophilic matrix core containing the drug dose. One or two impermeable or semipermeable polymeric coatings (films or compressed) applied on both sides of the core (Conte and Maggi 1996). This kind of three-layer device has been used in the L-dopa/benserazide treatment of parkinsonian patients (Ghika et al. 1997). Night-time problems and early-morning symptoms of Parkinsonism can be avoided by use of a dual-release Geomatrix® formulation, which allows daily doses of drug to be reduced and leads to extent of bioavailability 40% greater than when a traditional controlled release formulation is employed[11,12, 13]

Press-coated systems

In recent years, various controlled release, especially time-controlled release, drug delivery systems based on compression coating technology have been studied. Most such formulations release drug after a lag phase, followed by a rapid dissolution of a core. Conte et al. (1992b, 1993) have developed a press-coated device in which the inner core contains the drug and the outer coat is made of different types of polymers. The outer barrier, controlling drug release can be either swellable or erodible. Lag times can be varied by changing the barrier formulation or the coating thickness. To achieve time-controlled delivery a press-coated formulation containing a swellable core and a less water permeable coat has been developed (Ishino et al. 1992). The core contains drug and disintegration agent. The outer shell delays commencement of drug release. A melted blend of hydrogenated castor oil and polyethylene glycol 600 has been used for coating. After a lag time of one to 10 hours release in vitro is rapid. Lag times depend on the composition of the blend used for coating. Matsuo et al. (1995) have developed a diltiazem hydrochloride formulation intended for use in treatment of time-related symptoms of ischaemic heart disease and hypertension.

The tablet consists of a core, containing drug, and a coat formed by compressing hydroxyethylcellulose. Diltiazem is rapidly released after a delay of several hours. Lag time can be controlled, primarily by changing the thickness of the outer polymer shell. Marvola and Sirkiä (1995) have developed a press-coated tablet formulation. Most of the total amount of drug is in the tablet core. Hydrophilic polymers such as hydroxypropylmethylcellulose and sodium alginates have been used in the coat to control drug release. The extent of bioavailability of furosemide, ibuprofen and salbutamol sulphate from the system developed have been found to be satisfactory (Sirkiä et al. 1992, 1994a, b, c).

Miscellaneous Systems

Elementary osmotic pumps can be useful for delivering drugs that need pattering based on chronotherapeutic requirements. One type of elementary osmotic pump can deliver salbutamol, initially at a constant delivery rate, then as a final pulse dose (Magruder et al. 1988). Such a system could deliver a dose during a nocturnal asthma attack. The first chronotherapeutic system for treatment for hypertension and angina pectoris, a controlled onset extended-release (COER-24) verapamil formulation has been developed and registered, e.g. in U.S.A (Cutler et al. 1995, Anwar and White 1998). This formulation has been tailored to the circadian rhythm of blood pressure and heart rate to better cover early morning symptoms of cardiovascular diseases. COER- 24 is osmotically controlled single unit system[14,15]

PULSINCAPÔ is a delivery system, which releases drug contents at a predetermined time or at a specific within the gastrointestinal tract (Junginger 1993,

Hedben et al. 1999). Each capsule is composed of a water insoluble body and a water-soluble cap. Capsule contains the drug dose and it is sealed with a hydrogel plug. At a predetermined time after ingestion the swollen plug is ejected from the capsule. Drug is then released into the small intestine or colon.

CONCLUSION

In order to achieve the development of chronopharmaceutical dosage forms, currently, the site specific and time controlled release preparation with a designated initial lag time phase without drug release followed by a rapid and sustained phase release system of the diseased condition is wide important phenomenon to consider. Drugs used for ideal treatment of disease should be administered only at the required time to maintain the therapeutic blood levels. Hence such a design can be used as a drug delivery system for chronopharmacotherapy. Success of the In vitro drug release studies recommends the product for further in vivo studies, which may improve patient compliance to the greater extent.

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