JChrDD | Vol 2 | Issue 1 | 2011: 23-29
ISSN: 2249-6785
Journal of Chronotherapy and Drug Delivery

Received: Mar 31, 2011
Accepted: May 6, 2011

Review

CHRONOPHARMACEUTICS: DOSAGE FORM DESIGN TO RHYTHMS IN DISEASE STATE

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Abstract

The term "chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time. There are various advantages of the Chronopharmaceutics are available which may includes decrease first pass metabolism, increase biological tolerance. Also there are various diseases in which chropharmaceutics are used which include cardiovascular diseases, anti-asthmatic disease, antiulcer diseases and very recently even antiglaucoma. There are various chronopharmaceutical delivery system are available which includes enteric coated drug delivery system, layered system, time-controlled explosion system, sigmoidal drug delivery system, press-coated system. The site specific drug delivery systems which include various patents which are available for the drug release at the site specific.

Key Words: Circadian rhythm, Chronopharmaceutics, Chronotherapeutics

Introduction

The term "chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time. Diseases, such as hypertension, asthma, peptic ulcer, arthritis, etc, follow the body's circadian rhythm.[2]This means that many diseases have rhythmic changes with time. Such disease includes osteoporosis, cardiovascular diseases and peptic ulcer. In osteoporosis which becomes sever during the day and most bothersome in the evening and in the rhythmic arthritis, peaks in the morning and decrease as day progresses.[1]

The goal in drug delivery research is to develop formulations to meet therapeutic needs relating to particular pathological conditions. Research in the chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy, and this has brought a new approach to the development of drug delivery systems. Most physiological, biochemical, and molecular processes in healthy organisms display robust, predictable changes on a 24-hour schedule. Chronotherapeutic products can synchronize drug delivery with circadian rhythms in order to optimize efficacy and/or minimize side-effects.[3]Also problem occurs with the diseases of heart such as cardiovascular diseases such hypertension and angina pectoris. By taking advantage of known biological patterns in disease manifestation, the goal of developing chronopharmaceutic products to optimize the desired effects of drug and minimize its undesired ones, can be obtained.

Advantages of chropharmaceutics [4]

Through chronopharmaceutics, appropriate delivery of drug can be achieved.

(1) *First pass metabolism*: Some drugs, such as beta blockers, and salicylamide, undergo extensive first pass metabolism and require fast

drug input to saturate metabolizing enzymes in order to minimize pre-systemic metabolism. This can be avoided be Chronopharmaceutics. For such drug Chronopharmaceutics is useful.

(2) *Biological tolerance*: Continuous release drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g., biological tolerance of transdermal nitroglycerin.

(3) *Special chronopharmacological needs*: It has been recognized that many symptoms and onset of disease occur during specific time periods of the 24 h day, e.g., asthma and angina pectoris attacks are most frequently in the morning hours.

(4) *Local therapeutic need*: For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects.

(5) *Gastric irritation or drug instability in gastric fluid*: For compounds with gastric irritation or chemical instability in gastric fluid, the use of a sustained release preparation may exacerbate gastric irritation and chemical instability in gastric fluid.

(6) *Drug absorption differences in various gastrointestinal segments*: In general, drug absorption is moderately slow in the stomach, rapid in the small intestine, and sharply declining in the large intestine. Compensation for changing absorption characteristics in the gastrointestinal tract may be important for some drugs.

Diseases in which Chronopharmaceutics used

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.[5]

Anti-inflammatory therapy

The non-steroidal anti-inflammatory agents (NSAIDs) such as ibuprofen may be more effective at relieving pain, if the drug is administered at least 4 to 6 h before the pain reaches its peak. It will be more helpful if arthritis patients take the NSAIDs before bed time if they experience a particularly high level of discomfort in the morning.[6]

Anti-asthma therapy

Symptoms of asthma occur 50 to 100 times more often at night than during the day.[7] Many circadian-dependent factors appear to contribute to the worsening of nocturnal asthmatic symptoms. The enhanced understanding of the chronobiological impact upon the pathology of asthma, and the pharmacology and pharmacokinetics of the drugs used in its management, have led to new approaches to disease management and enhanced patient care.

Cardiovascular therapy

The differences in patterns of illness between day and night for cardiovascular disorders such as hypertension, angina, heart attack, sudden cardiac death and stroke have been documented. Medications have been formulated, and dosing schedules established, in an attempt to provide appropriate concentration of a drug in the target area of the body when the drug is most needed.[8]

Anti-ulcer therapy

It is well established that patients with peptic ulcer disease often experience the greatest degree of pain near the time that they go to bed, as the rate of stomach acid secretion is highest at night. The timing of administration of ulcer medications has a significant impact on their therapeutic effect.

Chronotherapeutic drug delivery systems

Controlled release formulations can be divided into subgroups of rate-controlled release, delayed-release and pulsed-release formulations. When constant drug plasma levels need to be avoided, as in chronotherapy, time-controlled or pulsed-release formulations are preferable, especially in the treatment of early morning symptoms. By timing drug administration, plasma peak is obtained at an optimal time and the number of doses per day can be reduced. Saturable first-pass metabolism and tolerance development can also be avoided.[10]

Enteric-coated systems

Enteric coatings have traditionally been used to prevent the release of a drug in the stomach. Enteric coatings are pH sensitive and drug is released when pH is raised above 5 in the intestinal fluid. These formulations can be utilised in time-controlled drug administration when a lag time is needed, e.g., anti-

asthemic drug such as salbutanol used by this route. The system contains a core which is film coated with two polymers, first with HPMC and then with a gastro-resistant polymer (Eudragit® L30D).

Layered systems

These are one or two impermeable or semi permeable polymeric coatings (films or compressed) applied on both sides of the core.[11] To allow biphasic drug release, a three-layer tablet system was developed.[12] The two layers both contain a drug dose. The 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 may also incorporate a drug-free hydrophilic polymer barrier providing delayed (5 h) drug absorption. Conte *et al* has also studied a multi-layer tablet system (Geomatrix®).It consists of a hydrophilic matrix core containing the drug dose.

Time-controlled explosion systems (TES)

These have been developed for both single and multiple unit dosage forms.[13] In both cases, the core contains the drug, an inert osmotic agent and suitable disintegrants. Individual units can be coated with a protective layer and then with a semi permeable layer, which is the rate controlling membrane for the influx of water into the osmotic core. As water reaches the core, osmotic pressure is built up. The core ultimately explodes, with immediate release of the drug. The explosion of the formulation can also be achieved through the use of swelling agents. Lag time is controllable by varying the thickness of the outer polymer coating.

Sigmoidal release system

For the pellet-type multiple unit preparations, SRS containing an osmotically active organic acid have been coated with insoluble polymer to achieve different lag-times.[14] By applying different coating thicknesses, lag times *in vivo* of up to 5 h can be achieved. Release rates from SRS, beyond the lag time, has been found to be independent of coating thickness.

Press-coated systems

Delayed release and intermittent release formulations can be achieved by press-coating. Press-coating, also known as compression coating, is relatively simple and cheap, and may involve direct compression of both the core and the coat, obviating the need for a separate coating process and the use of coating solutions. Materials such as hydrophilic cellulose derivatives can be used and compression is easy on a laboratory scale.

Recent research in site specific chronotherapeutic system

The PULSINCAP dosage form releases its drug content at either a predetermined time or at a specific site (e.g., colon) in the gastrointestinal tract.[15]The drug formulation is contained within a water-insoluble capsule body and is sealed with a hydrogel plug. Upon oral administration, the capsule cap dissolves in the gastric juice and the hydrogel plug swells. At a controlled and predetermined time point, the swollen plug is ejected from the dosage form and the encapsulated drug is released. But in the majority cases, no measurable amount of drug observed in the blood due to instability of the drug in the intestine.[16]

US patent 7048945 explains a system flexible enough to form into timed controlled drug delivery system. The inventors prepared the active drug particle by coating drug on to sugar spheres or by granulation or extrusion-marumerization techniques and coated the drug particle with a plastisized enteric coating with polymers like cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), polyvinyl acetate phthalate (PVAP), pH-sensitive methacrylic acid-methamethacrylate copolymers, shellac etc., forming a plasticized enteric coated drug particle; and coating said plasticized enteric coated drug particle with a mixture of a water insoluble polymer such as ethyl cellulose (EC), polyvinyl acetate (PVA) and neutral copolymers based on ethyl acrylate and methylmethacrylate and an enteric polymer. The second and third operations can be interchanged and this feature affords flexibility in modulating the release profile from said drug particle. The researcher also added an alternative of applying an organic acid which is fumaric or succinic acid containing membrane between the second and third coating operations to further modulate the lag time and release profile from the drug particle. While the membranes can be applied in any order, the enteric polymer membrane is usually applied as the innermost membrane.[17]

US patent 5914134 describes pulsatile technology for diltiazem hydrochloride. This technology is based on drug layering of diltiazem hydrochloride in a suspension form on Nu Pareils (sugar spheres,

30/35 mesh). Thereafter, the drug layered pellets were precisely divided into three fractions for subsequent application of multiple membrane coats of quaternary polymethacrylate. Depending on the number of membrane coats applied, the delivery system was designed to deliver about 40% of the total dose in a pulsatile, site-specific manner, in the proximal segment of the small intestine and about 60% of the total dose in a Sigmoidal, site-specific manner in the distal segment of the small intestine and the large intestine. The films of quaternary polymethacrylate are not sufficiently flexible. Even with 10% plasticizer they showed some brittleness. Furthermore, a 20% plasticizer resulted in considerable increase in the elongation of break, whereas tensile strength at break was lowered. Therefore, the optimum film properties were found in between the two concentrations (10% and 20%) of the plasticizer.[18]

US patent 6217904 also describes in a similar way a pharmaceutical dosage form for pulsatile delivery of d-threo-methylphenidate and a CNS stimulant. The formulation included three fractions of beads; first fraction of beads being prepared by coating an inert support material such as lactose with the drug which provides the first (immediate release) pulse. A second fraction of beads was prepared by coating immediate release beads with an amount of enteric coating material sufficient to provide a drug release-free period of 3-5 h. A third fraction was prepared by coating immediate release beads having half the methylphenidate dose of the first fraction of beads with a greater amount of enteric coating material, sufficient to provide a drug release-free period / lag phase of 7-9 h and thereafter releasing the drug in the colon.[19]

US patent 5439689 discloses a once-a-day oral formulation of diltiazem hydrochloride having a stair stepped release profile Generated by two populations of diltiazem beads which released the drug at two different intervals of time, 3-9 h following lag times of 3 h and 15-21 h following a lag time of 15 h. [20]

US patent 5834023 (Andrx Pharmaceuticals Inc., Cooper City, US) described a once-a-day controlled release diltiazem formulation which includes 20 to 50% by weight of enteric polymeric membrane coated pellets comprising a polymer membrane coated core which comprises of a biologically inert core which is coated with a first layer which consists essentially of diltiazem and a polymeric binder; and a second layer which comprises a membrane comprising a pH dependent polymeric material. [21]

Patent CA2215378 assigned to Andrx Pharmaceuticals Inc., USA, describes unit dosage forms of diltiazem hydrochloride which comprise a two fraction system, enteric polymeric membrane coated pellets and delayed pulse polymeric membrane coated pellets.[22]

US patents 6605300 and 6322819, issued to Burnside et al., give method of preparing an oral pulse dose drug delivery system. The present invention comprised of a core or starting seed, either prepared or commercially available product. The methods of preparing the core given in the patent were extrusion-spheronization, high shear granulation or solution/suspension layering. The diameter of the core pellets was kept in the range of 100-800 μm. A protective coating layer (HEC, HPC, HPMC, PVP, PVA, EC and the like) was applied (2-4% coating level) immediately outside the core (drug-containing or drug-layered) by conventional coating techniques such as pan coating or fluid bed coating using solutions of polymers in water.

The enteric polymers used in this invention were modified by mixing with other known coating products that are not pH sensitive which included a water penetration barrier layer of a semi permeable polymer e.g. cellulose acetate butyrate, cellulose acetate propionate, EC, fatty acids and their esters, waxes, zein, and aqueous polymer dispersions such as Eudragit RS and RL 30D, Eudragit NE 30D, Aquacoat, Surelease, cellulose acetate latex etc. which were successively coated after the enteric coating to reduce the water penetration rate through the enteric coating layer and thus increasing the lag time of the drug release.[23]

Patent CA2305762 describes a targeted drug delivery system accompanied with burst release of drug after a well defined lag time to one or more specific location in the alimentary canal. The delivery system contained a core and a coating. The core contained a drug in combination with a carrier material (e.g., calcium pectinate, calcium alginate and pectin) which had the property of swelling upon in contact with an aqueous medium. Other important components of the core included a disintegrant (e.g., crosspovidone) and a hardness enhancer (e.g., microcrystalline cellulose). Due to the presence of disintegrant, the core had a

characteristic of disintegrating rapidly after the coating is broken. [24]

US patent 6200602 provides a drug delivery composition for colonic delivery comprising a polar drug, an absorption promoter comprising a mixture of a fatty acids and a dispersing agent. A particularly preferred mixture of fatty acids used was AKOLINE (available from Karlshamns, Sweden). Akoline is a mixture of mono-diglycerides of medium chain fatty acids. Dispersing agent functioned to position itself at the interphase between the formulation phase and the aqueous phase in the colon and thereby reducing the interfacial tension between the two phases and promote the dispersion of the formulation in the lumen of the colon. Dispersing agents included polyglycolyzed glycerides (eg., LABRASOL), polyoxyethylene sorbitan fatty acid esters, e.g., polyoxyethylene 20 sorbitan monolaurate (Tween 20), polyoxyethylene, etc. The ratio of the fatty acid to the dispersing agent was kept in the range of 1:3 to 3:1. The composition was formulated as a capsule formulation using hard or soft gelatin capsules or starch capsules, the polar drug being suspended in the dispersing agent-fatty acid mixture or the dispersing agent-di-triglyceride mixture or the dispersing agent-mono/diglyceride mixture. [25]

The patent US6555136 explains the use of hydrocolloid gums to be effective to provide for colonic delivery, e.g., guar gum, locust gum, bena gum, gum tragacanth, and karaya gum. Other materials suitable for effecting colonic drug delivery include polysaccharides, mucopolysaccharides, and related compounds, e.g., pectin, arabinogalactose, chitosan, chondroitin sulfate, dextran, galactomannan, and xylan. The invention is based on pharmaceutical dosage form for pulsatile delivery of methylphenidate and explains the use of three kinds of minitablets or bead or particle fractions in a capsule which have different drug and polymer coating levels out of which the third tablet or bead or particle fraction provides for release of the active agent in the colon, in which polymeric or other materials were used that enables drug release within the colon. [26]

Gazziranga et al. developed a site specific (colon targeted) pulsatile drug delivery system consisting of a drug containing core coated with different amounts of low viscosity grade HPMC, which maintained the lag time which was proportionally prolonged with increase in the HPMC amount. However higher amounts of HPMC coating resulted in slower release after the lag phase.[27]

Fan et al. designed a time dependent release tablet system, which avoided the release in stomach and released the drug in intestines after a predetermined lag time of 3 h. The system was made up of a core containing the drug and cross linked PVP as swelling layer and a coating of a mixture of ethyl cellulose and Eudragit L. Eudragit L was used as an enteric coating as well as pore forming polymer which dissolved above pH 6. Ingress of water from the surrounding medium in to the system caused expansion of swelling agent which eventually led to burst and complete release of drug in one pulse.[28]

Sinha and Kumria did an *in vitro* evaluation of xanthan gum, guar gum, chitosan and eudragit E as binders for colon drug delivery out of which xanthan gum as a binder was regarded as best suited for time-controlled release systems for colon targeting which initially retards the drug release due to the lag time required for swelling and after swelling, a rapid drug release was obtained. Systems formulated using chitosan (3%) as binder seems to be highly site specific due to the release of majority of drug only upon the breakdown by the bacterial microflora of the colon.[29]

Marvola et al. investigated the possibility to delay the drug release in a new way, by preparing film coated matrix pellets using enteric polymers as both matrix binders and coating materials. [30]

Sangalli et al. performed *in vitro* and *in vivo* evaluation of Chronotropic™ System for time and site specific (colon targeted) drug delivery after a predetermined lag phase, the duration of which depended on the thickness of the polymer layers applied on the cores.[29] Both the pharmacokinetic and scintigraphic data pointed the capability of the system of releasing drugs in the GIT after a programmed lag and a colon-specific drug delivery to be attained in the case of gastro resistant systems.

Conclusion

Compared to conventional dosage forms, CDDS can easily mimic circadian rhythm of several diseases. The application of biological rhythm to pharmacotherapy may be correlated by the appropriate timing of dosing of these drug delivery systems to synchronize drug concentrations to rhythms in disease state. CDDS are now better understood for selected disease such as cancer,

peptic ulcer, sleep disorder, hypertension, glaucoma etc. CDDS appear to have choice of future as many pharmaceutical companies are developing such systems and already a number of chronotherapeutic products. Development of some more technologies for the large scale production and research at academia of chronotherapetuic systems needs to be initiated.

Declaration of Interest

It is hereby declared that this paper does not have any conflict of interest.

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