In the field of oral delivery, growing attention has lately been focused on the potential of systems able to release drugs after a programmable lag phase commencing at administration time, i.e. in a pulsatile mode. While triggered pulsatile release is started by different external stimuli, only inherent mechanisms operate to delay the onset of drug liberation from time-based devices regardless of environmental variables such as pH, ionic strength and temperature. Accordingly, time-controlled pulsatile release may also be referred to as delayed release.

The interest in pulsatile delivery has been developing in close connection with emerging chronotherapeutic views. In this respect, it is by now well established that the symptoms of many pathologies, as well as the pharmacokinetic and pharmacodynamic profiles of most drugs, are subject to circadian variation patterns. Hence, the possibility of accomplishing effective drug levels in accordance with the specific temporal requirements of an illness state holds considerable appeal in that it could improve the therapy outcome on one hand, while limiting the incidence of adverse reactions related to an unnecessarily prolonged patient exposure to the active molecule on the other.

As far as widespread chronic pathologies with mainly nocturnal or morning symptoms are concerned, such as cardiovascular disease (CVD), bronchial asthma and rheumatoid arthritis, remarkable efficacy, tolerability and compliance benefits could arise from modified release medications that, after bedtime administration, would allow the onset of therapeutic drug concentrations to coincide with the time at which disease manifestations are more likely to occur. In principle, pulsatile delivery performances appear especially appropriate to fulfill such a goal. Particular emphasis is laid on the potential advantages of a chronopharmacological approach to the management of systemic hypertension. In this specific case, evening-dosed formulations intended for delayed release would be expected to lower the risk of morning cardiovascular events without increasing that of nocturnal stroke and ischaemic optic neuropathy connected with an excessive hypotension condition possibly resulting from bedtime intake of conventional dosage forms.

In addition to being potentially suitable for chronotherapy, pulsatile release is also exploited to target proximal as well as distal colonic regions via the oral route. Colon delivery is being extensively investigated as it may yield improved topical inflammatory bowel disease (IBD) treatments and is even suggested as one means of enhancing the poor oral bioavailability of peptides, proteins, oligonucleotides and nucleic acids. For the purpose of time-controlled colon targeting, delayed-release systems have to be presented in an enteric-coated configuration so that the high intra- and inter-subject variability in gastric residence may be overcome, and provide, following stomach emptying, a lag phase roughly corresponding to fairly reproducible small intestinal transit time (a mean ± standard deviation of three ± one hour).

Based on the relevance of potential therapeutic applications, a variety of design strategies have been attempted in pursuit of pulsatile release. Overall, delayed delivery systems are categorized into reservoir, capsular and osmotic devices. Reservoirs constitute the largest and most diversified group of formulations. These may be proposed in single or multiple units and, according to their functional coating characteristics, be differentiated as rupturable, erodible or increasingly permeable systems. Rupturable reservoirs are subject to a volume increase resulting from water uptake through a moderately permeable membrane, generally composed of ethylcellulose (EC) blends with plasticizing and pore-forming auxiliary substances applied by spray-coating technique. When the consequent rise in internal pressure is sufficient to cause disruption of the release-controlling membrane, the core contents are exposed to the external fluids and a fast delivery (in principle) of the drug can take place. The influx of water is driven by osmotic and/or highly swellable excipients, such as sodium croscarmellose and low-substituted hydroxypropylcellulose (L-HPC). An early example of rupturable device is the pulsatile release tablet (PRT), comprising a calcium carboxymethylcellulose-containing core and an outer...
double-compression coating based on co-melted hydrogenated castor oil and polyethylene glycol (PEG) 6000 mixtures. Further rupturable systems reported in the literature are those presented in the form of gelatin capsule or tablet cores provided with an inner sodium croscarmellose and an external EC layer; the swelling controlled release system (SCRS) consisting of an EC-coated tablet incorporating polyvinyl alcohol as the swelling agent; and, finally, a device in which EC is mixed with the enteric acrylic resin Eudragit™ L to form the tablet coating and cross-linked polyvinylpyrrolidone is used as the superdisintegrant. The performance of the latter system has been explored in volunteers versus an immediate-release dosage form. The appearance of a detectable drug amount in the plasma was clearly delayed by the device, whereas neither the area under the concentration/time curve (AUC) nor the peak concentration (C_max) turned out modified. Moreover, rupturable multiple-unit formulations have also been described. In particular, the time-controlled explosion system (TES) is based on inert sucrose seeds covered by overlapping drug, L-HPC and EC layers, respectively. A human bioavailability study has pointed out consistency of in vitro release and in vivo absorption data. Another multiple-unit device has been obtained from pellets provided with a sodium chloride osmotic charge and externally coated by a semipermeable cellulose acetate film. Alternatively, the core expansion responsible for break-up of the release-controlling membrane has been accomplished by carbon dioxide development following water dissolution of effervescent additives contained within a tablet core.

Reservoir systems based on erodible coating layers are mainly prepared with swellable hydrophilic polymeric materials, such as hydroxypropyl methylcellulose (HPMC), hydroxyethylcellulose (HEC) and hydroxypropylcellulose (HPC), which ensure consolidated safety profiles, ease of handling and availability in several grades. Upon contact with aqueous media, such polymers typically undergo combined swelling, dissolution and mechanical erosion phenomena, which contribute to delay the onset of release. Hydrophilic swellable coating agents are applied by press-coating or, more innovatively, through spray-coating and powder-layering techniques. The earliest pulsatile delivery system based on swelling/erosion processes is a three-layer tablet, within which two different drug compartments are separated by an intermediate HPMC barrier. The whole external surface of the bottom drug compartment and of the HPMC barrier is covered by an impermeable film, whereas the free surface of the top layer is allowed to interact with the bulk fluid. Double-peak plasma concentration curves of the model drug ibuprofen have been achieved, and the lag phase prior to the latter peak has turned out programmable by varying the overall viscosity of the intermediate HPMC barrier. The Chronotopic™ system, consisting of a drug core and an HPMC coating, has subsequently been proposed. In the course of development of this technology, the release-controlling layer has been obtained by different techniques, such as press-coating, soon abandoned because of the operational and versatility constraints involved; hydro-alcoholic spray-coating, which has been ceased, despite process and performance advantages, due to well-known organic-solvent-related issues; and, finally, aqueous spray-coating, which has been shown to afford the best balance among a number of key items. Systems prepared by low-viscosity HPMC aqueous spray-coating have yielded, in healthy volunteers, concentration profiles characterised by a lag phase dependent on the coating polymer amount, followed by a fast rise in the drug levels. Notably, an agreement between in vitro and in vivo lag times has been found. Such pharmacokinetic results have been supported by γ-scintigraphic studies as well. Furthermore, the Chronotopic™ system has also been attained from gelatin capsule cores suitable for conveying dispersed and multiparticulate formulations, which are described as potentially beneficial to the oral bioavailability of peptides and proteins. More recently, the use of novel techniques, such as tangential spray-coating in rotary fluid bed and powder-layering, is being explored to improve the scalability of this delivery platform by reducing the time and enhancing the yield of the relevant coating process.

Combinations of high- and low-viscosity HPMC grades have been employed for the preparation of a different press-coated reservoir system. When increasing the low-viscosity HPMC percentage, shorter lag phases and a faster absorption have been observed. Moreover, double-peak concentration curves have been achieved when splitting the drug dose between the core and coating formulations. In addition to HPMC, HEC and HPC have also been utilised as the release-controlling polymers for press-coated erodible systems. Even in those cases, in vitro and in vivo lag times have been proven to lengthen as a function of the amount and viscosity grade of the employed polymer. Differently, the erodible layer of the Time Clock® system has been prepared with hydrophobic blends of natural waxes and surfactants applied onto tablet cores by spray-coating in water dispersion at rather elevated temperatures. In this instance, the delay in drug release is accomplished by dispersion of the hydrophobic coating materials into the aqueous fluids. In vivo pharmacokinetic and γ-scintigraphic investigations have pointed out reproducible lag times regardless of food intake. ■

This article is continued, with full references, in the Reference Section on the website supporting this briefing (www.touchbriefings.com).