Right on Time

Time-delayed, controlled-release formulation can be a powerful tool in the treatment of conditions that display circadian patterns, but often presents some technical challenges.

Many of the formulation concepts in time-delayed, controlled-release formulation development have been driven by our increased understanding of the importance of chronobiology and its role in human disease.

The circadian rhythm is a daily cycle that regulates physiological processes, and disruptions in circadian homeostasis can have a pronounced impact on physiological functioning and disease susceptibility (1). Many diseases – including asthma, hypercholesterolemia and cardiovascular disorders – have been shown to demonstrate a circadian pattern.

Further, there is an expanding body of evidence concerning the relationship between circadian rhythms and the responsiveness of the body to drugs. As a direct consequence of this relationship, the absorption, distribution, metabolism and elimination of a drug and its subsequent therapeutic efficacy and/or toxicity can vary considerably with the circadian cycle (2).

Temporal control of drug release may offer particular advantages in the treatment of diseases that demonstrate a circadian pattern. In addition, the development of delayed-release formulations that deliver drugs at optimal times can enhance therapeutic effects while potentially reducing required doses. This is particularly beneficial for drugs with a narrow therapeutic window.

Although there are clear therapeutic benefits to time-delayed drug delivery, the associated technical challenges are considerable:

- The system must be robust enough to perform independently of the widely variable conditions (pH, agitation and availability of water) found at different points within the gastrointestinal (GI) tract.
- The influences of various environmental factors such as stomach content or alcohol need to be understood.
- There should be no leakage of drug before the targeted delivery time.

Although a number of time-delayed delivery systems have been reported, their design has typically fallen into one of three main release-controlling mechanisms: osmotic control, coatings or plugs.

### Osmotic Control

Osmotic drug delivery systems use osmotic pressure to control drug release. They are chiefly applied to drugs with low solubility and those requiring pulsatile release, allowing targeted and sustained release, unaffected by the physiology of the GI tract. The release rate is affected by solubility; thus, it may be unsuitable for sustained release of highly soluble drugs.

The most widely cited commercial example of osmotic-controlled drug delivery is Covera HS®, which provides controlled onset release of verapamil. This formulation was designed to be taken at bedtime by hypertensive patients, enabling a four- to five-hour delay before the release of its active ingredient, which targets the known early morning rise in blood pressure and heart rate.

Covera HS utilises OROS® technology, comprising a swellable osmotic 'push' layer situated below a drug-containing layer. The bilayer tablet is then surrounded by a hydrophilic barrier coating and an outer, semi-permeable membrane. As fluid slowly penetrates the system through the outer rate-controlling layers, the osmotic component swells, forcing out the drug through a precision laser-drilled orifice. OROS technology was modified by the addition of a hydrophilic polymer layer, which causes a delay prior to fluid reaching the swellable osmotic 'push' layer.

### Coatings

Coatings of varying compositions can surround either single- or multiple-unit solid drug-containing cores to control the onset of drug release. The level of coating used determines the lag time in these devices, while the coating agent(s) selected determine the mechanism of release with erodible, rupturable...
or diffusive systems predominating. These are discussed further below.

**Erodible Systems**

Erodible systems generally comprise an erodible barrier layer surrounding a core tablet that contains the drug. The controlled erosion of the coating delays the core tablet’s exposure to the surrounding media, ultimately enabling release of the drug contained in the core.

The Time-Clock® system described by Pozzi et al is an example of this approach, where an outer layer composed of a mixture of hydrophobic and surfactant components provides an erodible barrier, preventing drug release from the core tablet for a period of time which can be controlled by its thickness (3).

A further example of erodible systems is a time-delayed controlled-onset technology developed at Drug Delivery International. This system is tunable to achieve a range of different controlled-onset release profiles, tailored to a particular therapeutic strategy (4). The time of drug release onset can be further influenced by the nature and ratio of hydrophilic/hydrophobic materials in the coating, and the thickness of this layer. The multi-component structure of this formulation offers the potential to manipulate the drug dissolution profile through modulation of the release behaviour from the core tablet (see Figure 1). Crucially, this formulation has been shown to be independent of pH, agitation and fat content *in vitro* (5).

**Rupturable Systems**

In a rupturable system, the drug is protected by a delay layer. On exposure to gastric fluids, this layer controls the rate of fluid ingress through the barrier coating until subsequent swelling of the core mechanically weakens the barrier, allowing rupture and delayed release of core contents.

The use of swell-rupture mechanisms for time-delayed controlled delivery has also been pursued by Liu et al, who have designed a multi-unit tablet for chronotherapeutic applications (6). The technology has an inner core tablet containing drug-loaded, sustained-release pellets. The pellets are formed by traditional spray-coating processes to provide a sustained release. The core tablet is firstly coated with an Opadry isolation layer, then a swelling coating layer of HPMC E5, and finally a rupturable coating layer of Surelease®. As fluid enters across the Surelease film coat, the middle coating layer expands and eventually ruptures the outer layer, allowing further ingress of fluid and disintegration of the inner tablet core with liberation of the sustained pellets. Using this approach, a lag time of four hours has been reported, followed by four hours of sustained isosorbide mononitrate release.

SkyePharma’s Geoclock™ is one such system where the formulation consists of a drug-containing core surrounded by a controllable delay layer – in this case composed of hydrophobic wax and brittle material (6). This formulation has achieved clinical success in the CAPRA-2 study (7), and a formulation developed in conjunction with Horizon Inc has recently been approved in the US for delivery of low dose prednisolone for chronotherapeutic treatment of early morning pain and stiffness in rheumatoid arthritis, under the proprietary name Rayos® (previously available as Lodotra® in Europe).

**Diffusive Systems**

Diffusive systems rely on the application of one or more polymeric film coats to provide
diffusion-controlled drug release. However, performance of the resultant system is heavily dependent upon reproducibility of film coat quality, and inter- and intra-gastric variation can also impact upon release behaviour.

Chronotherapeutic Oral Drug Absorption System (CODAS®) technology consists of drug-containing pellets which are coated with a combination of water-soluble and -insoluble polymers. On exposure to fluid, the soluble polymer gradually dissolves away, leaving pores in the remaining water-insoluble polymer through which the drug can diffuse, controlling the time and rate of release. It is currently used commercially in products such as Verelan PM (Schwartz/Elan), which is taken at bedtime to deliver verapamil at around four to five hours post-dose (8).

Diffucaps®, marketed by Aptalis, are beads composed of a drug layered onto an inert core, further surrounded by one or more layers of release-controlling polymer. This technology has been used to develop Innopran XL®, which delivers propranolol in a capsule to be taken at bedtime. It produces maximum plasma concentrations prior to waking by means of a four-hour delay before releasing the drug.

**Plugs**

These delivery systems rely upon the ejection of a ‘plug’ from the device to provide time-delayed drug release. The plug acts as a seal to separate an impermeable chamber – which contains the drug – from the GI environment. The composition of the plug and its placement in the chamber are critical to the resulting performance of the system, entailing a high pharmaceutical and engineering design burden.

The Egalet® device provides an alternative means of delivering controlled onset of drug release, and variations on the basic design are currently at multiple stages of development. The device consists of a non-permeable, injection-moulded polymer outer case, which forms an elliptical cylinder with openings at either end. As the surface area for erosion of excipients from these openings remains constant, the drug and excipients can then be layered and arranged within the impermeable shell to control the time and rate of drug release. This technology has been demonstrated in vivo (9).

**Summary**

Time-delayed, controlled-release drug delivery devices can be readily manufactured using conventional pharmaceutical processing equipment. With skilful identification of excipients and construction of the devices, these systems will undoubtedly prove to have powerful therapeutic applications in disease states where there is a strong chronobiological component that is poorly addressed using pre-existing technologies.

References