There are many benefits offered by controlled drug delivery systems. For example, sustained-release technologies allow prolonged delivery of a therapeutic dose, thus reducing the number of times that a patient needs to take their medication while maintaining a steady state of drug in the bloodstream, and time-delayed release introduces a lag time before dose release, providing pulsatile delivery of drug to specific sites, such as the colon, or at a specific time.

Temporal control of drug release has particular advantages in the treatment of disorders that demonstrate a circadian pattern, such as cardiovascular disorders, asthma, anxiety and hypercholesterolemia. In such cases, the development of controlled-release formulations that deliver the payload at an optimal time can greatly enhance the therapeutic effects of the drug and reduce the dose required. This is particularly beneficial for drugs with a narrow therapeutic window.

Further, there is an expanding body of evidence concerning the relationship between circadian rhythms and the responsiveness of the body to drugs. As a 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.

Drug Delivery International (DDi) is a start-up formulation development company that specialises in providing solutions for “difficult” formulations, such as those for drugs with poor solubility, poor bioavailability or other properties that prevent APIs from reaching the market or achieving their full therapeutic potential.

DDi has an expanding intellectual property portfolio, providing licensing or collaborative research opportunities in controlled release and chronopharmaceutics.

DDi has developed a series of novel delivery systems, based on compressed tablet technology, that can be readily configured to provide immediate, biphasic (two pulses of drug(s) separated by a defined delay) or time-delayed sustained release patterns of one or more drugs for a wide range of medical applications.

Drug Delivery International Ltd has developed oral drug delivery preparations that provide a range of drug-release profiles that can be developed for single- or multiple-drug delivery. The profiles can combine separate pulse releases, or an initial release combined with delayed, sustained release.

Here, Carol Thomson, PhD, Chief Operating Officer, Drug Delivery International, explains how the preparations’ behaviour in man has been demonstrated using the nuclear imaging technique, gamma scintigraphy. Dr Thomson outlines how potential applications in sleep maintenance, pain management and cardiovascular disease have been demonstrated in this way, although the formulations are not limited to these therapeutic areas; indeed, they could be applied to a broad range of drugs and disease groups.

“THE ABSORPTION, DISTRIBUTION, METABOLISM AND ELIMINATION OF A DRUG AND ITS SUBSEQUENT THERAPEUTIC EFFICACY AND/OR TOXICITY CAN VARY CONSIDERABLY WITH THE CIRCADIAN CYCLE.”

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technology is unique and distinct from other delivery technologies in the marketplace and offers the following advantages:

• Widespread applicability to different drugs and dosages
• High degree of flexibility in manipulating drug release profiles
• Simple assembly and production processes
• Formulations are not pH-sensitive.

These formulations have been developed for three therapeutic areas: sleep maintenance; cardiovascular disease; and pain management. Formulations have been clinically evaluated using the non-invasive imaging technique of gamma scintigraphy to visualise the release of the drug.

The gamma scintigraphy work was carried out by Bio-Images Research Ltd (Glasgow, UK), a complete clinical research services company which, with a high level of expertise in drug delivery systems, provides clients with early-stage guidance in the drug development process.

SLEEP MAINTENANCE

Sleep maintenance insomnia is characterised by frequent and prolonged nocturnal awakenings, typically in the second half of the night. It is a common problem which has increased incidence with age and detrimentally impacts on the quality of life of individuals. Difficulty in resuming sleep has been associated with reduced sleep quality, leading to anxiety, mood disorders and consequently daytime impairment. DDHi has developed a time-delayed hypnotic formulation that provides a two-hour-delayed release of zolpidem for the treatment of sleep maintenance insomnia. Gamma scintigraphy and pharmacokinetic analysis was used to monitor the in vivo performance of the formulation.

In vitro validation was carried out by standard dissolution studies. The mean time to onset of radiolabel release was 95 min (n=3) post-dose and the mean time to completion of radiolabel release was 171.7 ±15.3 min (n=3) post-dose (see Figure 1).

Clinical evaluation was carried out using gamma scintigraphy in six healthy male volunteers. The mean time to onset of radiolabel release was 98 ±10 min post-dose and the mean time to completion of radiolabel release was 153 ±8 min post-dose. This gave a mean time of 55 ±16 min for complete dispersion, from onset to completion.

These data correlate with the in vitro results and show the tablet’s barrier layer to prevent drug release successfully until close to the target time of two hours post dose. Onset of radiolabel release occurred in the stomach in five subjects and in the small intestine in the remaining subject. Complete release was noted in the stomach for four subjects and in the small intestine for two. Figure 1 shows scintigraphic images of key events in the GI transit of a tablet in Subject 001.

Almost immediately after radiolabel release was confirmed by scintigraphy, the subjects reported feeling drowsy and fell asleep. No clinically significant deviations from normal blood pressure and pulse ranges were noted. The formulated tablet proved successful in delivering the drug after a predicted time delay. The release parameters were comparable among the six subjects, indicating robustness of the formulation in providing accurate time-delayed release. The physiological effects of the sleep tablet coincided with the scintigraphic confirmation of release.

CARDIOVASCULAR

Hypertension has been shown to follow a circadian pattern. Specifically, both heart rate and blood pressure blood pressure peak early in the morning and in many people with hypertension there is a marked rise in blood pressure...
upon awakening called “the a.m. surge”. DDi has developed a formulation for the delivery of anti-hypertensive drugs in the middle of the night, prior to wake-up, when the risk of fatal heart attack is greatest.

The formulation provides a delayed release of verapamil. In vitro, around 20% of the drug is released 3-5 hours after administration, with the remainder of the drug being released in a sustained manner over the following 4-5 hours, thereby covering the pre-wake-up period of greatest cardiovascular risk. This ensures that peak plasma levels of verapamil are achieved during the night in a targeted manner consistent with the chronopharmacological nature of cardiovascular disease.

This formulation was validated clinically using gamma scintigraphic imaging in six healthy male volunteers, demonstrating delayed sustained release of verapamil in vivo (see Figure 3 on previous page).

**PAIN THERAPY**

People with rheumatoid arthritis suffer significant problems with pain and stiffness upon awakening, severely impacting on their normal daily functions. DDi has developed a formulation that provides an immediate night-time release of diclofenac, followed by a seven-hour delay before pulsatile release of a second dose of the drug. This formulation offers immediate pain relief at night time, allowing pain-free sleep, and subsequently provides delivery of pain-relief prior to waking. This will be particularly useful in the treatment of patients suffering from chronic pain that has a significant inflammatory component.

The formulation has been demonstrated in vitro to be highly reproducible. Further studies are being carried out to validate the formulation in vivo.

**COLON TARGETING**

Colon targeting is desirable for treatment of diseases specific to the large intestine. Two formulation strategies have previously been proposed for the delivery of drugs to the colon:

1. The use of pH-sensitive coatings that dissolve at specific pHs in the small intestine.
2. The use of microbial flora of the colon to selectively metabolise a portion of the coating.

Before employing such strategies it is important to consider the environment in the small intestine and colon in the disease state as the pH and microbial organisms may differ from that understood to be present in the healthy population.

**DDI COLON DELIVERY TECHNOLOGY**

DDi has developed patented technology for time-delayed formulations based on a detailed understanding of the erosion of dosage forms in the GI tract. The barrier layers developed by DDi operate independently of pH and are relatively unaffected by agitation conditions, leading to excellent in vitro/in vivo correlation of erosion performance. However, gastric residence is a very variable event in a population and depends significantly on the fed state of the subject. In the presence of food, gastric emptying is delayed. Since the dietary habit of patients is virtually uncontrollable, gastric emptying will be very variable in a patient population. This means that employing time-delay alone is not a useful technique for the delivery of drugs to the colon, since gastric residence will be variable and will result in delivery to a range of intestinal sites.

The addition of a gastroresistant coating to a DDi time-delay formulation successfully eliminates the variability of gastric emptying. The erosion of the time-delay layer only begins following dissolution of the gastroresistant coating, which can only occur in the higher pH environment in the small intestine, following gastric emptying. Since small intestine transit time is very reproducible, at around 3-4 hours, it follows that an enteric coated time-delayed dosage form with a time-delay of around three hours will successfully target the colon.

We have successfully used this strategy for the development of a range of colon-targeting versions of time-delayed dosage forms.

Drug Delivery International Ltd and Bio-Images Research Ltd are part of the Bio-Images Group – providing integrated pharmaceutical development solutions.

**REFERENCES**