MEDICATION ADHERENCE

It is estimated that 33-69% of all medication-related hospital admissions in the US are due to poor medication adherence, with a resultant cost of approximately US$100 billion a year.1-6 Taking medications exactly as prescribed and following appropriate lifestyle recommendations is highly beneficial and may reduce the impact of side effects.

Practitioners should always assess adherence to therapy and may improve adherence by emphasising the value of a patient’s regimen, making the regimen as simple as possible, and customising the regimen to the patient’s lifestyle.7 Simple dosing (one pill, once daily) can help maximise adherence, particularly when combined with reinforcing visits / messages from healthcare practitioners, despite the fact that 10-40% of patients on simple regimens continue to have imperfect dosing adherence.8,9

WHY AREN’T ONCE-DAILY ORAL DOSAGE FORMS AVAILABLE FOR ALL DRUGS?

As the orally administered pharmaceutical dosage form passes through the human gastrointestinal (GI) tract, drug should be released from the dosage form and be available in solution at or near the optimal site for drug absorption to occur.10-12 The rate at which the drug is released from a dosage form and goes into solution is important for the kinetics of drug absorption. The dosage form and hence the pharmaceutical ingredient (API) is subjected to varying pH levels during GI transit.13-16 Specifically, pH varies from a minimum of about 1.2 to a maximum of around 7.4 (stomach pH: 1.2-2.5, which increases to 3.5-6.1 upon consumption of food; bile pH: 7.0-7.4; pH 5.0-6.0 in small intestine; and pH: 6 to 7 in the large intestine).

GI fluid volume and agitation can vary significantly, which has substantial impact on drug dissolution and absorption.17 Moreover, transit time may vary significantly in individual parts of the GI tract, depending on individual size and prevailing local conditions.18 Truly once-daily dosage forms of many weakly basic drugs are not commercially available. Several attempts have been made in the past at developing once-daily delivery systems of weakly basic drugs, such as carvedilol, ondansetron, and dipyridamole, with limited success.19-22 This is largely because the absorption of a weakly basic drug is critically affected by its solubility and the required total daily dose. The ability to maintain these drugs in a soluble form as the drug passes through the GI tract throughout the day has been a substantial challenge for oral formulators.

SOLUBILITY ENHANCEMENT BY ORGANIC ACIDS

The solubility-enhancing property of organic acids23 is exploited during the manu-
facture of customised-release (CR) dosage forms using Diffucaps® technology. The potential for in situ formation of acid addition compounds is averted by using a sustained-release (SR) coating membrane between the inner organic acid layer and the weakly basic drug layer. The SR-coating membrane thus applied, precisely controls the release of the organic acid ensuring drug is not retained in the dosage form for lack of solubilising acid in the Diffucaps® formulation.

DIFFUCAPS® TECHNOLOGY

Diffucaps® technology in its simplistic form (see Schematic of the Time Pulsatile Release / Time Sustained Release (TPR/TSR) bead shown in Figure 1) involves the preparation of:

1) drug-containing cores by drug-layering on inert particles
2) customised release (CR) beads by coating immediate release (IR) particles with one or more functional dissolution rate controlling polymers or waxes
3) combining one or more functional polymer coated Diffucaps® bead populations into hard gelatin or hydroxypropyl methylcellulose (HPMC) capsules.

MECHANISM OF DRUG RELEASE FROM TPR/TSR BEADS

The water-insoluble and enteric polymers are dissolved in a common solvent mixture and the solution is sprayed onto drug particles. These two polymers may exist as molecularly dispersed or as molecular clusters in the lag-time coating membrane applied on the drug cores (Figure 1).

During dissolution testing in two-stage dissolution media (first two-hour dissolution testing in 700 mL of 0.1N HCl and thereafter testing in 900 mL of pH 6.8 buffer obtained by adding 200 mL pH modifier) or upon oral administration, water or body fluid is blocked from imbibing into the core as the polymeric system is impermeable in the acidic medium or gastric fluid. When the pH of the medium is changed to 6.8 or following exit from the stomach, the penetrating dissolution medium or intestinal fluid selectively dissolves the enteric polymer molecules or molecular clusters starting from the outermost membrane layer, thereby creating tortuous nanopore channels for dissolved drug to pass through. The tortuosity increases with increasing coating thickness and/or decreasing enteric polymer content, and consequently, the drug release from the TPR beads having no barrier coat becomes sustained with increasing thickness of the TPR coating.

DEVELOPMENT OF ONCE-DAILY DOSAGE FORMS OF WEAKLY BASIC DRUGS

Below is shown the method for the preparation of CR drug delivery systems comprising one or more IR, SR, TPR/TSR, Delayed-Release (DR) bead populations, themselves containing a weakly basic, nitrogen moiety-containing API such as ondansetron, carvedilol, dipyridamole, lamotrigine or iloperidone, which is moderately soluble at pH <4, but it is practically insoluble at a pH >6, and at least one pharmaceutically acceptable organic acid as a solubiliser (see the schematics of SR organic acid bead & TPR/TSR bead containing a weakly basic drug shown in Figure 2). The method comprises the following steps:

a) layering an organic acid on 25-30 mesh sugar spheres;
b) applying an SR coating on acid-layered beads with a water-insoluble polymer to control the rate of release of the acid;

Figure 1: Diffucaps®– Customised Drug Release Bead (A) soaked in pH 1.2 or resident in the stomach and (B) soaked in pH 6.8 or in transit in the intestinal tract.

Figure 2: Diffucaps®: Customised Drug Release Bead for pH-sensitive Drugs (e.g. Ondansetron HCl).
Radiotherapy-induced nausea and vomiting (RINV), chemotherapy-induced nausea and vomiting (CINV), and postoperative nausea and vomiting (PONV) remain the most common and distressing challenges facing patients receiving these cancer therapies or following surgical procedures under general anaesthesia (occurring in up to 80% of cases).25-33

Nausea and vomiting very often occur together but can also occur independently. RINV and CINV during cancer therapy can have a direct and significant impact on adherence to primary therapy. Some of the most highly prescribed anti-emetics suffer from a short-half life requiring multiple daily doses for control of emesis. Between doses, the plasma levels of the anti-emetic can drop well below efficacious levels increasing the risk for breakthrough nausea and vomiting, particularly when subsequent doses are not taken exactly as scheduled. Proper control of acute and breakthrough nausea and vomiting therefore can be achieved with a higher probability and a higher level of confidence with a customised-release (CR) dosage form for oral administration, preferably administered prior to the procedure.

Weakly basic ondansetron HCl dihydrate

Ondansetron HCl dihydrate, the API in the branded product, *Zofran*® Tablets (4 and 8 mg base equivalent) and *Zofran*® Oral Solution, marketed by GlaxoSmithKline, is a selective serotonin 5-HT3 blocking agent (an antiemetic). The API in *Zofran*® ODTs (orally disintegrating tablets, 4 and 8 mg) is ondansetron base. All products are immediate release (IR) formulations. Ondansetron is indicated for the prevention of nausea and vomiting associated with radiotherapy (adults: 8 mg bid) and/or chemotherapy (adults: 8 mg bid to tid) and prevention of postoperative nausea and/or vomiting (adults: 8 mg bid).

Ondansetron is a weakly basic drug having a pKa of 7.4 and an elimination half-life averaging approximately 3.8±1 hours. It is practically insoluble in the pH environment of the intestinal tract. However, there is a dramatic increase in solubility in aqueous organic acid solution, making it a good candidate for developing once-daily dosage forms based on the organic acid approach of *Diffucaps*® technology.

**Modified release (MR), once-daily dosage forms of ondansetron HCl dihydrate using *Diffucaps*® technology**

Pharmacokinetic/biopharmaceutical modeling and simulation of possible plasma profiles based on available pharmacokinetic data as a guide in the design of customised-release (CR) dosage forms in order to be suitable for a once-daily dosing regimen is typically performed using *WinNonlin*® and/or *GastroPlus*™ computer simulation and modeling techniques. The CR capsule product was designed to comprise appropriate amounts of both IR and TPR components wherein the TPR component used SR-coated organic acid beads as inert cores to design multiple TPR bead populations with different lag times.33 The use of such methods resulted in reduced feasibility development time and enhanced the probability of success of the program.

For the IR component of the formulation, rapid release (RR) granules comprising ondansetron, mannitol, and organic acid were developed, which are designed to release the drug faster than, or similar to, *Zofran*® IR tablets even under alkaline pH conditions.33 Ondansetron HCl CR capsules were designed to comprise appropriate amounts of both RR granules and TPR beads. Three CR formulations were prepared for pharmacokinetic (PK) testing in healthy volunteers.33

A randomised, four-way crossover pilot PK study was conducted that included 12 healthy male volunteers, aged 18-55 years, with a washout period of seven days. Each volunteer was dosed with one of three test formulations of Ondansetron MR at 0800h, or two *Zofran*® (8 mg) at 0800h and 1630h after an overnight fast. Figure 3 shows the mean plasma concentration-time profiles achieved. The relative bioavailability compared with 8 mg IR bid reference was approximately 0.85 for all test formulations (Test Formula 1, 2, and 3) at the end of 24 hours.

Based on these results, Test Formula 3, given the product code EUR1025, was advanced into pivotal PK studies which have been completed.34 In these trials, single and repeated oral administrations of 24 mg EUR1025 resulted in similar rate and extent of exposure as 8 mg *Zofran*® tid. Steady-state concentrations of Treatment 2 (8 mg *Zofran*® bid) and Treatment 3 (8 mg *Zofran*® tid) are equivalent to that of single administrations of two and three 8 mg *Zofran*, respectively.34 The total exposure of ondansetron (AUC0-24) from EUR1025 on day six was approximately 13% higher than that observed on day one, suggesting minor accumulation following repeated dosing.

Figure 3: Pilot PK Study - Ondansetron QD versus Ondansetron IR (*Zofran*®).

c) preparing IR beads by layering the weakly basic nitrogen moiety-containing API and applying a protective seal-coat with a water-soluble polymer;
d) preparing SR beads by applying a barrier (SR) coating of a water-insoluble polymer on the IR beads to sustain the drug release over several hours (if needed);
e) preparing TPR beads by applying a lag-time coating on IR beads or SR beads (called TSR beads) comprising water-insoluble and enterosoluble polymers for a weight gain sufficient to achieve a lag time (a time period of less than 10% drug release) of 2-6 hours followed by a sustained-release profile; and
f) filling into a capsule a mixture of IR beads and one or more TPR bead populations at appropriate amounts to achieve a target pharmacokinetics profile suitable for a once-daily dosing regimen.

The following examples demonstrate how Aptalis Pharmaceutical Technologies utilised the above process to formulate once-daily dosage forms of ondansetron and iloperidone.

**NAUSEA AND VOMITING FOLLOWING CHEMOTHERAPY, RADIATION THERAPY, OR SURGERY**

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The total exposure of Treatment 1 (24 mg EUR 1025) appears to be nearly equivalent to that of Treatment 3 (8 mg Zoferan® tid) at steady state. The product is now ready to enter Phase III clinical development.14

ILOPERIDONE TPR BEADS AND RELEASE PROFILES

The Diffucaps® organic acid approach used with ondansetron is applicable to any weakly basic drug, which is at least slightly soluble at a pH≤3, but is poorly soluble or practically insoluble above pH 6. Iloperidone, the API in Fanapt®, is a weakly basic, dopamine and serotonin receptor antagonist exhibiting antipsychotic activities. Iloperidone (12 mg) is dosed twice daily.

The incidence of adverse effects differs in patients treated with Fanapt® 20-24 mg/day were twice that occurring in patients treated with Fanapt® 10-16 mg/day indicating an MR, once-daily formulation may improve the side effect profiles. Initial studies indicate that by combining IR and TPR bead populations at appropriate quantities (as determined by simulation and modeling) to provide desired in vitro release profiles, it would be possible to achieve target plasma profiles suitable for a once-daily dosing regimen.

ADVANTAGES OF CR DIFFUCAPS® DRUG DELIVERY SYSTEMS

Controlled-release drug delivery systems consisting of coated multiparticulates, particularly based on Diffucaps® technology, which typically have a particle size in the range of 200-600 μm, exhibit characteristic target in vitro profiles, as well as target plasma concentration-time profiles to be suitable for a once-daily dosing regimen.

Multiparticulate drug delivery systems, such as Diffucaps®, offer the following advantages over conventional controlled-release monolithic dosage forms such as matrix or coated tablets including osmotic delivery systems:

• Dispersed along the GI Tract for more effective delivery
• Predictable and consistent GI transit time thereby minimising food effect
• Low probability of dose dumping
• Reduced inter- and intra-subjectvariability
• Easy adjustment of multiple dose strengths

In addition, the Diffucaps® technology offers incremental advantages:

• Easy adjustment of target plasma profiles including combining bead populations exhibiting differing release profiles
• Ability to create combination products of incompatible actives or actives requiring differing target plasma profiles
• Capability to create micro-environments:
  – Create a sustainable acidic pH micro-environment within coated bead to solubilise the weakly basic drug (which is practically insoluble at pH 6.0 or above) in order to extend its release into the GI tract
  – Create a sustainable alkaline pH micro-environment within coated bead to moderate the solubility of a weakly basic drug (which is extremely soluble in the entire physiologically relevant pH range of 1.0 to 8.0) to avoid dose dumping
• Improve patient adherence due to reduced frequency of dosing, ease of oral administration, reduction in incidence of adverse events, and/or improved safety profile
• Additional product patent protection

CONCLUSIONS

Adherence to oral medication regimens, and therefore effective therapy, is a common issue for patients across multiple indications. Although simple dosing regimens (one pill, once daily) as provided by extended release (ER) formulations for a number of products are available, there are still many drugs for which an ER, once-daily form has proven to be exceptionally challenging to develop. These challenging molecules frequently have water solubility issues which may also be complicated by limited molecule half-life.

The Diffucaps® technology is one approach that effectively overcomes such challenges, allowing for straightforward development of ER, once-daily formulations that help to improve adherence, which can result in improved efficacy and patient quality of life.

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