New Technology Combo Drives Once-Daily Drug Formulation

The use of a remote-controlled drug delivery capsule combined with gamma scintigraphy enables a drug to be assessed for development as a modified-release formulation.

By Dr Karen Jones at Pharmaceutical Profiles Ltd

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A once-a-day oral dose is widely considered to be the ideal strategy for the administration of drugs. This is the easiest and most convenient method for patients, thus maximising compliance. Clinicians have long believed that the best drug is the one the patient actually takes. Pharmaceutical companies understand that this simple regimen is needed to obtain sufficient market penetration and an acceptable return on investment.

This creates a drug discovery/development challenge, however, as achieving this once-a-day goal via a conventional, immediate release (IR) dosage form is unrealistic for many drugs. Instead, a modified release (MR) formulation must be developed – something that poses significant challenges to development scientists.

AN EARLY UNDERSTANDING

Knowing how a drug performs during its transit through the human gastrointestinal (GI) tract provides the key to understanding drug absorption and determining what is possible in terms of developing an oral formulation. The complex mix of physicochemical properties of a drug, its dosing regimen and formulation type, and the variation in physiology of the human GI tract mean that reaching this understanding can be far from straightforward (see Figure 1).

An added complicating factor is that a compound only resides in the stomach and upper intestines for a total of around five hours but commonly remains in the colonic region for 24 hours or more. Therefore, a drug needs to show adequate absorption from the colon if it is to have any potential as an MR formulation.

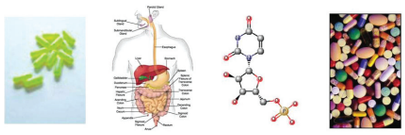
The complexity of bioavailability studies means that they are frequently delayed until a point when they can be avoided no longer. Establishing these basic facts early can save considerable time and resources later. Human regional absorption studies using a remote-controlled drug delivery capsule (Enterion™, Pharmaceutical Profiles) provide valuable insight into a drug's gastrointestinal absorption (see The Enterion™ capsule, see page 69). Study results reveal whether once-a-day dosing is ever achievable, and how optimal bioavailability can be attained by designing formulations and delivery technologies that target the right place in the GI tract.

THE RULE OF THUMB

At Pharmaceutical Profiles, we have performed more than 100 studies assessing the regional absorption of drugs delivered to specific sites via the Enterion capsule. The drugs have covered a range of development stages, mechanisms of action, target indications and physicochemical properties. The results of 37 such studies showing the measurement of relative bioavailability following colonic delivery are shown in Table 1.

To determine whether or not MR development was feasible, we developed a 'rule of thumb': if relative colonic bioavailability

Figure 1: Key drivers of oral bioavailability



Administration	Regional variation	Drug properties	Formulation
Fasted versus fed	pH	Solubility/dissolution	Particle size
Number of units	Fluid volume	Molecular size/shape	Excipients
	Surface area	Lipophilicity	Unit dose
	Gut wall enzymes	Ionisation	IR versus MR
	Transporters	Permeability	
	Transit time		

Table 1: Results of 37 human drug absorption studies using the Enterion capsule performed by Pharmaceutical Profiles

Relative colonic bioavailability	Impact on MR[1] dosage form development (the 'rule of thumb')	% compounds tested by PP within each category
<30%	Very difficult and probably impossible	38
30-60%	Challenging, but should be achievable	19
>60%	Straightforward MR development	43

[1] Assuming conventional sustained or extended release formulations

Table 2: Comparison of relative colonic bioavailability for NCEs versus marketed drugs

	% compounds tested at PP within each category	
Relative bioavailability following colonic delivery	NCE (n=17)	Marketed (n=19)
<30%	59	21
30-60%	6	32
>60%	35	47

were less than 30 per cent, MR development would be very difficult and probably impossible; 30-60 per cent relative bioavailability would make MR development challenging but it should be achievable; and if relative bioavailability is over 60 per cent, MR development should be more straightforward.

A GROWING PROBLEM

Half of the studies included in this analysis (19) involved the assessment of drugs on the market, with the remainder involving drugs still in development. The trend for these two sub-groups was similar to the combined data, with the majority of drugs exhibiting relative colonic bioavailability of 60 per cent or less. However, a very different split was observed within the 0-60 per cent relative bioavailability bracket (see Table 2).

These data support the concept that drug development is becoming more challenging as a result of the sub-optimal physicochemical properties of new drugs entering development. They also underline the need to proceed into formulation development with definitive information on bioavailability from the human GI tract.

NEXT STEPS

Having performed a feasibility assessment of a drug using the rule of thumb described above, a prototype MR formulation can be designed and produced. If the drug is well absorbed from the ileum and colon, then conventional sustained or extended release dosage forms can be developed. However, if the results identify an absorption window (for example, the drug is only absorbed from the jejunum) then this standard approach will not provide sustained systemic drug levels. Instead, a gastro-retentive dosage form should be developed to sustain delivery of drug to the upper intestine. Prototype formulations can then be assessed using *in vitro* methods.

Following this *in vitro* phase, the most important step is to test in the target population – man. Testing in animal models offers no benefit as gastrointestinal composition, permeability and transit times vary significantly between humans and animals.

If the excipients used in the prototype formulations are generally recognised as safe (GRAS-listed), then toxicity testing is not required and preclinical assessments are not necessary.

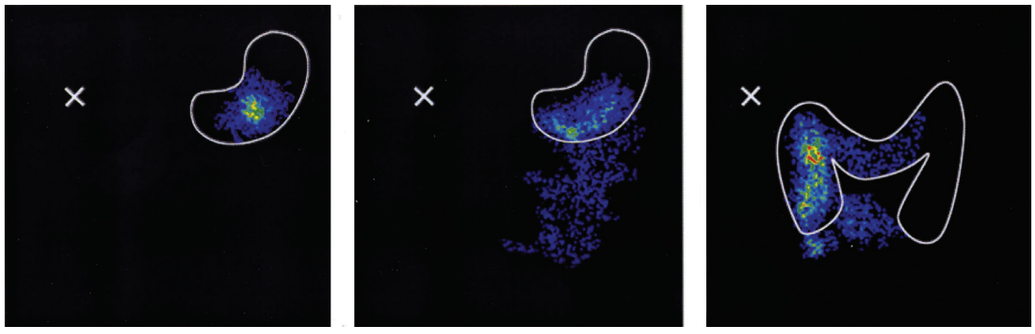
A COMBINED APPROACH

Instead of relying on pharmacokinetic (PK) data alone, it is better to combine it with the technique of gamma scintigraphy ('pharmacoscintigraphy') to assess the performance of the dosage form in man.

In these studies, the dosage form is radiolabelled and administered to volunteers or patients. Images are acquired using a gamma camera, permitting visualisation of the dosage form in the body in a non-invasive manner. The performance of the dosage form is tracked both qualitatively and quantitatively, and the resultant data provides detailed information on the time, GI location and rate of drug release.

Parallel assessment of the scintigraphic and PK data enables detailed understanding of performance. Gamma scintigraphy uses short half-life, gamma-emitting radionuclides as a marker for the performance of

Figure 2: Sample scintigraphic images



formulations. Commonly-used isotopes include technetium-99m (^{99m}Tc, half-life 6 hours), indium-111 (^{111}In, half-life 67 hours) and samarium-153 (153Sm, half-life 47 hours). The radionuclide is incorporated into the formulation, so that it acts as a marker for a particular event – usually release of the drug.

Following administration to healthy volunteers or patients, scintigraphic images are acquired at regular intervals. This is a non-invasive process and each image takes approximately 50 seconds to acquire. Images are acquired at 10-20 minute intervals resulting in a series of snapshots of the dosage form in the GI tract – an effect similar to time-lapse photography (see Figure 3). The scintigraphic images are interpreted by experienced data analysts to identify key events such as gastric emptying, colon arrival, initial release of drug and so on, and to quantify processes such as rate of tablet erosion.

A PRACTICAL EXAMPLE

A study was undertaken to establish whether a new anti-infective compound was amenable to MR formulation development. A formulation strategy was required that would overcome challenges associated with the compound, namely:

- Small molecule (MW ≈ 450)
- Excellent solubility
- Highly lipophilic
- Rapidly absorbed
- Short half-life
- Dose dependent
- Metabolised by CYP3A4

For this compound, a formulation that releases the drug in the colon was tested against an IR capsule. In addition to the potential for prolonged exposure in the colon, the level of CYP3A4 is reduced here, thereby helping to reduce any adverse effect on bioavailability due to gut wall metabolism.

Eight healthy volunteers received two administrations of the anti-infective compound, with a wash-out period of at least seven days between them. The reference formulation was an IR capsule administered after an overnight fast. The test formulation comprised the same dose, administered directly to the colon using the Enterion capsule.

The results showed an average relative bioavailability of 151 ± 68.6 per cent when delivered direct to the colon compared with the IR formulation (see Figure 3). The early peak in absorption seen with the IR formulation was absent and the absorption profile was prolonged when the drug was delivered to the colon.

The study suggests that MR formulation development would be possible for this compound, and that a formulation strategy that bypassed the upper GI tract and targeted drug release to the colon could enhance systemic exposure.

CONCLUSIONS

Technologies such as gamma scintigraphy combined with the Enterion capsule have proven pivotal in the development of oral modified-release formulations and for optimising oral drug bioavailability. Because they provide a straightforward and efficient way to understand human intestinal bioavailability with a wide range of different formulations, these studies can pinpoint the causes of poor bioavailability and show whether conventional modified-release formulation development will be feasible for the drug in question. Studies can be conducted with small amounts of material early in the development cycle.

This approach removes the need for parallel tracks of formulation development, shaving months off development time-lines. Importantly, those drugs that have poor biopharmaceutical properties can be identified and effort concentrated on others, with more favourable profiles.

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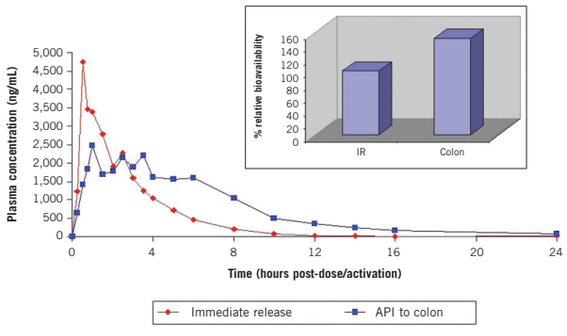
Figure 3: Enterion capsule delivery to colon increases oral bioavailability – pharmacokinetic data from IR (red) and colon delivery (blue) from one trial subject



The Enterion™ capsule

The capsule is a remote-controlled drug delivery device which delivers any form of a drug to targeted regions of the human GI tract. A gamma-emitting radionuclide sealed inside the tracer port of the capsule enables it to be tracked in real-time as it passes through the gut.

The volunteer takes a drink containing a second radionuclide which provides an outline of his/her stomach and colon. When the capsule has reached the target site, the volunteer stands inside an activation unit which sends an electromagnetic signal that triggers the instantaneous release of the capsule contents.

The plasma concentration data are then analysed to generate pharmacokinetic profiles and relative bioavailability.