

# Analysis of modified release products

A recent meeting in London provided an insight into the analysis of modified release products, including the use of dissolution testing and *in vitro*–*in vivo* correlations. Joseph Chamberlain reports

Vinod Shah, a consultant from the US, gave a thought-provoking presentation on the future of dissolution testing or, more accurately, drug-release testing. The dissolution test is well established, reliable and reproducible. It is used as a process control test and also to assess batch-to-batch quality. Increasingly *in vitro* dissolution testing is relied on to assure product performance.

For medicinal products having a systemic action, bioequivalence testing is usually based on a comparison of the plasma concentration profile of the medicinal product at issue with the profile obtained with the reference preparation. However, in some situations such a bioequivalence study may be replaced by *in vitro* dissolution testing. When such a substitution is allowed by registration authorities it is referred to as a biowaiver. Several regulatory guidances have been developed to provide biowaivers based on dissolution profile comparisons for lower strengths, for test product based on the biopharmaceutics classification system, and for certain scale-up and post-approval changes. Thus the dissolution test has brought about significant changes in regulatory perspectives.

The concept of dissolution — or *in vitro* release — can be easily extended to other dosage forms. Examples of these include *in vitro* release from semisolids and transdermal patches. Development of such performance tests for other dosage forms is under investigation. Dissolution testing remains essential, and its future is strong, asserted Dr Shah.

A working definition of *in vitro*–*in vivo* correlation (IVIVC) is that it is a predictive mathematical treatment describing the relationship between an *in vitro* property of a dosage form, such as the rate or extent of drug dissolution and a relevant *in vivo* response usually plasma drug concentrations or amount of drug absorbed. Harald Rettig, of Biovista, Switzerland, was a firm believer in such correlations, particularly for modified-release products. If successfully established, such correlations provide strong support for biowaivers, with considerable savings in time and costs.

A correlation can usually be expected when drug release from the product is the step governing the subsequent absorption step. Normally this is an essential design element for a modified-release dosage form. For

oral dosage forms the *in vitro* drug release is routinely measured and characterised as dissolution rate.

Some compound properties will prohibit the successful application of IVIVC, such as those with a narrow therapeutic window, those with a variable first-pass effect, endogenous compounds, prodrugs, or those with multiple response populations.

The relationship between the *in vitro* and *in vivo* characteristics is expressed by a linear or non-linear correlation. However, the plasma concentration profiles cannot be related directly to the *in vitro* release rate, and must be converted first to the underlying *in vivo* release or absorption profile, either by pharmacokinetic compartment model analysis or by a model independent treatment.

The IVIVC becomes more robust when two or more different formulations are tested in the same *in vivo* study. Also, the release-controlling excipient in the formulations should either be identical or very similar. The corresponding *in vitro* dissolution data can be obtained with different test conditions. The IVIVC with the best predictive power is then selected for further use.

## Modified release and PAT

Since the US Food and Drug Administration launched its process analytical technology (PAT) initiative in 2003 there has been an increase in activities to better understand pharmaceutical manufacturing processes. PAT has been successfully applied to blending and granulation processes although other parts of the manufacturing process, including the coating processes have received significantly less attention. However, said Alex Pysik, of Pfizer, Sandwich, Kent, it is widely recognised that coating processes are important and in order to achieve “quality by design” for these manufacturing steps it is necessary to identify and assess the key quality attributes and key process parameters. There are many assessment tools available and the outcome of such a risk assessment is used to decide on how to gain a better process understanding. This can be achieved in a variety of different ways, including the use or implementation of PAT technology.

Osmotic pump tablets and multiparticulates in capsules are common examples of modified-release drug delivery systems. Both of these dosage forms can incorporate functional and active coating components that are critical to product performance. Different approaches to monitoring the coating processes using near-infrared (NIR) spectroscopy have been tested and compared. Good correlations between NIR reflectance spectra and weight gain, coat thickness and drug release performance have been demonstrated.

Therefore, it has been shown that application of PAT provides significant benefit in enhancing monitoring, improving end-point determination and understanding of the associated coating processes. Furthermore, this can help understand and reduce intra-batch variability in product drug release performance and potency.

## The physiological environment

In an overview of gastrointestinal physiology, illustrated by the view of a camera-in-a-pill on its journey throughout the entire gastrointestinal tract, Abdul Basit, of the University of London School of Pharmacy, emphasised that the environment was wholly unlike the environment of medical devices being tested in dissolution testing. For example, the volume of fluid in the fasting stomach was approximately 45ml, a far cry from the litre volume specified in dissolution tests, and the buffering capacity of the intestinal fluids is relatively weak compared with phosphate buffers. The varying conditions *in vivo* mean a more acceptable way of assessing the behaviour of a dosage form is by direct observation *in situ*. Gamma-scintigraphy is a well established, non-invasive imaging technique for disease diagnosis in many areas and has been adapted for following the transit and transformation of orally administered medicines and devices. A radio-nuclide is incorporated into the formulation and a gamma camera used to track its location. Thus a liquid formulation can be seen to be relatively smoothly removed from the stomach compared with a pellet formulation.

The difference in performance (based on drug plasma concentrations) of an osmotic pump extended release tablet in two healthy volunteers could be dramatically demonstrated as due to different residence times at the main release site (the colon). Dr Basit used the example to point out that single component devices such as this were susceptible to catastrophic removal from the proposed absorption site, explaining the variability in performance.

Dr Basit concluded that pharmacokinetic assessment of modified-release formulations provides an incomplete and often misleading picture of gastrointestinal performance and the use of visualisation techniques, not just scintigraphy, can help to explain *in vivo* variability and aid formulation development.

# Characterisation and performance of parenterals

Brian Clark, of AstraZeneca Macclesfield Cheshire, described the characterisation and performance of parenterals based on poly-(lactide-co-glycolide), a polymer often used as a release-controlling excipient in sustained release parenterals for subcutaneous or intramuscular administration.

Duration of release is determined by several factors, including the characteristics of the active substance, drug loading, size, shape and morphology of the delivery system, polymer characteristics including molecular weight, lactide:glycolide ratio and other parameters, such as residual solvent levels.

Because the efficacy of the product is largely dependent upon the rate and extent of drug release *in vivo*, the development of an *in vitro* drug release test which is relevant to the physiological situation is important.

Based on an understanding of the factors that influence release, a factorial experimental design approach was used to maximise discrimination *in vitro* for batches known to perform differently in *in vivo* animal models.

This approach was used to establish an *in vivo-in vitro* relationship for an experimental microsphere formulation.

Parenteral preparations are often intended to release drug over a period of up to six months. It is therefore also desirable to develop a valid accelerated drug release test, particularly at the formulation design stage where the researcher needs to evaluate dose dumping, assess the duration of action, minimise the number of animals required, evaluate product stability, and establish the effect of changes in processing conditions.

Drug release can be accelerated by use of elevated temperature, extreme pH, reduction in ionic strength or the use of a catalyst to increase the rate of polymer degradation. Above all, however, the accelerated test must not distort the physiological environment. Although accelerated testing is feasible, it may be relatively insensitive to the morphological factors which mediate the initial "burst" release often observed with such formulations, concluded Mr Clark.

Jayne Lawrence, of King's College London, also tackled the problem of modified dosage forms for parenterals, concentrating on microemulsions and vesicles. Microemulsions are thermodynamically stable, transparent dispersions of oil and water, stabilised by a surfactant often in combination with a cosurfactant, such as butanol. Vesicles are spherical structures consisting of one or more bilayers entrapping a central aqueous core and with a layer of water trapped in each bilayer.

Both microemulsions and vesicles are used as vehicles for drug delivery, and a variety of physicochemical techniques have been applied to characterise them. This is necessary to understand their structure and their capabilities so as to aid in design of drug delivery systems. For example, phospholipid vesicles are rapidly removed from circulating blood by a process of opsonisation (coating with protein). To extend the plasma half-life of such vesicles, they can be coated with poly(oxyethylene) chains, said Professor Lawrence.

## Understanding the physical chemistry of modified-release systems

The properties of water-soluble polymers are of considerable importance in industrial and biotechnology processes, said Simon Ross-Murphy, of King's College London. Their dissolution — which may be defined as an increase in viscosity — is complex and depends on temperature, concentration, molecular weight and particle size.

Professor Ross-Murphy focused on investigations on the effect of particle size on the hydration rate of macromolecules over a wide range of particle sizes. The model system studied was guar gum, used in pharmaceuticals to control release in the gastrointestinal tract or as a bulk-forming laxative. Unsurprisingly, small particles are hydrated faster than large particles, as shown by simple plots of viscosity versus time. Attempts to establish a more precise relationship, however, proved problematic as larger particles take such a long time to achieve even 80 per cent of their final hydration level. Log-log plots did not seem to throw any further light until a shift factor was introduced for the time axis and superimposable curves were obtained. Although this shift factor is, at present, an arbitrary figure, its value (somewhat closer to 2 than 3) suggests it may be related to surface area, rather than volume. Establishing an accurate figure for the shift factor would allow prediction of hydration time for any other particle size of interest and the model allows some new physical insights to be developed. Further work is needed on different molecular weight

samples of controlled particle size, concluded Professor Ross-Murphy.

Temperature and pH-responsive polymers offer a number of important advantages for controlled release systems compared with conventional release systems, said Brian Saunders (School of Materials, University of Manchester). They have enabled new designs for temporal and distribution-controlled release devices. Microgel particles are crosslinked colloidal particles that swell under appropriate conditions. Poly(N-isopropylacrylamide) is a temperature-responsive polymer with a lower critical solution temperature of about 32°C in water, meaning that the microgel will swell and collapse, respectively, when the temperature is below and above this temperature. Poly(diethylaminoethyl methacrylate) is a pH-responsive polymer with a pKa of about 6.8. By combining either type with a poly(ethylene oxide) macromonomer it is straightforward to prepare a range of systems with varying characteristics. Architectural control during construction of the devices provides considerable flexibility in tailoring the release properties of delivery vehicles. Through strategic use of the polymers it is possible to design delivery systems that behave in different ways *in vivo* even though responsiveness originates from the same polymer. Model polymers demonstrate principles that also apply for biocompatible responsive copolymers, said Dr Saunders.

### Joint Pharmaceutical Analysis Group

The Joint Pharmaceutical Analysis Group is a focus for the presentation and discussion of matters of importance to those interested in pharmaceutical analysis. The remit of the group is "to encourage, assist and extend the knowledge and study of pharmaceutical analysis and quality control by the holding of scientific meetings, by the promotion of lectures, practical demonstrations and discussion, or by any means consistent with the aims and objects of the sponsoring bodies and the with the rules of the group".

The group normally holds scientific meetings in January, March (with the group's annual general meeting), May, October and December. The meetings are generally held on Thursdays at the Royal Pharmaceutical Society's headquarters in London. The group also encourages joint meetings with other organisations. In some years, one or more sessions are organised within the annual British Pharmaceutical Conference.

The group's sponsoring bodies are the Royal Pharmaceutical Society and the Royal Society of Chemistry. Membership of the group is open to member of either society and is free to members of the Royal Pharmaceutical Society.

Pharmacists wishing to join the group should apply in writing, giving their registration number, to the Secretariat, Joint Pharmaceutical Analysis Group, Room 403, Royal Pharmaceutical Society, 1 Lambeth High Street, London SE1 7JN. A programme of forthcoming meetings is available from the secretariat.