UKICRS JANUARY 2002 MEETING

ORAL ADMINISTRATION OF 'DIFFICULT' DRUGS

For several years, one of the principle activities of the UKICRS has been to organise a one-day meeting in January on a topic of current interest associated with drug delivery. This year the group, led by Dr Rupi Pannu and Dr Karen Lewis, organised a symposium on the perennial problem of oral drug delivery from molecules whereby effective absorption is a problem. We were fortunate in being able to bring together a highly renowned international group of speakers from both academia and industry, resulting in an oversubscription for attendance for the first time in the history of the organisation. The meeting was held at AstraZeneca R&D Charnwood on 17th January 2002, with final the delegate number being 140.

The meeting began with an overview from Professor Sandy Florence (School of Pharmacy, University of London) who began by defining 'difficult' drugs in terms of their intrinsic properties including lability, low aqueous solubility or low lipid solubility and hence poor permeability. The post-administration challenges were then outlined, including adsorption to gut contents, precipitation and mucus entrapment amongst others. Professor Florence discussed some of the approaches that are currently under investigation to overcome these difficulties. These approaches include the use of dosage forms such as microemulsions, nanoparticles and solubilisation techniques to overcome poor aqueous solubility. The subject of p-glycoprotein was also touched upon, outlined in greater detail later in the meeting. Focussing on some of the above approaches in more detail, Professor Florence suggested that the wide spread use of drug solubilization had been hampered by a lack of fundamental knowledge regarding the interrelationship between the chemistry of the drug, the delivery system used and the interaction with the site of absorption. Other related approaches that are currently emerging include the use of bilosomes, (bile-salt based vesicular systems) and dendrimers, while the use of self-assembling drugs such as certain peptides and proteins may present a new and exciting drug delivery opportunities whereby the protein or peptide can act as its own delivery vehicle. Professor Clive Wilson (University of Strathclyde) discussed the latest approaches to imaging drugs and dosage forms within the GI tract but began by suggesting that the drive towards the selection of increasingly high potency molecules, defined by the receptor-ligand interaction, has led to difficulties in terms of the delivery of molecules that are unable to easily overcome the natural barriers to drug absorption. Professor Wilson then gave an overview of the use of gastrointestinal imaging techniques in relation to drug delivery. For example he described the use of endoscopy to establish the role of folds within the GI tract in prolonging dosage form retention. Gamma scintigraphy allows a

Back row: Duncan Craig of Queen's University Belfast (Chairman UKICRS), John Hempenstall of GlaxoSmithKline, Hans Lennernas of Uppsala University.

Front row: Clive Wilson of Strathclyde University, Maurice Clancy of Elan Pharmaceuticals, Ali Rajabi-Siahboomi of Colorcon Pharmaceuticals, Christos Reppas from University of Athens, Paul Gellert from AstraZeneca, Sandy Florence from the London School of Pharmacy and Rupi Pannu from AstraZeneca (Secretary of UKICRS).

more sophisticated and compartmental analysis of the transport process, particularly allowing a greater understanding of the nature and importance of the residence time in each region of the tract. The use of gamma scintigraphy has facilitated the development of dosage forms such as floating systems whereby the residence time of the dosage form in the stomach could be modulated to the benefit of the patient. One of the disadvantages of gamma scintiigraphy is the requirement for radiolabelled markers. More recently, magnetic resonance imaging (MRI) has allowed the imaging of non-radiolabelled material within the GI tract and represents a useful furtherance of the field. An interesting issue that is rapidly becoming prominent is the study of the real-time dynamic movement of dosage forms within the gut over limited distances. As a consequence of these studies it is now believed that dosage forms may move via a series of discrete steps rather than as a continuous, steady passage as previously believed. This observation has implications both for the reliability of imaging methods, as a dosage form may have appeared to have broken up due to the apparent presence of several hot spots whereas in reality the multiple sites are due to the dosage for being visualised in several discrete locations due to the timeframe of the experiment. A further related consideration is the importance of mixing within the gut, an area in which not enough is yet known but which may have profound implications for our understanding of dosage form transit. Professor Wilson concluded his talk by suggesting that the next methodology to be explored for imaging purposes may be ultrasound, although research in this field is at a very preliminary stage. The issue of drug absorption was addressed in detail by Professor Hans Lennernas (University of Uppsala). After an introduction to the principles of the widely used biopharmaceutical classification scheme, Professor Lennernas described the use of the Loc-I-Gut instrument for perfusion experiments. This technique allows distinct sections of the gastrointestinal tract to be isolated by inflating selected regions of the device, thereby allowing study of the dissolution and absorption patterns of drugs in a location-specific manner. This methodology has led to a number of surprising insights, and in particular has highlighted significant discrepancies between in vitro and in vivo dissolution behaviour. These discrepancies include greater in vivo dissolution, as is found with carbamazepine due to its favourable permeability in the gut leading to near-sink conditions in the gastrointestinal lumen. The Loc-I-Gut approach also allows the study of the role of efflux transport proteins such as p-glycoprotein and has cast some important new considerations on the importance of these efflux systems in a practical setting. For example, verapamil, a high lipophilicity/high permeability drug that is both a substrate and inhibitor for p-glycoprotein is nevertheless rapidly absorbed due to the high gut permeability of this molecule and the rapid saturation of the efflux mechanism, despite the impression to the contrary being given by cell line studies. Similarly, fluvastatin is a substrate for efflux proteins and as a consequence shows variable transport across CaCo-2 cell lines in the presence of inhibitors but shows high absorption in a practical clinical setting. The key consideration for these drugs seems to be that their high gut permeability overrides the efflux process, hence the latter may not be as relevant in the clinical setting as cell line studies suggest. For drugs with lower gut permeability the absorption may be more strongly influenced by p-glycoprotein. However, the intestinal absorption of fexofenadine, a low permeability drug and proposed P-glycoprotein substrate, was not affected in the presence of PGP inhibitors such as ketoconazole and verapamil. Nevertheless, the process here is more complex than it may first appear. This therefore indicates that there may be other factors involved in determining absorption of these drugs other than those that are currently recognised. During his presentation Professor Lennernas outlined the current state of the field regarding the absorption of peptides, which is very much an emerging discipline in terms of understanding the fundamental science underpinning the absorption process.

The theme of peptide drugs was expanded on by Dr Maurice Clancy (Elan Pharmaceuticals), with the majority of these being administered via the parenteral route. There is therefore a clear opportunity for improving peptide formulation strategies to increase the percentage of peptides that may be successfully delivered via the oral route. Dr Clancy outlined some of the enzymatic processes associated with peptide and protein degradation and discussed the possible strategies that may be adopted to improve oral absorption. These include the presence of enzyme inhibitior or permeation enhancers in the formulation, the use of formulation of the peptide in an appropriate dosage form such as liposomes or microemulsions thereby protecting it from the contents of the gut. Other strategies include chemical modification via pegylation or the substitution of D amino acids for L amino acids. Dr Clancy then went on to describe some encouraging result to emerge from Elan's oral peptide programme, demonstrating that suitable formulation strategies can result in significantly enhanced peptide absorption. One of the primary tools we currently utilise for predicting bioavailability at an early stage is the use of dissolution tests. Professor

Christos Reppas (University of Athens) gave a comprehensive overview of the rationale and practicalities underpinning the use of dissolution testing as a means of mimicking in vivo conditions. There are numerous difficulties associated with both the methodologies employed and the assumptions utilized regarding the correlation between dissolution and absorption, the latter being reflected by the categorisation within the bioclassification system. In terms of the methodology used, Professor Reppas outlined the current thinking regarding the choice of dissolution media used to represent different regions of the gastrointestinal tract. Typically, the stomach in the fasted state is represented by a medium containing HCl, sodium dodecyl sulphate and sodium chloride in distilled water, possibly including pepsin, while the fed state may be represented by, for example, whole milk. There are issues associated with these strategies, not least of which being the inclusion of a surfactant that has limited biorelevance, although it was pointed out that dissolution in the stomach is often not a key issue for many drugs in any case. The upper small intestine may be represented by more complex systems including buffers, bile salts and lecithin and sodium hydroxide with equivalent compositions having been put forward to simulate the fed state (although these tend to neglect the important influence of food lipids). An alternative approach is to use human aspirates, although there are associated logistical issues with the quantity and ease of availability. In addition, the issue of gastrointestinal motility was raised, with in vitro tests having limited propensity to mimic this effect. Overall, however, when properly conducted in vitro tests may yield valuable insights into the prediction of the effects of formulation and food on the absorption of drugs and may also allow insights into the likely plasma profile of a new chemical entity.

Chairman Professor Sandy Lawrence presents poster winner Andrew Baldwin with his prize

Chairman Professor Sandy Lawrence presents poster winner John Murphy with his prize

In addition to understanding the absorption of difficult drugs, it is essential to have a range of formulation strategies available in order to enhance the bioavailability of such substances. The use of amorphous drugs in general and melt-extrusion technology was discussed by Dr John Hempenstall (GlaxoSmithKline). An overview was given of the use of amorphous materials within the pharmaceutical sciences, with the point being made that the amorphous state represents a promising means by which dissolution and hence possibly bioavailability may be enhanced. The discussion included the use of solid dispersions in amorphous polymeric carriers such as polyvinylpyrrolidone (PVP). While the approach may undoubtedly lead to enhancement of dissolution profiles, there are a number of issues associated with the preparation of such dispersions and their subsequent stability. One recent approach that has attracted considerable interest has been the development of melt-extrusion technologies, whereby the drug and carrier (in the cases presented PVP) are heated to a suitable softening point and extruded through a small orifice. The resulting extrudate hardens on cooling and may then be milled to produce a solid dispersion that may be subsequently tabletted or filled into capsules. The advantage of this method is that it removes the necessity of using solvents, a factor that has traditionally severely limited the use of PVP as a solid dispersion matrix. The use of oral controlled release systems were reviewed by Dr Ali Rajabi-Siahboomi (Colorcon). Several now-familiar known strategies have been employed in the development of these devices, including the use of matrices, ion exchange resins and osmotic pumps. More recently there has been a greater emphasis on developing novel strategies for defining specific release characteristics, using geometric design technology and material science in addition to utilising non-traditional materials to improve performance. Dr Rajabi-Siahboomi then went on to give a review of some of the methodologies that have been developed on the back of the traditional systems such as

hydrophilic matrices. Examples of these approaches include the Ringcap system, whereby an insoluble polymer band is wrapped around a hydrophilic matrix caplet, the release profile being determined by the thickness and geometry of the polymer band. Similarly the Smartrix system involves the use of geometrically defined release in that a multilayer tablet is prepared whereby a non-erodible matrix is coated with one or more erodible layers, the combination of these two regions resulting in zero order release. Other new developments include the Accudep system whereby precise quantities of drug are electrostatically deposited on to the surface of a polymeric film which may then be formed into a laminate and covered with a rate controlling membrane. Other well-known systems such as Geomatrix and Pulsincap technologies were also described. Dr Rajabi-Siahboomi concluded this talk by stating that at present the emphasis is on the design of new systems from existing materials rather than the development of novel polymers or controlled release molecules, a fact largely driven by regulatory considerations.The final presentation of the symposium was given by Dr Paul Gellert (AstraZeneca) who presented an industrial perspective of the issues associated with oral drug absorption. In particular Dr Gellert pointed out that 76% of the top 100 drugs are orally administered, hence the problem of difficult drugs is particularly commercially relevant. The speaker went on to give an industrial viewpoint regarding the use of the biopharmaceutics classification system but also outlined the development issues associated with bringing such molecules on to the market, including the need to develop a reliable "best assessment" of the possibilities for successful development at an early stage. Similarly, one needs to bear in mind the changes in the strategies used at the discovery stage, including the use of genomics and combinatorial chemistry. It was the view of the speaker that most drugs brought to initial development from these sources also tended to have extremely low aqueous solubilities, hence the difficulties are likely to remain or worsen in the future. There is a range of options available to overcome these problems, including chemical modification and a number of formulation strategies that may improve dissolution or absorption. Similarly, problems associated with metabolism or degradation in the GI tract can, once recognized, be overcome by the use of protective formulations or the addition of enzyme inhibitiors to the formulation. Problems in permeation may also be overcome by the use of penetration enhancers or efflux inhibitors. It is clear that with a with greater fundamental understanding of the problems of getting intact drug into the systemic circulation via the gastrointestinal tract a growing range of solutions are becoming available. Dr Gellert also touched on what is clearly becoming an increasing important issue, that of oral peptide delivery, and discussed some of the problems and strategies that may be used for this important class of molecule.

The chairman Professor Duncan Craig concluded by thanking the speakers for providing with audience with a highly stimulating and relevant series of presentations that were of clear interest to both academics and industrialists. Congratulations were also forwarded to the winners of the poster competition, namely John Murphy (Queen's University of Belfast) for his poster entitled "The use of micro-thermal analysis as a means of characterising particulate systems" and Andrew Baldwin (University of Nottingham) for his poster "Investigations into cationic liposome:DNA binding during lipoplex formation". Both winners receive £500 and free registration for the forthcoming CRS meeting in Seoul.

David Brayden
Duncan Craig