Drug delivery strategies for the new Millennium

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The annual meeting of the American Association of Pharmaceutical Scientists (AAPS) took place on 29 October–2 November 2000 in Indianapolis (IN, USA), with a theme of *Unmet medical needs: therapies for the new Millennium*. Symposia from invited speakers and contributed poster sessions covered the entire range of pharmaceutical activities from basic pharmaceutics through prediction of oral absorption to formulation studies, analytical development, *in vivo* pharmacokinetics and drug metabolism, regulatory issues and pharmacy practice. This overview highlights some of the work presented in the fields of oral delivery (both of proteins and of conventional molecules), the mechanics of formulations and gene therapy.

Oral drug delivery

Aqueous solubility and drug solubilization

William J. Curatolo (Pfizer, Groton, CT, USA) discussed the importance of solubility and permeability to identify lead drug candidates in terms of their effect on the oral bioavailability of drugs. The range for absorption rate constants for most molecules of pharmaceutical interest is ≈40-fold [through the gastrointestinal (GI) tract], whereas the range for the solubility of these same compounds is over one million-fold. Therefore, the recommended strategy during pharmaceutical development is to improve the solubility of the lead molecule even if the permeability of the molecule is compromised as a result.

Guidelines were also presented to assess the bioavailability and hence the commercial value of a chemical library. These guidelines were generated based on observations of chemical properties of currently approved drugs. Wei-Qin (Tony) Tong (GlaxoWellcome, Research Triangle, NC, USA) indicated that, as a result of combinatorial chemistry and high-throughput screening, there are many more hits and potential drug development candidates than ever before with a large reduction in the time it takes to screen potential candidates.

Another challenge is the difficulty of predicting crystalline energy in the solid-state because of the requirement for complex intermolecular modeling. If a potential drug candidate with high crystalline energy is identified, it is recommended that the crystal structure should be disrupted to increase the solubility of the compound. Michael Hageman (Pharmacia & Upjohn, Kalamazoo, MI, USA) presented a comprehensive overview of various strategies used to increase the solubility of poorly water-soluble drugs. The more common strategies using pH control and ionization, cosolvents, complexation, ion-pairing, prodrugs or the partitioning of lipophilic drugs into amphoteric or lipid-based systems, such as micelles, liposomes, microemulsions and emulsions, were discussed.

Prediction of oral bioavailability

The need to accurately predict oral bioavailability of potential candidate molecules is becoming increasingly important within the pharmaceutical industry. Carleton Sage (Trega Biosciences, San Diego, CA, USA) described the use of a neural-network system to investigate the relationships between various one-, two- or three-dimensional molecular descriptors and the effective permeability of over 200 molecules through CaCo-2 cells. With the models thus developed, they could predict the permeability of compounds not included in the initial data set to a reasonably high level of accuracy.

Increasing attention is being focused on the interactions between drugs and p-glycoprotein as a determinant of oral bioavailability and drug distribution. Chad Stoner and colleagues (Parke-Davis, Ann Arbor, MI, USA) have developed a high-throughput robotic screening method for assessing whether a drug is an inhibitor of p-glycoprotein. The effect of added test compound on the passage of tritiated vinblastine through CaCo-2 cells with functional p-glycoprotein expression can be determined, without the need to develop analytical methods for each test compound. Using cyclosporin A as a positive control, the inhibitory potency of the test compounds can be assessed. The authors claim that their system can process approximately 120 compounds a week (n = 3), which is a vast saving of time compared with conventional techniques.

Oral delivery of proteinaceous drugs

The oral delivery of proteinaceous drugs, such as insulin and heparin, is a holy grail within the pharmaceutical sciences. Catherina O'Shaughnessy (Emisphere

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Technologies, Tarrytown, NJ, USA) demonstrated that the presence of amidated acids could improve the CaCo-2 permeability of heparin and increase the absorption of the drug following colonic instillation in rats. Andrea Leone-Bay (Emisphere Technologies) and colleagues have performed a Phase I volunteer study on the effectiveness of oral delivery of heparin using this technology. Capsules containing heparin and the amidated acid were well tolerated by the volunteers. Dose-dependent elevations in activated partial thromboplastin time (aPTT) of up to three times baseline values were observed, indicating some GI absorption of heparin had occurred.

Other workers presented novel delivery strategies for enhancing the oral absorption of peptides. For example, F. Abedin Dorkoosh and coworkers (Leiden University, Leiden, The Netherlands) developed a bioadhesive 'superporous' hydrogel system for the oral delivery of peptides. The superporous hydrogel, containing small drug-laden cores, was filled into a hard gelatin capsule, which was subsequently enteric-coated. It is envisaged that, following breakdown of the enteric coat in the intestine, the hydrogel would adhere to the intestine wall, swell rapidly and release the drug close to the site of absorption. *In vitro* studies demonstrated a burst release of the drug, following lag periods to enable disruption of the enteric coat and swelling of the hydrogel.

The approach taken by Vikas Agarwal and colleagues (Texas Tech University HSC, School of Pharmacy, Amarillo, TX, USA) was to reduce the degradation of the protein in the GI tract by co-administering an enzyme inhibitor. *In vitro* studies indicated that duck or chick ovomucoids could reduce the degradation of insulin by α-chymotrysin and enhance its GI absorption. Whether such a biochemical approach will be successful in the long run remains to be seen.

The gene therapist's toolbox

For diseases such as hemophilia and cystic fibrosis, gene therapy represents a potential cure as opposed to mere mitigation of the disease state through chronic administration of medications. Therefore, the successful delivery of genes (DNA) to patients lacking these genes or possessing faulty genes and the subsequent expression of the gene product (protein) represents a superior treatment approach. The two broad approaches for formulating DNA are viral-based and non-viral-based systems.

Viral gene delivery

John Monahan (Avigen, Alameda, CA, USA) described the use of adeno-associated virus (AAV) vectors as a flexible technology platform to deliver genes to cells. The vectors are derived from a common non-pathogenic human virus to take advantage of the natural efficiency by which viruses deliver genes to cells. These vectors are prepared by removing the viral genome and replacing it with the therapeutic gene of interest, thus eliminating the risk of an undesirable immune response. Manufacturing and purification challenges were overcome to achieve substantial yields of product with high purity. Preliminary data in humans indicates that a single intramuscular or intrahepatocyte (liver cell) administration of the hemophilia gene significantly reduces the hemophiliac patient's need for self-administering Factor 9. This reduction has been observed for the length of the study, 2.5 years, and is ongoing. It is proposed that this effect will last as long as the cells into which the genes were incorporated remain viable.

Non-viral gene delivery

Igor Gonda (Aradigm, Hayward, CA, USA) presented *in vitro* data on the use of non-viral formulations that are being developed to deliver genes to the human lung via aerosol. The presentation focused on formulation and characterization of the DNA–surfactant complexes after aerosolization by a highly efficient electronic inhaler. The DNA in the formulation is not tightly packaged; rather it resembles strands of DNA with various globules of lipids (referred to as a 'spaghetti and meatball' model). Through the use of gel electrophoresis, the stability of the formulation after aerosolization has been demonstrated. Aerosol delivery represents a non-invasive approach to deliver genes to the lung.

Leaf Huang (University of Pittsburgh, Pittsburgh, PA, USA) also focused on non-viral gene delivery and presented freeze-fracture electron micrographs of lipid–protamine–DNA (LPD) complexes. These LPD nanoparticles contain a condensed DNA core that appears as a perfect sphere with a uniform dark colour. A lighter sphere of uniform size and density surrounds this inner sphere. This lighter sphere represents the lipid membranes used in the formulation. Because the non-viral approach can be used to package the DNA tightly into a sphere as discussed in this presentation or loosely in strands as discussed previously, there was some debate as to the relative uptake efficiency of the two systems.

Although no conclusive data were reported, there was an indication that DNA arranged in loosely complexed strands might have a higher uptake efficiently owing to increased interactions with the cell receptors. Leaf Huang also presented data on efficient endothelial uptake of naked DNA in organs with occluded arteries. He hypothesized that DNA binds weakly to cell surface receptors and is endocytosed but this process is ineffective under conditions of normal blood flow.

Drug–herb interactions

On a more clinical note, the importance of assessing the potential for interaction, not only of conventional polytherapy, but also between conventional medication

and herbal remedies was highlighted in two posters by Bill Gurley and colleagues (University of Arkansas for Medical Sciences, Little Rock, AR, USA). In a controlled volunteer study, they established that St John's Wort (used as an antidepressant) induced CYP3A4 and CYP2D6 activity, whereas gingko biloba (used to improve vascular and neurological conditions) reduced CYP2D6 activity. They then described two case studies whereby renal transplant patients had self-medicated with St John's Wort, leading to a significant reduction in the blood levels of cyclosporin A, and in one case, acute graft rejection. In both cases, stopping St John's Wort administration allowed the return of blood cyclosporin A concentrations to therapeutic levels.

The mechanics of formulations

Gregory E. Amidon, (Pharmacia & Upjohn, Kalamazoo, MI, USA) emphasized characterization of the active pharmaceutical ingredient and the excipients used in various formulations. There is an active USP (United States Pharmacopoeia) effort to review and draft new test methods for physical property characterization. Currently, there is an art to selecting excipients and excipient levels in formulations. It is argued that with proper characterization of the active drug and excipients, this process could be done more scientifically. This could lead to a more robust formulation with reduced development timelines especially when the drug compound of interest is in short supply. To expedite formulation development, the following four factors should be considered and evaluated carefully:

- physicochemical properties;
- mechanical properties;
- biological/permeability properties; and
- the desired drug release profile.

The concluding slide was, 'Those who take the time to understand and take advantage of the physicochemical and mechanical properties of drugs and excipients will have a competitive advantage by being able to more efficiently develop tablet formulations.' Of course, this message applies to all types of formulations.

Conclusions

Overall, although the AAPS 2000 was less well-attended than in the past, it was an enjoyable conference with much good work presented.