Modern drug design and the development of drug delivery systems consider not only the pharmacological activity of a compound but also the drug’s ability to be absorbed and to reach its intended site of action. Novel delivery devices can assess human absorption studies employed in early drug development to rationalize possible strategies for drug delivery. This approach has helped to integrate drug delivery into the discovery/development process. A number of innovative drug delivery approaches have been devised including macromolecular assemblages, gene regulating therapeutic oligonucleotides, molecular bioengineering, and selective tissue delivery of drugs. All these form an encouraging basis for further attempts to establish the possible clinical applications of targeted and site-specific drug delivery for treating human diseases that currently require frequent chronic parenteral drug administration.

Introduction

Advances in biochemistry, molecular biology, cell biology, immunology, genetics, and information technology are transforming drug discovery and development, paving the way for more effective drug products with fewer side-effects than before, that will benefit patients of all ages and stages of life. New active ingredients are only part of the arsenal against disease, however, because the drugs must somehow get to the right place at the right time by means of an appropriate drug delivery system.

To convert molecules into effective drug products, pharmaceutical companies need access to a ‘tool-kit’ of drug delivery technologies. At a minimum, any innovative drug delivery system should provide optimal delivery and have a reasonable chance of being commercially viable, whether the technology is novel or pseudo-novel. Furthermore, drug delivery companies work to devise new dosage forms for older medications. Historically, this has meant product life-cycle management, a process in which a pharmaceutical company looks for ways to set apart a product reaching the end of its patent lifetime from inevitable competition from generics. For example, a company might tinker with a drug that patients must take several times a day and reduce that frequency to a single daily dose.

This review describes recent developments in the chemical, biological, and pharmaceutical fundamentals of drug delivery that might determine present and future technological opportunities. It emphasizes the effects of molecular design and the solid-state properties of drugs on delivery, cellular response and targeting, and site-specific delivery.

Drug delivery as enablement technology during molecular design

Managing the attrition rate of new chemical entities (NCE) and compressing the timeline from the discovery to the launch of a drug product are two factors critical to success facing today’s pharmaceutical companies. One way to increase the probability of developing a successful drug is to build ‘deliverability’ into every NCE, thereby maximizing its chances of success. To achieve this purpose, companies use NCE development assessors such as Pfizer’s ‘Rule-of-Five’, which offers a simple calculation algorithm that flags NCEs with potential development liability. The Rule-of-Five prediction is based on the fact that poor absorption is more likely to occur when there are more than 5 H-bond donors, more than 10 H-bond acceptors, when the molecular weight is greater than 500, and when the value of log P is greater than 5, where P is the n-octanol–water partition coefficient. The name, Rule-of-Five, comes from the cut-off for these parameters, which are all close to 5 or to a multiple of 5. While there are many exceptions to this rule, the parameters offer a reasonable target around which libraries of compounds can be designed with good solubility and permeability across membranes (Table 1). The ideal biopharmaceutical properties of a ‘perfect’ molecule for oral drug delivery are:

- Aqueous solubility to allow the drug to dissolve in 100–400 ml water.
- Apparent log P of ~2.
- Little first-pass metabolism.
- Terminal half-life appropriate for dosing schedule.

Further, in areas of unmet medical need, those molecules with poor or limiting biopharmaceutical properties (that is, poor solubility/poor bioavailability, peptide/protein/gene-related therapeutics, etc.) may be turned into potential winners if drug delivery issues can be overcome. Drug delivery technologies that accelerate the early biopharmaceutical evaluation of these difficult-to-deliver (or formulate) NCEs can offer significant value in predicting success earlier in the drug delivery pipeline. The Enterion® capsule (Fig. 1) has recently been developed in Nottingham in the U.K. by Phaeton Research, for targeted delivery of a wide range of different drug formulations into any region of the gut. This capsule can be loaded either with a liquid

<table>
<thead>
<tr>
<th>Compound</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Good</td>
</tr>
<tr>
<td>Caffeine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Good</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>Good</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Poor</td>
</tr>
</tbody>
</table>

1 = Yes to the rule; 0 = no to the rule.

Rule A: there are more than 5 H-bond donors (expressed as the sum of OHs and NHs); Rule B: the molecular weight is over 500; Rule C: log P is over 5 (or M log P is over 4.15); Rule D: there are more than 10 H-bond acceptors (expressed as the sum of Ns and Os).
formulation (for example, in solution or suspension) or with a particulate formulation (such as powder, mini-tablets) through an opening, which is then sealed by inserting a push-on cap fitted with a silicone O-ring. The floor of the drug reservoir is the piston face, which is held back against a compressed spring by a high-tensile strength polymer filament. A radioactive marker is placed inside a separate sealed tracer port to allow real-time visualization of the capsule location using the imaging technique of gamma scintigraphy.

When the capsule reaches the target location in the gastrointestinal (GI) tract, the contents are actively ejected by the external application of an oscillating magnetic field. The power induced in the coil by the magnetic field is fed to a tiny heater resistor located within a separate sealed electronics compartment inside the capsule. The heater resistor is in direct contact with the restraining filament, causing it to soften and break with the increase in temperature. When the filament breaks, it releases the spring and drives the piston. The resulting increase in pressure within the drug reservoir forces off the O-ring sealed cap and rapidly ejects the drug or drug formulation into the surrounding fluids of the gastrointestinal tract. The movement of the piston also operates a switch, which diverts some of the electrical energy away from the heater and uses it to transmit a weak radio signal. Detection of this signal externally confirms that the capsule has opened successfully.

This capsule design offers the opportunity to obtain data on the intestinal absorption of drugs in humans using a range of complex formulations easily and efficiently. Delivering the drug in different physical forms into a specific region of the intestine makes the respective contribution of intestinal permeability and/or in vivo dissolution to bioavailability easy to assess. By mapping out the human absorption profile, it is possible to fast-track drug development by selecting optimal enabling technology for the molecule, determining whether or not a change of delivery route is required, and deciding whether or not to terminate drug development.

These are examples of assessor tests and novel delivery devices used to evaluate human absorption studies in early drug development to rationalize possible strategies for drug delivery. This approach has helped to integrate drug delivery into the interface between discovery and development and has placed the selection of appropriate enabling technologies at the heart of drug development.

Particulate architecture and drug delivery

Traditionally, changing particulate characteristics to affect drug delivery concentrated on reducing particle size so as to increase the dissolution rate. Classic examples of the effect of particle reduction on drug dose are spironolactone and griseofulvin. Micronisation to below 10 µm has reduced the required dose of these drugs by twenty- and twofold, respectively. Another compelling example is the potential conversion of insulin from an injectable formulation to one that can be inhaled, that has become a possibility for the first time since injections were introduced 75 years ago; if approved, patients with insulin-dependent diabetes would be freed from multiple daily injections.

The alveoli in the lungs can be effectively targeted for drug absorption by delivering the drug as an aerosol with a mass median aerodynamic diameter less than 5 µm. A technique employing supercritical fluids has important applications in micro-particle formation for inhaled drug delivery. A supercritical fluid (such as CO₂) is a material that can be either liquid or gas, used in a state above the critical temperature and critical pressure where gases and liquids can coexist (Fig. 2). Supercritical fluids can perform in ways that baffle our common sense. They are dense like liquids, yet can also flow freely as gases. These unique properties allow supercritical fluids to penetrate readily into apparently solid materials. Many are also excellent solvents. The use of supercritical fluids in the formation of micro-particles minimizes the use of organic solvents, allows the particles to be formed directly in a totally enclosed single-stage process, and permits the controlled preparation of micro-particles under defined working conditions.

Rapid expansion of supercritical solutions (RESS) and the gas anti-solvent method (GAS) are two techniques currently used in pharmaceutical particle formation. RESS allows for a solute to dissolve in the supercritical fluid and then expand across a nozzle at supersonic velocities. It has been used to produce polymer particles of DL-PLA enveloping lovastatin needles, and microspheres containing lovastatin needles. RESS’s principal limitation is that its use is restricted to compounds that are soluble in carbon dioxide, mainly non-polar substances. The gas anti-solvent method offers an alternative to RESS for polar compounds in that the compound is first dissolved in an organic solvent. This technique is commonly used, for example, in the...
formation of protein and peptide powders such as insulin, where biosynthetic human insulin is precipitated from solution in a halogenated alcohol, using supercritical CO₂ as anti-solvent, followed by de-agglomeration. Particles of insulin with narrow size distributions and means in the 1–5-µm size range can be obtained without seriously degrading the insulin or reducing its potency.

Results from a Phase 2 trial that tested inhaled insulin micro-particles in comparison with injected insulin were presented at the American Diabetes Association Convention in Chicago in June 1998. This study involved 70 people with Type 1 diabetes and 51 people with Type 2 diabetes. Researchers found that blood sugar control was equivalent when inhaled Regular® insulin was compared to injected Regular® taken before each meal. Another study found statistically indistinguishable intra-patient variability of inhaled compared to subcutaneously injected insulin; shorter T_{max} for inhalation, allowing for dosing closer to the start of a meal; relative bioavailability of 16%; and similar safety profile of inhaled compared to subcutaneous administration. To date, the main problem with this approach is the inability of inhaled insulin micro-particles to deliver more precise insulin doses than subcutaneous injection.

Size alone, however, does not determine the suitability of drug particles for delivery. The morphology, including crystal form, size, shape, surface geometry, surface constitution, degree of crystallinity, inter-particle friction and tendency to aggregation — collectively the particle architecture — influences the success of drug application. In particular, the polymorphic behaviour of organic solids can be of crucial importance in the pharmaceutical industry. Properties that vary among polymorphs include stability (that is, the shelf life of drugs), crystal shape, compressibility and density (important in formulation), and dissolution rate (a factor that determines bioavailability). Some polymorphs may be inactive or, at the other extreme, even toxic.

Each pharmaceutical compound has an optimal therapeutic blood concentration and a lethal concentration. If the drug can crystallize in two or more polymorphs with different bioavailabilities, the optimal dose depends on the polymorph used in the formulation. Some drugs show a narrow margin between therapeutic and lethal concentrations. It is thus vital to understand the bioavailability of each polymorph in detail and to control the crystallization and formulation of the desired form.

Chloramphenicol palmitate (CAPP) is a broad-spectrum antibiotic known to crystallize in at least three polymorphic forms and one amorphous form. The difference in bioactivity between the most stable form, A, and form B is a factor of 8. This creates the danger of fatal dosages if the unwanted polymorph is unwittingly administered owing to alterations in production and/or storage conditions. The dissolution rate of CAPP is known to be quickened by enzymatic hydrolysis, which separates the insoluble fatty acid chain from the bioactive compound.

Since enzymes attack at specific sites, the nature of the groups exposed at the CAPP surface is vital. To facilitate better understanding of molecular-level processes on the particle’s surfaces, simulation technology can be used to predict the morphology of all possible CAPP polymorphs. Researchers studying the exposed functional groups then gain insight into the likely dissolution behaviour of the compound. The low bioavailability of the most stable CAPP form, A, is explained by the inaccessibility of the key ester groups on the crystal surfaces (Fig. 3). Although the crystal structure of the less stable form B has not yet been determined, its much higher bioavailability (by a factor of 8) can probably be explained by a morphology that makes key ester groups on the surface readily accessible for hydrolysis. This work shows that modelling of surface chemistry can be used to rationalize the biological activity of a particular crystalline form of a drug.

There is also a practical need, during the manufacture of delivery systems, to characterize all solid forms of a drug substance. Poorly soluble or unstable forms can be produced by standard pharmaceutical processes such as crystallization, exposure to solvent vapour, freeze drying, heating, melting, milling, precipitation, quench cooling, slurry conversion, spray drying, solid dispersion, wet granulation, and ‘accelerated’ storage. Once a drug has been crystallized, it is normally the crystal form that is patented. Some companies have sought to use patentability of polymorphs as a means to extend the monopoly protection of...
a known active ingredient. The company SmithKline, for instance, applied for a patent on a polymorph of cimetidine approximately five years after the original patent had been granted. That later patent, however, was nullified in the U.K. and other countries on the grounds that the polymorph was inevitably obtained by applying the process already claimed in the original patent. Another example is the case of ranitidine. The patentee obtained in the United States two patents for a second polymorph that expired in 2002 and 2004 as distinct from 1995 for the main patent. The first patent covered the ranitidine crystallized as the Form 2 polymorph per se and the other covered specific processes for synthesizing Form 2. The claims in both of these patents characterize Form 2 by means of an infrared spectrum with 29 identifiable main peaks.

Pharmaceutical compounds can exist in numerous solid forms that may possess different physical and chemical properties. This variety presents both a challenge to pharmaceutical scientists who wish to produce drug delivery systems of consistent quality, and an opportunity for materials scientists interested in understanding the structure–property relationships in organic solids. The potential impact of changing crystal forms during late-stage drug development, in terms of cost and product delay, also justifies systematic and early characterization of polymorphism, because a thorough understanding of polymorph characteristics allows selection of the best form to market.

Targeting cellular and paracellular pathways for oral drug delivery

Conventional ways of administering non-absorbable drugs and peptides often rely on parenteral injection, because the intestinal epithelium is a major barrier to the oral absorption of these therapeutic agents. Carrier-mediated, transcellular active transport is limited to small molecules, such as sugars and amino acids, but paracellular pathways are theoretically available for the oral delivery of drugs and vaccines, because they do not require the presence of specific carriers for the trans-epithelial transport of molecules (Fig. 4). Transcellular passive transport may be enhanced by entrapment of the active components in microspheres that are more efficiently taken up through the membranous epithelial cells (M cells). Particles absorbed through intestinal epithelial cells (enterocytes), however, are subject to degradation by lysosomes and, therefore, are less efficiently absorbed. Furthermore, the quantity, quality, predictability and reproducibility of oral drug delivery through the transcellular pathway limit the clinical use of this technology.

The paracellular pathway may, however, be used for drug and peptide delivery when the permeability of tight junctions is modulated. Tight junctions are the most important cellular junction involved in drug absorption. They form when specific proteins in two interacting plasma membranes make direct contact across the intercellular space. A tight junction is one of the most important morphological and functional characteristics of the epithelial membrane. Without tight junctions, the cells can diffuse, and membrane polarity and composition can change. These junctions also help to seal neighbouring cells together to create a continuous sheet of cells, which restricts the free movement of molecules, even those that are relatively small (such as mannitol, which has a molecular weight of 182).

Currently, many researchers are exploring the regulation of intestinal tight junctions as a paracellular pathway for drug delivery. One study describes the potential of the recently established technology of protein encapsulation in biodegradable poly(lactic-co-glycolic) acid (PLCG) microspheres for site-directed delivery of microspheres to the intestinal tight junctions. This delivery system disrupts the protein barrier of the tight-junction opening, access to the paracellular route, and basolateral membrane; the encapsulated protein is thereby absorbed into the systemic circulation in a controlled and reproducible manner. In ongoing studies various proteins are being cloned using molecular biology techniques, for expression in *Escherichia coli*, and these proteins are then conjugated to fluorescent microspheres, so that their transport properties can be monitored using cell culture models.

Although it is generally accepted that uptake of solid particles, such as starch, across the intestine by pinocytosis or phagocytosis happens when the absorptive cell engulfs the material, various unresolved issues remain, such as intracellular trafficking and degradation of delivered macromolecules. Particle uptake may be easier to exploit clinically for the oral delivery of vaccines because the predominant sites of uptake, Peyer’s patches, are the inductive sites for the mucosal immune response. Peyer’s patches are lymphoid follicles, similar in many ways to lymph nodes, that are located in the mucosa and extend into the submucosa of the small intestine, especially the ileum. It has been shown that orally administered microcapsules are taken up primarily by gut-associated dendritic cells and are found ultimately in Peyer’s patches, mesenteric lymph nodes and in the spleen. In contrast, orally administered free virus is found only in Peyer’s patch macrophages; the same is true for PLCG microcapsules, another frequently used vaccine-delivery system. Chitosan derivatives as particulate delivery systems are also used for vaccine targeting the Peyer’s patches together with novel adjuvants to increase IgA and IgG production.

In addition to the delivery strategies described above, other innovative drug delivery approaches have been developed, including entrapment of drugs, proteins and peptides within small vesicles and passage through the space between adjacent intestinal cells. All this experimentation represents an encouraging basis for further studies to establish the possible clinical applications of targeted trans- and paracellular drug delivery for treating human diseases that currently require frequent parenteral drug administration for chronic conditions. Oral delivery of drugs and vaccines still represents the ‘Holy grail’ of pharmaceutical biotechnology.
Site-specific drug delivery

Site-specific drug delivery means a system designed to carry the drug to those locations in the body where the disease is prevalent. Although difficult to accomplish, this strategy for drug delivery works well for compounds, with a narrow therapeutic window, that are toxic to healthy or disease-free tissue.

For years, site-specific drug delivery focused on the formulation of delivery systems that would enhance the presentation and acceptability of transdermal delivery products. This focus has led to drug application in matrices that are thin, conform to skin contours, and flex with the movement of the body. For example, comparison of the delivery of oestriadiol by an envelope structure (Estraderm®) and a matrix structure (Fematrix®) showed that the matrix system allowed drug release by diffusion through the matrix into the skin, resulting in a smoother delivery profile appropriate for hormone-replacement therapy than the envelope system.

Many cytotoxic anti-tumour agents have a narrow therapeutic window and, for these, drugs encapsulation in liposomes provides a safe vehicle for delivery to specific sites of disease, while limiting the extent of exposure of normal tissue. Anthracycline antibiotics (doxorubicin) benefited substantially from liposomal encapsulation, especially after the surface of the liposomes had been coated with inert materials to provide ‘camouflage’. A major advance in this surface-modification method is the development of polymer-coated liposomes and, in particular, poly(ethylene glycol) (PEG), which led to the development of ‘Stealth™’ liposomes. Doxid® (Caelyx®) was one of the first Stealth liposome formulations available on the market and is used mainly to treat Kaposi’s sarcoma. Stealth liposomes avoid the body’s natural defence systems, thereby reaching the site of action at the maximum possible dosage.

Another topic of current interest in drug delivery is the use and novel applications of human mononuclear phagocytes (MNPs) in the development of a breast-cancer vaccine. The function of mononuclear phagocytes is integrated with, and dependent on, the action of the adaptive immune system. Antigenic fragments may be expressed on the surface of MNPs in association with normal cell surface molecules (MHC molecules) in such a way as to facilitate the response of the adaptive immune system. MNPs can kill tumour targets directly by a variety of lymphocyte-independent mechanisms. The phagocytes can become activated killer monocytes (AKMs) by incubation with certain substances, the most widely used being IFN-γ. Intravenous infusions of these suspensions given to patients with incurable cancer resulted in stabilization and even regression of the disease. The future may see the development of a non-toxic immuno stimulation intervention that could maintain the MNP anticancer defence in healthy individuals.

The gene therapy field has expanded its search to find gene-delivery vectors that achieve high-efficiency, non-toxic transgenic expression. Numerous materials have been studied as potential vectors for gene delivery, with varying results. Among these materials are dendrimers, which are branched three-dimensional macromolecules with highly controlled structures, a single molecular weight, a large number of controllable ‘peripheral’ functionalities, and the tendency to adopt a globular shape once a certain size is reached. Dendrimers constitute a unique class of synthetic polymers, in which growth emanates from a central (initiator) core molecule such as ammonia, ethylenediamine, propyldiamine, or benzene tricarboxylic acid chloride. Their features have made the application of dendrimers particularly attractive in pharmaceutical and medicinal chemistry. Their use as gene-delivery vehicles and magnetic resonance imaging agents, and their potential for applications in drug delivery have sparked the development of several such compounds. One compound, polyamidoamine (PAMAM), has been found to be safe and non-immunogenic, and can function as a highly efficient cationic polymer vector for delivering genetic material into cells (Fig. 5). PAMAM dendrimers have been used as a non-viral gene-delivery vector ever since the discovery of this capacity.

Another part of the human body that may require site-specific drug delivery is the central nervous system (CNS). Currently, the growth of the neuro-pharmaceutical industry is limited because 95% of all new CNS drugs do not cross the blood–brain barrier (BBB); 99% of all CNS drug development is devoted to CNS drug discovery, whereas only 1% is directed towards CNS drug delivery. The BBB ‘bottleneck’ may be navigated in the future if CNS drug development programmes begin to focus on BBB drug delivery strategies that target the endogenous transport systems within the brain capillary endothelium. Just as molecular neuroscience provides the platform for CNS drug discovery, the molecular and cellular biology of the brain capillary endothelium provides the platform for CNS drug delivery.

Many pharmaceuticals are thus ineffective in treating cerebral diseases because of the inability to deliver and sustain activity in the brain. General methods to enhance brain delivery are therefore of great interest. Bodor and Buchwald published an extensive review on targeting neuro-pharmaceuticals by chemical delivery systems (CDS), in which various aspects and strategies for brain delivery as well as an extensive list of drugs, are described and referenced. Drugs obtained by CDS design provide site-specific or site-enhanced delivery through multistep enzymatic and/or chemical transformations. CDS design together with soft drug design are part of the so-called retro-metabolic drug design approach that integrates structure–activity and structure–metabolism relationships.

Chimeric peptide technology is a universal brain-drug delivery mechanism and can convey peptide-based pharmaceuticals, nucleic acid-based therapeutics and small molecules to the brain using liposomes. This means of delivering therapeutic nucleic acids to the brain will require further optimization to allow for endosomal release of the conjugate into the cytosol, following transport across the blood–brain barrier and receptor-mediated endocytosis into brain cells. Gene medicines may be delivered to the brain by entrapment of the plasmid gene within a liposome...
that is then pegylated and conjugated to BBB-targeting monoclonal antibodies.

Recent studies indicate a widening role in many therapeutic areas for adenosine receptors, because they are widely distributed throughout the body. These receptors are involved in immunological and inflammatory responses (such as arthritis and asthma), respiratory regulation, the cardiovascular system, the kidney, various CNS-mediated events including sleep and neural protection, as well as central and peripheral pain processes. A clear understanding of the specific interactions and physiological role of adenosine receptors in these key areas is likely to lead to new uses of adenosine receptor agonists and antagonists in a wide range of diseases.

The search for new classes of antibiotics to stem the global emergence of drug-resistant bacterial pathogens is perhaps one of the greatest challenges facing the pharmaceutical industry. Many contemporary antibiotics were introduced more than 25 years ago during the ‘golden era’ of antimicrobial drug development. Researchers, however, have started to focus on the observation that infection of a host by pathogenic bacteria requires that the bacteria bind to the target tissue to colonize and/or begin the process of invasion. This adhesion event involves specific interactions between receptors on the host tissue and external surface structures produced by the bacterial cell. Gram-positive bacteria use a special class of surface-anchored proteins for this purpose, whereas Gram-negative microorganisms exploit a more complex structure, called a pilus, to achieve the same end. In both cases, a highly conserved pathway is used to export, assemble and anchor these surface structures. As such, these pathways are targets for antibiotic development. Compounds that prevent the assembly of bacterial surface proteins cripple the ability of bacteria to interact with and colonize host tissue, so that the bacteria are rapidly eliminated from the body. The compounds are not intended to kill the pathogen but to remove it from the host by allowing physical mechanisms and innate immunity to remove the organisms. It is believed that treatment of infectious disease by attacking these pathogenic agents in this way will have less of a tendency to lead to the development of resistant organisms than conventional drug regimes. Furthermore, because bacterial pilus and surface-anchored proteins are continuously produced and recycled throughout the course of infection, such antibiotics will theoretically exhibit therapeutic as well as prophylactic properties. We still await the identification of a compound that efficiently blocks bacterial adherence and its delivery to sites of infection.

A need also exists to improve glycemic control in Type 2 diabetes, to prevent diabetic complications. There seem to be two promising possibilities. First, since we have not yet achieved completely normal physiological control of glucose homeostasis, it would be desirable to devise novel hypoglycemic agents that can maintain blood glucose levels within a narrow range. Second, it would be helpful to develop a targeted insulin sensitizer to contribute to the improvement of glycemic control, since some patients do not respond to thiazolidinediones, which are drugs that have no effect on glucosamine-induced insulin resistance. Drugs targeted at improving pancreatic b-cell functions associated with glucose homeostasis (for example, a drug that restores the responsiveness of b cells to glucose) would be desirable as insulin sensitizers.

These are examples of areas of drug research in which the development and improvement of site-specific drug delivery would be very beneficial. A major concern with site-specific drug delivery, however, is the lack of techniques to follow closely and accurately the distribution of the drug at and around the target. In vivo imaging techniques are vital in the pharmaceutical development process. Gamma scintigraphy, comprising two-dimensional ‘planar’ imaging, is used widely to visualize and to quantify drug delivery, particularly by the oral and pulmonary routes. However, three-dimensional imaging modalities — single photon emission computed tomography (SPECT), positron emission tomography (PET) and magnetic resonance imaging (MRI) — may also be applicable. SPECT and PET offer potential advantages over gamma scintigraphy for assessing regional deposition of drugs in the lung from aerosol inhalers, but these advantages are currently greatly outweighed by the practical problems of conducting SPECT and PET studies. For the near future, therefore, gamma scintigraphy is the imaging modality of choice in assessing the delivery of new oral and pulmonary drug products. However, continuing developments in 3-dimensional imaging techniques to overcome practical problems with SPECT and PET are likely to improve our ability to monitor drugs at specific sites of action more closely than ever before.

Advances in biotechnology and pharmaceuticals involve progress towards controlled, site-specific drug delivery for the dual purposes of increasing efficacy and reducing side-effects. According to estimates, controlled drug-delivery products will account for 20% of all pharmaceutical sales by 2007. Some advantages of using controlled site-specific drug delivery systems include the maintenance of drug levels within a desired range, the need for fewer administrations, optimal use of the drug in question, and increased patient compliance.

Advances in additives used in drug delivery systems

Traditionally, additives, also called excipients, in drug formulations have been regarded as inert, but in many instances these compounds have been shown to have a significant effect on the biological availability of the drug. Many drug–excipient interactions affect the process of dissolution. In fact, an interaction between a drug and an excipient that alters the dissolution of some hydrophobic drugs has been shown to have a marked influence on the absorption and bioavailability of that drug, where, for instance, dissolution is the rate-limiting step in absorption. A drug–excipient interaction can be used to the advantage of the formulator of medicinal products to increase the bioavailability of the drug (for instance, complexation with cyclodextrins or solid dispersion technology). There are also cases, however, in which interactions were not expected, and when they adversely affected the bioavailability of a drug (for example, where the mechanism of the interaction was surface adsorption or where it increased GI transit time).

Excipients still form a major part of any drug delivery system, however, and advances in their development have been reported. One such development involves sugar-based additives that are popular for pharmaceutical formulations for many reasons – they have a pleasant taste, for example, which helps to mask an unpleasant one. Many sugar-based excipients on the market today are beneficial in certain applications. Two new sugar-based additives, crystalline maltose and directly compressible sucrose (containing sorbitol), can be used in direct-compression tabletting. Since both are compressible and palatable, exhibit excellent flow, and can help the flow of other ingredients, they present new options for tablet formulations. Formulators have also begun to realize that many products contain excipients that can be classified in a general sense as stabilizers. Using suspending agents to prevent sedimentation, adding a preservative to prevent microbial spoilage, or incorporating a buffer to adjust pH for optimum stability, are all good
reasons for adding excipients to enhance product stability. By choosing additives that have an appropriate effect on the molecular integrity of the active ingredient, fundamentally unstable drugs can be transformed into viable delivery systems. What is an appropriate strategy for stabilization? In the era of combinatorial chemistry and genomics-based research, the predominant view seems to be that unstable entities should be ‘selected out’ early in the discovery and development process, because poorly stable therapeutic agents are likely to progress slowly (or not at all) to the market-place. Especially in the environment promised by genomics, it is postulated that there will be an embarrassment of riches in terms of compounds to select for clinical evaluation. Attempts to stabilize a relatively unstable material might therefore seem unwarranted. There are other reasons, however, why the ability to stabilize labile materials should remain an option for the formulator of medicinal products. Activity, specificity, and freedom from toxicity might be directly related to molecular fragility. Materials derived from biotechnological or other natural sources are a case in point.43

Another major development in drug delivery is the increased number of potent compounds available for promoting drug transport, especially those targeted at promoting cellular uptake of drugs. One such compound is the VP22 protein. It is a component of the herpes simplex virus particle, which, together with another structural protein, VP16, comprises the main part of the tegument of the virus and its inner nucleocapsid core.44 It is claimed that the ability of VP22 to enter and exit cells, together with its DNA-binding capabilities, mean that the protein has great potential as a drug delivery vehicle for molecules that are intended to function in cell nuclei. Other small molecules that aid drug uptake are oligomeric molecular transporters that enter cells and tissues with ease and enhance the uptake of drugs.45 One such oligomer is a segment of the protein Tat, which helps the human immunodeficiency virus to enter cells.38 Tat consists of nine residues, six of which are L-arginine, and is well known to cross the plasma membrane of cells efficiently. The transporter oligomers can be attached to their cargo with ease. Most compounds with oxygen, nitrogen, sulphur, or phosphorus groups can be attached in one to three steps. These oligomers have been tested to deliver cyclosporin A into both human and mouse skin and peptides to heart cells.46

Using appropriate excipients might be the only way in which many newly developed therapeutic agents can be converted into viable products. All drug-delivery systems should be developed so that the pharmaceutical agent retains its quality while in close association with other formulation components. Turning an unstable drug into a stable product also offers possibilities for intellectual property claims. Thus, there are potential commercial advantages for companies with the skills and the will to make the effort to provide inventive approaches to stabilization either by developing innovative delivery systems or by using excipients that increase the drug’s stability.

Pharmacokinetic considerations in drug delivery

Since the early 1980s, the importance of pharmacokinetic considerations in drug design has been recognized and studied extensively. Quantitative structure–pharmacokinetic relationships have great generalization value and are particularly important in the design of drug delivery systems.42,43 The basic experimental pharmacokinetic parameters invoked include absorption, elimination, rate constants, half-lives, clearances, volume of distribution, rate of metabolism, mean residence time and fraction of bound drug, in which descriptors such as pKₐ, log P/log D, solubility, Van der Waals volume, Hammet constant, molecular weight and connectivity indices are used.46 Pharmacokinetic/pharmacodynamic (PK/PD) relationships and modelling link the concentration–time profile and intensity of response, and thus allow the description of the complete time course of the effect of drug therapy.47

A concept that goes hand in hand with the above is ‘soft drug design’, whose aim is to produce safer drugs with increased therapeutic efficacy by integrating considerations of metabolism into their design.50 This is especially viable for compounds that are substrates for the cytochrome P-450 system, as distinct substrate preferences and predictable metabolism of these substrates for these enzymes are known.51 Several drugs obtained by successful application of these considerations are on the market and many more promising candidates are under investigation.52

A reason for developments in pharmacokinetic evaluation is the pressure on pharmaceutical companies to reduce time-to-market and improve the success rate of new drug substances, so higher-throughput pharmacokinetic (HTPK) support has become integral to many drug delivery programmes.41 This new paradigm employs a strategy where issues can be flagged early through reference to data on previous compounds and/or cheminformatic predictions. To resolve these issues timeously, a higher-throughput (HT) and parallel testing cascade are put in place to address the properties of molecules through suitable in vitro and in vivo assays. For many years, HTPK was hampered by lack of analytical sensitivity. Advances in mass spectroscopy (MS) now offer many intriguing possibilities for the further development of HTPK. Triple quadrupole MS systems continue to improve in sensitivity with the development of enhanced vacuum pumping systems and ion optics. The requirement for method development is negated by improvements in selectivity and detection limits such that instrument optimization for ultimate performance is no longer required. In addition, such instrumentation as is available allows PK investigation at more pharmacologically relevant doses.

All the information gathered from pharmacokinetic studies can be used to streamline the drug development process and dose optimization. This means that broader application of PK/PD concepts in clinical therapy provides a more rational basis than before for the design of drug delivery systems that can be used for patient dosage and individualization, and that may thereby guide applied pharmacotherapy to a higher level of performance.

Conclusion

Modern drug discovery and the design of drug delivery systems not only focus on the pharmacological activity of a compound but also consider its ability to be absorbed and to reach its intended site of action. Some of the exciting new developments in potential therapeutics are quite different from our standard repertoire of chemical and biochemical entities that we call drugs. They are diverse in nature and disease targets and therefore need more innovative delivery systems. Novel methods should take into account the physicochemical and biological properties of the drugs. They have several hurdles to overcome, but also display great potential. The prospect of in vivo barrier permeability, in particular intestinal absorption, site-specific delivery, cellular uptake and passage through the blood–brain barrier are also substantial concerns in the development these new delivery systems.

It is predicted that, based on advances in drug delivery technology, the rate of growth of a number of peptide and protein
drugs on the market will increase significantly. Epoetin a
(Epogen®), for anaemia-associated diseases, and interferon a
(Intron A®), are examples of drugs that have enjoyed dramatic
increases (>20%) in global sales. Almost all current peptide and
protein drugs are still marketed as injectables, however, and
there remains great commercial potential for delivery systems
that use alternative routes. These include pulmonary protein
delivery, including the potential for systemic therapies, and
oral administration of peptides and proteins using lipid systems.

Other important developments not addressed in this re-
view but which in future will influence the design of drug
delivery systems are genome mapping, pharmacogenomics,
combinatorial chemistry, high-throughput screening, and
cassette dosing. Furthermore, performance-to-cost ratio and
early market entry will remain major goals in the development
of a drug delivery system. When these commercial consider-
ations are combined with a highly competitive market, the
pressure to reduce the timescale for the development of a drug
delivery technology will be even greater.

Today 2(1–3), 49–57.
ing-based capsule dosing. Furthermore, performance-to-cost ratio and
early market entry will remain major goals in the development
of a drug delivery system. When these commercial consider-
ations are combined with a highly competitive market, the
pressure to reduce the timescale for the development of a drug
delivery technology will be even greater.

Today 2(1–3), 49–57.
ing-based capsule dosing. Furthermore, performance-to-cost ratio and
early market entry will remain major goals in the development
of a drug delivery system. When these commercial consider-
ations are combined with a highly competitive market, the
pressure to reduce the timescale for the development of a drug
delivery technology will be even greater.

Today 2(1–3), 49–57.
ing-based capsule dosing. Furthermore, performance-to-cost ratio and
early market entry will remain major goals in the development
of a drug delivery system. When these commercial consider-
ations are combined with a highly competitive market, the
pressure to reduce the timescale for the development of a drug
delivery technology will be even greater.

Today 2(1–3), 49–57.
ing-based capsule dosing. Furthermore, performance-to-cost ratio and
early market entry will remain major goals in the development
of a drug delivery system. When these commercial consider-
ations are combined with a highly competitive market, the
pressure to reduce the timescale for the development of a drug
delivery technology will be even greater.

Today 2(1–3), 49–57.
ing-based capsule dosing. Furthermore, performance-to-cost ratio and
early market entry will remain major goals in the development
of a drug delivery system. When these commercial consider-
ations are combined with a highly competitive market, the
pressure to reduce the timescale for the development of a drug
delivery technology will be even greater.

Today 2(1–3), 49–57.
ing-based capsule dosing. Furthermore, performance-to-cost ratio and
early market entry will remain major goals in the development
of a drug delivery system. When these commercial consider-
ations are combined with a highly competitive market, the
pressure to reduce the timescale for the development of a drug
delivery technology will be even greater.

Today 2(1–3), 49–57.
ing-based capsule dosing. Furthermore, performance-to-cost ratio and
early market entry will remain major goals in the development
of a drug delivery system. When these commercial consider-
ations are combined with a highly competitive market, the
pressure to reduce the timescale for the development of a drug
delivery technology will be even greater.

Today 2(1–3), 49–57.
ing-based capsule dosing. Furthermore, performance-to-cost ratio and
early market entry will remain major goals in the development
of a drug delivery system. When these commercial consider-
ations are combined with a highly competitive market, the
pressure to reduce the timescale for the development of a drug
delivery technology will be even greater.

Today 2(1–3), 49–57.
ing-based capsule dosing. Furthermore, performance-to-cost ratio and
early market entry will remain major goals in the development
of a drug delivery system. When these commercial consider-
ations are combined with a highly competitive market, the
pressure to reduce the timescale for the development of a drug
delivery technology will be even greater.

Today 2(1–3), 49–57.
ing-based capsule dosing. Furthermore, performance-to-cost ratio and
early market entry will remain major goals in the development
of a drug delivery system. When these commercial consider-
ations are combined with a highly competitive market, the
pressure to reduce the timescale for the development of a drug
delivery technology will be even greater.