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Commentary

Drug delivery systems for challenging molecules

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Abstract

The development of delivery systems for challenging drug molecules is discussed with particular reference to the products of biotechnology and unmet medical needs. A proper understanding of the properties of the drug molecule, the disease to be treated and the destination in the body is often essential before an appropriate delivery system can be developed. The outsourcing of drug delivery to specialist companies is also discussed.

Keywords: Challenging molecules; Delivery systems; Drugs

1. Challenging drugs

Some years ago we visited a major UK Pharmaceutical company to discuss 'Advanced Drug Delivery Systems'. Our meeting with the Research Director was most illuminating. He could not see the need for such technology since in his words 'our drugs deliver themselves'! He appeared to be correct since the candidate products then under development were apparently stable, low molecular weight, reasonably lipophilic compounds that would be well absorbed from the gastrointestinal tract; the preferred route of administration. Even today, some drugs are (relatively) easy to deliver. They are soluble in biological fluids at physiological pH and are stable. They can be transported satisfactorily across cellular barriers into the blood and to their sites of action. These drugs do indeed 'deliver themselves' and do not require sophisticated delivery systems. However, for an increasing number of compounds the situation is

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different. Most of the 'simple' or 'easy to deliver drugs' have been discovered and the drugs of tomorrow, needed for the treatment of unmet medical needs, will be far more challenging. They will be more complicated, and may well be larger in size. They may also be less stable, less soluble and less permeable. They may take the form of complex carbohydrates, peptides and proteins, oligonucleotides or DNA. Insulin and heparin can be considered to be ancient prototypes. Such materials will be much harder to deliver by conventional routes than 'classical molecules'. Injection may be the only means (at least to start with). In order to provide better treatment we will need to find new ways to deliver these drugs and to control their absorption and distribution in the body. Novel methods for delivering drugs to and across mucosal surfaces will be required (nose, lung, intestines, etc.) as will targeting to specific sites, that include tissues, organs and cells. For the case of DNA delivery in the emerging field of gene therapy, there is the added need to deliver the 'therapeutic agent' to a specific site in the cell; the nucleus.

Advances in biotechnology, high throughput drug screening and combinatorial chemistry can be cited as reasons that many of tomorrow's drugs will be different to those of today. New screening methods are impressive in their ability to identify target molecules that demonstrate activity in in vitro screens. Whether such screening methods will lead to molecules that perform well in vivo is yet uncertain. The molecule that displays the 'best' result in a pharmacological screen may not be the best to develop if it is unable to reach its site of action in a patient. Thus, while structure–activity relationships are important they are not everything. The related aspects of structure-delivery also need to be addressed. Critical factors such as drug solubility, membrane permeability, metabolic pathways and stability need to be considered at the earliest stages of drug candidate selection. Unfortunately, high throughput preformulation measurements are still in their infancy. Furthermore, the voice of those with experience in drug delivery issues is not always given due consideration in the choice of drug candidates. Drug delivery staff need to be involved in the early decision making processes. To that end, better training, communication and authority may be needed so that the choice of a drug candidate is truly a shared decision and responsibility.

Not only do we face the future spectre of more challenging drugs but also challenging diseases that reflect demographic, social and environmental changes (AIDS, Alzheimer's disease, BSE-CJD). Advances in biotechnology have led to the availability and rapid production of complex natural molecules for disease treatment (growth factors, interferons, cytokines, response modifiers, etc.). Similar advances that rightly are to be expected from gene therapy, will likewise be dependent on the availability of suitable delivery systems. It is impressive how quickly molecular biologists can produce plasmids encoding for therapeutic proteins. Consequently, in gene therapy the rate limiting step in product development, will surely be the availability of stable non-viral vectors that will result in long term expression at selected tissue sites.

Some would consider that we have only touched the tip of the iceberg. A greater understanding of the human genome will lead to an identification of the causes of disease and new treatments. In a recent article by Jurgen Drew in a Nature supplement entitled 'Intelligent drug design' (November 1996), the importance of the Human Genome project and the identification of gene products and other proteins in signalling pathways was discussed. New opportunities for disease intervention were identified with the suggestion that there could be from 300–10000 drug targets! These new targets would include nuclear receptors and DNA. The importance of the selection of genes and the isolation of proteins to develop screening assays for potential drug leads was strongly emphasised. We subscribe to this view of the future but would wish also to emphasise the need for appropriate drug delivery systems

Such considerations for novel drug delivery can also be applied to vaccines and in some cases to the new generation of diagnostic agents.

2. Novel drug delivery

Drug delivery can be of importance for both new chemical entities as well as established drugs (Table 1). Consequently, drug delivery systems can have a wide variety of applications and benefits. At one extreme it is possible to imagine how a drug delivery system could be instrumental in the successful therapeutic use of a new chemical entity; especially in those situations involving drug targeting or improvement of the absorption of a poorly bioavailable compound from the gastrointestinal tract. More mundane applications of drug delivery include the development of over-the-counter products, improving patient compliance with once-a-day formulations, establishment of a market differentiation or the extension of the patent life of a product. The complexity of a chosen delivery system does not necessarily mirror the severity of the disease being treated or the novelty of the drug. Indeed, some of the most sophisticated delivery systems currently available can be found applied to over-the-counter products and line extensions. Novel delivery systems also find a place in the generic market, either in the development of copies of innovative products (avoiding patent conflicts) or in the development of so called 'super-generic' systems.

We are still surprised when people ask us for details of for example, our 'vaccine delivery system' or our 'DNA delivery system' as if in each case there should be some form of universal delivery modality. Clearly the delivery system will depend on the nature of the material to be delivered (e.g. whole virus, surface protein, peptide, lipopeptide, etc. for a vaccine) and the route (destination), e.g. parenteral, mucosal for the case of vaccines; the muscle, lung endothelia, lung epithelia, liver hepatocytes, tumour tissue, gastrointestinal tract, etc. for gene therapy. For the challenging drugs of the future a wide variety of delivery methods will be required. Unfortunately, but not surprisingly, there is no universal delivery system for drugs, vaccines or for that matter, DNA. Each case needs to be considered on its own merits. One should evaluate carefully whether an appropriate delivery system exists already (or can be modified to serve the special needs of the drug) or whether it is necessary to develop a delivery strategy from scratch. A delivery 'tool kit' rather than a single delivery tool will be the order of the day.

Table 1
The role of novel drug delivery

New chemical entities
Established drugs
• Essential for successful product concept
• Reduction of adverse reactions and side-effects
• Site specific delivery or better access to target site
• New application or therapeutic indication
• More convenient mode of administration
• Improved patient compliance
• Extension of product life

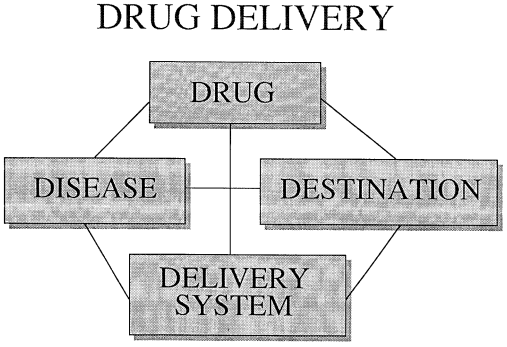

Fig. 1. The essential components of drug delivery.

Any discussion of opportunities in the field of drug delivery, and the use of delivery systems for improving the characteristics of challenging drug molecules, can be approached in a number of different ways. In our work we use the diagram shown in Fig. 1 comprising drug, disease, destination and delivery system. We believe it is logical to adopt a 'market pull' approach and to consider first the *drug*, the *disease* and the *destination* (in terms of where in the body the drug should achieve its effect or the preferred route of administration). Then, only after these factors have been well addressed is it appropriate to consider what is the most appropriate delivery system. In some cases a technology may already exist which can be applied readily to the delivery problem. However, in many cases it is necessary to develop a delivery

system de novo in order to meet specific problems and needs. We believe that this approach of first evaluating the special needs of the drug is far preferable to that of developing delivery systems and then to seek out diseases and drugs. This second, alternative approach is known as 'technology push'. By starting with the drug and the disease, it is normally possible to consider carefully the properties or 'personality' of the drug molecule and the required performance specifications that will include the best route of administration, the needs of the patient, physician, marketing departments, etc. Some of the aspects that should be taken into account when considering the development of a novel drug delivery system are listed in Table 2. They include pharmaceutical, pharmacological, pathological as well as economic factors.

For instance, in the emerging field of peptide and protein delivery, molecules that are relatively similar in their characteristics (polypeptides), may present very different opportunities in delivery system development. Insulin and calcitonin are two good examples. The former is a very challenging drug where one needs to deliver the molecule according to precise requirements of time and quantity and probably site of action. Thus, parenteral (subcutaneous) as well as nasal and pulmonary delivery would be routes of choice. Oral delivery, because of the imprecision and lack of reproducibility could conceivably be used for basal delivery of insulin but not for prandial pulsatile delivery of the drug. In contrast, calcitonin is a drug that has a wide therapeutic index and consequently it can be given by many different routes. Some calcitonin delivered daily (or less frequently) appears to be beneficial in the treatment of post menopausal osteoporosis. Parenteral, nasal, pulmonary and oral routes should all be acceptable. The choice of route will depend more upon patient preference and cost of goods rather than a need to have a precise delivery pattern. In the same area of therapy for osteoporosis, the delivery requirements for the polypeptide drug, parathyroid hormone, are far more stringent than those for calcitonin. Not only is the drug less stable but needs to be given in a pulsatile fashion to avoid the opposite clinical effect to that intended.

Table 2
Factors in drug delivery

- Drug polarity
- Drug size
- Drug stability
- First-pass metabolism
- Therapeutic index
- Cost of goods
- Patient acceptability
- Regulatory hurdles
- Time to market
  - Quality/quantity of deliver
  - Acute/chronic treatment
  - Preferred route
  - Pharmacokinetics/
  - Pharmacodynamics
  - Onset/duration

3. Drugs

This commentary is focused on delivery systems for challenging drug molecules. As discussed above, we are now witnessing the development of a wide range of novel materials. Some of these have been discovered through the efforts of biotechnology and genomics whereas others have been discovered through high throughput screening and combinatorial chemistry. Many of these new molecules are large, polar in nature and some have limited stability. These materials include peptides and proteins, carbohydrates, oligonucleotides and nucleic acids in the form of DNA.

In our own work on novel delivery systems, we include not only therapeutic applications but also the development of vaccines and diagnostic agents since the challenges in delivery are often very similar, especially where targeting applications are concerned. Challenging molecules can also have the opposite physicochemical characteristics, namely compounds that are poorly soluble in water and in a whole range of organic solvents. These compounds are often likened to 'brick dust' and need to be solubilised. Materials such as cyclodextrins, emulsions, liposomes or the production of small particulates (through methods such as supercritical fluid technology or novel methods of comminution using sophisticated milling and grinding processes) are under active investigation. Many of the new anti-cancer agents, (e.g. taxol), antifungal agents (e.g. itraconazole), are known to be problematical in this regard.

The essential properties of a drug that will influence the choice of delivery strategy can be defined by preformulation experiments. Here the stability, solubility, partitioning properties of the molecule can be determined along with essential physicochemical data such as melting point, polymorphic forms. Ever increasing today in pharmaceutical industry are preformulation studies that include the measurement of membrane permeability using for example, intact layers of cells in culture (CaCO-2) or epithelial sheets or even by basic experiments in animal models such as the rat. In many companies there is now the need to develop rapid screening methods that can keep up with the large number of successful 'hits' that have been found by high throughput screening techniques. Methods for the rapid determination of solubility and drug permeability have been described.

The results of a preformulation database can be used to provide insight into the problems that one may face with the formulation of a new chemical entity or when trying to develop a line extension of an existing drug. For example, poor stability may preclude the development of certain types of formulation as can a limited absorption from different regions of the gastrointestinal tract. A special problem for orally administered drugs is poor colonic absorption as found with polar compounds. This will often mean that it will be hard, if not impossible to develop sensibly a once-a-day formulation. In order to better understand the competing factors we have developed computer models for the various routes of administration of drugs into the body. It is then possible to calculate pharmacokinetic profiles that show the local concentrations of drugs in the blood, selected tissue compartments or within a body cavity. Such computer models can be used to investigate possibilities and problems and to conduct detailed sensitivity analyses to answer the question 'What if?'; What if the drug was released more slowly from its dosage form? What if the drug was less stable? What if the drug was retained through a bioadhesion mechanism within a given lumen for an extended period of time? What if the permeability of a given epithelial barrier was increased? What if the dissolution rate of the drug was dramatically improved? We have found that this type of analysis can be highly instructive and can lead to a more rational choice of the best route of administration as well as the best delivery system.

4. Diseases

In theory, novel delivery systems could be beneficial in treating almost every disease condition, to include both therapeutic and prophylactic applications. Knowledge of the particular disease state, (its site of action in the body, its dissemination, its severity and length, whether acute or chronic, associated sequelae, etc.) can be of critical importance to the design of an appropriate delivery system. This knowledge of the disease condition is important, not only since it is relevant to aspects of direct treatment, but can provide vital information on pathologies that can affect physiological processes such as gastrointestinal transit, drug metabolism, drug elimination, etc. The development of delivery systems for self limiting acute conditions, can be different to that for the treatment of critical diseases such as cancer. The sophistication of the delivery system, its cost, potential for side effects, etc. are all relevant parameters. The period of time the drug will be administered and age of the intended recipient are also important. For example, in the development of delivery systems for growth hormone, it is critical to the development of a suitable delivery system whether the product is to be used over a long period of time, for example in children for the treatment of pituitary dwarfism, or for the use in the elderly or in cancer patients, AIDS treatment, etc.

5. Route of administration—destination

The preferred route of administration will be dictated by various factors to include the nature of the disease, the drug, along with patient preference. Obviously for an over-the-counter product, the number of routes that are acceptable will be more limited than for drugs intended for the prescription market. Drugs which are intended to

act locally will often dictate the nature of the delivery system required. Whereas, for other drugs that act systemically, it is possible to find a number of different routes competing in terms of efficiency, cost and patient preference. With vaccines, the route of administration may well dictate the type of response that is obtained; for example the mucosal delivery of antigens can give rise to a very different immune responses than the parenteral administration of the same antigenic material.

Some sites of administration will be convenient and easy to reach, such as the nasal and buccal cavities and the skin. Some sites may be more challenging to access, for example the colonic region of the gastrointestinal tract. The brain is of special importance with efforts being made to develop formulation strategies to circumvent the blood/brain barrier. Specific pathologies, e.g. tumours, can be especially problematical. Much is made about drug targeting, but there are relatively few examples of pharmaceutical delivery systems that function strictly in this capacity. Conjugates of drugs with monoclonal antibodies have the propensity to target, but to date, clinical success has been disappointing. In the liposome field, particles coated with polyethylene glycol are known to avoid capture by the elements of the reticuloendothelial system and to reach tumour sites and sites of inflammation (probably through processes of passive diffusion rather than active targeting).

Table 3
Future research in drug delivery

1.	Development of non-viral gene vectors for the delivery of vaccines and therapeutic agents
2.	Surface modified nanoparticles and liposomes for the site specific delivery of anticancer agents, DNA, etc.
3.	DNA polymer complexes for drug delivery
4.	Oral delivery systems for targeting to the terminal ileum, ascending colon
5.	Bioadhesive systems that provide retention of drugs in body cavities
6.	Gastroretentive formulations that deliver drugs for local treatment or for enhanced uptake from absorption windows in the small intestine
7.	Nanoparticulate systems for DNA delivery based upon cationic polymers and cationic lipids
8.	Novel permeation enhancers that provide enhanced transport across cells by paracellular and/or transcellular routes
9.	Oral delivery systems designed to avoid food effects
10.	Particulate systems for approved delivery to mucus-associated lymphoid tissue
11.	Particulate and polymer systems for targeting to tumours following intravenous administration
12.	Targeting systems for lymph nodes
13.	Electrotransport systems for improved transdermal delivery
14.	Liquid and powder injector systems
15.	Polymer implants for conventional drugs and polypeptides
16.	Improved systems for the nasal delivery of drugs used for the treatment of migraine

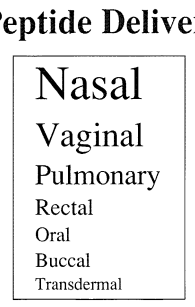

Fig. 2. Peptide delivery, opportunities for quantity and quality.

The delivery of DNA to specific cells is a clear example of the potential that appropriately designed delivery systems could bring to the success of a new mode of therapy. Here, it will be necessary for the gene construct to be delivered first to the required organ, then to the required cell and subsequently to the required structure within the cell (the nucleus). Gene delivery represents an excellent example of the need for specific delivery and a third order level of targeting. Success will demand a detailed knowledge of different sciences, to include molecular and cell biology, pharmaceutical formulation, colloid science, etc.

Today, almost all conceivable routes of delivery are being considered for the delivery of challenging molecules such as peptides and proteins and related polar macromolecular pharmacological agents. Transmucosal delivery is a popular option with nasal, buccal, pulmonary, oral, vaginal delivery systems under active evaluation. It is often possible to rank the different routes of adminis-

tration in terms of their membrane permeability and hence the delivery to the systemic circulation. It is possible to include in such a rank order, not only issues such as absorption but also items such as convenience and cost (Fig. 2). It is interesting that this preference, based largely on our own work and recent publications (to include the patent literature) mirrors well the known permeability of the different routes as measured in animal models. There are of course, exceptions to any generalisation, but we have found for small molecular weight polypeptides that one can obtain the best systemic absorption from the nose, followed by vagina, lung and the other tissues in descending order. We greatly value studies conducted in man and published in refereed journals. Data obtained in animal models can sometimes be misleading and studies in cell culture are normally useful for initial screening exercises, rather than prediction of final product performance.

6. Delivery systems

It is not surprising from the foregoing discussion, that the Pharmaceutical scientist can be faced with a bewildering number of delivery opportunities currently available. However, once detailed performance characteristics have been drawn up, many options will be found to be no longer suitable. Client companies (particularly their Marketing departments) will often have a strong preference as to the nature of the delivery system and the intended route. Hopefully one will be able to meet such demands but not always. The stability of the drug, its metabolism in the liver, the intended site of drug action and associated side effects may dictate the nature of the system that is developed. The delivery system may be required to be localized at a specific site of pathology, eg. in the stomach through the use of gastroretentive concepts or in the colon through the use of a colon targeting system. Prototype systems can be tested in animal models, but it is essential that delivery systems are evaluated in man as soon as practicable. In our own work we use the sheep for nasal, vaginal, rectal and parenteral administration. The pig is used as a model for buccal absorption measurements and for studies in the gastrointestinal tract to include studies on absorption of challenging drugs from the large bowel.

Table 4
When to outsource?

• Transdermal
• Pulmonary
• Nasal
• Controlled release (oral)
• Implants (microspheres)
• Drug emulsions
• Liposomes
• Solubilization techniques

Delivery systems can take many shapes and forms, varying from patches to capsules to colloidal systems such as emulsions, liposomes and more recently nanoparticles. Some of these systems may well gain a new lease of life. It is interesting to note that in the emerging field of gene therapy, plasmid DNA compacted using cationic lipids or cationic polymers can be transformed into a particle of about 100 nm in size. Consequently, the technology that has been developed for the formulation and characterisation of nanoparticles (to include their evaluation in vivo) can now be applied directly to the various strategies currently being proposed for gene therapy.

Products developed for the administration of drugs and vaccines can be used for the administration of diagnostic agents. Similarly, but vice versa, formulation concepts developed originally for diagnostic agents can be applied to the successful formulation of targeting systems and vaccines. Some of these newer delivery approaches (and in particular those involving newer therapeutic agents) present special problems and challenges both in formulation and especially subsequent characterisation. Vaccine and gene therapy systems (to include microspheres, nanoparticles, polymer conjugates) can usually benefit from a detailed physicochemical characterisation. The biological read-outs obtained for these 'biopharmaceuticals' when evaluated by in vitro (and especially) in vivo tests can be highly complex in nature and involve multi-faceted cascade phenomena. The term 'fuzzy end-points' can

Table 5
Some key factors leading to successful collaboration between companies

- Proven expertise and core competence in drug delivery technology
- Good, open communication between both companies
- Experts and product champions in both organisations
- A thorough understanding of the drug and the product specification
- Sufficient funding for the completion of the project as defined by agreed milestones
- Dependable and flexible staff
- A clear appreciation of the time it takes to develop new product concepts through scale-up to production

be used to describe this situation. Under such circumstances, extensive detail of essential physicochemical properties, the content (and location) of active components, degradation processes and impurities as they relate to the delivery system can be invaluable when attempting to relate biological performance to formulation strategies.

It is not possible in this review to provide details of individual delivery systems and their advantages and disadvantages. However, excellent reviews can be found in various journals to include Journal of Controlled Release, International Journal of Pharmaceutics, Pharmaceutical Research, Advanced Drug Delivery Reviews, Journal of Drug Targeting, Journal of Microencapsulation, etc. Some of these journals also provide details of patent applications. Some key research areas for novel drug delivery where future work would be beneficial are given in Table 3.

7. Outsourcing of drug delivery

It is now well understood by staff in most companies (to include those directly at the bench and senior management) that it is difficult and costly to do everything in-house and that it can be beneficial to use the expertise of outside specialist companies in order to move forward rapidly. Some of the reasons given to outsource are given in Table 4. Following down-sizing and the various ever frequent mergers, there is a growing tendency for large pharmaceutical companies to out-source their needs in drug delivery. However, this is not necessarily an easy matter. There are many competing technologies available from different companies. Some technologies are more proven than others and for hard data, especially quality data obtained in man can often be in short supply. Small companies can also respond quickly to new discoveries and combine these into their research and development plans with competitive advantage. There is often a 'David and Goliath' situation where large companies carry with them (an inevitable?) inertia.

For a successful collaboration between a large company and a small drug delivery organisation, there are a number of essential requirements. These are listed in Table 5.