SEGUNDO CONGRESO DE BIOFARMACIA Y FARMACOCINETICA

SECOND EUROPEAN CONGRESS OF BIOPHARMACEUTICS AND PHARMACOKINETICS

PROCEEDINGS - VOLUME I
BIOPHARMACEUTICS

BAJO LOS AUSPICIOS DE LA FIP

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RECENT ADVANCES IN BIOPHARMACEUTICS - DRUG DELIVERY SYSTEMS

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INTRODUCTION

The prime objective in rational drug therapy is to achieve a controlled pharmacodynamic effect at the desired site of action, through the selective modification of some known biochemical or biophysical process. Examples include the interaction of drug molecules with receptor sites in certain tissues, the destruction of bacterial and tumour cells by chemotherapeutic agents, and the effect of drug molecules on transport processes.

In some cases it is a requirement that the administered drug reaches a multiplicity of sites in the body in order for it to have a therapeutic effect. However, with a large number of substances a selectivity of effect can result in both therapeutic benefit and minimal adverse reactions and side effects. This is not a new concept. Almost 100 years ago Paul Ehrlich (13) advanced the aim of specific chemotherapy, the extermination of an invading organism without injuring the host. Similarly, the concept of selective toxicity has been championed by Adrian Albert (1).

The temporal concentration profile at a given site in the body will be determined by the pharmacokinetic factors absorption, distribution and elimination (metabolism and excretion) which in turn are related to the physicochemical properties of the drug, the interaction of the drug with body systems and the nature of the delivery system.

In Ehrlich's day the role of the pharmacist was simply one of 'compounding' the prescribed ingredients in order to produce a medicine that contained the correct materials in the required amounts, with little or no thought about aspects of drug release and its appearance in the body. Not until the 1960's, with the advent of the science of biopharmaceutics did the pharmaceutical scientist move from physicochemical considerations such as formulation and stability testing to those of a more

biological nature (bioavailability, pharmacokinetics). This trend in pharmaceutics has continued and will do so even more actively in the future. The design of appropriate delivery systems for tomorrow's drugs as well as for the better use of existing compounds will involve not only a proper understanding of physical pharmacy and pharmaceutical technology but also a detailed knowledge of the interaction of pharmaceutics with physiology, pathology, biochemistry, immunology, cell biology etc. As a consequence, biopharmaceutics will become a multidisciplinary field. These changes are already reflected in the names given to new research groups, books and journals; Drug Delivery Research, Drug Delivery Systems, Drug Targeting. Unfortunately in some cases the science has not always kept pace with etymology. Space does not permit a detailed analysis of all recent developments in the field of biopharmaceutics. Instead the changing pattern of research and development within the field will be illustrated by reference to joint interrelated areas that encompass the research interests of the Pharmaceutics Group at the University of Nottingham

- membrane transport
- the gastrointestinal tract
- controlled release systems
- colloidal drug carriers

MEMBRANE TRANSPORT

Before a drug molecule can reach its site of action it will need to cross a variety of membranes. The general picture of the biomembrane is as a lipid bilayer, containing protein and glycoprotein functions (11). Drugs can cross this membrane by a simple process of passive diffusion, or by more specific mechanisms involving facilitated and active transport. Membrane permeability can be defined in terms of exact physicochemical quantities such as the diffusion coefficient and lipid solubility of the compound. Consequently, in theory at least it is possible to modify the structure of a molecule by making an analogue or prodrug that will provide more beneficial permeability characteristics (25). However, as with all such theoretical analysis, care has to be taken to ensure that the model proposed has physical reality. The lipid nature of membranes is an important but not exclusive factor when considering drug transport. The diffusion of a drug through the membrane will be controlled not only by

the nature of the membrane but also by unstirred layers (of water) adjacent to the membrane. These unstirred layers can become important when the molecule has a certain (optimal) lipid solubility. As a consequence the rate determining control is shifted from membrane to unstirred layer, and further increase in lipophilicity of the compound will not increase drug transport, instead it will lead to reduced water solubility and thence reduced biological availability through a dissolution limited process (14).

Studies on model systems comprising stirred liquid phases, and diffusion cells with well defined hydrodynamics have been invaluable in providing basic information about rate processes. They also yield data on the effect of molecular structure and ion pair systems for facilitated transport. These model membrane systems can be further modified to include biological samples such as human skin and used to assess the efficacy and perhaps eventually the mechanism of transport to include studies on so-called skin penetration enhancers.

Liposomes (which will be discussed further below) can be used with success as model membrane systems notwithstanding the difficulties created by their somewhat ill-defined structure. Various research groups have used liposome systems above and below their phase transition temperature to follow the uptake and release of model drug compounds and to answer structural and thermodynamic questions (11). Different modes of ionophore mediated ion transport have been examined using compounds such as crown ethers and and cyclic peptides (11).

The membranes lining the gastrointestinal tract readily permit the absorption of lipid soluble unionised species, by a process of passive diffusion, as well as low molecular weight solutes and ions by passage through aqueous pores and channels between cells. Ionized species and high molecular weight material (peptides) are normally little absorbed. Attempts are being made to improve the gastrointestinal absorption of poorly transported species through the use of chemical modifications (prodrugs) as well as so-called absorption enhancers. T Higuchi and others (20) have reported extensively on the use of salicylates and related compounds together with non-ionic surfactants for increasing the intestinal and rectal absorption of antibiotics and peptides (insulin).

Success has been demonstrated in animal models and also more recently in man. The mode of action of the enhancers has yet to be elucidated. What is certain is that the drug and enhancers have to be administered concurrently and that for rectal administration the lymphatic system is in some way involved.

For some drugs so-called absorption windows within the gastrointestinal tract have been proposed, but these have been difficult to find in practice. Similarly, active transport systems that can be exploited to enhance drug uptake are few in number. Earlier studies with liposomes containing insulin suggested that these colloidal particles could be used to enhance the oral absorption of peptides (12). However, such results have not been substantiated in subsequent investigations, although it is still believed that colloidal particles can be absorbed intact from the intestinal mucosa under certain circumstances. The possible role of 'M' cells which are associated with Payers Patches in the small intestine is worthy of investigation. Claims that 'large' amount of colloid are transported across intestinal mucosa are probably only valid for the immature gastrointestinal tract.

The buccal route of administration is another site that could usefully be examined for drug delivery. Although its absorption characteristics are similar to those of the lower intestinal tract, the drug absorbed from the buccal site is transported directly to the systemic circulation without passing through the liver, thereby avoiding the 'first pass' effect. Sustained release systems for the delivery of low doses of vasodilators have already been developed (19).

Various attempts are being made to increase the uptake of complex species from the gastrointestinal tract. However, the chances of success are rather limited because of the hostile environment (pH and enzymes). Other routes such as the nose and lung have more to commend them since the lining membranes are known to be very different to those within the gastrointestinal tract. Oxytocin is already administered intranasally and other compounds; besides cocaine and nicotine! (in the form of tobacco and snuff) should be examined (22). Fundamental studies on the nature of the nasal membrane and its discriminatory ability are urgently required. What is certain is that the nose and the

lung are well permeable to polar compounds such as disodium cromoglycate which is non-absorbed to any significant extent from the intestines. Once the physiological characteristics of these potential absorption sites have been evaluated, appropriate drug delivery systems can be designed which will need to take into account pathological conditions (eg asthma, rhinitis). Scintigraphic methods of evaluation using formulations labelled with gamma emitting radionuclides have already proved useful for this purpose.

THE GASTROINTESTINAL TRACT
Biological Availability

Since earliest times the oral route for drug delivery has been the one of choice; largely as a matter of convenience. As discussed above some drugs are poorly absorbed by this route while others are absorbed only to be metabolised extensively by the liver. Despite the widespread use of oral therapy surprisingly little is known about the fate of drugs in the gastrointestinal tract and the gastrointestinal transit of delivery systems. The correct values for basic physiological variables such as the pH in the stomach or colon are still in dispute as are the transit properties of different formulation types.

The research group at the University of Michigan (14) have made a significant contribution to our understanding of the inter-relationships between intestinal permeability, gastrointestinal transit, drug solubility and the resultant drug availability. They have used a physical model approach to identify the important physiological variables and physicochemical factors thereby enabling the definition of the required characteristic for a formulation in order for it to provide complete absorption of the drug from the small intestines. The model approach can be usefully extended to consider drug stability since an increasing number of new chemical entities present problems not only because of being poorly soluble but also their instability at physiological pH. Classical approaches to overcoming bioavailability problems (enteric coating, reduced particle size) are sometimes successful but in certain instances the normal pharmaceutical approach can be inappropriate. A good example is the new anticonvulsant progabide (6). This is a weak base that is poorly soluble in intestinal fluids, but very soluble in acid.

However, at stomach pH the half-life of the compound in short, being less than 20 minutes. A first approach would be to enteric coat a tablet containing micronised drug. However, if this is done the bioavailability is poor. Instead it has been found that by dosing the compound unprotected, the biological availability is good. These effects can be predicted using a computer simulation that takes into account the competing factors of relative solubilities in acid and alkaline media and their effect on dissolution, the stability of the drug in solution and the gastric emptying characteristics of solids and liquids. The computer model showed that the optimum sequence was one of rapid dissolution of the drug in the acid contents of the stomach followed by rapid emptying of the dissolved drug into the intestines (followed by further steps of precipitation and redissolution) (6).

This type of simulation exercise that uses not only preformulation data but can also include permeability values from in situ gut loop experiments and realistic estimates of physiological variables (pH values, transit times) should lead to a much more rational approach to the design of appropriate delivery systems.

Gastrointestinal Transit

Knowledge concerning the transit behaviour of drug delivery systems in the gastrointestinal tract is required for the proper design of controlled release dosage forms of different types as well as for delivery to specific sites. Transit times (gastric emptying, small intestine, colon) can be obtained using the technique of gamma scintigraphy (8). The method also provides a means of measuring in vivo release rates and their inter-correlation with pharmacokinetic data (blood levels) and the position of the delivery system in the gastrointestinal tract. The main conclusions that can be drawn from these studies so far is that the transit of a delivery system (be it solution, pellet or single unit form) from mouth to colon is largely determined by gastric emptying and that gastric emptying is dependent on the physical nature of the system (liquid or solid) and food intake. Once the formulation empties from the stomach the transit to the colon is almost independent of pharmaceutical and physiological variables. The average transit time in the intestines for liquids and solids is of the order of 3 to 4 hours. The unfed stomach

empties delivery systems rapidly, whereas in the fed state single units systems can remain in the stomach for many hours while small pellets empty in a progressive manner. Thus a controlled release system intended to give delivery of a drug over a 24 hour period must be retained in the stomach by some means (eg floating system, muco-adhesion) or alternatively the drug must have significant absorption in the large intestines. These scintigraphic results obtained with various drug delivery systems are in agreement with recent studies in animals and man using labelled foodstuffs and non-digestible markers. They indicate clearly the profound effect that diet can have on gastric emptying and colon motility, as well as the inherent inter- and intrasubject variation that can occur. Any attempt to design controlled release delivery systems with a desirable property, for example good spreading throughout the gastrointestinal tract must take such factors into account. Scintigraphic methods will also allow the examination of the concept of preferential absorption sites (windows for absorption) and methods for targeting drugs to selected areas of the gastrointestinal tract for local effect; particularly the colon.

Lymphatic Transport

The majority of drugs that are absorbed from the gastrointestinal tract are transported via the mesenteric blood supply into the portal blood circulation and thence to the liver. However, an alternative pathway exists for very lipid soluble compounds, the lymphatic route. Certain drugs such as some steroids and highly lipid soluble materials like Probucol and DDT can be taken up by the fat digestion pathway and thus find their way into the circulation in the chylomicrons fraction that enters the blood via the lymphatics at the thoracic duct. In doing so these drugs can avoid the possibility of first pass metabolism by the liver. Lymphatic uptake can be enhanced through the use of appropriate delivery systems in the form of lipid vehicles comprising selected vegetable oils that follow the normal fat digestion pathway that involves micellar solubilization by bile salts (21). Fractionated oils of short chain length and mineral oils do not enhance lymphatic transport. Attempts are now being made to improve the bioavailability of drugs using lipid soluble analogues and prodrugs of optimal lipophilicity and structure.

CONTROLLED RELEASE SYSTEMS

It could be claimed that the upsurge of interest in controlled release delivery systems was as a result of the formation of the Alza Corporation in the United States over 15 years ago. Certainly their philosophy of developing exclusively novel drug delivery systems, rather than new chemical entities, was a radical departure. Their early products were based largely on the sound application of physical chemistry and polymer science. The Ocusert for drug delivery to the eye, progestasert for drug delivery to the uterus, both comprised drug reservoirs that released the therapeutic agent in a controlled and predictive manner by means of diffusion control via biocompatible membranes (3).

The systems were elegant in terms of physical chemistry but were not successful commercially. The osmotic pump device from Alza, Oros, which is essentially a tablet that embibes water through a semi-permeable membrane and releases the drug through a small orifice, will surely gain acceptance despite a temporary setback in the form of the Osmosin affair. Other sophisticated (and less sophisticated) controlled release systems are available for delivery via the gastrointestinal tract. These include matrix systems based on polymers and waxes as well as various multiparticulate systems such as coated pellets and coated crystals. In some instances the systems so developed are clearly based on rational therapeutic and pharmacokinetic premises, but one also meets examples of controlled release systems for which the main rationale would appear to be one of commercial benefit and extension of patent life. This is not unexpected since today and no doubt in the future, the costs of developing new successful chemical entities are enormous. Yesterday's drug packaged in tomorrow's delivery system can make both commercial and therapeutic sense. Certainly if it were possible to deliver highly active drugs in a more selective way not only could present drugs be used more effectively but it would open up the possibility of re-examining compounds discovered in the past that had beneficial pharmacological activity, but were unsuitable because of a poor therapeutic ratio or limiting side effects. A dramatic example of the way in which selective delivery can lead to the use of highly toxic materials is the work on the ricin conjugate as selective immunotoxic agents (24).

Biocompatible and bioerodable polymer devices have been developed for the prolongation of release of drugs following their implantation into body tissues. The success of these systems is dependent not only on their release properties but also their minimum interaction with the body (4). The use of polymeric microspheres will be discussed below.

COLLOIDAL DRUG CARRIERS

It was mentioned in the Introduction that the concept of selective delivery of a drug to a specific site is not a new one. Indeed Paul Ehrlich proposed that suitable vehicles might be found which would have this ability, but it is only recently that the concept has been explored in earnest. Three different types of drug carrier can be identified; prodrugs, macromolecules (to include antibodies) and colloidal particles (12,24,25). Whatever the system chosen, a number of criteria need to be met if the chosen objective is to be achieved. The carrier must be able to reach the desired site through some form of homing effect or recognition. Next the carrier must concentrate at the selected site and release the drug there in such a manner to provide the desired response. The drug carrier system should be stable before administration and be biocompatible and biodegradable (the last either as a part of the release process or occurring soon after the drug has been released). The carrier system should be non-toxic and non-allergenic.

Various research groups (largely outside the established field of pharmaceutical sciences) are extremely active in this area at the present time. Many of them have the stated aim of delivering cytotoxic agents to tumours (and more importantly to metastases) since cancer chemotherapy represents an excellent example of the problems of attempting to deliver an agent to a designated pathogenic site without affecting the normal tissue. Colloidal carriers will be selected for detailed discussion since they provide useful insight into future developments with biopharmaceutics and possible limitations. They also demonstrate the basic and essential requirement of understanding the nature of the relevant biochemical and physiological processes, that can determine drug delivery. In effect, before one can develop a sensible targeting system one must first know the target! More often than not in the past, assumptions have been made about biological processes that were incorrect and