

Novel Drug Delivery Systems

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The number of drugs made available for clinical practice is increasing. However, many of the drugs used do not achieve their maximal potential in therapy, partly because of the poor or less suitable system of delivery used. Research for new delivery systems for traditional drugs are continuously being carried out to improve therapy. Drug delivery takes into account elements such as carrier, the route and the target using processes or devices designed to enhance the efficacy of the drug through controlled release. The 3 articles on aerosol therapy in this issue of the Medical Journal of Malaysia highlight the increasing importance of novel drug delivery systems.

Advantages of new drug delivery systems over traditional systems include the ability to deliver a drug more selectively to a specific site; easier, more accurate and less frequent dosing; decreased variability in systemic drug concentrations; absorption that is more consistent with the site and mechanism of action; and reduction in toxic metabolites. Four fundamental strategies govern the mechanisms of advanced drug delivery, i.e., physical, chemical, biological and mechanical¹.

Rapid growth and development is expected of drug delivery systems in the near future². Genetic engineering has mandated the development of new strategies to deliver biotechnically derived protein and peptide drugs and chemoimmunoconjugates¹.

Ideally, drugs should be administered so that the optimal amount reaches the target site to cure or control the disease state. Sophisticated systems containing different carriers are being developed. Macromolecules are promising examples. Amongst these are liposomes³, antibodies^{4,5}, polymers^{6,7,8,9}, polysaccharides and polyanions.

Liposomes are vesicles consisting of one or more concentrically ordered assemblies of phospholipid bilayers. Phospholipids have been used in conjunction with cholesterol and charged amphiphiles such as stearylamine or phosphatidic acid³. Liposomal affinity for various tissues can be changed by making liposomes containing phospholipids with various fatty acid chain configurations so that these microparticles may be either solid or liquid at defined temperatures^{10,11}. The alteration of surface charge has been shown to enhance drug incorporation and also influence drug release. Negatively charged vesicles enter the cell by fusion which allows the drug to be discharged into the cell cytoplasm. Neutral vesicles are incorporated into the cell by phagocytosis, which exposes the drugs to the lysosomal digestive system of the cells. Positive and neutral liposomes are cleared more slowly than negative ones. These factors allow researchers to design specific liposome carriers for certain pharmacologic agents. Liposomal entrapments include a variety of pharmacologically active compounds such as chemotherapeutic agents including anticancers, prostaglandins, steroids and bronchodilators to name a few^{12,13,14,15,16,17,18}. The liposomal entrapment has been shown to have considerable effect on the pharmacokinetic and tissue distribution of administered drugs. Liposomes have been used in a variety of routes of administrations, including intravenous, intramuscular, intraperitoneal and oral^{19,20}. To achieve site-specific delivery, a ligand such as monoclonal antibodies may be attached to its surface to permit it to preferentially attach to the target cells¹³. Despite the potential value of liposomes as unique carriers, the major obstacles are the targeting of a systematically given liposome to site of action;

physical stability and manufacture of the liposomal products^{2,3}. These problems still remain to be overcome.

Monoclonal antibodies are purified antibodies produced by a single clone of cells. They are engineered to recognise and bind to a single specific antigen. Accordingly, when administered, monoclonal antibodies home in on a particular circulating protein or cells that have the corresponding antigenic structure on their surfaces. It is the specificity of monoclonal antibodies that has made them valuable tools for delivering drugs to specific targets. They have been used to deliver cytotoxic drugs to malignant cells or enzymes to specific cell types.

Polymers are a class of ubiquitous materials possessing an inexhaustible variety of molecular architecture and they may be used for the fabrication of drug delivery devices. A number of polymers have been studied systematically and there is every indication that they can be clinically valuable. The potential of these promising polymers is still far from being exhausted and there is a strong possibility that many important developments will be seen in the near future^{6,7}.

Recent work in advanced oral delivery has been primarily focused on liposome technology and the concept that substances that are normally destroyed by the stomach can be protected long enough before they could be absorbed downstream. For cost and patient convenience, oral delivery is certainly attractive. The nature of biologic substances, however, will probably limit greatly those that can be delivered orally. Besides, where delivery rate control is critical, oral delivery, even when possible, would probably be insufficiently precise. Oral delivery would also limit the substance to bloodstream delivery to the disease site.

A number of drugs have been applied to the skin for systemic treatment. Transdermal therapeutic systems have been designed to provide controlled continuous delivery of drugs via the skin to the systemic circulation. The relative impermeability of the skin is well known. Elucidation of factors that contribute to this impermeability has made the use of skin as a route for controlled systemic drug delivery possible²¹. Basically, there are 4 systems available; the microsealed system (a partition-controlled delivery system that contains a drug reservoir with a saturated suspension of drug in a water-miscible solvent homogeneously dispersed in a silicon elastomer matrix), the matrix-diffusion controlled system, the membrane-permeation controlled system and the gradient-charged system²². Additionally advanced transdermal carrier includes systems such as iontophoretic²³ and sonophoretic²⁴ systems, thermosetting gel and liposomes. Many drugs have been formulated in transdermal systems, and others are being examined for this (e.g., nicotine, antihistamines, beta-blockers, calcium antagonist, non-steroidal antiinflammatory drugs, contraceptives, antiarrhythmia drugs, insulin and other hormones, alpha-interferons, etc.). Research also continues on various chemical penetration enhancers that may allow delivery of therapeutic substances, e.g., azone for larger-sized molecules such as proteins and polypeptides^{25,22}.

In comparison with many of the other drug delivery systems, implantable pumps and implants for variable rate delivery general are at a crude stage of development²⁶. The typical implantable pump consists of an electromechanically complex mechanism to regulate drug delivery from a percutaneous refillable system. The potential for electrical or mechanical failure is high and the systems are not yet sufficiently convenient to recommend in routine therapy. Problems with refilling of an apparently well-designed implanted reservoir have been observed while at the same time cutaneous energy transmission systems are not well-established. This system has been mainly developed to deliver insulin.

The potential for drugs to cure and relieve illness could be maximised if the drugs given could reach the target of required action in sufficient amount over sufficient time. Development in drug delivery systems are towards this objective. With the implementation of the Patents Act in many countries, pharmaceutical companies are more inclined to invest in developing effective delivery systems to maintain their

competitive edge against generic products while at the same time developing other new chemical therapeutic compounds. As such, one would expect rapid advances in drug delivery systems in the future.

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