

CHAPTER 1: THE NEED FOR AND ADVANTAGES OF DELIVERY SYSTEMS

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1.1 Problem statement and rationale

All drugs have to be absorbed in sufficient quantities from the site of administration, then be transported to its site of action and released from its formulation in an effective way to ensure the maximum therapeutic effect and minimal toxic effect for the patient. This whole process is reliant on the effective delivery of the drug at its target site in a cost effective way. Many drugs that have been in therapeutic use for years are characterized by low bioavailability, generally as a direct result of either inadequate absorption or delivery or both.

Since the 1990's there has been a growing trend that not only the design, but also the formulation and delivery of drugs need to be based on biological premises. Furthermore, the acceleration in the discovery of new therapeutic moieties (chemical, biological, genetic and radiological) has ensured that there are ample numbers of particularly efficient therapeutic agents readily available to eliminate both chronic and opportunistic diseases. The rapid progress in the design of new generation of drugs has not been matched by the development of safe and effective delivery systems for these compounds. According to Tang *et al*,

approximately 40% of new chemical entities exhibit poor and generally variable bioavailability due to their poor aqueous solubility, high hydrophobicity with limited solubility in the aqueous phases of the body and high intra-subject/inter-subject variability and lack of dose proportionality (Tang *et al.*, 2008). For such new candidate drugs to become therapeutically useful, effective dosage forms and formulations to improve the bioavailability of such drugs is needed.

During drug design, predominant attention is often placed on the therapeutic effectiveness achieved, while other aspects such as stability and dosage form are neglected, leading to failure of the drug. Toxicological and stability profiles are important criteria in the evaluation of therapeutic agents. Ideally, the bioavailability, biodistribution, pharmacokinetics and, ultimately, the therapeutic effect characteristic of the administered moieties need to be predictable and controllable. The above factors have led to an increasing demand for delivery systems capable of protecting, transporting, and selectively depositing those therapeutic agents at desired sites.

1.2 The concept of drug delivery

Delivery systems are not limited to drug delivery systems but are extensively applied in medicine and biotechnology, as well as in the food and cosmetics industries. These systems consist of the most versatile classes of biomaterials. An application of the Pheroid™ delivery system to the cosmetic industry is discussed in Chapter 4.

Unsophisticated delivery systems had their origin at least as far back as the mixing of Arabian glue with pigments by the ancient Egyptians. Delivery systems of various degrees of sophistication have been developed during the last millennium, starting with simple emulsions. Applications in the pharmaceutical industry include a variety of drug delivery systems and/or drug carriers with different routes or modalities of administration (Whittlesey and Shea, 2004; Teeranachaideekul, 2008), carriers of immobilized enzymes and cells (Fernandes *et al.*, 2006), biosensors (Reimhult and Kumar, 2008), 'smart' materials that are reactive to biosignals (Stayton *et al.*, 2005), bioadhesives (Guo *et al.*, 2008), tissue scaffolding and implant carrying drugs, tissue-engineering matrices (Whittlesey and Shea, 2004) and the components of diagnostic assays (Mansur *et al.*, 2005).

Common sense will dictate that the process of drug delivery encompasses a number of interdependent steps, each with its own characteristic challenges to be overcome. The dosage form is dependent on the site or mode of administration of the drug, which in turn is dependent on the desired therapy and the drug used for the therapy. For a drug to be transported to its site of action, it has to cross biological barriers. These barriers are determined by both the site of administration and the site of therapeutic action. The drug should not be deactivated, degraded or cleared during the transport processes. Once the drug has arrived at its site of action, it has

to be released from the delivering biomaterial without losing its efficacy through chemical or stereo-chemical instabilities or interactions with surrounding body components (see also figure 2.1).

The term drug delivery system is itself used to describe a variety of systems. In the so-called "Trojan horse" systems the drug is entrapped inside a particle or body during manufacturing or after manufacturing by a mixing process. The entrapment is generally a result of the interplay of electrostatic forces. These systems are useful when the drug needs to be masked by the biomaterial and should allow some measure of protection against harsh environments and enzyme degradation. In drug carrier systems, the drug is conjugated to the carrying material either by covalent or electrostatic linkage. In these systems the drug would more often be exposed to the environment, with concomitant advantages and disadvantages. In addition, if the bond is covalent, it will have to be broken for the drug to be released and to fulfill its therapeutic role. Where drug entrapment or conjugation is based on electrostatic forces, those forces will have to be overcome or negated for the drug to be released. In an ideal drug delivery system the chances and rate of physical delivery of the drug to its site of action would be supported or maximized by the pharmacokinetic processes inherent in the delivery system or the biomaterial used to design the delivery system (Petрак, 2006).

The identification of an active drug molecule is only the first step in the creation of an effective and marketable pharmaceutical product. Development of a new drug also requires a safe, reliable, stable and effective method of administration and of delivery. The process involves multi-disciplinary aspects, such as physical and analytical chemistry and analysis, biological function analysis, pharmacology, toxicology, pharmaceuticals and formulation, and chemical engineering. This thesis will not attempt to address all of these aspects, but will touch upon some of them in the following chapters.

1.3 Design of a delivery system

During the design of a delivery system, cognizance has to be taken of nonspecific interactions occurring between the drug-carrier conjugate and the environment of the systemic compartment (i.e. blood and lymph), which compartment is mainly an aqueous, polar medium. According to Van Oss (2003), the more than 17 types of reported non-covalent interactions in polar media may be represented by a combination of electro-dynamic interactions, electrostatic interactions and hydrogen bonding. The most obvious approach is to try to eliminate all interactions. The approach used by most delivery system or biomaterial designers is to use water-soluble, inert macromolecules as drug carriers or carrying material and to try to get the biomaterial to mask interactions between the drug and the environment. Again the concept of 'Trojan horses' comes to the fore, with the biomaterial to some extent 'tricking' the body to

overcome the biological and disease barriers presented by the body, such as gastro-intestinal absorption, opsonization, clearance, blood-brain barrier, access to malignant cells, and penetration of bacterial cell walls (Petрак, 2006).

For all administration routes, with the exception of the parental route, the drug has to cross major physical and/or chemical barriers that could hamper drug absorption and delivery. The different routes of drug administration thus differ as to their individual environments and have to be analyzed as to their inherent permeability, enzyme activity and mucus secretion. Optimized delivery across these barriers is not easily achieved and this frequently results in ineffective therapy and dosage forms.

Numerous efforts have focused on the development of drug carrier systems able to enhance the therapeutic efficacy of drugs. A variety of polymeric molecules and lipid-based systems have been investigated as carriers of both covalently bound and physically entrapped drug molecules. Delivery systems are used in order to

- improve their water solubility;
- decrease their toxicity;
- increase their permeability;
- protect them from possible enzymatic degradation or hydrolysis; and/or
- increase the site-specific delivery of drugs.

1.4 Objectives in the development of a drug delivery system

When developing new drug delivery systems, the main objective is the ability to rationally manipulate the pharmacological profiles of drugs and their concomitant therapeutic indices. Such delivery systems may then be used to modify potential therapeutic agents towards:

- (i) the creation of new pharmaceutical moieties;
- (ii) an improvement in the effectiveness or reduction of the side-effects of an existing therapeutic;
- (iii) the extension of the patent lifetime for an already marketed drug;
- (iv) drug delivery processes across biological membranes in order to enable more efficient bioavailability and delivery of drugs;
- (v) the development of novel cost effective drug delivery systems; and
- (vi) the development of the physico chemical aspect of formulation for the industry.

The design of delivery systems is directly related to each specific therapeutic or diagnostic application. A delivery system for an anti-neoplastic drug molecule to the brain will need

inherently different characteristics than that of a system required for the delivery of a DNA vaccine to the lung. The ideal delivery system would be one that can be manipulated to:

- (i) prolong the retention of the drug in the circulation;
- (ii) enhance the deposition or accumulation of the therapeutic molecule in a particular target tissue or organ;
- (iii) target either actively or passively, the therapeutic molecule to a particular cell population, such as the macrophages;
- (iv) target the therapeutic molecule to a specific intracellular component, such as the nucleus or mitochondria;
- (v) prolong the retention of the therapeutic molecule within the body or within a specific organ; or most probably
- (vi) a combination of any of the above.

The listed objectives are daunting and although generalized it is a good starting point for drug delivery and biomaterial design. In practice, these objectives relate to a much simpler list of objectives if biomaterials with well-defined structures and with specific chemical, physicochemical, mechanical and biological properties are used within the physiological framework of the body.

1.5 General requirements of drug delivery systems

Besides being an effective delivery system and complying with the objectives stated above, some general requirement may be added. These requirements do not pertain to properties related to a specific administration mode or specific barrier functions; those will be discussed within the ambit of each application of Pheroid™ technology.

1.5.1 The material should be non-toxic and non-antigenic

Since ancient times, even before Hippocrates (Breast, 1944) and in the times of Isocrates, the first premise in medicine has been to do no harm. That means that the medicine must be non-toxic. This may be even truer for a biomaterial that is in itself not an active pharmaceutical ingredient (API). Non-toxicity of the delivery system itself is a requirement in terms of genotoxicity, cytotoxicity and systemic toxicity. No toxicity should be present when acute, chronic reproduction and mutagenic toxicity tests are performed. Oral doses can be safely administered. None of the components should present a toxicological hazard when administered orally, parenterally or intravenously. In fact, one of the contributions that can be made by the delivery system is a decrease in the toxicity of the API (Pettrak, 2005).

1.5.2 Biocompatibility

Besides being non-toxic, the material used in the manufacturing of a drug delivery system must be biocompatible. The majority of synthetic materials suffer a general lack of biocompatibility and synthetic delivery systems are therefore often associated with inflammatory reactions, which limit their use. For this reason, the study concerns itself with biomaterial as starting material for delivery systems, with reference to synthetic systems only when relevant or pertinently informative. Biocompatibility specifically concerns the reaction of the biomaterial with blood and / or tissues, depending on the site and purpose of use. For blood-contact applications, biocompatibility is determined largely by specific interactions with blood and its components. For applications not involving blood contact (e.g. transdermal applications), the choice of formulation generally depends on its tissue biocompatibility.

1.5.3 The delivery system should be biodegradable

Since complete clearance of all ingested or parenterally ingested drugs are not guaranteed, the delivery system should be degradable at a reasonable rate or within a specific time limit without chemical interference. No accumulation of the material should occur. The degradation may be the result of enzyme interaction normally present within the body and should not rely on degradation by the conditions present in the stomach or GI tract alone.

1.5.4 The delivery system and API(s) should be compatible

Ideally, a delivery should be non-reactive towards the API it carries or holds, as APIs with a large variety of chemical characteristics is available to be used as drugs. Furthermore, the material should preferably be non-reactive towards systemic biological components. Totally inert biomaterials are scarce or non-existent and this requirement may be one of the most limiting.

1.5.5 Delivery systems should be versatile

Following from the above, it should be possible to use a biomaterial for more than one application, more than one API, and more than one administration route and dosage form. This implies that the biomaterial should have readily adjustable properties. As the degree of sophistication increases one would expect better versatility, but the opposite seems to be true: a high level of sophistication is generally associated with specialized systems while emulsions still seem to be the system with the highest versatility.

1.5.6 Delivery systems should be stable

Numerous drug delivery systems have been developed, but clinical success is still relatively rare, often due to a lack in the stability of the biomaterial or the API-biomaterial combination. Therefore, despite the large number of existing delivery systems, additional studies in this field, concomitant with an often lengthy regulatory-approval process, are motivated by the need for more stable biomaterials for delivery systems.

1.5.7 Manufacturing of delivery systems should be reproducible

One of the principal stumbling blocks to overcome in the development of delivery systems is the establishment of reproducible production methods for both the bulk material from which the delivery system is composed, as well as the delivery system itself. Generally, the higher the structural complexity of the system, the more modification is required and the less stable is system. Additionally, significant batch-to-batch variations occur in most biomaterial-based delivery systems because of their inherent instability and problems in bulk preparations. If the system is to be prepared by aseptic processing and sterilized or disinfected before use, the sterilization method should not cause structural or undesirable chemical changes.

1.5.8 Manufacturing should preferably be environmentally friendly

The cleaner and greener the manufacturing of both the components of the delivery system and the delivery system itself, the better. Preferably the total manufacturing process should be environment friendly, with no major chemical plants required for manufacturing, or toxic waste produced during the manufacturing process.

1.5.9 Cost and ease of preparation

In designing a delivery system for application to local diseases, cost is a major factor. Working within the financial constraints of both the final product and the finance available for drug development, the delivery system must of necessity be

- composed of relatively inexpensive material;
- simple in design;
- inexpensive to manufacture.

The evaluation of inexpensive, versatile, commercial biomaterials produced by optimized processes is thus well-worth investigating.

1.6 Conclusion

The above being the case, the biomaterials used in the composition of the delivery system must be easily available and inexpensive, the manufacturing process cannot be sophisticated and should contain as few steps as possible and the equipment needed for the manufacturing plant should not be expensive with limited quality control required overall. The selection of biomaterials is challenging, especially since a wide variety of materials is available for different applications and no simple set of rules can be used to screen the biomaterials. The next chapter (Chapter 2) will evaluate colloidal systems within the objectives and requirements stated above, while chapter 3 is an attempt to define a rational basis for the success of the Pheroid™ carrier of compounds, be they of a therapeutical or agricultural nature.

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