Essential properties of drug-targeting delivery systems

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How, if at all, can drug delivery help to create ideal drugs? After four decades of trying, an effective site-specific drug-delivery system has not yet been developed. This review draws attention to the pharmacokinetic conditions that must be met to achieve a successful performance by site-selective drug–carrier delivery systems. In a drug–carrier approach, a drug is attached to a macromolecular carrier via a chemically labile linker. The carrier transports the drug to its site of action and releases it at the target site. For this simple approach to work, several fundamental conditions (nonspecific interactions, target site access, drug release and drug suitability) must be satisfied. The importance of these essential requirements, not always recognized in the development of drug-delivery systems, is discussed and illustrated by recent examples selected from the literature.

Can drug delivery help to create ideal drugs? Over a century ago, Paul Ehrlich [1] described a drug that is aimed precisely at a disease site and that would not harm healthy tissues as a 'magic bullet'. However, at therapeutic concentrations, very few drugs bind solely to their intended therapeutic target. A concept of site-specific drug-delivery systems was formed and, according to this concept, a drug would be attached to a carrier that would take the 'pay-load' (the drug) to the target (attached to the carrier via a targeting ligand) and release it at the target site. The practical realization of this concept has fascinated and eluded scientists ever since.

After early attempts by Wade *et al.* [2], four decades of research have not yet produced an effective, generally applicable, site-specific drug-delivery system [3]. Only 'target-homing' drugs that specifically recognize their pharmacological target have achieved any degree of site-selective delivery. For example, Rituxan® was the first therapeutic antibody approved by the FDA (in November 1997) for treating cancer. Rituxan® works by binding to a particular protein (the CD20 antigen), located on the surface of normal and malignant B cells, that recruits the body's natural defenses to attack and kill the marked B cells. Stem cells (B-cell progenitors) in bone marrow lack the CD20 antigen, allowing healthy B cells to regenerate after treatment, returning to normal levels within months. So, although this antibody does not differentiate between normal and malignant cells, its action is limited to one particular, renewable cell type. Serious adverse events (fatal infusion reactions, tumor lysis syndrome and severe mucocutaneous reactions) are, nevertheless, still associated with this antibody treatment.

Essential properties of drug-targeting delivery systems

For a drug to exert its desired effect it needs to be in physical contact with its physiological target, such as a receptor. Site-selective drug delivery ensures

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1359-6446/05/$ – see front matter PII: S1359-6446(05)03698-6

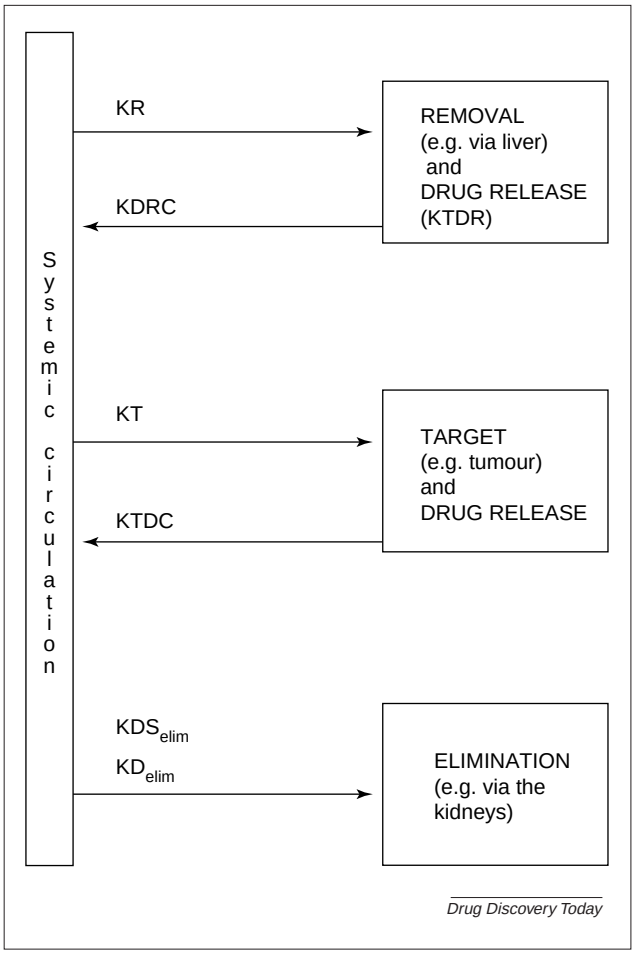

FIGURE 1

After systemic administration of a drug–carrier conjugate into the central (blood–lymph) compartment of the body, the access, retention, release and elimination of the conjugate and its individual elements to the relevant organ, tissue and, ultimately, to the drug target are determined (in the main) by the following rate processes: elimination of drug–carrier conjugate (KR), release of free drug at the non-target site (KDRC), delivery of drug–carrier conjugate to the target site (KT), release of free drug at the target site (KTDR), removal of free drug from the target site (KTDC), elimination of the drug–carrier conjugate (KDS$_{elim}$) and the free drug (KD$_{elim}$) from the body.

that such interactions take place only in the desired anatomical location of the body. Although, in principle, every drug might benefit from site-selective delivery not every drug is equally suitable for the process. Drugs that are not retained at the site of action for a long enough period of time will not benefit from site-specific release. Also, drugs that have the same site for efficacy and toxicity will not improve through site-selective delivery and their effect:side-effect ratio could even get worse. Evidently, drugs that already have an inherently high specificity for reaching and interacting with their targets, for example therapeutic antibodies, do not need to be considered for targeting. Several publications offer mathematical analyses of targeted delivery kinetics [4–7] and specify the properties needed for the site-specific delivery approach to work. It appears, however, that realizing these requirements has, to date, proved to be elusive.

The minimum requirements for a targeted drug-delivery system to have any chance of returning the 'wished for' performance must be considered. Focusing on the drug–carrier conjugate to be administered into the systemic compartment of the body, the key events governing such drug delivery are shown in Figure 1. The events are discussed in terms of rate constants corresponding to each depicted event. In an ideal delivery system the pharmacokinetic processes would progress at a rate that would maximize the chances of the eventual physical delivery of the drug to its target.

Rate of elimination of drug–carrier conjugate (KR)

It is essential that the drug–carrier conjugate is not removed too rapidly from the circulation. If it is eliminated from systemic circulation more rapidly than it is delivered to the target site, the amount of conjugate at the target site might never be enough to provide the required concentration of free (unbound) drug. The design and the production of the delivery system need to eliminate all nonspecific interactions occurring between the drug–carrier conjugate and the environment of the systemic compartment [8,9]. The central compartment of the body (blood and lymph) is essentially an aqueous, polar medium. Van Oss [10] noted that at least 17 different types of noncovalent interactions in polar media were reported in scientific literature and demonstrated that it is always possible to represent them (for aqueous media) by a composite of the three primary forces: electrodynamic, electrostatic and hydrogen bonding. In the design of a drug-delivery carrier, one needs to consider the contributions of these three primary forces to the carrier's overall properties. The most frequently employed approach is to use water-soluble, inert macromolecules as drug carriers, or to attach them (covalently or by adsorption) to the surface of drug-carrying particles. The function of the carrier is to mask all unwanted interactions between the drug and the environment until the drug is released from the carrier at the target site.

Rate of release of free drug at the non-target site (KDRC)

Depending on the amount of drug, the release of drug away from the target site could nullify any benefits that might potentially come from delivering the drug to the target site. This could be because the amount of drug reaching sites of systemic toxicity might become too high or, second, the amount of free drug that reaches the target site after it has been released from the conjugate at non-target sites might be greater than the amount of drug actually being delivered to the target using the delivery system. Every claim that a drug-delivery conjugate delivers the drug preferentially to the target site should be documented by measuring the actual amount of drug delivered; it should not be inferred from an observed change in the apparent efficacy of the drug conjugate. Examples of this will be given later in this review.