The Role of Payload Hydrophobicity in Nanotherapeutic Pharmacokinetics

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ABSTRACT: Although drug delivery with nanovectors is regarded as one of the paradigm-shifting advances in modern medicine, the compatibility and performance of drug–vector formulations have not been systematically studied in terms of their physicochemistry and pharmacokinetics (PKs). The drug delivery systems (DDSs), currently available in clinics or trials, were analyzed based on hydrophobicity and anatomical therapeutic chemical (ATC) classification of drug payloads. Four major types of DDSs differentiated based on DDS structure and drug hydrophobicity, where payload hydrophobicity decreased: micelles, serum albumin, liposome membrane, and liposome interior. A strong relationship between the increase in half-life in DDS formulation and drug hydrophobicity was found with up to 200-fold greater increase for hydrophilic drugs. The analysis results seemingly integrated PKs, ATC, and hydrophobicity to reinforce the development or optimization of drug delivery vectors and their formulations. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: log *P*; liposomes; albumin; micelles; nanoparticles; formulation vehicles; formulation; lipoproteins; pharmacokinetics; physicochemical

INTRODUCTION

Advances in nanotechnology and material sciences have spawned many approaches to enhance drug delivery.[1–3] The majority of these methods rely on nanoparticles and microparticles, which span a wide range of sizes and shapes. These particles serve as delivery vectors[4–6] for the transport of image-contrast agents[7,8] and drugs. A large variety of particles are available as vectors, such as lipid particles,[9] liposomes,[10] micelles,[11] serum albumin particles,[12] fullerenes,[13] carbon nanotubes,[14] dendrimers,[15] silica, metallic particles (gold, iron oxide, etc.),[16] polymeric particles [e.g., poly(lactic-*co*-glycolic acid)],[17] and hydrogels.[18] Drugs that employ vector-based drug delivery systems (DDSs), such as Doxil™, have been extensively used in clinical medicine.[19] Over the last decade, more DDSs have entered clinical trials, and even more have been actively studied,[20] especially in the treatment of cancers.

Some drug delivery strategies involve the modulation and differentiation of vector biodistribution in organs or tissues. Therefore, such approaches increase the delivery of the therapeutic payload in certain organs.[21] DDSs have gained benefits over classical drugs in pharmacokinetics (PKs), such as increasing circulation time or reducing toxicity. However, the magnitude of benefits is sometimes poorly defined, as is referenced in several papers.[22,23] Vectors have their own PK profiles that may differ from those of therapeutic substances because of their size and surface properties. As a result, the vector's circulation and interactions with cells may be impacted, thus resulting in altered biodistribution. Carriers can also employ the enhanced permeability and retention (EPR) effect.[24] The EPR effect is a result of two properties of tumor tissue: leaky vasculature with fenestrations of up to several microns in size,[25] and greater than normal retention within the tumor's interstitial fluid. Because of EPR, most polymeric drugs accumulate in tumor tissues at concentrations that are five to 10 times or 10 times higher than those in plasma or normal tissues, respectively.[24] PEGylated (also referred to as sterically stabilized or Stealth™) liposomes display inhibited interactions with plasma proteins and mononuclear phagocytes, resulting in prolonged circulation times and increased accumulation in the interstitial fluid of tumors at levels comparable to those of reticuloendothelial system-rich organs.[26] The mononuclear phagocyte system (MPS), which consists of phagocytic cells in the lymph nodes, spleen, or Kupffer cells in the liver, sequester circulating particles, including carriers.[27] This effect is not desired frequently, and delivery agents can be chemically altered to make them invisible to MPS. An example of this alteration is a modification with PEG.[28] Because of the EPR effect and MPS, the PKs of vectors are very different from those of small molecule drugs. A drug that is associated with a carrier will adopt the carrier's PK profile,[29] both with advantages and negative consequences.

The efficacy of DDSs depends on many properties, including how much of a drug can be loaded into a carrier. If no covalent binding is involved to retain drugs inside the carrier matrix, the loading and release of drugs from such DDSs rely on diffusion and concentration gradients, as well as the degradation of the carrier. Because many different materials of varying compositions are possible for the production of vectors, each DDS will have a specific affinity for a particular drug. Drug hydrophobicity may influence its loading and release, making it more or less efficient.[30–38] Moreover, the hydrophobicity of a carrier may

Abbreviations used: ATC, anatomical therapeutic chemical; DDS, drug delivery system; MPS, mononuclear phagocyte system; HSA, human serum albumin; BSA, bovine serum albumin; MTD, maximum tolerated dose; AUC, area under the curve.

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also have the same effect.[39–41] However, the carrier's influence is not significant because of the tendency for different immiscible systems to have comparable partitioning[42] (Fig. A.1).

Log *P* is the logarithm of a partitioning coefficient between the water and octanol phases for a chemical compound. The partitioning of drugs is a complex process that depends on many physicochemical aspects, where log *P* provides an integrated phenomenological measure. Log *D* is an alternative parameter that accounts for the charge of drug at different pH levels. However, scarce experimental data are available for log *D*. In addition, it is less reliable than log *P* because of cumulative error in log *P* and pK_a measurements.[43] Log *P* is one of the five parameters in the Lipinski rules for drug likeliness, and is employed in drug discovery.[44] Because log *P* can be easily evaluated with good accuracy using computational algorithms,[45] it is widely accepted and can be found in many databases.

In addition to the drug's interactions with the drug media and vector matrix, drug loading and release may also be affected by the surrounding physiological media, which can be expressed in terms of the log *P* value of the drug. Studies investigating the systemic basis of how drugs and vectors may be coupled are limited.[46] Because log *P* may affect both drug delivery and PK, DDSs can be created in response to specific therapeutic aims to maximize the synergism of the drug's and vector's physiochemical properties.

We assume that there should be certain level of compatibilities between drug vectors and drugs. Therefore, we have analyzed DDSs by investigating the physicochemical, PK, and therapeutic properties of drugs to establish relations leading to better systemic knowledge about existing and future DDS.

METHODS

Drug Information

DrugBank is a freely available database, which contained 6711 total entries at the time of the study.[47,48] The entire dataset, including small molecules and biomolecules, was parsed in XML format and analyzed with Knime software.[49,50] Drug properties, including log *P*, bioavailability, and half-life ($t_{1/2}$), were extracted with the accompanying structures. The parsing and analysis of the dataset were automated to prepare information for further statistical evaluation. Most of the log *P* values for salt-free drugs were taken from an extensive study by Hansch and Leo.[51] In this study, we will refer to experimentally established log *P* values in the octanol–water system, unless otherwise stated. Missing log *P* values in Table 1 were supplemented by calculations with Xlog *P* implementation in Knime software,[49] and they are marked with asterisks. The performance of Xlog *P* was validated with DrugBank drugs, and the results are displayed in Figure A.2. Drug bioavailability and $t_{1/2}$ were extracted with regular expression text analysis tools, and then verified by visual inspection.

After DrugBank was updated on August 2, 2013, the experimental log *P* values of several drugs (doxorubicin, daunorubicin, floxuridine, and fluorouracil) were altered, although the official database snapshot was not updated at the time of manuscript submission. The changes for both floxuridine and fluorouracil were very minor (0.2 and 0.1 log *P* units). However, the log *P* values for doxorubicin and daunorubicin drastically increased from −0.5 and 0.1 to 1.27 and 1.83, respectively. This change seemed ambiguous because of the known solubility of these compounds. Therefore, we averaged the log *P* values that were documented in various studies. The calculated average log *P* value for doxorubicin and daunorubicin were −0.26,[44,52–58] and 0.72,[57–59] respectively. All of these values were determined at pH 7–7.2 for salt-free drugs.

Data regarding the anatomical therapeutic chemical (ATC) classification was collected, along with defined daily doses and admission routes.[60,61] Most of the drugs in DrugBank have ATC codes assigned to them, and some have several codes because of the use of the same chemical compound for different indications. The ATC code consists of several levels that describe the anatomical, therapeutic, and pharmacological classification of a specific chemical moiety (http://www.whocc.no/atc/structure_and_principles/). An extensive ATC code description is given in Tables A.1–A.2. In this study, drugs in DrugBank were grouped according to the first, ATC (1), and second, ATC (2), levels of ATC classification: anatomical location and therapeutic action.

Statistical Analysis

The extracted data were analyzed using the StatSoft Statistica 10 software. We chose to directly analyze log *P* values instead of the partitioning coefficient (*P*), because log *P* exhibits normal distribution, which was also observed for all different subgroups of drugs. *P* distribution is highly asymmetric and cannot be easily parameterized. Datasets that were categorized into ATC (1) and ATC (2) classifications and exhibited normal distribution was evaluated using parametric one-way analysis of variance. After the heterogeneous categories were identified and homoscedasticity was proven by the Levene test, pairwise comparisons of categories were performed with Tukey's honest significant difference test for samples with unequal *N* (Spjotvoll/Stoline). This approach allowed us to identify significantly different drug groups at both ATC (1) and ATC (2) levels (Tables A.3. and A.4.). For box-and-whisker plots with both normal and nonparametric distributions, only categories with more than four members were used.

Pharmacokinetics

Detailed PK analyses were performed for DDSs with sufficient data. We used the mean values of PK parameters at the same dosage levels, and preferentially selected the maximum tolerated dose (MTD) or the most commonly used dose of the free drug if the MTD was unknown. In the case of paclitaxel, there was no carrier-free formulation of the drug; therefore, we used Taxol™ as a reference, regardless of its use of CremaphorEL.

RESULTS

This study depended on well-defined reference data. What makes a good DDS depends on the purpose of that particular system. To provide the least-biased analysis, we assumed that DDSs that are currently employed in clinics or clinical trials are sufficiently well developed. Their usage in clinics suggests that the given DDS meets some clinical and engineering expectations. Therefore, the study began with a brief analysis of such DDSs, where the physicochemical boundaries were evaluated and compared against available drugs and therapeutic classifiers. The second part of the study dissected the PK properties of the DDSs, and established correlates to couple the properties of drugs and DDSs with their PK. Less relevant data related to