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Excipient pharmacokinetics and profiling

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ABSTRACT

Novel pharmaceutical excipients, and new derivatives of currently used excipients, are new chemical entities and as such have to go through extensive pharmacokinetic and toxicologic evaluations before they can be approved for use in pharmaceutical products. The high cost of these safety studies, long development timelines and risks of failure have hampered development of new excipients and drug delivery systems. Various, relatively simple, methods are used for prediction of pharmacokinetic properties of new drug candidates based on their physicochemical properties. Similar methods can be applied to predict pharmacokinetic and ADME properties of new excipients. Simple methods, like the Rule-of-Five and the Biopharmaceutics Classification System, can be applied for early prediction of pharmacokinetic and ADME properties of new excipients and drug delivery systems although the aims can be different. While the objectives in new drug development are to maximize drug bioavailability and pharmacologic response the objectives in new excipient development can be reduced excipient bioavailability and enhanced rate of elimination. Here pharmacokinetic properties of some currently used excipients are reviewed and shown how some of the simple methods used to predict drug-like properties can be applied to predict desired properties of novel excipients and drug delivery systems.

1. Introduction

Pharmacokinetics is the kinetics of drug absorption, distribution, metabolism and excretion (ADME). These four criteria all influence drug levels and kinetics of drug exposure to tissues and hence influence the performance and pharmacological activity of a drug. ADME profiling and toxicological (ADME/Tox) screenings are conducted during drug discovery and development processes. ADME/Tox properties of a new biologically active compound will determine if it can be developed into a useful pharmaceutical product (a drug product). However, a pharmaceutical product, such as tablet or parenteral solution, does not only contain an active pharmaceutical ingredient (API) but also several inactive ingredients that are commonly called pharmaceutical excipients or simply excipients (from Latin excipere meaning 'to except' or 'other than' [the API]). While an excipient is considered to be inactive pharmaceutical ingredient it enables delivery of API to a patient. Frequently, the API makes up only small fraction of a drug product with the rest being a mixture of excipients such as tablet fillers used to increase volume or weight of tablets, binders and disintegrants. Sometimes drug release modifiers are included to provide sustained drug release and colorants to give the product a distinctive look. Liquid products frequently contain buffer salts for pH control, solubilizers, polymers for enhanced viscosity, antioxidants and antimicrobial preservatives. Although a pharmaceutical product may contain much larger amount of excipients than of the API there is no independent regulatory approval process for new excipients in the EU and US. It is not known if a new excipient will be approved until it has been included in a new approved drug product. Although excipients are by definition pharmacologically inactive their regulatory requirements are in praxis comparable to those of new drug substances regarding, for example, toxicological evaluations and in vivo performance, with development processes that can take seven years at a cost of between 10 and 50 million USD (DeMerlis et al., 2009; EMA, 2007; IPEC, 2014; Osterberg et al., 2011). In this context the pharmacokinetics of a new excipient should preferably be determined in animals and humans during new product development. ADME profiling should be an integral part of new chemical development in drug delivery, including development of new chemicals and novel drug delivery systems such as nanocarriers and enabling polymers, all of which are characterized as new pharmaceutical excipients.

Physicochemical properties of excipients, such as their aqueous solubility, ionization (pK_a), lipophilicity, number of hydrogen bond (H-bond) donors and acceptors, polar surface area, physical and chemical stability, and molecular shape and weight, will affect their fate in our body. Good understanding of how physicochemical

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properties of pharmaceutical excipients affect their interactions with our body is of essence to pharmaceutical scientists in their search for ever more effective excipients and drug delivery systems. Rules and guidelines that were developed for rapid profiling of new drug candidates, such as Lipinski's Rule-of-Five and the Biopharmaceutics Classification System, can be applied during development of new excipients and drug delivery systems (Kerns and Di, 2008).

Here the relationship between physicochemical properties and pharmacokinetics of some currently used excipients will be reviewed and shown how the methods used for rapid profiling of new drug candidates can be applied during development of new excipients.

2. Pharmacokinetic parameters

When a compound, such as a drug or an excipient, is injected into the systemic blood circulation (i.e., administered by intravenous (IV) injection) it is rapidly distributed within the body and then more slowly eliminated by metabolism and/or as intact compound in urine (Fig. 1). Likewise, an orally (PO) administrated compound is absorbed from the gastrointestinal (GI) tract into the blood circulation and then eliminated. Various pharmacokinetic parameters are used to characterize ADME such as volume of distribution (V_D), elimination half-life ($t_{1/2}$), clearance (Cl) and bioavailability (F), and most often the pharmacokinetic processes follow first-order kinetics (Loftsson, 2015). V_D describes how the compound is distributed within the body. A compound with small V_D (e.g. $\leq$0.2 L/kg) is mainly located in the blood plasma while a compound with large V_D (e.g., much larger than the body volume) might be highly tissue bound. Elimination $t_{1/2}$ of a compound is the time it takes to reduce its blood plasma concentration by 50%. Cl is another parameter that indicates how rapidly drug is eliminated from the body. It can be divided into hepatic clearance (Cl_H) and renal clearance (Cl_R), which are the two main elimination pathways. Cl_H is associated with metabolism of the compound in the liver while Cl_R is associated with elimination of unmetabolized compound in urine. The total body clearance (Cl_T) is the sum of Cl_H and Cl_R (i.e., $Cl_T = Cl_H + Cl_R$). Bioavailability is the fraction of a compound that is absorbed from the GI tract into the general blood circulation. While high bioavailability (i.e., close to complete absorption [$F \approx 1$]) of API is desired after PO administration low excipient bioavailability ($F \ll 1$) is favored with most of the excipient metabolized in the gut or excreted unchanged in feces.

In the kidneys drugs are mainly excreted from the blood circulation by glomerular filtration (Loftsson, 2015). Glomerular filtrated drugs may be passively reabsorbed in the peritubular capillaries. Only unbound hydrophilic molecules with a molecular weight (Mw) below approximately 25 kDa are filtered through glomerulus. In humans, dextrans with Mw less than 15 kDa are mainly excreted unchanged in urine with a renal clearance close to the glomerular filtration rate (GFR) ($Cl_R \approx 125$ mL/min = 7.5 L/h), whereas dextrans with Mw above about 50 kDa are mainly degraded in the liver to lower Mw products (i.e., metabolites) that are then excreted in urine.

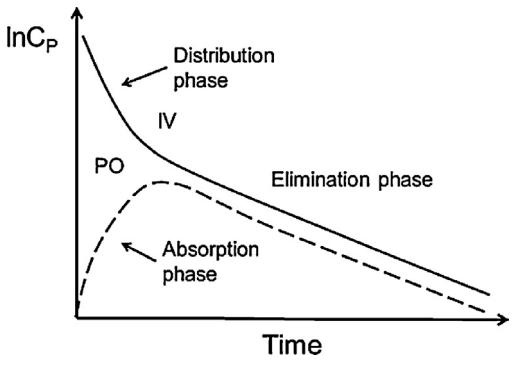

Fig. 1. Sketch showing the natural logarithm of the plasma concentration (C_P)–time profile for a compound after intravenous (IV) injection (solid curve) and per oral (PO) administration (broken curve).

3. Lipinski's Rule-of-Five and other methods used for rapid drug profiling

Various methods or "rules of thumb" are used in rapid profiling of new drug candidates to predict their drug like properties, mainly bioavailability after oral administration. Some of these same rules of thumb can be applied for profiling of new excipients although the aims can be different. While the objectives in new drug design are to maximize bioavailability and pharmacologic response, the objectives in new excipient design can be to reduce its bioavailability and enhance its rate of elimination from the body and detoxification.

Lipinski et al. evaluated drug-like properties of couple of thousands biologically active compounds (i.e., drugs and drug candidates) and came up with what is known as the Lipinski's Rule-of-Five (Lipinski et al., 1997). Due to its simplicity, this method is widely used by researchers to predict not only absorption of compounds from the GI tract but also overall drug-like properties of biologically active compounds. The Rule-of-Five applies only to passive absorption and excludes compounds that are substrates for biological transporters such as some antibiotics, antifungals and vitamins. It consists of four prerequisites that are based on the number 5 and state that poor absorption from the GI tract or permeation through biomembrane is more likely when:

- there are more than 5H-bond donors (expressed as the sum of all OHs and NHs),
- there are more than 10H-bond acceptors (expressed as the sum of Ns and Os),
- the molecular weight (Mw) is over 500, and
- the log $P_{octanol/water}$ is over 5.

The physicochemical rational for the Rule-of-Five is based on the fact that in aqueous solutions H-bonds are formed between water and dissolved molecules and these H-bonds must be broken when the molecules partition from the aqueous exterior into a lipophilic membrane. The more H-bonds there are the more difficult it becomes for a molecule to partition from the aqueous exterior into a membrane. The molecular weight refers to the size of the molecule and the fact that the diffusion coefficient of a molecule as well as its solubility decreases with increasing size. Increase in lipophilicity (e.g., increased log $P_{octanol/water}$) of a compound will also decrease its aqueous solubility. Furthermore, if log $P_{octanol/water}$ of a compound is greater than 5 then dissolved molecules will partition into the lipophilic membrane but will have less tendency to partition from the membrane on the receptor side into the aqueous internal layers. The Rule-of-Five is based on oral absorption but with some modifications it can be applied to predict permeation through biomembranes in general (Table 1). Although there are numerous exceptions from Lipinski's Rule-of-Five it still gives important information of how physicochemical properties of a compound direct its fate within our body.

The Biopharmaceutics Classification System (BCS) is based on the fact that close to half of drug failures in development can be traced to poor dissolution or poor permeability (Amidon et al., 1995). According to the BCS, orally administered drugs are divided