Permeability, absorption, and bioavailability of a drug and drug dissolution testing

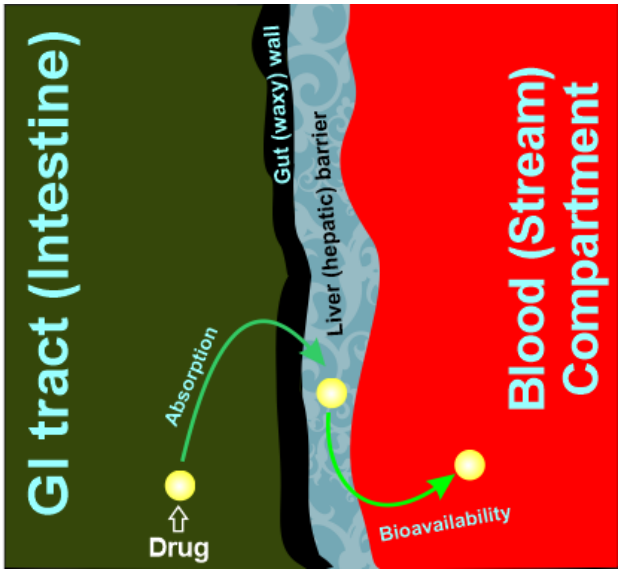
Saeed A. Qureshi, Ph.D. (www.drug-dissolution-testing.com)

The quality of a solid oral dosage form, such as a tablet or capsule product, may be defined as its ability to provide expected and consistent (reproducible) drug levels in plasma/blood. The product is introduced into the GI tract through the oral cavity (mouth) to release its drug, which gets dissolved in the aqueous milieu and gets transferred into the blood stream to produce its therapeutic effects.

This transfer of a drug from the GI tract to the blood stream is described by different terminologies, often interchangeably, such as permeability, absorption and bioavailability of the drug. However, these terminologies have distinct meanings, and for clarity purposes should not be interchangeably used. The purpose of this article is to describe and explain these terminologies to facilitate an appropriate development and evaluation of the products in particular for the use of in vitro drug dissolution testing.

From the analysts' perspective and understanding, it can be assumed that the GI tract and blood vessel, or compartment, is separated by a thick waxy/fatty wall (See Figure). Further, one can assume a gap (sort of like a creek or a drain) which a drug has to cross, or jump, to appear in the blood stream. Usually drug particles do not interact very well with the waxy/fatty wall and they should be in a solution form to be partitioned into the wall. The force for pushing the drug into the waxy/fatty wall is the concentration gradient i.e. higher concentration of the drug in the GI tract vs in the waxy/fatty wall. On the other hand, a higher concentration in the waxy/fatty wall compared to the blood compartment forces the drug out of the waxy/fatty wall and towards blood stream. Such a movement of the drug from the GI tract to blood stream is commonly referred to as "passive diffusion".

Another name for this process of transfer can be "permeation" or "permeability" of the drug i.e. how easily the drug will enter and leave the waxy/fatty wall. From a chemistry perspective, if the compound (drug) has to penetrate through a waxy/fatty wall, it should preferably be in a non-polar (or un-dissociated) form for easier penetration or diffusion. Often, this non-polar characteristic of a drug is measured by determining the partition (coefficient) of a drug between octanol and water and denoted by logP value (link). The higher the logP value the higher the partitioning in octanol and consequently higher the permeability. It is very important to note that this logP value, or permeability, is an inherent (basic) property of a drug just like the



Schematic representation of absorption/bioavailability process

aqueous solubility of the drug. One can only measure it but cannot alter it. So, permeability is a drug property and reflects its potential ability of crossing the GI tract barrier or the waxy/fatty wall.

Absorbability of the drug can be the same as of the permeability i.e. ability of crossing the wall of the GI tract. However, these terminologies can be very different at times, which may be explained as follows. Suppose a drug having a certain permeability characteristics is introduced into the GI tract in a solution form, however, due to the presence of a certain ingredient (e.g. complex formation) transference or absorbability of the drug gets reduce significantly, thus now much less drug will crossover. In this case, as stated above, permeability cannot be changed so what has changed here is the absorbability (crossing over) and thus one would see much less drug on the blood side. Therefore, under normal or common situations both permeability and absorption will be the same however they can also be different reflecting the impact of certain environmental deviants. It is very important to note that it is not the absorption characteristics of the drug which has changed, as it is a drug property and cannot change. It is the availability of a smaller amount of drug for absorption, which manifests as lower absorption.

Once the drug is transferred (permeated or absorbed) from the GI tract into the blood side, as stated above, now it has to jump the creek/drain to actually appear into the blood. The jumping ability, and then its appearance into the blood stream, is known as bioavailability of the drug. The ability of a drug to jump the creek would be dependent on the attributes of both, the drug's own ability of jumping and the "width/depth" of the creek. If the drug can jump the creek without any problems (without falling into creek or going into drain) then this would reflect that the absorption and bioavailability of the drug are the same or similar. If not, then the bioavailability will be less than the absorption.

In real life, this creek or drain analogy in fact represents the liver. Before reaching the drug in the blood compartment after absorption from the GI tract it first has to pass through liver, which may chew-up (metabolize) part of drug depending on the nature of the drug. This "chewing-up" of the drug by liver is known as the "first pass" effect. This first pass effect is dependent on both drug characteristics and the liver's (enzyme) ability of chewing-up (metabolizing) the drug. It is almost impossible to predict these aspects but can be determined experimentally, and individually, for drugs.

The extent of drug appearance in blood after it crosses the gut (waxy/fatty) wall is known as bioavailability. If the liver does not metabolizes the drug and it appears unchanged in the blood compartment then absorption and bioavailability become the same or similar. However, it is quite common that the drug gets absorbed fairly easily and efficiently but appears in blood to a lesser extent, representing low bioavailability. For example, for a well-known cardiovascular drug diltiazem absorption is as high as 90% (logP = 2.8, indicating non-polar characteristics and potentially higher absorbability) but bioavailability is only 44%, which means about 56% of the absorbed drug is chewed-up or metabolized by the liver.

So with this background, how should one link these parameters together and make them useful for product development and evaluation? Note that all three parameters are drug properties and practically unchangeable.

When a product is prepared, or manufactured, of a drug, basically all it (the product) can do is control the availability of the drug in the GI tract for absorption. For example, for immediate release products the idea is that the drug should be released more or less as a burst. The product becomes only a vehicle/means for convenient delivery of the drug into the GI tract. On the other hand, for a controlled (or extended) release product, the drug should be released (for absorption) in a controlled manner. It is very important to note that with formulation, or product development, one is only controlling and/or adjusting the release of drug from the product. Once the drug is released, then the system (GI tract environment) takes over and the drug will behave as per its inherent (basic) characteristics of solubility, permeability, and bioavailability as if the drug was delivered in a powder form into the GI tract.

As stated earlier, as a drug does not usually crossover (absorb) in particle form but from the solution form, even if the drug is released from the product, it is the drug in the solution form which is the most important for absorption and bioavailability. The evaluation of drug dissolution in the GI tract becomes not only relevant or important but one of the most critical attributes to monitor, or assess, the quality of a drug product. The in vitro drug dissolution testing is conducted to assess this in vivo drug dissolution testing.

When conducting a drug dissolution test at least two requirements should be met: (1) the experimental conditions must simulate the testing environment appropriately as observed in vivo; (2) the experimental conditions must be product independent as is the GI tract environment.

As the current practices often use experimental conditions which are not relevant to in vivo or the GI tract environment e.g. lack of stirring and mixing, product dependent experimental conditions, such testing, or results obtained from them, would not be relevant and/or useful for the development of products as well as assessment of their quality.

Another important thing to note is that people often try to relate or predict absorption and/or bioavailability from dissolution characteristics which is not correct because both absorption and bioavailability are drug properties while drug dissolution is a product property and are independent from one another. However, all three (dissolution, absorption and bioavailability) are linked together to reflect plasma drug levels or profiles. This linkage which is based on combining, or convoluting, dissolution, bioavailability and other pharmacokinetic parameters results in prediction of plasma drug levels forms the basis of drug dissolution testing and its use for product development and their quality assessment (link).

In conclusion, the terminologies of permeation, absorption and bioavailability parameters are explained along with their relevance to drug dissolution testing. It is important to note that absorption and bioavailability are drug properties and dissolution is a product property and are all independent from one and other. These are combined (convoluted) together to provide plasma drug levels or profiles, which is a needed exercise to develop and evaluate drug products. A mandatory condition in fulfilling this requirement is that dissolution tests must be conducted using physiologically relevant experimental conditions which must also be product independent.