Are low solubility drugs really problematic? Maybe not!

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Drug absorption from the GI tract is generally dependent on dissolution characteristics of a product which in turn is dependent on the aqueous solubility of the drug. In general, it is assumed that the higher the solubility, the higher the expected drug absorption will be, and vice versa.

Before considering the link between absorption and solubility, it should be prudent to define and establish the solubility characteristics of a drug for absorption purposes. In this regard, it is a well-known fact that drugs are mostly absorbed from the intestinal part of the GI tract (link). The liquid phase in the intestine is aqueous-based having a pH in the range of 5 to 7. For all practical purposes one may consider a pH of 6 (average of 5 to 7) for the intestinal fluid. Thus, to represent intestinal fluid, for dissolution testing, one may use water itself, which usually has pH around 6 or a (phosphate) buffer having a pH of 6. Therefore, in the following discussion, solubility of drugs in water will only be considered.

The solubility values for compounds/drugs in water are commonly described in the literature. The reported values are often for room temperature, however, for dissolution testing purposes one would require solubility values at 37 ^{o}C. To be precise, one should determine the solubilities at 37 ^{o}C. However, as a rule of thumb, one may use solubility values of room temperature, as solubilities at a higher temperature (i.e. 37 ^{o}C) would most likely be higher, an advantageous situation for dissolution testing.

It is important to note that for absorption purposes it is the solubility of the base (or native) form of the drug is relevant and not that of the salt form. Drugs are often available and administered as salts such as chloride, sulphate, phosphate etc., however, these salt components get dissociated. The drugs then exist in an undissociated form in equilibrium with a dissociated form with a counter ion depending on the nature of the environment. The absorption of the drug usually occurs from the undissociated form as explained in detail in other articles (e.g. see link).

Table 1: Description of solubility terms (link)

Descriptive terms	Parts of solvent needed for 1 part solute
Very soluble	< 1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000
Practically insoluble or insoluble	> 10,000

For dividing drugs into groups of high or low solubility, one first has to define or establish criterion for this classification. An appropriate approach in this regard would be the one recommended by the pharmacopeias (e.g. USP, BP). Pharmacopeias usually define solubilities in units of parts (drug) in parts (solvent). Commonly, these are reported as how many parts of solvent (water) would be required to dissolve one part of

a drug, usually in grams (~mL) of water (link). Table 1 provides the description of different solubility levels. As per the table, any drug which would require 30 parts (or 30 g) of water or less to dissolve 1 part (or 1 g) of drug is considered as soluble. However, if the drug requires more than 30 parts (30 g) of water then it will be considered a low solubility drug.

The next item to consider is the absorption i.e. what does it mean and how is it reported? First of all, it is important to note that, just like the solubility, absorption is a drug property as well and is not the property of the products. Different products can have different absorption profiles of the same drug e.g. IR (immediate-release) vs ER (extended-release) products where for IR products absorption would appear faster while for ER products it would appear slower. This difference in (rate of) absorption is not because of the drug, but due to the release of the drug from the product at the absorption site which in most cases is the small intestine. The drug dissolution tests are conducted to assess this release, or differences in release, of a drug from the products.

Another important consideration is that often in literature it is described that dissolution test is used for the prediction of absorption which is not accurate. Dissolution does not predict absorption, but linearly relates/links to absorption. It is similar to how the concentration of a drug in solution does not predict UV (coefficient of) absorption, as UV absorption is a drug characteristic. However, UV absorption of the solution is directly proportional to the concentration of the drug in the solution. Similarly, dissolution would not describe the absorption characteristics of the drug in humans, however, higher and faster dissolution will proportionally provide a higher and faster absorption outcome.

The absorption characteristic of drugs is a standalone property and is to be determined experimentally. In most case, for product evaluation purposes, this absorption value can be obtained from literature. In this regard, one should be clear regarding the differences in the absorption and bioavailability terminologies. The differences in these two may be explained as follows: Disappearance of a drug from the intestine (assuming no degradation or metabolism in the GI tract) represents absorption while appearance of the drug in the blood stream represents bioavailability. If a drug disappears from the intestine and appears in blood, without any loss, then absorption and bioavailability becomes the same or equivalent. However, if a drug disappears from the intestine, and appears in lesser amounts in blood then it means that the drug has a lower bioavailability. The loss between disappearance from intestine and appearance in blood is commonly known as “first pass effect” and represents “filtering” or metabolic conversion of the drug by liver (link). For example propranolol is a drug which is rapidly and almost completely (>90%) absorbed, however its bioavailability is only 36%. This means that liver chews up about 64% of the absorbed drug and the blood sees only 36%. For dissolution testing purposes, it is only the absorption part which is relevant and applicable, because bioavailability or the metabolic effect of liver is a drug property and this effect occurs after the drug leaves (or disappears) the intestine. From a drug dissolution testing aspect, one should focus on the drug absorption (not the bioavailability per se) characteristics. Often absorption is reported as “rapidly and completely absorbed” or in percentages (X%).

Now let us evaluate the relationship between these two properties, solubility and absorption. For the purpose of the discussion, one may divide drugs into two groups i.e. drugs which require 30, or less, parts of solvent for 1 part of the drug as "high" solubility drugs and the ones which require greater than 30 parts as "low" solubility drugs. The solubility and absorption characteristics of some commonly used drugs were obtained from literature and are reported in Table 2.

In Table 2, the drugs are listed with decreasing solubilities i.e. requiring increasing amounts of solvent to dissolve the same amount (1 g) of drug. However, note that all drugs with few exceptions show rapid and complete absorption, without any particular order. In addition, it is to be noted that majority of the drugs in this list are of low solubility to practically insoluble. Now if one considers the commonly held belief that solubility and absorption are linked or linearly related then absorption characteristics of the drugs listed in Table 2 should also linearly decrease. However, this is not the case.

It should be interesting to note that out of these 30 drugs only 4 would meet the criteria of being in the soluble category, while the rest would be sparingly to practically insoluble. On the other hand, the interesting aspect is that most of the drugs show very high absorbability characteristics. What this means is that absorbability of drug is not directly linked/related to solubility of the drug in a "traditional sense". This observation is not in line with the currently held view where it is believed that low solubility drugs may cause absorption difficulties.

So, how should one explain this discrepancy? One of the possible explanations is that while considering the solubility aspect, unfortunately, it is assumed that the physiological system (GI tract, especially intestinal) is a closed system i.e. all the drug is expected to be in solution form in the available volume at a given time. However, the GI tract provides an open or continuous extraction site which can continuously extract extremely small amounts ***of dissolved drugs*** repeatedly for absorption, thus neither requires large volumes of solvent nor high solubility of a drug (link).

Secondly, people have become accustomed to considering paddle and basket vessels/apparatuses as the dissolution tester, representing the GI tract environment or "pot". This is not an accurate view or assumption either. The stirring environment within a dissolution vessel is such that not only does it not facilitate dissolution, it in fact retards and hinders dissolution. Consider for example, dissolution testing of USP prednisone PVT tablets. The drug is capable of dissolving completely in 900 mL of water, however, it often shows dissolution of around 40% in 30 minutes. The reason being, the drug (prednisone) just sits at the bottom of the vessel without any stirring and mixing. The dissolution testers do not provide an efficient mixing environment as one observes in vivo, thus dissolution would appear to be problematic in particular for lower aqueous solubility drugs. It is not the dissolution or absorption problem but the stirring and mixing problem within a dissolution tester.

Thirdly, people have accustomed to the view that the drug or dose has be dissolved in 900 mL of volume to be considered as soluble drug. However, this practice of using 900 mL volume is for our convenience or tradition, in reality it can be 500 mL or 2000 mL. This limitation of the volume can easily be addressed by adding a small amount of solubilizer to enhance the solubility of

the drug in the dissolution medium. As long as the medium remains aqueous and at a pH around 6 with or without solubilizer, not changing the chemical nature of the drug or excipient, this should be an acceptable dissolution medium for dissolution testing.

Table 2: Solubility and absorption characteristics of various drugs. Solubility values are reported as number of parts (g) of water required to dissolve 1 part (g) of drug.

Drug	Solubility	Absorption (Bioavailability=BA)
Isoniazid	8	Readily absorbed (BA=91%)
Stavudine	12	Apparently fast absorption (BA 86 - 100%)
Lamivudine	14	BA > 82%
Doxycycline Hyclate	20	>95%
Ciprofloxacin	33	Rapid absorption (BA ~ 70)
Levofloxacin	40	Rapid (BA~100%)
Ranitidine	40	Rapidly absorbed (BA 50 - 60%)
Zidovudine	50	Rapidly and almost completely absorbed
Pyrazinamide	67	Fully absorbed
Acetaminophen	68	Readily absorbed (BA=62%–89%)
Cimetidine	88	Rapidly, yet incompletely (BA 56-68%)
Metronidazole	100	Rapidly absorbed with BA > 90%
Ibuprofen	571	Rapid and complete (BA 100%)
Acyclovir	714	Erratic (BA 10 to 30%)
Rifampicin	714	Well absorbed (BA ~93%)
Atenolol	1010	Incomplete absorption, (BA 40 -60%)
Acetazolamide	1389	rapidly and almost completely
Quinine	2000	Rapidly and almost completely absorbed
Prednisolone	4348	Rapidly absorbed (BA > 75 – 98%)
Metoclopramide	5000	Rapid absorption (BA 30-100%).
Prednisone	8333	Rapidly absorbed (BA 80 – 100%)
Propranolol	16207	Almost completely absorbed (>90%)
Furosemide	54795	Fairly rapidly absorbed (BA 60 – 70%)
Choroquine	94340	Rapidly and almost completely (BA ~ 89%)
Efavirenz	100000	Absorption? (BA 40-45%?)
Ketoprofen	100000	Readily absorbed (BA=92%)
Verapamil	223714	Rapidly and almost completely (BA 10-20%)
Diclofenac	421941	Rapid and complete (BA ~ 60%)
Amitriptyline	500000	Well absorbed (BA ~ 48%)
Amodiaquine	>1000000 (?)	Readily absorbed

Source: Int. Pharm. Fed. (FIP Link) and Drug Bank (Link). Accessed November 8, 2013

The condition of limited volume and/or poor stirring environment within dissolution vessels often creates problems for proper dissolution assessment which people tend to extend to in vivo as well. However, this is purely an in vitro and analytical problem and does not reflect an in vivo situation. It is important to note that low solubility drugs do not seem to be problematic for absorption as described above. However, in vitro they do because of a lack of stirring and mixing and availability of small volume of medium in particular for paddle and basket apparatuses. This issue should be addressed by adding some solubilizer and improving the stirring and mixing environment. The use of a crescent spindle addresses this problem very well and most dissolution tests can be conducted using a simple and single set of experimental conditions (link). In short, as long as system/testing is based on using a medium in a vessel capable of dissolving an expected amount of drug present in a product and availability of a gentle but thorough stirring/mixing set-up, it should be able to reflect in vivo dissolution/absorption characteristics, appropriately.

On the other hand, if a drug is indeed insoluble (like sand particles) in water or aqueous buffer (pH 6), then the question should be asked how is it getting absorbed through the GI tract, because absorption require dissolution. In such cases, the drug may be getting absorbed through other mechanisms (such as pinocytosis) which are not diffusion based. Here dissolution or its testing should not be required and one should not be conducting a drug dissolution test at all for such drugs for their products developments and/or evaluations. However, fortunately, such situations are rare and should be considered as exceptions. Most drugs are indeed absorbed by diffusion

mechanism which would require a dissolution step as a pre-requisite.

In conclusion, for absorption purposes, solubility characteristics of the base (undissociated) drugs should be considered. Drugs having low aqueous solubility often provide better absorption characteristics in vivo, however, may provide some challenges in monitoring dissolution characteristics in vitro. In such situations, if appropriate testing conditions (stirring and mixing with solubilizers) are used for dissolution testing then the products with low solubility drugs can be developed and evaluated as easily as the high solubility drugs.