Impact of dissolution and ionization of drugs, and their interactions, on the absorption through gastrointestinal (GI) tract

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This article provides an overview of mechanism of the drug absorption from the GI tract based on solubility/dissolution and dissociation/pH characteristics of a drug. It is argued that although pH values of the environment (stomach and intestine) may play a role, it is the availability of the large surface area of the intestine which predominantly is responsible for the drug absorption for both acidic and basic drugs. Furthermore, in the GI tract drugs exist in three forms i.e. solid (outside solvent/solution) and solid and ions in solution which are in equilibrium with one another. However, it is only the drug in solution form which is relevant for the absorption purpose. The roles of the interactions between drug (solid), drug/ions in solution and the surface areas are discussed in providing efficient drug absorption. Considering the absorption mechanism, the role of in vitro drug dissolution testing is also highlighted.

It is commonly considered that higher dissolution in aqueous medium and the undissociated drug molecules provide the best combination for drug absorption. However, in most cases these two conditions mutually contradict each other, as often undissociated drugs show lower aqueous solubility thus low dissolution characteristics. On the other hand, higher solubility/dissolution is achieved with products which ionize to a larger extent, however, ionized drugs tend to get absorbed to a limited extent. So, how should one explain the efficient absorption of drugs occurring in the GI tract? Furthermore, it is often suggested that acidic drugs should absorb better from stomach (lower pH to provide more undissociated drug) and basic drugs may be absorbed better from intestine (higher pH to provide more undissociated drug), as absorption is often likely to occur from undissociated molecules. In reality, this assumption is incorrect as it considers a simplistic approach of absorption based only on the pH of the environment. On the other hand, it is a well established fact that most drugs preferentially get absorbed from the intestine. This article describes the scientific considerations for the absorption of drugs from products (tablets/capsules) and their relevance to the drug dissolution testing.

Let us first consider solution formation (Figure 1) steps for a drug. The upper box in Figure 1 shows a schematic of the processes of drug solubility/dissolution and dissociation/pH. The most important thing to note here is that it is a **closed** system and it is in equilibrium between the solid drug (outside the solvent), drug in solvent (i.e. drug in solution) and dissociated ions in the solvent/solution. There are in fact two equilibriums here not one; the equilibrium between solid drug outside solvent (consider it as precipitate) and drug inside solvent/solution, and the drug in solution and ions in solutions. Both of these equilibriums are in equilibrium between themselves as well.

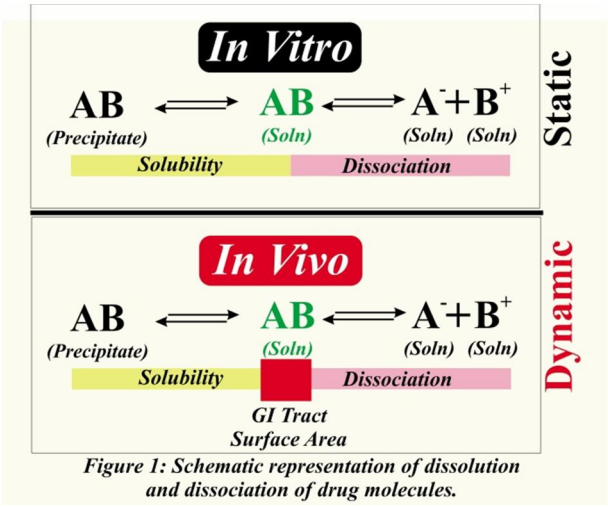

Figure 1: Schematic representation of dissolution and dissociation of drug molecules.

The overall equilibrium will be disturbed by an external event such as by the addition of a small amount of acid (or decreasing pH as in the stomach). Assuming that equilibriums are representative of a weak acidic drug where $B^+=H^+$), then the equilibrium (ionization) will shift from right to left. This will reduce the ionization, and to compensate for that, it will result in lesser drug in solution by pushing out the drug from solution i.e. as precipitate or solid, commonly known as the salting out effect. On the other hand, with the addition of a base (or increasing the pH as in the intestine), the equilibrium will be shifted to the right i.e. more ions in solution. Then to compensate for this disturbance in equilibrium more of the drug will be moved into solution and lesser drug in solid (outside the solvent). Exactly the opposite will happen in the case of weak basic drugs, (decreasing pH as in the stomach) will shift the equilibrium to the right with higher drug in solution as well as in solution, and by increasing the pH as in the intestine, decreasing the drug in solution as well as ions in solution.

From a drug absorption aspect, the most critical thing to remember is that one should watch for the (**undissociated**) drug in solution, which is often overlooked. The undissociated drug in solution is the one which is relevant for the absorption. It is to be noted that undissociated drug will always be present and available for absorption for both types of drugs (acidic and basic) both in the stomach and the intestine in small or large concentrations depending on the environment and the nature of the drugs. Confusion often occurs if one relates the appearance of drug in solid form (or precipitate) as a reflection of lack of drug in solution form, which is not correct. It is the invisible (**undissociated**) drugs in solution form, in equilibrium with the invisible ions, which is important and critical for drug absorption. For low solubility drugs one often sees solid/precipitate, which is not relevant for absorption purposes. It is like sand to the body or GI tract. On the other hand, for soluble drugs one does not see presence of the solid drug. However, in this case, the drug in solution exists and again in equilibrium with ions just like in the case of low solubility drugs. Note that just like the solid drug outside the solvent is irrelevant for absorption, ions in solution are almost equally irrelevant for absorption. These equilibriums between drug (solid) and drug in solution and drug in solution and ions have to be considered or watched for the drug absorption to occur **efficiently.**

Before, moving further it is important to consider the **relative** concentrations of the dissociated and undissociated species in the stomach and the intestine. The ratio is defined by an equilibrium constant which is as follows: $K_e=[A^+][B^-]/[AB]$. Let us assume that $K_e=1$ for two drugs here, where one drug has high water solubility (e.g. acidic) and the other one low water solubility (e.g. basic). If equal amounts of these drugs are delivered to the stomach where pH is low, the acidic drug is expected to dissolve in a limited extent (with significant quantity of undissolved solid) compared to the basic drug which will most likely be completely in solution form. Although equal amounts of the drugs are delivered, and both drug are assumed to have same K_e values, concentrations of drugs and ions in solution form will be different in these cases which will be lower in the case of the acidic drug and higher for the basic drug. This is completely opposite to common understanding where it is often assumed that stomach would have a higher concentration of undissociated acidic drugs compared to the basic drugs. In fact, stomach will have a smaller amount of drug in **solution**, thus absorption, for acidic drugs as compared to the basic drugs on an equal amounts and K_e basis. This situation will be reversed in the intestine where pH is higher, therefore, acidic drugs should be more in solution, thus should absorb well than basic drugs.

Now, if the drug absorption is to depend on drug in solution **only**, then certainly basic drugs should preferentially be absorbed from the stomach and acidic drugs should preferentially be absorbed from the intestine. However, the assumption here is that the system is a closed and static one, and both the stomach and intestine physiologies are the same. However, the body or physiological (in vivo) system is neither closed nor static and have different stomach and intestine physiologies. This makes the described absorption model not bio-relevant while the observed absorption behavior of drugs is very different than described here.

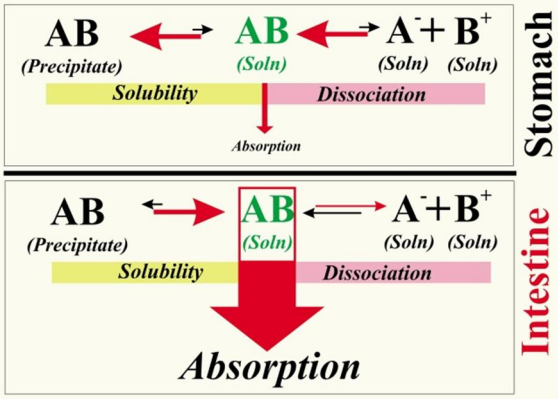

Figure 2: Schematic representation of dissolution and dissociation of weak acidic drug molecules.

In the physiological system (GI tract), there is another major contributing factor which is the availability of the surface areas of the GI tract or the absorption site/capacity with their associated blood flows. In addition, the availability of the surface area in the GI tract is further complicated by its uneven distribution between the stomach and intestine. The available surface area for absorption is almost negligible in the stomach, compared to the enormous surface area in the intestine, which for all practical purposes can be ignored. However, the surface area and its associated blood flow play a major role for the drugs absorption in the intestine. Now, let us see how the combination of the two variables solubility/dissolution and dissociation/pH, and their equilibriums, interact together to provide appropriate drug absorption.

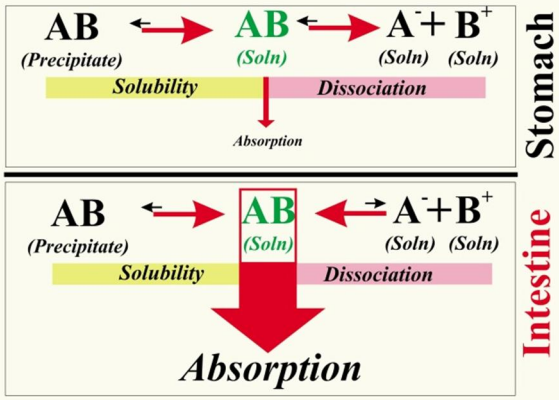

Figure 3: Schematic representation of dissolution and dissociation of weak basic drug molecules.

As the drug appears first in the stomach, it will behave as explained in Figures 2 and 3, i.e. the drug in solution form will be in equilibrium and also will get absorbed (or leaks into) into the stomach lining according to the availability of the drug in solution form. However, as the drug moves into the intestine, the equilibrium will be disturbed not only by the pH of the environment but also by the extraction capacity of the large surface area of the intestine. The large surface area of the intestine or its absorption capacity will have enormous impact on the equilibrium and concentration of the drug in solution. Here (**undissociated**) drug from solution will be absorbed (extracted) in large quantities (drain vs a leak). This will force the equilibrium to move greatly from undissolved drug to the dissolved drug (drug in solution) or the dissociated ions towards the dissolved drug (drug in solution). Although pH will have its impact on the equilibrium (as shown in Figures 2 & 3) but the major impact will be due to the surface area. It is to be noted, from Figure 3, that higher pH and higher surface area of the intestine concurrently increase the solution formation for basic drug thus absorption. This is a commonly known observation that basic drugs are absorbed more efficiently from the intestine compared to the acidic drug while both types of drugs get absorbed efficiently in the intestine.

Therefore, it is the intestine, because of its large absorption capacity, which plays the major role for drug absorption through the GI tract for both types of drugs i.e. acidic and basic. The pH of the environment (stomach and intestine) plays a relatively smaller role in drug absorption. This explanation is for drugs which get absorbed through passive absorption mechanism, i.e. absorption based on undissociated molecules through cellular lipid layers, which in general represents absorption for majority of the drugs. It is important to note that drugs would seldom be in solution form completely all the time. However, the extraction/absorption step keeps the solid drug moving into solvent/solution form that is the dissolution of drug which is necessary for the absorption of a drug.

So, if one likes to study absorption of a drug from a ***product***, then one needs to evaluate the rate and extent of the drug going into solution form which is evaluated in vitro by dissolution testing. It important to note that dissolution test is used to evaluate only the formation of drug solution. Furthermore, as the formation of solution is important for the absorption of drugs, which is required in the intestine, therefore, a dissolution test should always be conducted using intestinal environment i.e. using medium having pH 5-7 and with appropriate stirring and mixing.

It is often suggested that as the product goes through the stomach, one should also evaluate the impact of this (acidic environment) on the product first. Certainly, but this will not be part of dissolution testing but the evaluation of stability of drug and/or its interaction with the excipients in stomach (acidic environment). It is similar to stability studies conducted under harsher conditions to evaluate the impact of temperature and humidity on the drug and its product. Drug dissolution tests are conducted only to evaluate, as stated above, availability of drug in solution form in the intestine.

Now, let us consider the situations that one conducts a dissolution test using intestinal conditions (i.e. aqueous medium pH 5-7 and with an appropriate stirring/mixing), and results are not reflected by in vivo results as measured by the plasma drug concentration-time profile. The current practices are that experimental conditions for dissolution testing be modified until the dissolution results match the in vivo results. This practice is obviously incorrect as the in vivo experimental (or environmental) conditions do not change with drug or product, they remain constant. Therefore, in vitro dissolution testing environment (or experimental conditions) must remain constant as well. The analyst should determine what the reason is that the amount/concentrations of solid drug and/or its solution formation were not as expected. This should be evaluated based on the chemical nature of the drug and the excipients and then making appropriate changes to the product (formulation and/or manufacturing attributes) in a systematic manner until a product is developed having desire dissolution characteristics and the corresponding plasma drug concentration-time profile.

For further reading on related topics, please see the articles provided with links e.g. science of drug dissolution testing, selecting an appropriate dissolution apparatus and dissolution medium, predicting plasma drug concentration-time profiles from dissolution results.