Chemistry aspect of drug dissolution/absorption in the GI (gastro-intestinal) tract

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When an oral product, usually a tablet or capsule, is taken, it almost instantaneously goes into the stomach (gastric compartment). The gastric environment can be described as an acidic (mostly HCl based) aqueous solution (pH 1 to 3) with a churning (moving and mixing) process. Assuming a disintegrating type product, the product will disintegrate into solid particles/aggregates. Once in this disintegrated form, the drug will behave exactly like granules in dilute acidic solution with mild stirring in a beaker or flask. In case of non-disintegrating type tablets, the drug will be released or leaked-out from the unit into the acidic solution.

If the drug is soluble then it will move into the intestine as a solution, otherwise as a slurry or suspension. The important thing to note here is that with some delay, the drug will move into the intestinal component. Here the acid solution or suspension will be mixed with a strong buffer turning the acidic liquid to basic, more accurately less acidic in the pH range of 5 to 7. Considering the variability in contents and the rates of entrance of the two solutions i.e. slurry from the stomach and the buffer from pancreas, it is almost impossible to accurately determine or establish the pH of the soup. However, it is a well-established fact that pH in this area of intestine ranges between 5 and 7. Therefore, for all practical and standardization purposes one can use pH of 6, an average of 5 and 7.

After reaching into the intestinal compartment, the drug will be in solution or suspension/slurry form as well depending on its solubility characteristics at a pH of 6 exactly how a drug would be in a beaker containing an aqueous solution having a pH of 6.

The point being that for dissolution and absorption purposes the drug may be considered exactly like a drug in a beaker, either in a weak acidic (HCl) solution or almost neutral (pH) aqueous solution. If one considers such behaviour of a drug, then it becomes much easier to understand and/or predict the behaviour of drug dissolution and/or absorption in the body.

To further illustrate the drug behaviour in this regard, let us consider the potential drug dissolution and absorption characteristics of a propranolol product.

Propranolol as a free base has a solubility of 61.7 mg/L. This means, a dose of 120 mg will not dissolve in 900 mL of water, which usually has a pH of 6, similar to the one in intestinal compartment, a commonly used solvent for in vitro drug dissolution testing. On the other hand, the drug will be freely and completely dissolved in the acidic (stomach) environment and will be in the protonated form. The drug (propranolol) is usually administered in HCl salt form, which may further help its dissolution. However, even if propranolol is administered in free base form, it will still be completely dissolved in the stomach considering the acidic environment.

On the other hand, once the drug is moved to the intestinal compartment, whether administered as free base or HCl salt, the drug will precipitate out as free base if the concentrations/amounts are more than 61.7 mL/L. In fact, most likely the drug will precipitate out because often liquid volumes available will be much less than 1L at any given time, may be around the 25 to 50 mL range. It is very important to note that the HCl coming from the stomach will be neutralized by the buffer in the intestine, therefore, the intestinal compartment will see the drug in its free base form, whether administered as free base or HCl.

In short, the drug will be mostly in ionic and in solution form in the stomach, however, in the intestine it will be in solution form to a lesser extent as dissociated and un-dissociated equilibrium and a significant amount as un-dissolved (precipitate) form. This summarizes the dissolution process, or stages, of the drug (propranolol and similar) in the stomach and intestine.

Now, let us see how the drug will behave from the absorption perspective in these two compartments. In the stomach the drug will be in ionic form which is generally known to be a less favourable state for absorption for most drugs. Moreover, the stomach offers limited surface area for absorption. Therefore, negligible absorption of the drug (propranolol) will occur from the stomach, if any at all.

In the intestinal environment, on the other hand, the two properties described above (dissolution and ionic state) will be the opposite. The drug will be in a non-dissociated (less soluble) form, which is favourable for absorption and the intestine provides significantly

higher surface area for absorption. Therefore drug absorption will occur here. It is important to note that as explained in previous articles (1, 2), even if the drug dissolves in small amount in the intestinal environment, it will provide sufficient undissociated drug for absorption.

It is further important to note that the purpose of this rather long explanation is to highlight the fact that the dissolution and absorption process in the GI tract are based on simple and well established chemical principles of dissolution, ionization and its equilibrium, and liquid-liquid partition. It is to note that contrary to commonly held beliefs, free base (or acid) or undissociated form of the drug, even at very low solubility, provides the most efficient absorption behaviour. It is not necessary that a drug has to be of high aqueous solubility, in fact opposite is generally should be preferred from the absorption perspective. The high aqueous solubility of a drug is required only for in vitro drug dissolution testing as explained here, and not for improved absorption or bioavailability characteristics in humans.

In conclusion:

1. Stomach and intestine can be considered to behave exactly like two vessels with mixers/stirrers, containing acidic and almost neutral (pH 6) aqueous solutions, connected to one another.

2. When the (acidic) content of the stomach is transferred into the intestine, acidic solution is neutralized with pancreatic buffer, exactly as one would expect to occur in vitro (test tube) with the addition of strong alkaline solution.

3. Drugs will react to the environment exactly like they would in any in vitro experiments following well-established ionization and dissolution/precipitation principles.

4. Absorption will occur from the intestinal part because of its high surface area again following basic and well-established principles of chemistry i.e. change in medium pH would force formation of non-polar specie and/or precipitation which will be absorbed in repetitive or continuous manner.

5. High aqueous solubility should not generally be considered as a requirement for drug absorption purposes.

6. Non-ionic (non-polar) and low solubility drugs should not be considered a limitation from dissolution/absorption perspective, but an advantage.