Solubility considerations for drug dissolution testing and product development

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Dissolution tests are conducted for solid oral products such as tablets/capsules to simulate/evaluate in vivo drug dissolution which is required for the absorption of drugs from the GI tract to exert their therapeutic effects. Therefore, for appropriate absorption, drugs should dissolve in the liquid present in the GI tract. The liquid present in the GI tract is simulated in vitro with water or aqueous buffers having a pH in the range of 1 to 7.

Commonly in literature three pH values are suggested which are 1, 4.5 and 6.8 to cover the range of pH of the GI tract. It is possible, in fact quite common, that a drug may be freely soluble at one pH but not the other. For example, acidic drugs such as NSAIDs (e.g. ibuprofen) would practically be insoluble in solution having a pH of 1 but will be freely soluble at pH 7. So, how should one decide, for dissolution testing purposes, whether such drugs are of high or low solubility characteristics and how should they be tested?

As stated above the purpose of conducting a dissolution test is to determine in vivo dissolution rate which is necessary for drug absorption. In this regard, it is very well recognized that a vast majority of the drugs, if not all, get absorbed from the small intestine where pH ranges from 5 to 7. Therefore, for dissolution testing purposes one should be concerned about the dissolution in this (intestinal) area and its (intestinal) pH range. For practical and standardization considerations one may use a pH of 6 (average of 5 to 7). Thus, for dissolution testing purposes using a medium that has a pH of 6, and drug solubility at this pH, should be considered the most important factor. In this regard, water itself or some dilute buffer may be used as a dissolution medium. ***It is important to note that one has, practically, no other choice but to use a medium having a pH of 6 (or around it) for appropriate and/or physiologically relevant dissolution testing***.

For absorption, the drug (dose) should dissolve at this pH. This is where the problem arises, because dissolution is not only dependent on the pH but also on the available volume of the medium. If the volume of the liquid is not sufficient then not all the drug will get dissolved in the GI tract which is quite often the case as volume is limited. Commonly scientists/analysts tend to assume that drug/dose must be completely dissolved in the GI tract at a given time. However, often it is neither possible nor required, because the environment within the GI tract is not static but dynamic where, as soon as the drug is dissolved it gets extracted or absorbed by the GI tract lining or blood. Therefore, a small amount of liquid provides a means of "dissolving" a vast quantity of the drug. For example, as reported in literature, drugs such as glyburide, glipizide, phenytoin, digoxin, nifedpine etc. with solubilities of 33µg/mL or less in a 6.5 pH buffer get absorbed quite efficiently. On the other hand, drugs having solubilities equal to, or greater than, 300µg/mL in a buffer (pH of 6.5) have been considered of high solubility [1]. However, in a traditional sense a drug having a solubility of 300µg/mL (or 0.03%) would be considered as very slightly soluble or practically insoluble as per USP definition.

Therefore, it is safe to conclude that for drug absorption purposes defining drug solubility in a traditional sense may not be appropriate or accurate as solubility of 40µg/mL or higher in water or buffer at a pH of 6 may be sufficient for efficient absorption purposes.

On the other hand, one would face difficulties when evaluating dissolution in vitro as here the system is static and not dynamic. Therefore, in vitro drugs such as carbamazepine having solubility of 169 µg/mL and having a dose of 200 mg would require more than 1.2 L of dissolution medium for complete dissolution of the drug, and for the dosage of 400 mg tablet volume requirements would be more than 2.4 L. Commonly, as drug dissolution testing is conducted in volumes of 900 mL or less, such drugs can be considered as low solubility drugs ***only*** for in vitro drug dissolution testing purposes. To overcome this limitation of solubility barrier in vitro, there are two possibilities; either one should install a continuous extraction system to mimic physiological extraction/absorption process or add some solubilizer (physiologically relevant such as SLS) so that all the available drug should be freely dissolved in 900 mL of the medium. As adding a solubilizer is a simple and least expensive option, thus it is commonly employed.

It is important to note that for absorption purposes low aqueous solubility of drugs should not be a concern. In fact, it may be an advantage as drugs with low aqueous solubilities (e.g. non polar, non-dissociated, non-ionized or so called BCS class II) drugs at intestinal pH get absorbed quite efficiently. However, such drugs may cause problems during in vitro dissolution testing because of closed or static system as described above.

Another important thing to note here is that it is not the in vitro drug release from the product which will be an issue here, because the drug will be released from the product whether it is of low or high solubility, however, it is the quantitation of the released drug which will be the issue. For quantitation purposes the drug must be in solution form. If the drug happened to be highly soluble in aqueous medium with a pH of 6 (e.g. ibuprofen) the analyst should not be concerned. However, if a drug has low solubility then one would require a solubilizer for its dissolution in the medium to quantify [2].

In conclusion, therefore, it should be noted that one may not be concerned about the solubility (low or high) of drugs from the absorption perspective as drugs with extremely low solubility get absorbed efficiently from the intestine. However, for in vitro testing, low solubility does create a problem which is not per se an issue of drug release assessment but that of the quantitation. Therefore, medium should be such that it should be able to dissolve the drug freely and appropriately while still maintaining its physiological relevance which is usually achieved using SLS.

Reference:

1. Varma, M.V. et al. "pH-Dependent Solubility and Permeability Criteria for Provisional Biopharmaceutics Classification (BCS and BDDCS) in Early Drug Discovery" *Mol. Pharmaceutics* 2012, 9, 1199−1212.

2. Qureshi, S.A. "Sink Condition: Solely an in vitro (analytical chemistry) and not the in vivo or physiological requirement" *Drug Dissolution Testing*, March 4, 2012, (Link)