Reflections on Dissolution Testing

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(Comments in red are mine, Saeed Qureshi)

Principal Message and Scope of Dissolution Testing

a. Dissolution testing is conducted to measure the drug release from a product. It is best (It should only be) conducted under test conditions simulating the GI physiological environment that is constant independent to any tested drug product. Specifically such conditions are:
   To use a standard apparatus of defined geometry for dissolution of a product to occur.
   Dissolution medium be aqueous with optional ~~presence of electrolyte~~, buffer and/or surfactant.
   The pH be that where the drug likely to be absorbed; mostly at the range of 5-7.
   Allow for thorough mixing at low agitation using a mixer of defined shape.
   Test at a fixed temperature of 37^{o}C.
   Test for a duration up to 12 (I am not sure about it, may be longer, but perhaps no longer than 24) hours.
   Albeit such conditions converge for developing a universal dissolution testing certain assertions are pre-requisite in doing so. These will be discussed below.
b. Role defines the effect a variable has to others that collectively produce a result (I am not clear on this). The role of dissolution testing is to estimate the in-vivo drug release.
c. Objective is the final result; as such the goal of dissolution testing is to establish ~~a relationship of the dissolution data to~~ the drug's blood concentration/time profile.

A Simplistic & Practical Approach

Viewing the bioavailability of a drug product as an input output process becomes the most straight forward approach relating the in-vitro data (input) to in-vivo outcome (output). In doing so where the rate limiting step occurs is not critical. The output will be greater or less pending (differences in formulation/manufacturing attributes) the existence of a rate limiting step independently where this occurs at the product level or the biological level. Only the underlying assertions allowing this approach being pragmatic need be determined. In this instance the in-vitro data are the extent of drug dissolution released from a product and the in-vivo outcome is the drug concentration levels in the blood over time (c-t profile). The basic principle of this approach is the transfer of in-vitro (amount/t) to in-vivo (concentration/t or c-t) profiles and from this other in-vivo characteristics are obtained.

Assertions

1. There must be sink conditions (at least 30% (that may need some form of agreement, I am OK with it though) less drug to its saturation solubility) to allow for uninhibited drug dissolution and

absorption to occur. Otherwise the outcome will be prone to variability and the relationship may not be possible.

2. The dissolution apparatus needs to be as bio-relevant as possible.
3. The approach may not be possible for oil soluble drugs available as soft gels for delivery since dissolution testing is done in aqueous media. Further absorption of oils in the GI follows a different pathway to that for soluble drugs. (I am hesitant agreeing to it, however, for the time being let us assume it is, as you are suggesting).
4. The sequence of processes, dissolution → absorption → blood levels →excretion (Perhaps elimination is more appropriate), is one way. Specifically the elimination rate (K_e) and the bioavailability factor (F) remain constant. In the event homeostasis effects (especially for nutrients) exist or drug absorption is site specific, then likely this approach will not be applicable (This point is not clear to me).
5. The approach needs determination of an F factor (bioavailability factor) (K_e and volume of distribution as well) obtained from drug solution in-vivo absorbance study? To obtain intrinsic drug in-vivo characteristics. This is a key parameter for the transfer of the two profiles as mentioned above.
6. The dissolution test relates well to the product in-vivo dissolution (fulfilling its main role). In this instance the closeness c-t profiles reflecting in-vivo dissolution depends on the value of the F factor; at F=100% (should work equally well with less than 100%) then c-t profiles represent in-vivo dissolution and if less all can be said is that there exists a relationship between in-vitro dissolution and in-vivo dissolution; (I am not a fan of using the word relationship but predictability is a better interpretation).
7. The method presupposes that absorption and dissolution results are linear related (proportional). This means that physiological effects on in-vivo drug dissolution rate and extent released, have an equivalent effect on drug absorption. (Drug dissolution applications are often used to evaluate the impact of formulation/manufacturing attributes, keeping the dose constant. Therefore, linearity or non-linearity in drug pharmacokinetics may play a limited role for the purpose of drug dissolution testing).

<u>Limitations Achieving Role & Objective of Dissolution Test</u>

1. Inadequate simulation of the GI environment.
2. Apparatus design deficiencies.
3. Inconsistency of dissolution conditions lacking universality.
4. Requiring multiple in-vivo efficacy outcomes to determine product specificity of dissolution testing.
5. Utilizing dissolution testing beyond its role and objectives.
6. Assertion # 7 cannot be met. This is the outcome when any one of assertions # 1, 3 & 4 cannot be met.

<u>Practical Considerations</u>

Dissolution testing is critical for 1) product development, 2) quality of product and 3) safety & efficacy of product. The discussion above addressed the dissolution test meeting its goal thus being bio-relevant. In doing so the test acquires significance since it associates the quality to the efficacy of a product. However, as such the dissolution test does not necessarily fulfill specific needs of product production in all instances since the assertions mentioned above are not always met. Consequently dissolution testing has branched into three specific applications:

I. Dissolution testing as research tool; emphasis is on discriminatory power among formulation prototypes.
II. Dissolution testing as a quality control tool; emphasis placed on consistency of manufacturing processes.
III. Dissolution testing as an efficacy evaluation tool, emphasis placed on bio-relevancy discussed above.

These three applications of dissolution testing are not necessarily always exclusive and can be inter-related (should always be inclusive and inter-related). The mistake made is when test results from I & II applications are associated or expected to reflect results for III application when using different experimental conditions than those for dissolution testing for III application (I, II and III should all have the same experimental conditions). This means one cannot infer dissolution rate outcomes for III application unless the dissolution testing from the other two applications is uniformly applied too; as mentioned above this may not be practical or even possible. For example, application # II pertinent to the quality of the tablet product that is expected to demonstrate a reproducible drug release; this reflects consistency but not necessarily efficacy of the product. Otherwise, a dissolution test reflecting both these attributes would necessitate being conducted under the same experimental conditions. (I am from a different viewpoint about experimental conditions. To me, for a valid dissolution test, I, II and III must be one and the same).

Any measurement in-vitro or in-vivo is plagued by variability and so does dissolution testing. Dissolution testing of tablets and capsules can vary significantly however this variability, when used for application # II above, needs be less than the variability originating from the product itself. To achieve this, the mode and rate of stirring of a dissolution test is critical and becomes ever so important with the extended release products since their testing lasts much longer. The introduction of appropriate modifications to the test apparatus to reduce such variability should be a continuous endeavor. Regarding application # III above the in-vivo variability of the bioavailability data is much greater than that observed from the in-vitro data when using a bio-relevant dissolution testing. So the advantage fulfilling the role & objectives of dissolution testing is allowing observing the origin of the greatest variability in the process noted from formulation to absorption to elimination.

Regarding adjusting dissolution test experimental conditions to correlate with bioavailability outcomes of a product, obviously this would be counterintuitive since in doing so the test loses its predictive quality intended for. Nevertheless, the bio-relevant conditions of the dissolution test, mentioned under scope of dissolution testing, would be expected to reflect universal experimental conditions that would be adequate with minor adjustments, if need be, unless one of the assertions stated above is not met.

Having said that, the adjustment of experimental conditions, albeit small per previous statement, can be done even retrospectively with the realization that in doing so the particular dissolution test then becomes very specific to a specific product formulation. Being so, it could then be used for applications I and II mentioned above for this specific formulation. (I do not agree with this view. Experimental conditions have to remain constant).

The introduction of a proposal to a universal dissolution testing is a convenient (should be the target) target and it's pursue has merit because it allows for establishing standard conditions of testing upon which comparative evaluations can be made on product release characteristics of actives (drug or nutrients). Such a universal testing albeit its broad applicability is prone to exceptions (maybe/maybe not). This stems from the simple fact that the set of variables originating from the properties of actives is greater than those a universal dissolution test can address. (I would like to think about environmental conditions from a physiological aspect, i.e., as all products in in vivo interact with the same physiological (GI) environment, therefore, they should also be evaluated under same in vitro environment). Four examples are presented herein reflecting this.

a. Nitrifurantoin tablets: This is an old drug prescribed for urinary drug infections; its bioavailability and efficacy has been measured from the concentration levels in the urine and the duration (time) to maintain a certain concentration level in the urine. Numerous studies using various dissolution tests, conventional, as in USP apparatus II and non conventional, dialysis, have shown poor relationships between in-vitro dissolution data and urine drug values. Nevertheless correlations between test data and biological outcomes have been found only when drug dosing is 50mg or less. This is due to a saturation bioavailability at the specific site of this drug's absorption. What this means is that beyond a certain concentration drug bioavailability becomes independent to dissolution outcomes. Indeed this may not preclude from developing a universal dissolution test; however, its relevancy to predicting in-vivo data would be confined to a lower drug concentration dosing. (This appears to be an example of non-linear pharmacokinetics. It appears to me that people often use drug dissolution testing for the prediction of pharmacokinetics, which in my view not correct. Drug dissolution testing utilizes pharmacokinetics to predict blood levels. It would be inappropriate to conduct dissolution tests of 20 mg and 40 mg products of a drug and compare their pharmacokinetic outputs with dissolution results. Here the output (pharmacokinetic) may (linear) and may not (non-linear) relate to dissolution results and as stated they should not be expected to. For dissolution testing purposes, products should have same dosage strength but different formulation/manufacturing. They should be evaluated using C-t profiles, as dissolution tests only evaluate product's attribute not that of the drug).
b. Niacin tablets: Niacin is an ionized active compound that its solubility is pH dependent; as such, the pH of the dissolution medium has an effect to the dissolution rate of the tablets containing niacin. In particular the dissolution of niacin from tablets is slower in water and faster in 0.1N HCl. In particular for time release tablets that are designed to release niacin over a period of 8 hours the following results were obtained.

Time (hrs)	0.1N HCl	H_2O
1	26.80%	12.97%
2	39.10%	22.63%
6	74.60%	50.75%
8	98.35%	73.00 %

A universal test utilizing one dissolution medium, a buffer at pH range between 5-7 would show a slower release rate than if the dissolution test was conducted in 0.1N HCl. The manufacturer established dissolution specs based on the release rate obtained from the acidic dissolution medium. If the design of a bio-relevant dissolution test is the basis for proposing a universal dissolution test then one has to consider situations of ionized actives (For selecting dissolution test conditions, including dissolution medium and pH, one should not be dependent upon the drug property such as ionic, but the environment through which the drug/product is going to go through. This (GI) environment remains the same so the dissolution medium should also remain the same, even for ionic drugs). In such instances it may be more bio-relevant during the dissolution testing to allow for changing the dissolution media from acidic the first few hours of testing to the more alkaline media at the later stages of testing (I do not agree with this school of thought. If such an approach be followed then it should be followed for all drugs/products. However, as you have also noted, my view with respect to dissolution testing is that one should evaluate dissolution characteristics under an environment which reflect an environment from where absorption is expected to occur). Needless to say that the manufacture's depiction of the dissolution results from the acidic medium to set product specs was arbitrary and self serving, but not necessarily wrong (if something is arbitrary and self-serving, then in my view, it is wrong).

c. Nifedipine tablets: Nifedipine is a heart medicine that is extremely insoluble in water and independent of pH. The addition of surfactants to enhance its solubility has been met with limited success, even more so when confined to bio-relevant surfactants such as lecithin, bile salts and SLS. Conducting dissolution testing aqueous media then is problematic since sink conditions are not possible. The manufacturer opted to resort to non-conventional dissolution testing in order to perform product formulation development. The dissolution test consisted inserting the tablet in 100ml glass cylindrical container filled with water and oscillated at ten oscillations/min; mixing was achieved by the air volume provided by the head space of the glass container. At pre-determined time intervals the container contents were emptied and fresh water was added and the test continued. The sampled dissolution medium containing all un-dissolved nifedipine that was released from the ER tablet was placed in a large volumetric flask and diluted to volume with organic solvent allowing the drug to dissolve and assayed. What all this means is the highly insoluble drugs yet impose problems for a universal dissolution test (If one believes in the fundamental principle of drug dissolution testing which is that for a drug to absorb it should be first dissolved. Based on this principle we can conclude that, in the GI tract environment, which remains constant, some sort of dissolution of nifedipine is occurring. If the corresponding dissolution is not happening in vitro, to me it means that we are not simulating the GI tract environment appropriately. One has to look at this situation from this aspect of

mismatching in vitro-in vivo environment. Changing an in vitro test environment or apparatus just to achieve expected dissolution behavior which in my view is not a scientifically valid approach. Otherwise, one can argue for the use of other harsh test conditions such as a blender for stirring and mixing, propanol to increase solubility, higher pH of let us say 10. Obviously that would defeat the purpose of dissolution testing.

d. Aspirin tablets: Aspirin solubility is prone too to pH variations, although in this particular example this is not of interest, rather the focus is on an aspirin product ZORprin which is an ER tablet consisting of 80% drug active at 800mg dose. The product is formulated so that aspirin is continuously released (zero order) almost independent of PH. This is achieved by granulating aspirin with ethylcellulose (an insoluble excipient) so that the drug release is mostly done by continuous erosion. In this instance a universal dissolution test could be used as long as the mode of mixing is bio-relevant. USP paddle and basket apparatuses have been unreliable for simulating the in-vivo behavior of this product. As a result often patients complain of noticeable product plugs (undissolved tablet) in their feces. The tablet is sizable enough requiring efficient and prolonged agitation to achieve sufficient erosion for a complete drug release. Obviously the paddle stirring mode is inefficient meeting such requirement. This particular example is an excellent application for the proposed crescent shape stirrer in place of the paddle mixer. The crescent shape stirrer would provide the mixing efficiency needed along with some mild attrition for an efficient erosion of this tablet product (We have done some work with very large bolus products, incidentally of aspirin. The dosage strength is 15.6 gm/bolus or tablet. The crescent-shape shaped spindle worked well. We have used 50 rpm, as at that time we had not proposed 25 rpm as an appropriate rpm, but in my view there is no reason that 25 rpm would not work as good as 50. You stated that for such applications crescent-shape spindle may be excellent choice, I would like to argue differently. If crescent-shaped spindle provided an appropriate stirring and mixing, to me that means that it should show an appropriate reflection of the GI tract stirring and mixing environment. If this was the case then such stirring and mixing should and could be maintained from product to product. This is based on the principle that has previously been stated that the properties of the GI tract environment remain consistent regardless of the type of the drug/product being tested.)