Drug dissolution testing for phase I clinical trials/studies

Saeed A. Qureshi, Ph.D. (www.drug-dissolution-testing.com)

I received a query by email seeking my opinion concerning the topic mentioned above. The email is attached (link), without reference of the sender, to provide a background of my response. My opinion is as follows:

First, what is a phase I clinical study? In general, a phase I clinical study is a study in which a drug is to be evaluated in humans for the first time, following successful animals studies, to establish its safety and tolerability in different dosage strengths. In principle, at this stage, there would not be any data available on human pharmacokinetics (absorption, metabolism, elimination, volume of distribution etc), and this phase of the study is generally used for determining these parameters. If the drug is to be administered as a solid oral product such as a tablet/capsule or suspension, then such a product is to be "developed". The question then becomes how can such product be developed to achieve "certain" desired drug levels in blood? As drug levels in blood are linked to drug dissolution in vivo (within GI tract), which are estimated by an in vitro dissolution test, the use of dissolution testing is linked to the phase I clinical studies.

As stated above, the in vitro dissolution is linked to the levels of drug in the blood, however, this link is not direct but through the use of the pharmacokinetic parameters of the drug. Therefore, in principle it is difficult, if not impossible, to design a product to achieve specific blood levels based on in vitro dissolution results for phase I clinical studies as the pharmacokinetic values are not available. However, once a phase I clinical study is successfully completed and provides the needed pharmacokinetic values, then indeed dissolution results can be used to determined blood levels for developing a new/different formulation/product.

The only option available at this stage, I believe, is making some educated guesses or extrapolations from the pharmacokinetic parameters (e.g., bioavailability, volume of distribution and elimination rate constant) based on scientists' experience from animal studies and available parameters for similar drugs or products.

The next step should be the selection of a dissolution apparatus and associated experimental conditions. It is essential that the dissolution test must be conducted using experimental conditions and apparatuses which can adequately simulate the in vivo (GI tract) environment. The critical requirement for a bio-relevant test is that it should be product independent and consistent. Current practices of dissolution testing do not meet this requirement. Products are tested using arbitrary and product dependent experimental conditions and apparatuses. Therefore, application of commonly used apparatuses, such as paddle/basket, offers a poor choice for such studies and should be avoided.

A modified apparatus based on a new spindle, known as crescent-shaped, has been proposed with guidance in developing product independent and bio-relevant testing. This particular apparatus, or similar, may be used for testing.

Considering my experience with the diltiazem products, in a publication that was referred to, when predicting/calculating blood drug levels, I would approach the situation in the following manner:

Based on the experiences from animal studies let us assume that the drug under consideration is of the same type as diltiazem. Thus, I would develop a number of formulations/products and test the dissolution rates in water using a crescent-shaped spindle set at 25 rpm. Applying respective pharmacokinetic parameters to dissolution results one will be able to predict the "expected" blood levels of the drug. I would choose one of the products for a clinical trial or prepare others by changing formulation/fabrication to achieve desired dissolution characteristics. I would certainly not change the experimental conditions to achieve certain desired dissolution rate, as the experimental conditions are linked to the GI tract environment which remains constant.

Now coming to your specific questions:

Q: "You have very clearly mentioned in the article that dose of the drug should not be changed. My Question is: which dose should i choose for dissolution method development, dose given to rats or its Human Equivalent Dose (right now i do not have the provision to go for its Human Pharmacokinetic Studies)."

***Response*:** My publication is about the use of drug dissolution testing for the development and evaluation of the products where human pharmacokinetic parameters are known and well established. Most of the dissolution tests are indeed conducted for such drugs to develop or assess the impact of changes in formulation and/or manufacturing attributes. For example, working with products of phase II clinical trials to marketed products, evaluating impacts of scale-up and post-approval changes (SUPAC), developing generics or conducting other needed bioequivalence studies (e.g. bio-waivers) forms the major portion of dissolution studies. Therefore, when one assesses the impacts of formulation/manufacturing variations then these can only be evaluated by keeping the dose (strength) of the drug constant. Your situation is different, as you stated that you are not comparing products but trying to achieving a certain desired blood level by changing/adjusting formulation or manufacturing. The requirement of the consistency of the dose (strength) does not apply in your case. You should select a dose based on requirements for the human usage.

Q: Solid Dosage forms are considered as ideal for IVIVC and I have administered drug to the animal in the suspension form , Should i convert the same dose to pellet/ tablet for dissolution studies or may use suspension only (with rat or human dose).

***Response*:** I would use a suspension form as it has been used in animals and that may provide better (less variable) absorption characteristics for determining pharmacokinetic parameters and would use these parameters to develop a tablet/capsule product if so desired.

I hope you will find this discussion useful. ***Please, note that the opinion provided here is general in nature and for the "common good" based on the limited information available. Relevancy and accuracy of the outcome cannot be guaranteed in any shape or form.*** Good luck with your studies.