Stirring environments with the paddle and the crescent shape spindles: A misconception

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There is a common belief within the dissolution community that not only should the stirring within a dissolution vessel be very gentle but the product should also be not in contact with the rotating spindle/paddle. Touching or moving of the product by the spindle is considered to be a harsh and undesirable testing environment that may result in loss of the discriminatory ability of the dissolution test. On the other hand, there are no standards or requirements describing such gentleness or softness of the stirring, other than the belief that the softer the environment/stirring is, the better it will be. Such a belief has resulted in the practice of the other extreme i.e. the commonly recommended stirring (e.g. 50 rpm) in fact provides no, or extremely limited, stirring which in reality makes the current practices of dissolution testing meaningless.

Figure 1: Accumulation of the drug product, also known as cone formation, because of a poor stirring environment.

An example of such suggested gentle stirring may be observed from the testing of the USP prednisone performance verification tablets, which clearly demonstrates that there is almost a complete lack of stirring within the vessel. The product, the tablet or its aggregate, sits at the bottom of the vessel without any appreciable interaction with the medium. The common or formal description of this lack of stirring and product/medium interaction is cone formation (as shown in the Figure 1). Unfortunately, rather than considering this as a flaw, this (softness or lack of interaction) is often suggested and promoted as a desired quality and requirement of a dissolution tester. However, in reality, dissolution tests conducted in such an environment should NOT be considered as dissolution tests at all, because these tests never describe the dissolution behaviour of the test products. For an appropriate dissolution test, the product and medium must intimately interact with each other, whether the product touches the stirrer or not. ***Therefore, it is important to note that the practice of dissolution testing with the condition that product should not be in contact with the stirrer is an entirely made-up and irrelevant requirement.***

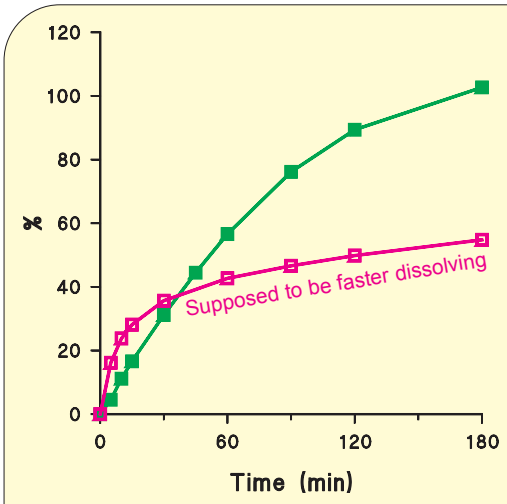

Figure 2: Dissolution profiles of the USP prednisone and diltiazem tablets using the paddle.

On the other hand, it is a common perception, based on the current thinking as described above, that the crescent shape spindle will provide a harsh stirring environment which would result in the loss of the discriminatory ability of the test, thus quality of the test and/or the product. However, in reality, the crescent shape spindle has been developed to provide this ability to remain in contact with the product, by moving the product around and/or spreading the aggregate in the dissolution vessel, to address the flaws of the paddle/vessel combination.

In the context of the stirring and mixing environment, relevant stirring would be the one which would show accurate dissolution characteristics of the test product i.e. faster dissolution results for a faster dissolving/release product and vice versa. In this regard, Figure 2 describes the dissolution behaviour of two products using paddle apparatus which are known to

have different dissolution characteristics; faster (USP Prednisone PVT Tablets) and slower (Diltiazem IR

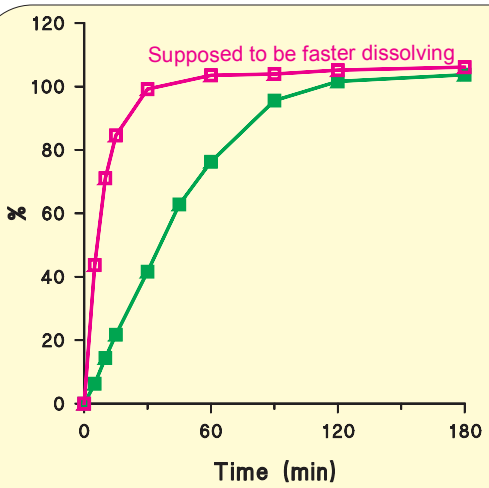

Figure 3: Dissolution profiles of the USP prednisone and diltiazem tablets using the crescent shape spindle.

Tablets). For further details regarding the tablet characteristics please see the link. The observed dissolution characteristics in this example are just the opposite as what is expected. Therefore, it is to be noted that the paddle does not provide a softer stirring environment but an inappropriate stirring environment, resulting in incorrect dissolution characterization of the products.

On the other hand, if the paddle is replaced with a crescent shape spindle, even at a lower rpm of 25, both products show expected and complete dissolution profiles (Figure 3). It is to be noted that dissolution characteristics using both spindles are similar for the diltiazem product, reflecting similar intensities of the stirring. However, in case of prednisone tablets, dissolution results are dramatically higher with the crescent shape spindle than with the paddle. As the intensity of stirring/agitation is the same or similar using both spindles, the higher results for prednisone are because of the spreading (higher surface area) of the aggregate, thus appropriately reflecting the faster release characteristics of the tablets.

A very clear conclusion from the above discussion is that the crescent shape spindle does not provide a harsh stirring environment, it is the paddle which provides too soft of a stirring environment to be useful for appropriate drug release characterization of drug products.