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USP Apparatus 4 - Applying the Technology

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USP Apparatus 4 is designed to determine the dissolution characteristics on a variety of dosage forms. Apparatus 4 is particularly useful for difficult dissolution analyses where the dosage form has poor solubility or the dosage form requires a pH change of the dissolution fluid. The article, "USP Apparatus 4 (Flow Through Method) Primer" (1), defined the general principles of Apparatus 4 and its advantages. This article will address the fundamentals of Apparatus 4 method development.

The Simple Reality of Apparatus 4

Three basic questions must be answered in order to begin USP Apparatus 4 method development. They are:

- What is the product form - tablet, capsule, powder, implant, etc.?
- What is the relative solubility of the product?
- What is the expected time of dissolution?

What is the product form?

In general, the product form will dictate the hardware configuration of the system - i.e., the cell that is most appropriate. Selection of cell type is the first and probably the simplest decision in the method development process. As pointed out in my previous article (1), there are five types of cells that are currently available. By far the most common cells are the "standard" 12mm and 22.6mm cells that are generally used to accommodate tablets, caplets, and capsules. In these cells, the product sample is placed in a holder within the cell and a filter system is placed downstream from the product. These cells are then closed and held in a temperature controlled environment. The analysis of some types of gelatin capsules and suppositories will benefit from the unique configuration of the suppository cell. As depicted in *Figure 1*, this cell allows the fats or gels to be separated from the active matrix and prevents their redistribution throughout the system, overcoming the sample matrix problems associated with these dosage forms. Powders and granular products obviously require another cell type *(Figure 2)*. This cell is designed to prevent "floating away" and filter obstruction problems commonly encountered with powder and granular product dissolution analyses. A final cell type is a very low volume cell for use with implants where extremely low flow rates (5mL/hour or less) are frequently required.

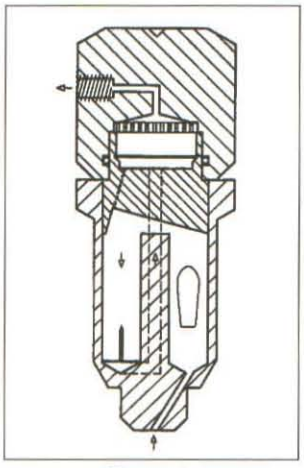

Figure 1.

The second implication of product form is its influence on the selection of flow dynamics. As a general rule, a method development routine for tablets will indicate the preference for a laminar media flow. The dynamics of this well-distributed flow will complement the tablet holder position and the geometry of the cell to distribute sufficient flow across the entire surface area of the securely positioned product sample. The theory is that this will affect disintegration of all sample surfaces relatively equally. Other less rugged or more dispersed sample types, i.e. powders, would benefit from a laminar flow as well. The laminar flow creates a gentler environment by passing the media stream through a bed of small glass beads generating a more consistent flow throughout the cell. The

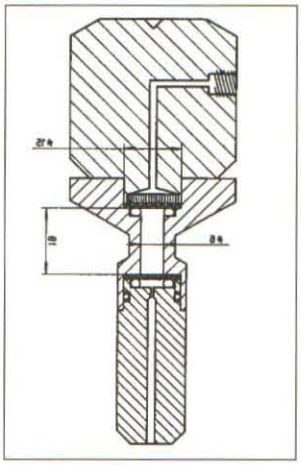

Figure 2.

laminar flow distributes media evenly to the product within the cell. Very durable, rugged products may benefit from the more turbulent flow that can be created by the omission of the glass bead bed.

What is the relative solubility of the product?

Many people will consider Apparatus 4 simply because of the poor solubility of their product. The basket and paddle methods (USP Apparatus 1 and 2, respectively) are limited in their ability to handle many poorly soluble products because of the limited media volume that they accommodate. Obviously, flow characteristics can greatly affect the ability of Apparatus 4 to address the solubility problem. Optimizing the rate of the continuously flowing fresh media across the sample allows for the exposure of the sample to a substantially increased volume of fresh media that increases the sample solubility. Most method development will start with the USP recommended 16mL/min flow rate. The flow rate can be increased to improve solubility of the product. The flow rate can be decreased, if necessary, to conserve media.

What is the total dissolution time?

Another primary reason Apparatus 4 may be considered is its ability to make on-line (complete or step-wise) pH changes. This is often a function of the total dissolution time. With the increasing proliferation of extended release products, more and more dissolution analyses extend over longer periods of time. Extended release products sometimes require a change in pH during their analyses. With Apparatus 4, pH change can be altered either manually or automatically by the introduction of a new media source or by the addition of a buffer. Due to the continuous flow of Apparatus 4 analyses, the problems associated

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with changing the media in USP Apparatus 1 and 2 systems (product loss, contamination, incomplete change), are overcome.

Final Consideration

The final consideration in developing an Apparatus 4 method is the applicability of automation. USP 4 can be conducted by manual procedures or can be batch automated for multiple unattended analyses. Samples can be collected to a fraction collector or analyzed on-line. Data can be analyzed, organized, reported, archived, and recalled in a variety of ways. The costs of automation are, of course, commensurate with the sophistication, but usually the added efficiency is greater than the investment.

References

1. Looney T. USP Apparatus 4 (Flow Through Method) Primer. Dissolution Technologies. 3:4;1997, 10-12.