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Advantages of USP Apparatus IV (Flow-through Cell Apparatus) in Dissolution Studies

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The basic characteristics of the flow-through cell apparatus (USP Apparatus IV) including the assembly and open/closed configuration of the apparatus have been described. The relative advantages of the flow-through cell apparatus over other release setups have been summarized. Finally, potential applications of this setup are presented.

Keywords: Flow-through cell apparatus, USP apparatus IV, Drug dissolution

USP Apparatus IV (flow-through cell apparatus)

The flowlow through cell apparatus which is described as Apparatus IV in the USP has gained recent acceptance into the dissolution world for its versatility in the testing of novel dosage forms where traditional dissolution apparatus and methods have failed [1]. Dosage forms including poorly soluble and extended release tablets, drug eluting stents, microspheres, suspension and injectable formulations, implants, soft gelatin capsules, and powders, all have provided exciting results and a solution to the troubles associated with the traditional dissolution methods.

Apparatus

The assembly consists of a resevoir containing the release medium, a pump that forces the release medium upwards through the vertically positioned flow-through cell, and a water bath. The pump usually has a flow rate delivery capacity between 4 and 16 ml min^{-1}, with typical flow rates of 4, 8 and 16 ml min^{-1}. Usually the bottom cone of the cell is filled with small glass beads of about 1 mm diameter and with one bead of about 5 mm diameter positioned at the apex to protect the fluid entry tube, whereas a filter (most frequently, a glass fiber filter) is positioned at the inner top of the cell. For orally administered solid dosage forms, two different cells are described: the large cell (22.6 mm i.d.) and the small cell (12 mm i.d.) [1]. USP Apparatus IV can be operated under different conditions such as open or closed system mode, different flow rates and temperatures. The diversity of available cell types allows the application of this apparatus for testing of a wide range of dosage forms including tablets, powders, suppositories or hard and soft gelatin capsules. It is the method of choice for extended release and poorly soluble products [2-3].

As diagrammed in Fig. 1, USP Apparatus IV requires the sampling pump to be on continuously throughout the analysis, as the dissolution rate is directly proportional to the flow rate of the medium that is pumped into the flow-through cell. Sampling for this technique therefore requires that continuous collection or measurement of the eluted sample be maintained. As the dissolution time increases, large sample storage may be required, which may not be practical. Fraction collectors have a finite number of positions that are reduced as the volume of samples to be collected increases, which can limit the number of time points that can be collected. Sample splitters can also be used to divert the eluent sequentially between collection and waste, thus reducing the volume of sample to be collected. More recently a dual sampling rack has been designed to

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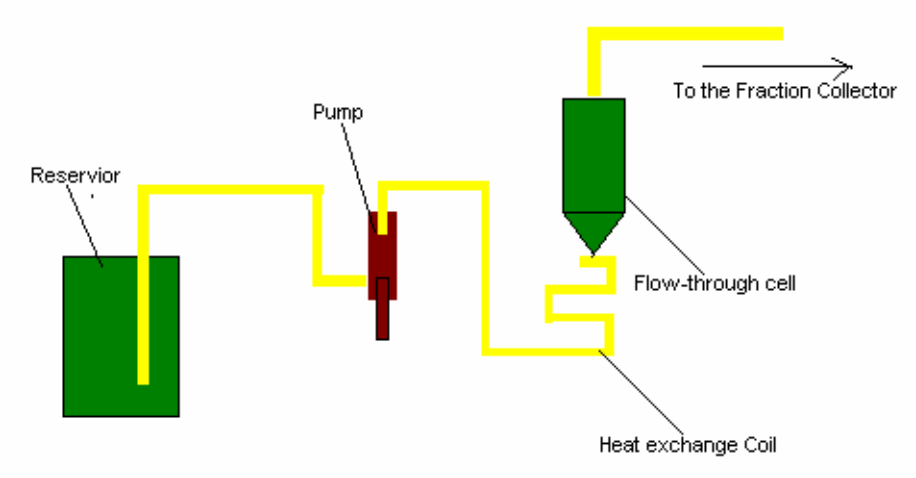

Fig. 1. Diagram of the USP Apparatus IV.

allow samples to be collected while simultaneously diluting, if required, and injecting into either an HPLC system or a UV spectrophotometer [4].

Open Configuration of USP Apparatus IV

Most often the flow-through cell apparatus is used as an open system with fresh solvent from the resevoir continuously passing through the cell where the dosage form is initially accomodated. Since the resevoir volume is not fixed, media volume can be increased to allow the maintenance of sink conditions for poorly soluble compounds or decreased to accomodate systems where the concentration of drug released would otherwise be below the detection limit (*e.g.* systems with low drug loading). The medium from the open system can be collected as the entire outflow over the sampling interval. The average concentration representing the cumulative mass dissolved in the total volume consumed is measured from the analytically determined concentration and the volume collected. This average concentration is divided by the number of minutes elapsed to give an estimate of the release rate over the time interval.

Closed Configuration of USP Apparatus IV

The flow-through cell apparatus can also be operated as a closed system by recycling a fixed volume of the medium. The medium passes the sample and is returned by the pump to the flow-through cell and the sample. A reservoir is placed in the line allowing the medium to be stirred, heated and sampled. By determining the concentration of analyte and the volume in the system, the cumulative release can be directly calculated.

Advantages

One distinct advantage of the open flow-through apparatus over the traditional closed apparatus (rotating paddle and/or rotating basket type) is that media and/or flow rate changes can be performed easily within the same run. This application is helpful in testing the robustness of the formulation with respect to the variations in the intralumenal environment. Intralumenal hydrodynamics are more efficiently simulated in this system than in other *in vitro* systems.

It is possible to sustain sink conditions in the open flow-through apparatus for longer periods. This application is especially important for poorly soluble drugs, making the development of *in vitro-in vivo* correlations easier for such drugs [5].

Furthermore, the floating and other special dosage forms can be more easily studied with USP Apparatus IV [6].

Some Reported Applications

Jack *et al*. [7] have compared USP Apparatus II and IV for the dissolution of soft gelatin capsule formulations of a poorly water soluble amine drug. Using an acidic medium with added surfactant, both apparatuses gave similar dissolution profiles. Apparatus II tended to give faster rates of dissolution but Apparatus IV was better able to distinguish between different formulations.

Sunesen *et al*. [8] developed in *vitro-in vivo* correlations for danazol hard gelatin capsules using the flow-through cell apparatus, media simulating the intraintestinal composition,

and higher than physiological flow rates (at least 8 ml min^{-1}). With this methodology, point-to-point *in vitro-in vivo* correlations were developed under both fasted and fed conditions. Correlations in the fed state were better when lipid digestion products had been included in the relevant release media. However, it has been shown that the improved *in vivo* dissolution of spironolactone particles and troglitazone tablets in the fed small intestine can be correctly predicted with the flow-through cell apparatus when physiologically relevant media and flow rates are used [9].

The flow-through cell apparatus has been successfully used for assessing the disintegeration of cross-linked gelatin capsules containing amoxixillin [10].

Emara *et al*. showed that for ER formulations of vincamine (a compound with pH-dependent dissolution characteristics) the *in vitro* release data with the flow-through cell apparatus could be correlated point-to-point with *in vivo* data only if used as an open system [11].

Fotaki *et al*. [12] were able to develop a point-to-point correlation of *in vitro* release data using the flow-through cell apparatus with *in vivo* absortion data of two monolithic extended release formulations of a highly soluble-highly permeable compound (isosorbide-5-mononitrate) in the fasted state by using physiologically relevant media and physiologically relevant flow rates.

CONCLUSIONS

The USP Apparatus IV is a viable option for dissolution experiments with novel dosage forms. The versatility of the apparatus with respect to alteration of flow rates can be used for studying the release characteristics from the dosage form. The *in vitro-in vivo* correlations of the poorly soluble compounds has been made easy with the flow-through apparatus. The method is more reliable, reproducible and discriminative than other systems.

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