Flow-Through Dissolution Testing

A comparison with stirred beaker methods

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Dissolution testing of solid dosage forms is well-established as a standard technique to assess drug release from tablets and capsules. It is currently the most useful in vitro method for assuring batch-to-batch uniformity, and is a valuable quality control procedure for comparing release profiles of different batches of finished products.[1]

The earliest dissolution apparata included Pernarowski's basket dissolution assembly[2] and Poole's paddle design.[3] Until recently, official dissolution testing methods were based entirely on modifications of these static models. However, these methods suffer from a number of disadvantages[4] and the need for a new official dissolution test was recognised, resulting in the introduction of the flow-through dissolution apparatus in the United States Pharmacopeia[5] and the British Pharmaceopoeia.[6]

Basic Design of Dissolution Apparata

The traditional dissolution apparata are based on a stirred-tank static system model, where the drug is dissolved in a relatively large, fixed volume of dissolution medium contained in a cylindrical vessel with a hemispherical bottom. The vessel is partially immersed in a suitable water bath to maintain the temperature of the medium at 37°C. A forced convection type of agitation is accomplished by means of a stirring, rotating or oscillating device, generally a motor-driven paddle or wire-mesh basket. Discrete samples are periodically withdrawn from the dissolution medium and analysed.

In flow-through methods, the assembly consists of a reservoir and pump for the dissolution medium, a thermostatically-controlled flow-through cell and a water bath that maintains the dissolution medium at 37°C (Figure I). The pump is separated from the dissolution unit in order to shield the latter against vibrations originating from the pump. The cell is made of transparent and inert material, and is mounted vertically with a screen and filter system that prevents escape of undissolved particles from the top of the cell. The bottom cone is usually filled with small 1-mm glass beads with one 5-mm bead positioned at the apex to protect the fluid entry tube. The dosage form under investigation is placed on the beads or on a wire carrier inside the cell and a continuous flow of the dissolution medium from the reservoir is forced upwards through the cell by the pump. The dissolution fluid is usually collected in a separate reservoir as it leaves the dissolution cell; fractions are removed at specified intervals and analysed.

Comparison of the flow-through method with static volume dissolution testing.

The advantages and disadvantages of the flow-through method are listed in Table I. Three particularly important issues warrant further discussion.

1. Flow characteristics of the dissolution medium

One of the factors responsible for the inherent lack of homogeneity in the beaker methods results from the agitation methods. Agitating the liquid by stirring with a wire mesh basket or a propeller creates a certain degree of turbulent solvent flow, which causes a variable shear rate of solvent transfer over the surface of the particles, resulting in excessive variations in the individual rates of dissolution. The movement of solute over any particle will depend on the position of the particle in the vessel and the character of the stirring process at each position

within the container. The latter varies markedly with the geometry of the vessel, the volume of the liquid, and the speed and form of motion created by the agitator.[4] The apparatus thus introduces an inherent variability into the dissolution process, which is extrinsic to the product under study. This can result in a lack of reproducibility, and consequently, these systems have to be greatly standardised, reducing investigative flexibility.

The objective of the flow-through design was to expose the dosage form to a homogeneous, non-turbulent, laminar flow, devoid of the problems associated with a stirring mechanism. However, achieving this goal can also be problematic, since both the nature of the pump[7,8] and, to a greater extent, the flow rate[9,10] can affect the pattern of flow inside the cell. Thus in earlier designs, at high flow rates, a column of solvent moved rapidly upwards and randomly dispersed after striking the upper screen and filter holder, with widespread turbulence. The drug particles resided in eddies within this type of flow, resulting in decreased dissolution rates. On the other hand, at relatively low flow rates, while the solvent entering the chamber had laminar characteristics, after striking the upper screen some of the solvent returned to the bottom of the cell, with laminar or turbulent characteristics, creating an undesirable two-directional flow. The best results were thus obtained with intermediate flow rates; within a certain range of flow rates, the dissolution rate was found to vary logarithmically with the flow rate.[9] The range of useful flow rates was increased when a bed of glass beads was added to the cell to act as dampers.[10]

Table I: Advantages and disadvantages of the flow-through dissolution apparatus

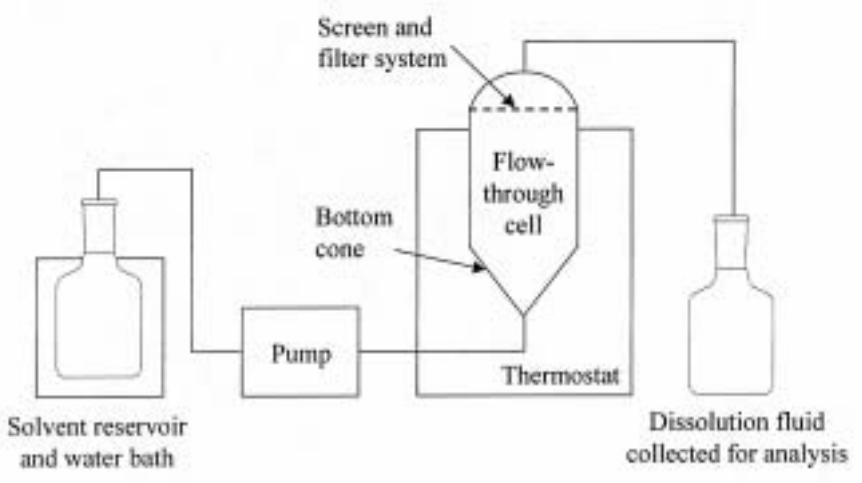
Advantages:

- Laminar flow characteristics over a wide range of solvent flow rates
- Infinite sink ideal for low solubility drugs
- Differential rather than cumulative time profile of dissolved drug concentration
- Dwell time of dosage form in medium is minimal, reducing risk of drug degradation
- pH modification of dissolution medium is easy
- Samples for analysis easily obtained without altering dissolved drug concentration

Disadvantages:

- Large volumes of media required to maintain flow rate
- Risk of clogging of filters
- Validation of flow rate during testing is difficult

Figure I: Schematic representation of a flow-through dissolution apparatus.



2. Liquid Volume

In the beaker methods, the liquid volume must be fixed beforehand; two major considerations require that the liquid volume be a large one.

a) Dissolution rate is directly proportional to the concentration gradient between the saturation solubility concentration at the solid/liquid interface, and the solute concentration in the bulk of the system. Since the former concentration remains constant, it is important that the bulk solute concentration be kept as low as possible in order to maintain a relatively constant concentration gradient. This is achieved by dissolving the dosage form in a large volume of medium.[4]

b) In all beaker methods the drug concentration in the liquid increases from zero up to either the saturation limit or the concentration which corresponds to the completely dissolved drug amount. This concentration increase is different from the in vivo process in which the dissolved material is removed continuously from the dissolution medium by absorption. In order to improve the chances of achieving good in vitro-in vivo correlations in this area, dissolution processes must be studied by methods in which the liquid acts as a perfect sink, that is, the concentration never exceeds 10-20% of the saturation. The need for a perfect sink necessitates using a relatively large volume of solvent.[4]

While the rate of agitation should be kept low in order to establish meaningful in vitro-in vivo correlations and to detect subtle differences between formulations, low agitation of a high volume system results in poor homogeneity, and the sample withdrawn for analysis might not be representative of the whole system. A relatively high rate of agitation is thus required, accentuating the lack of homogeneity in flow patterns mentioned previously. Thus, there is an inherent disagreement existing in these systems between the requirements for homogeneity, large volumes, and low

the major advantage of the open flow-through apparatus is that perfect sink conditions can be maintained without the use of large vessels, while maintaining relatively low degrees of agitation.

3. Data Generation

The beaker methods are based on the concept of a fixed volume and thus produce data expressed as an integral function, since the dissolved molecules are accumulating in the solution. On the other hand, since the flow-through technique continuously exposes the dosage form to fresh solvent, data generation occurs non-cumulatively in a differential form.[4] Consequently, the beaker methods produce average dissolution rates at best, making it difficult to detect subtle but possibly important differences in formulations, which are more readily detected in the data generated by the flow-through apparatus.

Comparative studies for the assessment of the flow-through apparatus

The first comparative evaluations of the flow-through apparatus relative to other apparata were performed in the 1970's.[11,12] More recently, a collaborative study involving four Swedish laboratories compared the dissolution of the USP salicylic acid calibrator tablet in the USP paddle apparatus and in a flow-through system.[13]

The results indicated a better reproducibility over a wide range of flow rates for the flow-through method than the paddle method. However, a similar study performed by the same group in 1989 using the USP prednisolone calibrator tablets yielded conflicting results.[14] Nevertheless the latter study showed the flow-through apparatus to be sensitive to formulation behaviour, and also capable of discriminating between different containers in the same batch - a factor of extreme importance for tablets of drugs which are sensitive to storage conditions, such as prednisolone. It was thus concluded that, in spite of the variability between the dissolution methods, the flow-through apparatus could be considered as capable as the beaker methods in generating reliable data, an assessment confirmed by the Scandinavian laboratories in a subsequent study using the sparingly soluble drug phenacetin.[15]

Conclusion

The official apparata all have their inherent advantages and disadvantages and are thus ideal for dissolution testing of different systems. While the conventional stirred beaker apparata are most suited for dissolution testing of immediate-release dosage forms of drugs with good solubility characteristics, the flow-through apparatus, whilst suitable for most solid dosage forms, yields maximum benefit in evaluating the dissolution of poorly-soluble drugs, primarily due to the fact that the system provides an infinite sink similar to that encountered under physiological conditions. ✶

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