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# USP Apparatus 4 (Flow-Through Method) Primer

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The Flow-Through Method (USP Apparatus 4), designed to test the dissolution characteristics of a wide range of dosage forms, is becoming increasingly popular among the pharmaceutical hierarchy. It has been incorporated into several international pharmacopoeias.

As early as 1957, a flow-cell method with closed liquid volume was developed in laboratories of the Food and Drug Administration and discussed between experts of the Pharmacopoeia.[1] In 1968, Pernarowski et al. published a "continuous flow apparatus" consisting of a 1000 mL flask with a stirrer/basket combination for hydrodynamic agitation and positioning, and a liquid flow of up to 70mL/min.[2] Since then, method development has proceeded on a broad base and several devices have been published, varying in the details but all based on the same principle.[3]

Using commercially available equipment, interlaboratory reproducibility of USP Apparatus 4 systems has been shown to be comparable to the USP paddle method (Apparatus 2) in many cases.

## General

When tested in the flow-through cell, a specimen is placed in a small testing chamber with a volume of about 20 mL (which is maintained at +37°C), and release is studied under continuous flow conditions. From a reservoir, the medium is pumped across a heat exchanger for temperature control and enters the cells from the bottom. The flow rate of the SOTAX piston pump, for example, is adjustable up to 50mL/min. while pump rates of 8-32 mL/min. have become the standard flow range. The solvent flows upward through the cell and a filter system which removes undissolved particles.

## Why Apparatus 4?

Apparatus 4 is well-suited to the determination of the dissolution rate of not only tablets and coated tablets, but also to suppositories, soft gelatin capsules, implants/micro capsules, powders and granules. It is particularly useful for sustained release products and analyses where pH changes are desired.

The following advantages are recognized, particularly in comparison with the more conventional stirrer methods (USP Apparatus 1 and 2).

1. There are very few apparatus parameters which affect the test and have to be standardized;
2. Ideal hydrodynamic conditions for turbulent and laminar solvent flow conditions exist;
3. Working with unlimited amount of solvent is possible, thus overcoming problems due to non-sink conditions;
4. pH changes may be easily performed stepwise since medium is exchanged very rapidly in the low volume cells (10-30 mL). (This allows adaptation of test parameters to physiologic conditions.);
5. Apparatus 4 allows for easy positioning and consistent testing of a wide variety of sample types, including powders, granules, implants/microcapsules, "floaters", suppositories, and soft gelatin capsules as well as conventional tablets and coated tablets;
6. Tests can be run either in an open or closed system (e.g. fixed or unlimited solvent amount).

## Parameter Selection

- **Cell Configuration**

The dissolution test apparatus' main module typically features assemblies for either 6 or 7 dissolution cells. Before reaching the cells, the solvent is pumped through heat exchangers which are placed in an electronically regulated thermostatted bath, assuring a test temperature of 37° ± 0.5°C, which is constantly controlled and displayed. The cells may be thermostatted as well.

Tests can be performed using any of the following individual cell types [Fig.1]:

*Cells with 12 mm and 22.6 mm internal diameters:* The cells with the internal diameter of 12 mm are used as standard. The 12 mm cells are commonly used for non disintegrating products and may, when compared to the 22.6 mm cell, increase dissolution rate due to higher flow velocity.

*Cell for powders and granulates:* Dissolution testing of powders and granulates is frequently dif-

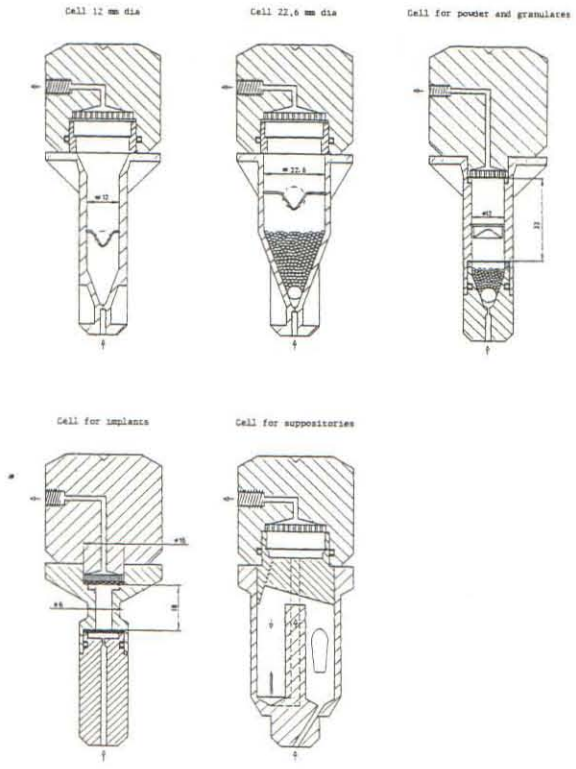


*Figure 1.*

ficult with standard methods because powders normally float up on the surface of the dissolution medium in the USP 1 and 2 vessels causing wetting problems. Even small agglomerates which are present in very fine powder, dissolve very slowly and with great variances. The cell for these materials has an insert with two screen plates. The powder is placed between the two screen plates and tested under laminar flow conditions. Suitable filters below the upper screenplate permit the removal of undissolved particles.

*Cell for suppositories and soft gelatin capsules:* This cell is preferably used for suppositories and is designed such that the lipophilic masses don't block the filters.

*Cell for implants/microcapsules:* This cell has a volume of only 1 mL and is preferably used for dissolution testing of implants which can last several weeks or even months. The small volume of the cell is required because of the very low flow rate (e.g. 5mL/hr.) for such types of dissolution tests. The required medium exchange in the cell can therefore be assured. Suitable fine filters prevent the removal of the non-dissolved particles.

- **Flow Conditions**

  Apparatus 4 testing may be carried out under conditions of laminar or turbulent flow by positioning the sample either on a bed of glass beads or directly into the cell. Usually, tablets and hard gelatin capsules, powders and granulates are tested under laminar flow, whereas turbulent flow offers clear advantages for testing of soft gelatin capsules and suppositories.

  After passing through the cells, the eluents are filtered within the filter heads and then either collected or transferred directly to the spectrophotometer for analysis. Usually a round filter with a retention capacity of 2.7 microns is suitable since it can be complimented with a second filter with a retention capacity of 0.7 micron.

The flow rate throughout the cell must be specified individually for each product. USP, for example, recommends a flow rate of between 240 and 960 mL/hour (4 to 16 mL/min.) 16 mL/min. is frequently used as the standard flow rate in pharmaceutical laboratories. The flow should be maintained at ± 5% throughout the entire test. The flow profile must be uniform.

The pump performance has been found to be absolutely critical to the successful implementation of USP Apparatus 4 analyses. SOTAX has developed a piston pump especially adapted to ensure the required flow profile in Apparatus 4 dissolution tests. It ensures high performance and superb delivery consistency. The valve heads are made of PVDF, assuring an inert flow path. The flow rate can be stepless adjusted up

to 50mL/min. by means of piston stroke adjustments, and each of the 7 channels can be switched ON or OFF independent of the others. The movement of the pistons (at 120 strokes/min.) ensures a clearly defined flow profile, thus the flow rate remains constant, independent of the flow resistance imposed, for example, by the filter in the cell head.

- **Sampling/Automation**

  Particularly for sustained release products and for other long term trials, manual sampling is not only time consuming but also tedious. Off-line automation is therefore the aim of most laboratories when using the flow-through method. On-line systems may also be configured.

  In off-line operation, the individual sample fraction can be automatically collected to a fraction collector, and, after a test run, analysis may be performed with a suitable system (e.g. HPLC, Spectrophotometer, etc.). Multi component analyses are also possible.[Fig. 2]

Schematic of Off-line Flow-Through (USP Method 4) Dissolution System with Medium Selector

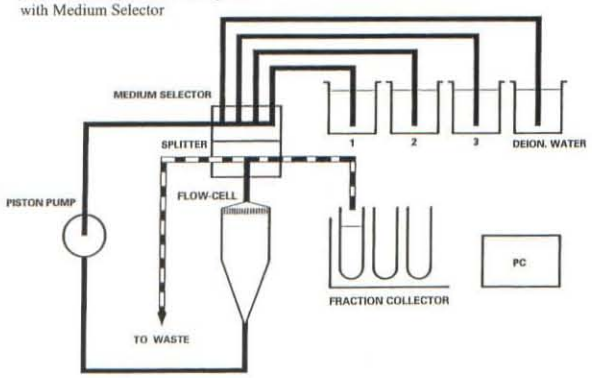


*Figure 2.*

Automated systems are generally interfaced to a PC which controls the bath, the pump and the test procedure, and processes the data. For each test, individual fractions can be collected at predetermined intervals. Multiple media can be pre-selected in order to provide pH change during the test. In the most sophisticated systems, the test preparation procedure before the test-start and cleaning procedure after the test, may also be automated. Batch samplers may allow up to six sequential sets of analyses to be performed completely unattended.

## The Future of Apparatus 4

Dissolution analysis using Apparatus 4 continues to grow in popularity. Many pharmaceutical companies in the United States and throughout the world are currently developing new methods utilizing Apparatus 4. As sustained release products continue to become increasingly important to the pharmaceutical community, Apparatus 4 utilization will continue to grow and its routine use will become more widespread.

## References:

1. Vliet, E.B., Letter sent to the USP Subcommittee on Tablets (August 23, 1957)

2. Pernarowski, M.,Woo, W., Searl, R.O., J.Pharm. Sci. 1968; Vol. 1419, page 57.

3. Langenbucher, F., Benz,D., Kurth,W., Möller,H., Otz,M., Standardized Flow-cell Method as an Alternative to Existing Pharmacopoeial Dissolution Testing 1989; Vol 51, Pages 1276-1281.