Dissolution Testing

USP 4
Flow-Through Cell

sotax

Flow-Through Dissolution Method.

The flow-through cell method allows you to see differences in your formulations that apparatus 1 and 2 simply do not show. The technique is also widely recommended for poorly soluble, modified / extended release, and low dose products. With the evolution of new drug delivery platforms, USP apparatus 4 has also been used for IVIVC studies and a growing range of dosage types.

Because of the highly flexible configurations, the ability to work in a variety of solubility conditions, different flow-through cell types, and enhanced control over the hydrodynamic environment, USP apparatus 4 continues to evolve to meet the changing needs of today’s in-vitro release testing.

SOTAX is the pioneer in flow-through cell dissolution technology designing and having manufactured the very first instrument in 1973. Today, SOTAX is 1st in class with hundreds of companies using the CE 7smart for their important dissolution workflow.

USP 4
Flow-Through Cell

For all applications.

Flow-through cells allow for testing of virtually all dosage forms. SOTAX was the first manufacturer to develop a standardized flow-through dissolution unit and has since helped pharmaceutical companies all over the world in designing robust methods for their applications – including new flow-through cells for novel dosage forms.

CE 7smart — Flexible. Precise. Predictive.

sotax.com/CE7smart

In-vitro drug release testing in compliance with USP apparatus 4, EP, and JP

High resolution dissolution

Ideal for small volume dissolution and poorly soluble compound testing

Configurations for various methods and analytical requirements

High resolution dissolution – see differences in formulations that apparatus 1 and 2 won't show

Streamlined filter validation with automated pressure detection

Specific flow-through cells for novel dosage forms

Simultaneous and easy loading / unloading of cells with a cell holder

Priming of all tubes and automatic test start once cells are inserted

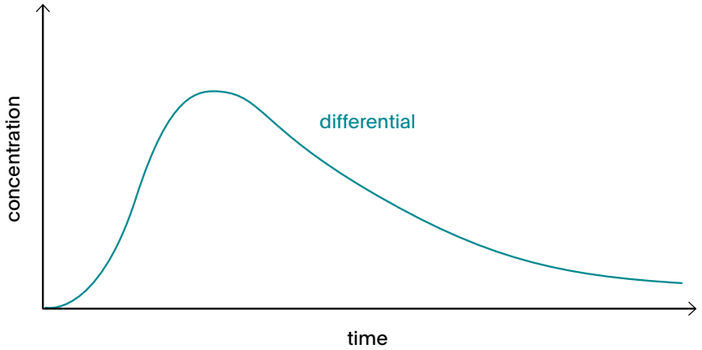
All test parameters are accessible during the test

Method setup and storage in instrument firmware

Automated cleaning process at the end of the test

Open loop setup.

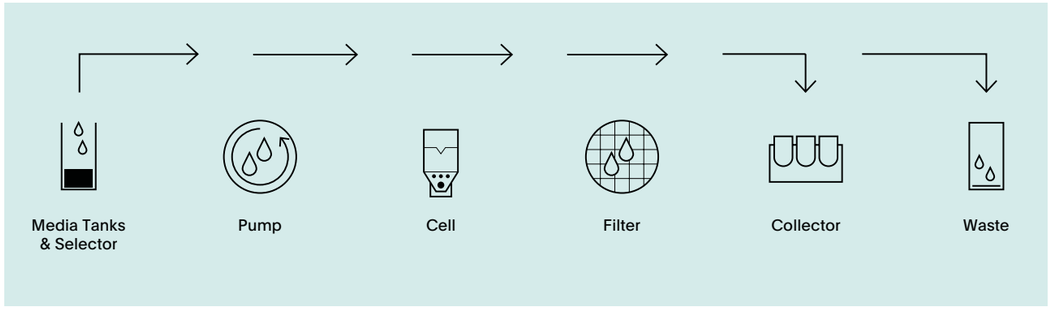
Originally designed for poorly soluble compounds where more than the compendial USP 1, 2 and 3 media volumes are required, the flow-through cell system has always been linked to “optimal sink conditions” allowing for flexibility in terms of media volume required.



Dissolution profile of an open loop setup

In the “open loop” configuration, fresh media crosses the dosage form. Samples are collected as fractions within a defined time interval, analyzed online by a UV-Vis spectrophotometer, or collected offline. The total amount of media is determined by the flow rate. This means that the influence of poor sink conditions on the test can be avoided altogether by using larger volumes of media without the need for solubilizing agents.

Open & Closed Loop Setup



Open loop setup with offline sample collection

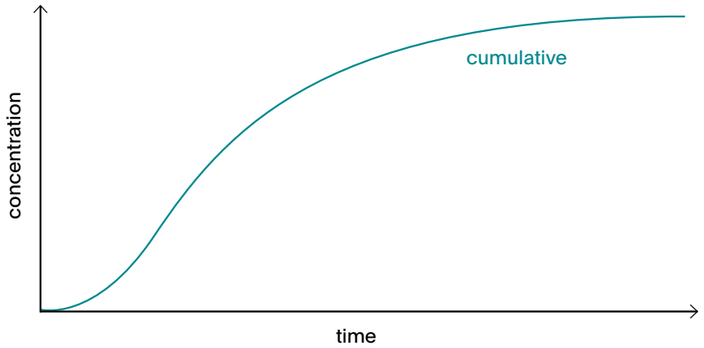
CE 7smart UV-Vis on-/offline in an open loop setup

Automated media change

In the open loop setup, it is possible to change the type of media that passes through the flow cell after predefined time intervals. Using the media selector, media is automatically switched to draw from a different source. Up to 3 different media can be programmed.
Bio-relevant dissolution media can be used depending on filter performance. This feature is useful for performing IVIVC studies where the dosage form is exposed to the different pH’s of the digestive tract. Studies have shown improved correlations due in part to maintaining sink conditions as well as differing hydrodynamics in the flow-through cell. It is also useful for enteric coated products, modified release and extended release products. Unlike the USP apparatus 1, 2 and 3 methods, where changing to a new media can be tedious, USP 4 simplifies this workflow allowing for a straightforward and documented media change.

Closed loop setup.

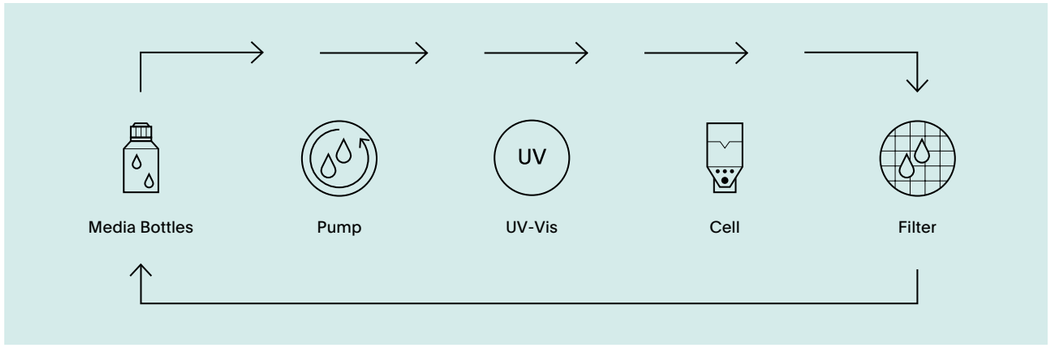
In a closed system, the flow-through method is conducted much like a USP apparatus 1 and 2 experiment where a fixed volume of media circulates across the dosage form. Samples can be taken at predetermined times by an autosampler or read by an online UV-Vis spectrophotometer.



Dissolution profile of a closed loop setup

Results are expressed as a cumulative dissolution curve. Closed systems are ideal for dosage forms where solubility and sink conditions are optimal in a volume range from 25 mL to 5 L. USP 4 offers another possible way to compare results with traditional 250 mL, 500 mL, 90 mL, 1 L, 2 L paddle, baskets, and USP 3 methods. This method also provides advantages over other USP methods such as different hydrodynamic and mixing effects eliminating the coning or dead zones as well as sampling issues or sample introduction effects sometimes seen in USP apparatus 1 and 2.

Open & Closed Loop Setup



Closed loop setup with UV-Vis online sample analysis

CE 7smart UV-Vis on-/offline in a closed loop setup

Small volume dissolution and elution testing

As a direct result of low dose formulations such as drug eluting stents, implants, coated medical devices, injectables, and microspheres, the USP 4 method has evolved to fulfill even lower media volume testing. Within the medical device field, the term “dissolution” has been replaced by “elution” where the amount of drug released from a polymer coating or drug depot is measured. These drug amounts are often so low that in order to meet LOQ issues for analysis, the total media volume had needs to be decreased. Note that (when compared with USP 1, 2) the dosage form remains in equivalent hydrodynamic conditions – whatever volume is used.

Cells — for virtually all dosage forms.

Apparatus 4 has become a powerful in-vitro release platform for a variety of dosage forms. Often times the standard setup can be used without the need for modification. Flow-through cell customization for specific product types can be helpful and cells are available in a flexible range of geometries.

Tablets (12 mm cell)

This cell is described in the EP, USP, and JP as a small cell for tablets and capsules. An optional tablet holder is also described. It can also be used for suspensions, injectables as well as small medical devices and stents.

- EP 2.9.3 “Dissolution”
- USP <711> “Dissolution”
- JP 6.10 “Dissolution Test”

Tablets (22.6 mm cell)

This cell is described in the EP, USP, and JP as a large cell for tablets and capsules. An optional tablet holder is also described. It can be used for parenterals, suspensions, and microspheres. There are a variety of holding devices developed for this cell. It is the most widely used of all flow-through cells.

- EP 2.9.3 “Dissolution”
- USP <711> “Dissolution”
- JP 6.10 “Dissolution Test”

Suppositories and soft gelatin capsules

This cell has a special 2-chambers design which traps the lipidic excipients and allows the dissolution media to pass up to the filter.

- EP 2.9.42 “Dissolution Test for Lipophilic Dosage Forms“
- USP <1004> “Mucosal Drug Products – Performance Test“

Drug-eluting stents

This cell is manufactured in PTFE and is used for medical devices like drug-eluting stents. It eliminates potential adsorption problems encountered with polycarbonate cells. The inner diameter can be custom manufacture to fit the medical device accordingly.

Powders and granulates

This cell is used to determine the apparent dissolution rate of pure solid substances (API characterization) and of active substances in preparations presented as powders. It is also used for granule and bead formulations.

- EP 2.9.43 “Apparent Dissolution”

Implants

This cell is used for small implants and has a small chamber to house the dosage form.

Large medical devices

This cell can be used for longer medical devices and has a maximum length of 83 mm.

Customized flow cells

Semi-solid adaptor

This cell is based on a 22.6 mm cell. An insert cup allows testing on gels, creams, and ointments with a permeation membrane.

- USP <1724 “Semi-solid Drug Products – Performance Tests”

Holding device for dialysis insert

This cell is based on a 22.6 mm cell. An insert holder allows testing on nanoparticles contained in a dialysis bag such as the Float-A-Lyzer®.

Holding device for ophthalmic lenses

This cell is based on a 22.6 mm cell. An insert holder allows testing on drug-coated ophthalmic lenses.

Flow rate — importance of the pump.

In the flow-through method, the pump is responsible for ensuring an important parameter: the flow rate of the media. The flow rate can be compared with the RPM speed of USP 1 and 2 or the DPM of USP 3.

The CP 7-35 digital piston pump has been specifically developed for the USP 4 method. This pump is equipped with 7 valveless ceramic pump heads ensuring a very high level of reproducibility and consistency. The flow rate can be adjusted between 4 and 35 mL/min, fulfilling the USP standard flow rate recommendations of 4, 8, and 16 mL/min. A useful method development tool is the pump's ability to have different flow rates per channel. This feature is advantageous during the development of a USP 4 dissolution method.

Valveless ceramic pump heads

Another unique feature of the CP 7-35 pump is the automatic calibration / validation option. For this purpose, the pump is linked to a balance (optional) and a printer (optional). The pump automatically checks and adjusts its flow rate channel per channel based on user-defined volumes. The calibration protocol is then automatically printed out.

Analytical configurations.

The CE 7smart can be fitted with either a UV-Vis spectrophotometer for online UV measurements or an autosampler for offline collection into HPLC vials.

Offline sample collection

For offline analysis, the CE 7smart can be connected to an autosampler. Both offline system configurations – open and closed loop – can be programmed via the firmware to collect sample volumes at predefined time points. Methods can be protected as well as connected to a printer for temperature and method reporting. For 21 CFR Part 11 / Data Integrity compliance, it can also be controlled by WinSOTAX®plus Dissolution Software.

Online analysis

For online analysis in an open loop setup, a wide range of UV-Vis spectrophotometers can be directly linked to the CE 7smart. Using WinSOTAX®plus Dissolution Software, online measurements can be taken at predetermined times. The system automatically reads the baseline for each cell, records raw absorbance data and corrected data, and calculates concentration and % drug release in a 21 CFR Part 11-compliant software package.

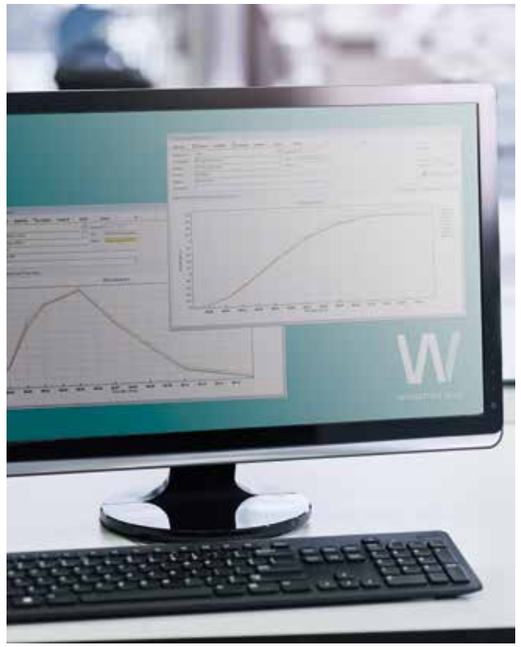
On-/offline analysis & sample collection

The UV-Vis on-/offline analytical configuration provides for even more flexibility: This combined configuration gives the user the benefits of both configurations and for the open loop setup, both offline collection and online analysis can take place simultaneously – providing real time UV-Vis results while allowing for back-up sampling. With WinSOTAX®plus, a single software package is used for raw data acquisition and flexible calculation of results.

WinSOTAX®plus Dissolution Software.

WinSOTAX®plus has been developed under the latest regulations including GAMP, GALP, ISO 9001 software standards and completely complies with the rules and regulations of 21 CFR Part 11 and Data Integrity set out by the FDA.

The software is an integrated dissolution package that controls the CE 7smart and all connected components. WinSOTAX®plus operates and has been validated on Windows 7. It is fully networkable and LIMS compatible. When installed, WinSOTAX®plus is supplied with a complete validation IQ / OQ package and supported by SOTAX-certified software engineers worldwide.



Other important features include:

- User-friendly method setup, results reporting, hardware control
- Real-time data collection in % dissolved, abs or concentration
- Single or multi-component analysis
- Placebo or impurity subtraction
- Standard calibration and standard bracketing
- Flow rate and temperature reporting
- Control of UV-Vis (different drivers available), sampling time points, sample volume collection
- Scanning function during the run
- Cell grouping (allows the collection of data by grouping different cells with different testing conditions, e.g. different flow rates, different dose etc.)

Analytical Services.

From method development to stability studies and commercial batch release in a US-FDA-inspected, certified Pharmaceutical Establishment with GMP-compliant quality system – our analytical services are a one-stop solution for pharmaceutical companies. Based on decades of experience and unique application knowhow, our team of experts will find a solution for your specific challenge.

R&D Services

- API screening and characterization
- Feasibility studies
- Method development
- Method automation
- Method validation and re-validation
- Method transfer

Routine Analytical Services (GMP)

- QC analysis
- Stability studies
- Clinical and commercial batch release

GMP CERTIFIED FDA

Support Services

- Troubleshooting and investigations
- Training
- Consulting
- Audits

Instrument Services.

Friendly and competent local service is the cornerstone of our business. A global network of service engineers and certified SOTAX partners assists you throughout the life cycle of your instrumentation – from on-site installation, qualification, and training, to preventive maintenance, regular re-qualification, and uncomplicated troubleshooting support in case of problems.

Compliance Services

- Installation
- Qualification (IQ / OQ / PQ)
- PVT / ASTM
- Routine calibration and qualification
- Computer system validation (CSV)

Support Services

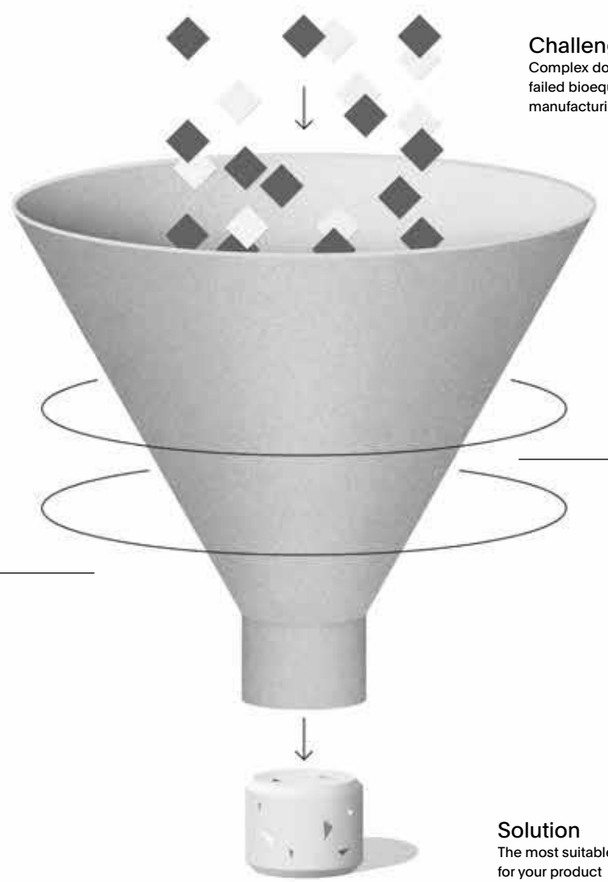
- Training
- Preventive maintenance
- Troubleshooting
- Repair
- Project management
- FAT / SAT
- LIMS integration
- Relocation services

sotax.com/services

For Experts.
By Experts.

SOTAX offers unique specialist know-how in close cooperation with SPS Pharma Services. Set in an independent cGMP-compliant and FDA-inspected facility, a team of scientists, analysts, and lab assistants helps companies worldwide in overcoming the various challenges associated with release testing of pharmaceutical dosage forms.

SPS Pharma Services



Challenge
Complex dosage form, failed bioequivalence study, manufacturing issue

Know-how
Formulation properties, methods, analytics, instrumentation capabilities

Equipment
Dissolution
(USP 1 / 2 / 3 / 4 / 5 / 6 / 7)

Content testing
(uniformity, assay)

Automated platforms

Physical testing

Solution
The most suitable method for your product

SOTAX Customer Services

		Analytical Services	Instrument Services
R&D Services	API screening & characterization	●	–
	Feasibility studies	●	–
	Method development	●	–
	Method automation	●	–
	Method validation & re-validation	●	–
	Method transfer	●	–
Support Services	Troubleshooting & investigations	●	●
	Consulting	●	●
	Training	●	●
	Project management	–	●
	LIMS integration	–	●
	Audits	●	–
	Relocation services	–	●
Routine Analytical Services (GMP)	QC analysis	●	–
	Stability studies	●	–
	Clinical & commercial batch release	●	–
Compliance Services	Installation qualification (IQ)	–	●
	Operational qualification (OQ)	–	●
	Performance qualification (PQ)	–	●
	PVT / ASTM	–	●
	Computer system validation (CSV)	–	●
	Routine calibration & re-qualification programs	–	●
	Preventive maintenance	–	●
	Repair	–	●

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