sotax
Solutions for Pharmaceutical Testing

35 years of Flow-Through Cell Dissolution: *35 years of Evolution and Flexibility*

From the first conceptual drawings from the creator of the flow through method, Dr Langenbucher at Ciba in the early seventies to the latest development for elution testing of drug eluting stents and injectables, the flow-through cell has always been the dissolution instrument of choice for novel dosage forms due to its *flexibility* and has evolved with the *evolution* of new drug delivery technologies.

Celebrate with us, the innovation SOTAX has delivered over the past 35 years.

1976 – 1978

CE 6 1978 – 1992

CE 70 1992 – 2001

CE 7smart 2001 – today

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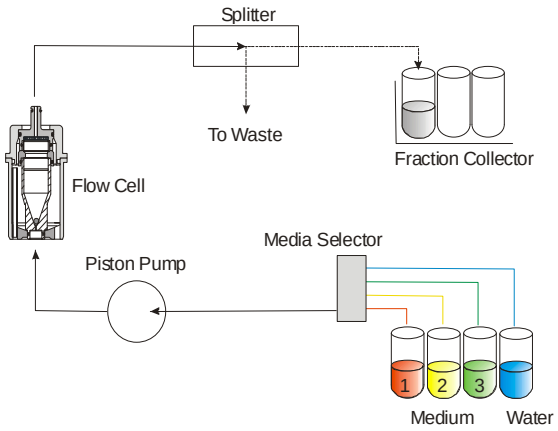
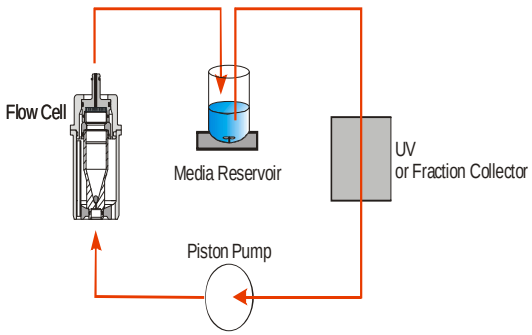
► *Flexibility in defining Solubility conditions with Media Volumes*

Originally designed for poorly soluble compounds where more than the compendial USP 1, 2 and 3 media volumes could provide, the flow-through cell system has always been linked to “optimal sink conditions” allowing for complete flexibility in terms of media volume.
In the *“Open Loop”* configuration, fresh media crosses the dosage form. The total amount of media is determined by the flow rate used. It is therefore more appropriate to link the FTC technique to the “sink conditions” in which the concentration of solute is from 5 to 10 times higher than the saturation concentration. In an *“Open Loop”* configuration, the total media volume is infinite. With the evolution of low dose products, it is also possible to use the same flow cell to work with a fixed volume of media in a *“Closed Loop”* configuration. In a *“Closed Loop”* set up, media is re-circulated across the dosage form. Media volumes in this set up can be as low as 10 ml (small volume dissolution) and as high as needed. It is now possible to compare 250 ml, 500 ml, 900 ml, 1 l, 2 l paddle, baskets and BioDiss methods to the FTC method. The FTC method provides advantages over the USP methods such as different hydrodynamic and mixing effects as well as eliminates the coning or dead zones effects seen in USP 1 and 2.



Open Loop configuration



Closed Loop configuration

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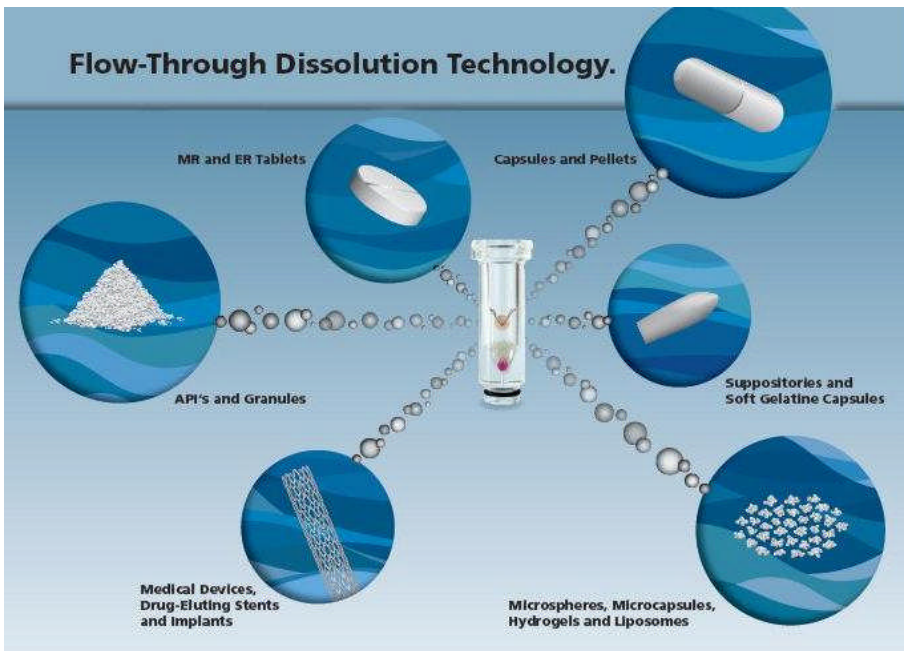
► *Evolution to Small Volume Dissolution Testing*

The small volume SOTAX CE 7smart system with MicroVolume Autosampler was developed in 2007 for release rate testing and elution testing of very low dose products such as drug eluting stents, implants and injectables. The microvolume autosampler can take accurate samples as low as 100 ul into capped vials. To increase throughput, two USP IV systems can be run in sequence to one autosampler.



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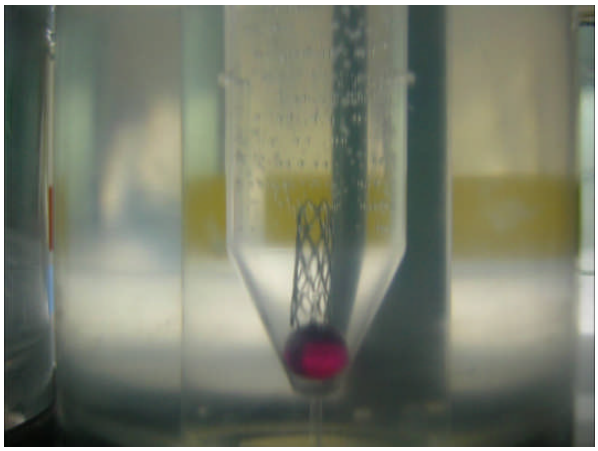
► *Flexibility of dosage form positioning*

The flow-through cell was immediately identified in R&D as a powerful technique due to the numerous possibilities in positioning the dosage form. Solid Dosage forms can be simply placed in the cell, positioned uniformly in a tablet clip holder or placed on glass beads. This all takes place before the test has even begun. This can eliminate variables caused by introduction of a tablet to a vessel, tablet sticking, swelling and floating.

Different tablet set ups



A Drug Eluting Stent in the FTC

As the FTC method evolved, new cells have been developed and optimized according to dosage form specificity. The position of the sample can be addressed by the choice of the cell and its internal arrangement. Possibilities include solutions for suspension and injectable introduction, powder and granule dissolution, drug eluting stents and implant positioning and oils and fats associated with soft gelatin capsules and suppository testing. Today, the FTC is used for IR, MR, ER tablets, capsules, API characterization, granules, pellets, suppositories, implants, drug eluting stents, suspensions, creams, gels, soft gelatin capsules, microspheres, buccal tablets, injectables and suspensions, ophthalmic solutions and lenses and much more.

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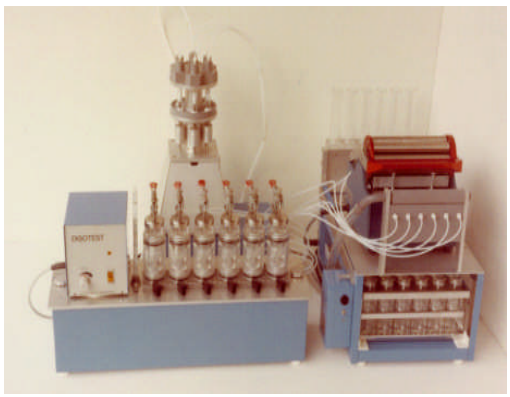
► *Flexibility of choosing analytical techniques and automation*

Since 1977, the first USP 4 Apparatus was connected to a fraction collector for automated sample collection.

Today many different configurations are available including:

a) Cost Effective Manual Sample collection
b) Open Loop with automated sample collection for HPLC analysis
c) Open Loop with On-line UV for real time Absorbance readings
d) Open Loop with both an On-line UV and fraction collector
e) Closed Loop with on-line UV
f) Closed Loop with autosampler for HPLC analysis
g) Open or Closed Loop with UV Fiber Optics



Open Loop with Fraction Collector 1977

Open Loop with Fraction Collector 2006

SOTAX entered a partnership with Thermo Scientific in 2005 to supports the integration of the Evolution 300 spectrophotometers for on-line analysis. With the use of WinSOTAX Advanced Dissolution Software, all methods, analysis, standard reading and reporting can be done in a 21 CFR Compliant environment. Today, WinSOTAX Dissolution Software can drive a number of brands of UV-Vis available on the market. WinSOTAX Dissolution Software was the very first Dissolution Software introduced by any vendor in 1998. Today, it has evolved into a client-/server software, networkable and ready for LIMS.

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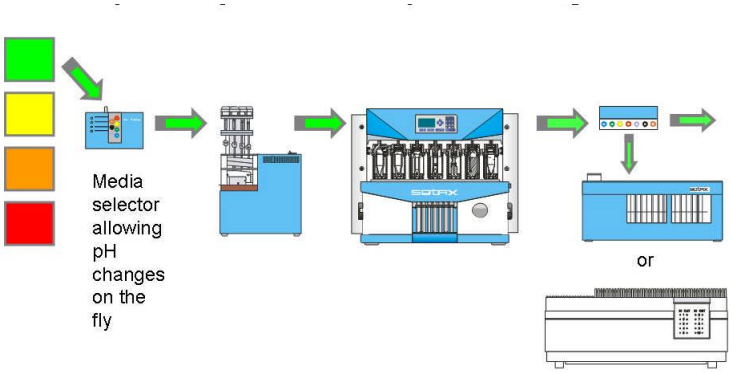
► *Flexibility of changing media*

pH and media changes are an important tool for IVIVC and especially critical for MR and ER products. Traditionally, it was time consuming with the other USP apparatus. In an open loop FTC a media selector allows pH changes after a predetermined time without movement of the dosage form. Unlike in USP 1, 2 and 3 methods where a physical movement must be made to move the dosage to the next media, the FTC media change is very simple. This is critical for light sensitive products and products that might disintegrate. When media changes occur in the FTC method, the flow rate and the cell temperature does not change or the position of the dosage within the cell. The FTC method is the only method that allows for a media change on a suspension and a powder.

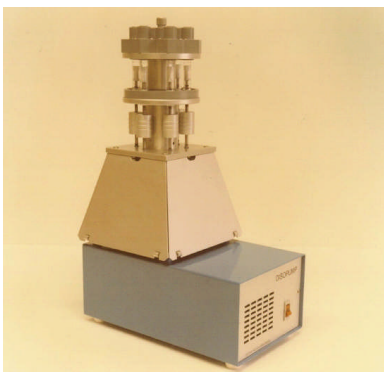


Open system for pH changes

► *Flexibility of flow rates*

The most important development parameter is the flow rate in the FTC method. The flow rate can be compared with the RPM speed of USP 1 and 2 or the DPM of USP 3. It is therefore extremely important to have a reliable and accurate pump. In the early USP 4 systems, a piston pump was developed over a peristaltic pump due to its reliability, strength to maintain flow rate and longevity. However with a need from industry for lower flow rates, SOTAX introduced a new digital pump that allows for very low and independent flow rates per channel.

The new digital CP 7 pump



First model of piston pump 1977

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► *SOTAX Application Seminars and Classes*

Annually since 2003, SOTAX hosts a gathering of regulatory, academia and industry experts to present applications of the Flow Through Method used within their labs. It's an opportunity to discuss with other companies how they are using the system, validating methods and useful experiences in method development. It also gives an update as to the regulatory and USP requirements for the FTC.

Here are a few of the many highlights:

- *"The method has been accepted by FDA as a release method for the elution of sirolimus in cardiovascular stents"* A Novel Method for the Elution of Sirolimus in Drug Eluting Stents, Cordis Corporation

- *"The impact of particle sizes and dissolution parameters can be discriminated using this instrument. Technique applied systematically to all suspensions development.*
- *The technique has been accepted by the FDA for our submission"* Experience with Bioequivalence study of suspensions – Relevance of InVitro data, Sandoz

- *"The preliminary results indicate that the modified USP flow-through method with open loop configuration shows potential to better simulate digestive system in development of model-free IVIVC for BCS I and II drug products"* In Vitro Dissolution Test with a Flow Through Cell CDER, FDA

- *"The in vitro dissolution methodologies are discriminating tests capable of measuring different degrees of product performance"* Performance Testing of a Suspension Dosage Form, Eli Lilly

- *"Apparatus IV can be used as an orthogonal, complementary tool in trouble shooting for problems arose from USP I/II dissolution testing and for decision making"* USP Apparatus IV Flow-Through Dissolution Testing--A Powerful Orthogonal Technique to the Conventional USP Apparatus I/II Dissolution Techniques, Genzyme

- *The laminar flow that the flow through cell provides mimics in vivo conditions more effectively than Apparatus I or II,* Drug Release in Ocular Implants Using Apparatus IV Dissolution with HPLC End Analysis, Intertek USA

- *" USP Apparatus IV was demonstrated as an important tool for dissolution in predicting and correlating in vivo performance of formulations"* Predicting BCS II and IV Compounds by Dissolution on Apparatus IV, Merck

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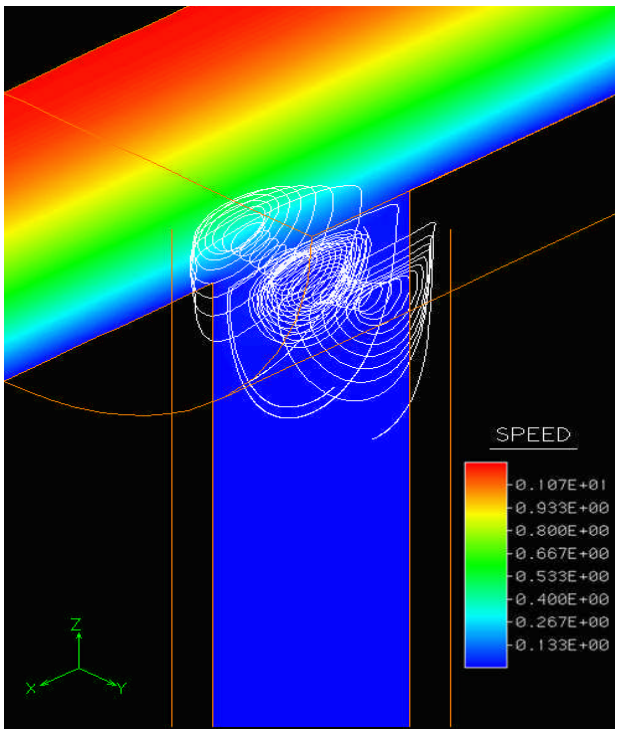
► *Today's Evolution of USP Apparatus 4*

New developments in the FTC method include the design of a T-Cell to study SR parenteral dosage forms where drug is transported via both a diffusion and convection process in vitro without the use of a membrane. Initial studies have been promising and work is continuing. Other new developments include holding devices for dialysis bags and contact lenses.

CE 7smart with two T-Cells



Diffusion convection principle

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► *The introduction of SPS Pharma Services, the first CRO dedicated to dissolution in 2007*

SOTAX Pharma Services, an independent company offers Feasibility studies, Method Developments and application training specific to USP 4. Another tool we have added to assist our global customers.

The flow-through cell has demonstrated for over 35 years, a complete dissolution technique offering flexibility in terms of media, volume, flow rate, analytical finish and dosage form handling. As the Flow-through cell method has evolved, so to have the instruments to meet our customers demand and the changing needs of Dissolution Testing. At SOTAX, we look forward to meeting your dissolution testing requirements and the needs of the *next* 35 years.

Do you need more information on specific applications?

You can contact us at:

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