Dissolution News

Issue #011 – January 2020

Welcome – Special Edition on the *Flow-Through Cell*

The Flow-through Cell Dissolution technique (FTC) has always played a particular role at SOTAX. From the pioneer days of pre-standardized dissolution experiments to the actual compliant use in QC, the FTC, JP3, or USP 4 technique has raised multiple milestones at SOTAX.

Due to its unique leading situation on the Pharmaceutical testing market, SOTAX has always been a unique observer and a partner of choice for ambitious dissolution developments. From Dr Langenbucher's work on poorly soluble compounds at CIBA (CH) to the long list of reference articles on microspheres from the Prof. Burgess and her team at the University of Connecticut (UCONN) USA, SOTAX has always been listening to the right experts at the right moment in order to offer the right systems at the right places.

Yes, indeed, from APIs to novel dosage forms, the FTC remains the "high resolution" dissolution technique, which says more. More discriminant, allowing easy media change for bio relevance, volume flexibility and ideal non-disturbing sampling, the FTC is the characterization tool that every dissolution department involved in formulation or re-formulation still requires to progress.

The recent successful years at SOTAX Asia have shown the importance of the FTC as a differentiation tool for all our pharmaceutical customers in emerging markets and SOTAX US have shown the way for decades organizing FTC events renowned as scientific exchange platforms of great value. European FTC projects never stopped whatever the general context was.

SPS Pharma Services, specialized in complex dosage form testing development for 10 years and an FDA-inspected company, remains the first place to support our customers worldwide. From an initial feasibility study to stability testing and batch release, SPS Pharma Services represents for our R&D customers more than ever the convenient highway to follow.

In parallel, SOTAX has also developed its internal support capacities everywhere and from scientific support to qualification expertise, our SOTAX experts are here to follow up on a daily basis.

In this FTC Special Edition of the SOTAX Disso News, you will read about software, hardware, events, and applications!

I want to thank all the committed supporters of the FTC (they will recognize themselves) for their efforts, which definitely gave a sweet flavor of success to the year 2019.

Enjoy the read.
I wish you and your families a nice year 2020.

Michel Magnier
Product Manager Dissolution USP 4

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New developments – Customer-specific features

Better accuracy on low flow rates (open system)
To achieve an industry requirement from a key customer on low flow rate testing, the firmware version 2.37 is now including a possibility of a “split factor” which is extending the collecting time, keeping the splitting ratio identical. This factor ensures a better accuracy for low flow rate methods. By default, this factor will remain to 1 and will not affect any functionality. Qualification documents have not been amended.

Semi-automated cleaning routines
The firmware version 2.37 also appeared with a new configuration parameter allowing a semi-automated cleaning more intuitive with user’s messages. An application note will be issued later on to describe these functionalities in detail. For all these new functionalities, the CE 7smart operating manual has been updated accordingly, do not forget to download and read regularly operating manuals. The previous cleaning modes are still available depending on the configuration.

Extended cells for oversized dosage forms or medical devices
Due to a method development project handled by SPS Pharma Services on long medical devices, we have developed a special version of our FTC instrument: the CE 7smart XTD. This unit has been designed to allow the use of extended cells. These cells have a diameter of 14 mm can hold 40 mL internal volume. The CE 7smart XTD unit is now used in a QC environment and remains user-friendly even used for highly potent products. As the CE 7smart design has been modified to allow the introduction of extended cells, this system is not compatible with standard cells. However, all the functionalities (e.g. test preparation) and possible system configurations (online, offline) remain equivalent. The CE 7smart XTD requires the firmware 2.38.

P/N	DESCRIPTION
22394-01, 22394-02	CE 7smart XTD
23081-01	Extended cell rack (inside the CE, 1 pc)
21490-01	Extended cell 14 x 260 mm (7 or 14 pcs)
22524-01	Bypass connector (option to work on less than 7 cells, 1-5 pcs)
23545-01	Extended cell rack assembly stand (outside the CE, to prepare cells, 1 pc)

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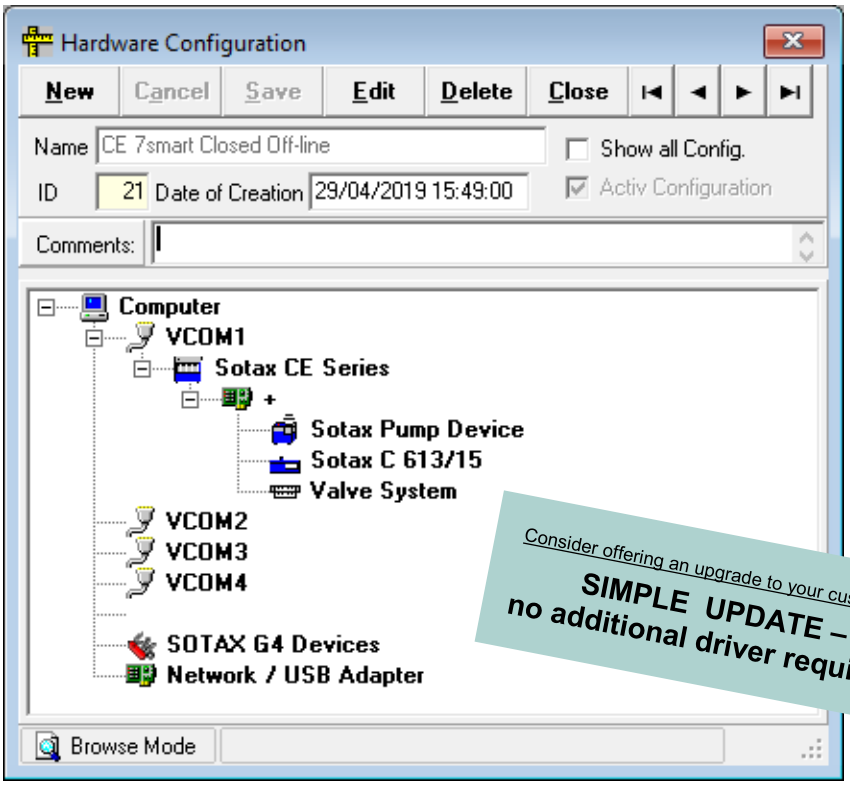
CE 7smart closed offline – Driven by *WinSOTAX®plus*

The CE 7smart closed offline configuration (CE 7smart, CP 7-35, and C 615) is also used in QC environments. Concerning data governance, it is therefore under the same level of scrutiny as other dissolution equipment is. So far, we had no possibility of controlling the CE 7smart closed offline system with a software.
This gap has now been filled with WinSOTAX®plus version > 2.70.
The CE 7smart functionalities remain the same, adding all current WinSOTAX®plus possibilities: user administration, report configuration, data export and audit trail. The only limitation is that users cannot do online UV-Vis measurement and offline sampling in the same test. It remains of course possible to sell an on-/offline configuration but user need to use one device configuration for online testing and another for offline testing. WinSOTAX®plus has been used to test this closed offline configuration driven by software in a real context: a big pharma QC lab in Europe. The users' feedback was good, so this functionality is now officially released.



Use of the CE 7smart – *at temperatures > 45 °C*

Testing microsphere drug release with the Flow-Through Cell has been extensively documented (list of publications on demand) and is sometimes involving accelerated testing. It important to mention that the CE 7smart has been designed to work at a temperature up to 45 °C.

Temperatures above are attainable based on firmware version (release note on demand) but requires user precautions and responsibilities as handling of hot water imposes. We also recommend a higher maintenance frequency in this case.

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The SOTAX SSA – *Semi-solid drug products and performance test*

In May 2020, the USP will describe products further according to their route of administration. Accordingly, semi-solid products are covered by chapter <3> “Topical and Transdermal Drug Products – Product Quality Test”.
In this chapter, semi-solid products are also linked to the informative USP chapter <1724> “Semi-solid Drug Products – Performance Tests” describing the equipment used for in-vitro drug release tests of semi-solid dosage forms such as creams, ointments, gels. In this chapter <1724>, apparatuses are mentioned such as the vertical diffusion cell, immersion cell, and “a special cell used with USP apparatus 4”. SOTAX and SPS were involved in a previous collaborative study to define this chapter and it may be important to describe this “special cell” briefly.

Firstly, all set-ups require a reservoir to contain the dosage form. This reservoir is the donor compartment. A membrane is used to separate the formulation from the receptor medium
There are three types of Vertical Diffusion Cell A, B, C, all having a limited volume.
There are also two types immersion cell, or enhancer cell (A, B) based on a flat bottom mini vessel and uses a mini paddle. Note that no mini-vessel type apparatus appears in a mandatory chapter.

Finally, the semi-solid adaptor (SSA) is a reservoir (donor compartment) containing a membrane and placed in a 22.6 mm cell (facing down the media flow under or above the tablet holder).
The SSA semi-solid adaptor is the only semi-solid system involving a compendial apparatus as described in chapter <711>: the 22.6 mm cell.
This also means that the SSA in Apparatus 4 is the only system, which can be used for other dosage forms.
The SSA also benefits from the inherent advantages of the flow-through cell: media volume flexibility (no need for media replenishment), non-disturbing sampling, sampling automation, dimensions consistency and possibility of using open and closed systems.
The SSA is available in three sizes (400, 800 and 1200 microliters) and is available with a punch to cut the membrane and a mounting tool to help placing the membrane on the top of the dosage form.
See comparison results in the scientific publication from University of Connecticut and FDA mentioned on page 5!

P/N	DESCRIPTION
11159-01	Semi-solid adapter for USP 4, v = 1.2 mL
11159-02	Semi-solid adapter for d = 22.6 mm cell, v = 0.8 mL
11159-03	Semi-solid adapter for d = 22.6 mm cell, v = 0.4 mL
11381	Mounting tool, for semi-solid adapter
R990-0001	Membrane-cutting punch, d = 18 mm, for semi-solid adapter

Printing – *directly* from the CE 7smart

The CE 7smart can be connected to parallel printers as the classical Epson label printer TM-U210 with a parallel port. This parallel printer is still available. As the number of printers with parallel port are decreasing, we also offer a parallel to USB port printer.
As it often happens with printers, it may not work with a specific printer model. So, take a demo device to try first. (Alternatively, connect a PC with WinSOTAx-plus…)

P/N	DESCRIPTION
C100-0051	Epson label printer TM-U210, with a parallel port
C100-0181	Parallel to USB port printer

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Good to know –
Regulation, publications, product news

Regulation –

Informative USP Chapter <1151> Pharmaceutical Dosage Forms:
Official in August 2019: This chapter describes the USP dosage form nomenclature and a complete description of each dosage form. It also includes the naming of Modified Release profiles (general term for alteration to an Immediate Release): Delayed-release as gastro-resistant oral products and Extended-release for a prolonged release.

Informative USP Chapter <1004> Mucosal Drug Products-Performance Tests:
This chapter describes the products dedicated to the mucosal route (membrane surfaces as optic, ophthalmic, nasal, oropharyngeal, urethral, vaginal, and rectal. The FTC is mentioned for lipophilic suppositories.

Publications –

"Orbito"
http://www.orbitoproject.eu/deliverables

"In-Vitro Release Test Methods for Drug Formulations for Parenteral Applications"
Vivian Gray, Susan Cady, David Curran, James DeMuth, Okponanabofa Eradiri, Munir Hussain, Johannes Krämer, John Shabushnig, Erika Stippler.
Available in "Dissolution Technologies", November 2018 issue.

"In-Vitro and Ex-Vivo Correlation of Drug Release from Ophthalmic Ointments"
Quanying Bao[1], Bryan Newman[2], Yan Wang[2], Stephanie Choi[2], Diane Burgess[1]
[1]University of Connecticut
[2]FDA / CDER
Available online or in "Control Release", 2018 April 28; 276: 93–101.
doi:10.1016/j.jconrel.2018.03.003.

New cells –

Some FTC cells are now declined in other material than PMMA. The PEEK cells can resist to any solvent and the ULTEM cells have the advantage of being transparent. So far, they are mainly used for R&D purpose.

P/N	DESCRIPTION
8220-02	22.6 mm cell in PEEK (same cap as usual)
8287-02	12 mm cell in PEEK (same cap as usual)
8388-02	Powder cell in PEEK (same cap as usual)
231667	12 mm cell in ULTEM® (same cap as usual)
231665	22.6 mm in ULTEM® (same cap as usual)
9155	5.5 mm in PTFE (requires cap 8457)

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Events 2019 – 14th Annual USP 4 Seminar at SOTAX Corp. in Westborough, USA

Representatives from more than 25 different companies participated in this year flow-through dissolution seminar hosted in Westborough, MA. This was the 14th annual meeting hosted by the SOTAX US team and an important part of the year for our customers looking to learn more and network with their peers.

After a wonderful introduction by our own Samir Haddouchi (SPS Pharma), the FDA and Zoetis both presented on bio-relevant dissolution testing and the modified use of the apparatus 4 for In-vivo Predictive Dissolution (IPD). The Zoetis work by Dr. Hao Xu[1] has already been published.

To start the afternoon, our new application scientist Vivek Shah gave an update to the group on some recent changes to the CE 7smart such as the improved cleaning procedure and the modified CE 7smart XTD (as described on page 2 of this Disso News edition), which can be used for long medical devices. Three customers then shared their experience using the flow through method to study novel products including a multi-component-gel formulation used to repair hearing loss and various case studies with parenteral products from University of Connecticut. Merck concluded the agenda with their success story where they have used the CE 7smart (in combination with an NMR) to understand the release characteristics of their nano-suspension formulations.

These annual meetings have become a critical part of both the flow-through and automation communities in the Americas. All presentations have been uploaded to our internal SharePoint and are available for public release.

[1] "Characterization of the Partition Rate of Ibuprofen Across the Water-Octanol Interface and the Influence of Common Pharmaceutical Excipients", Xu, Hao et al., Journal of Pharmaceutical Sciences, Volume 108, Issue 1, 525-537

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Events 2019 – Seminar “Current & emerging trends in drug development, R&D, Quality and Regulatory” in India

SOTAX India conducted a scientific seminar series titled “Current and Emerging Trends in Drug Development, R&D, Quality & Regulatory” which took place in Mumbai, Ahmedabad, and Hyderabad between 08-12 July 2019. This 1-day program was designed for USP 4 dissolution apparatus users and attended by around 280 professionals from the pharmaceutical industry and academia. The seminars covered the overview of the USP 4 apparatus, applications, regulatory considerations, and data integrity.

Jean Louis Raton, Head of Business Asia Pacific & Member of the SOTAX Group Management, explained the basics and fundamentals of USP 4 in detail while Samir Haddouchi presented the applications of non-conventional dosage forms on USP 4 (e.g. liposomes, microspheres, eye suspensions, OSDs, slow / sustained / modified release, medical devices, nano-formulations, etc.). He also spoke about the data integrity software for the USP 4 apparatus. Suhas Yewale, Head of the SOTAX India Application Lab, presented case studies involving injectable and eye suspensions. Dr. Umesh Banakar, Professor and President of Banakar Consulting Services USA, spoke about the various challenges in predicting bioavailability from in-vitro dissolution. Another highlight of the event was a live demonstration made by R. S. Pal, Vice President Technical and Service Support at SOTAX India.

In Mumbai, SOTAX jointly conducted the event with the FDA Lab (CDTL & CDSCO), and another with the Bombay College of Pharmacy. The event at CDTL & CDSCO was attended by Dr. Raman Singh, Director, CDTL, and Deputy Drugs Controller (India) at Central Drugs Standard Control Organization – Dr. P. B. N. Prasad and Dr. Rubina Bose.