Exploring Promising Alternatives to In Vitro Performance Testing of Dry Powder Inhalers

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Overview

- Overview of Dissolution
- Pulmonary Delivery and Challenges in Release Rate Testing
- Case Study I using an Enhancer Cell
- Case Study II using Small Volume Apparatus 7 (400-DS)
- Promising option using NanoDis – IR and ER Case Studies
- Summary & Key Takeaways

What is Dissolution?

Dissolution is the Determination of a drug's rate of release In Vitro under a specific set of conditions.

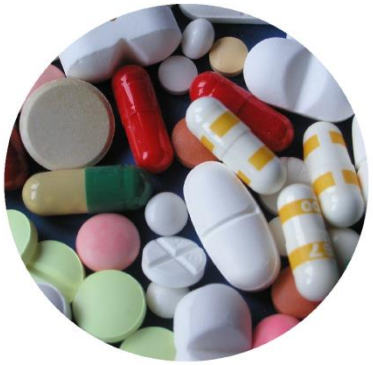
This release rate is correlated to in vivo data and can be used to determine the acceptability of a formulation for use.

The Importance of Dissolution

Of all the tests performed on pharmaceutical products, dissolution is the only one that determines the ***performance*** of a formulation**.**

Dissolution is essential in making sure that drug is administered in a **safe and effective** manner at all stages.

What do we test?

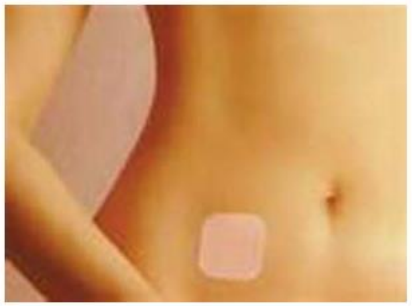


Tablets/capsules

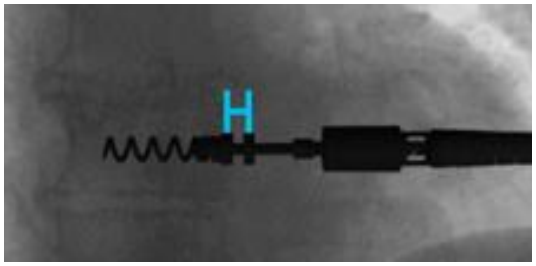
Suspensions

Dissolution is not just about orally ingested products. It is used for tablets, capsules, powders, ointments, creams, gels, osmotic pumps, transdermal patches, implants, bone cements, ocular implants, drugs on chips, medicated contact lens, stents, coated beads, catheters, wound care products, etc.…

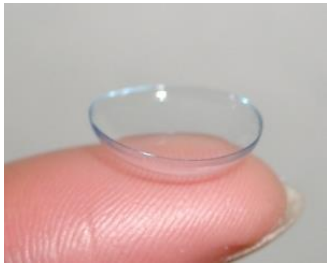
Ointments



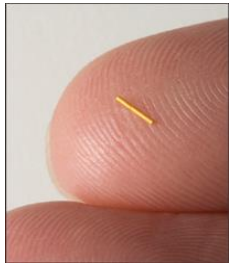
Transdermal patches



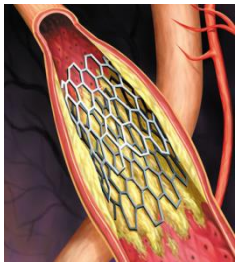
Pacemaker Lead



Contact Lens



Ophthalmic Implant



Drug Coated Stents

Dry Powder Inhalers

Inhalation Route of Administration offers many advantages for drug delivery:

- Non-invasive
- Avoids 1st pass liver metabolism
- Large epithelial surface area with good permeability
- Direct transport into the bloodstream allows optimal systemic delivery

Dry Powder Inhalers

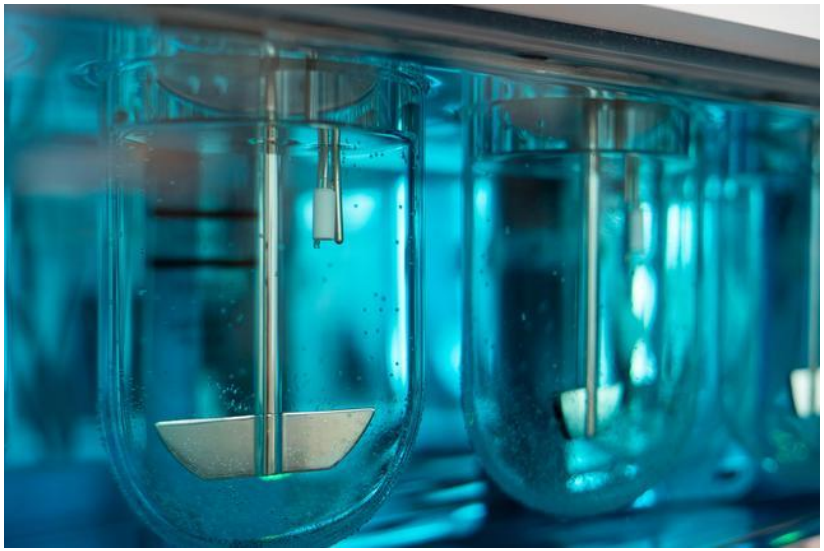
- Particle sizes are typically sized 0.5 – 4.0µm
  - <0.5 risks being exhaled
  - >4 can get trapped in the brachial airways and cleared through coughing or swallowing
- Prior to Dissolution Testing, proper fractionation of the dose from the inhaler should be obtained.
- USP <601> Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powder – Performance Quality Test discusses particle evaluation equipment

Dissolution Attempts with Dry Powder Inhalers

Dissolution Testing with Dialysis Chambers has been attempted for DPIs but there are significant issues with this approach:

- Insufficient mixing within the dialysis chamber itself
- Permeation through the membrane becomes the rate limiting step
  - Sink condition may not be maintained
  - Critical burst phase may not be captured

Float-A-Lyzer with holder and evaporation cover (p/n 12-2066).



Promising Options for Metered Dose Inhaler Dissolution

- Enhancer Cell for use with Modified USP Apparatus 2
- USP Apparatus 7 Small Volume System (400-DS)
- NanoDis nanoparticle filtration system for use with USP Apparatus 1 and 2

Case Study I: Dissolution of Fine Particle Fraction from Truncated Anderson Cascade Impactor with an Enhancer Cell

In this study, the collection of fine particle fractions (FPF) utilized a special PTFE funnel over the final small collection plate (sCP) contained in the truncated ACI.

After determining the FPF for the drugs under study, various stages were removed to truncate the ACI which allowed a simplified and robust means of collecting only the fine particles on the final sCP.

The sCP was coated with a film of silicon oil to retain the particles. Next, a portion of adhesive tape equivalent in size to the 4.0 cm^2 Enhancer Cell was used to recover the dose deposited on the sCP and mounted in the Enhancer Cell for testing facing upward.

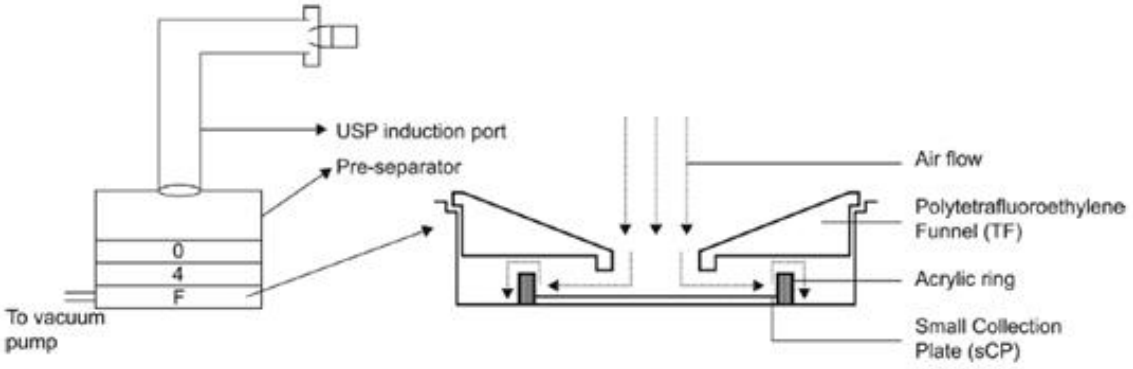


Fig. 1. Schematic diagram of truncated ACI set up with the cross-section of the additional insert on stage F for the collection of FPF on single stage.

Case Study I: Dissolution of Fine Particle Fraction from Truncated Anderson Cascade Impactor with an Enhancer Cell

- Described in USP <1724> Semisolid Drug Products as Immersion Cell Model A
- Works in a traditional Apparatus 1 and 2 system
- Typically used for testing semisolids
- Good alternative to Franz Cell testing, allows use of existing systems
- Available in 0.5, 2, and 4cm2 openings
- Membrane selection dependent on application

Case Study I: Dissolution of Fine Particle Fraction from Truncated Anderson Cascade Impactor with an Enhancer Cell

Method Parameters:

- 50 RPM Apparatus 2 with mini-paddle
- 200mL mini-vessel set up with Enhancer cell
- Media: Gamble's Solution with 0.2% v/v Tween 80 to mimic simulated lung fluid at 37°C
- Paddle placed 1cm above enhancer cell
- 2mL samples taken with media replacement

Case Study I: Dissolution of Fine Particle Fraction from Truncated Anderson Cascade Impactor with an Enhancer Cell

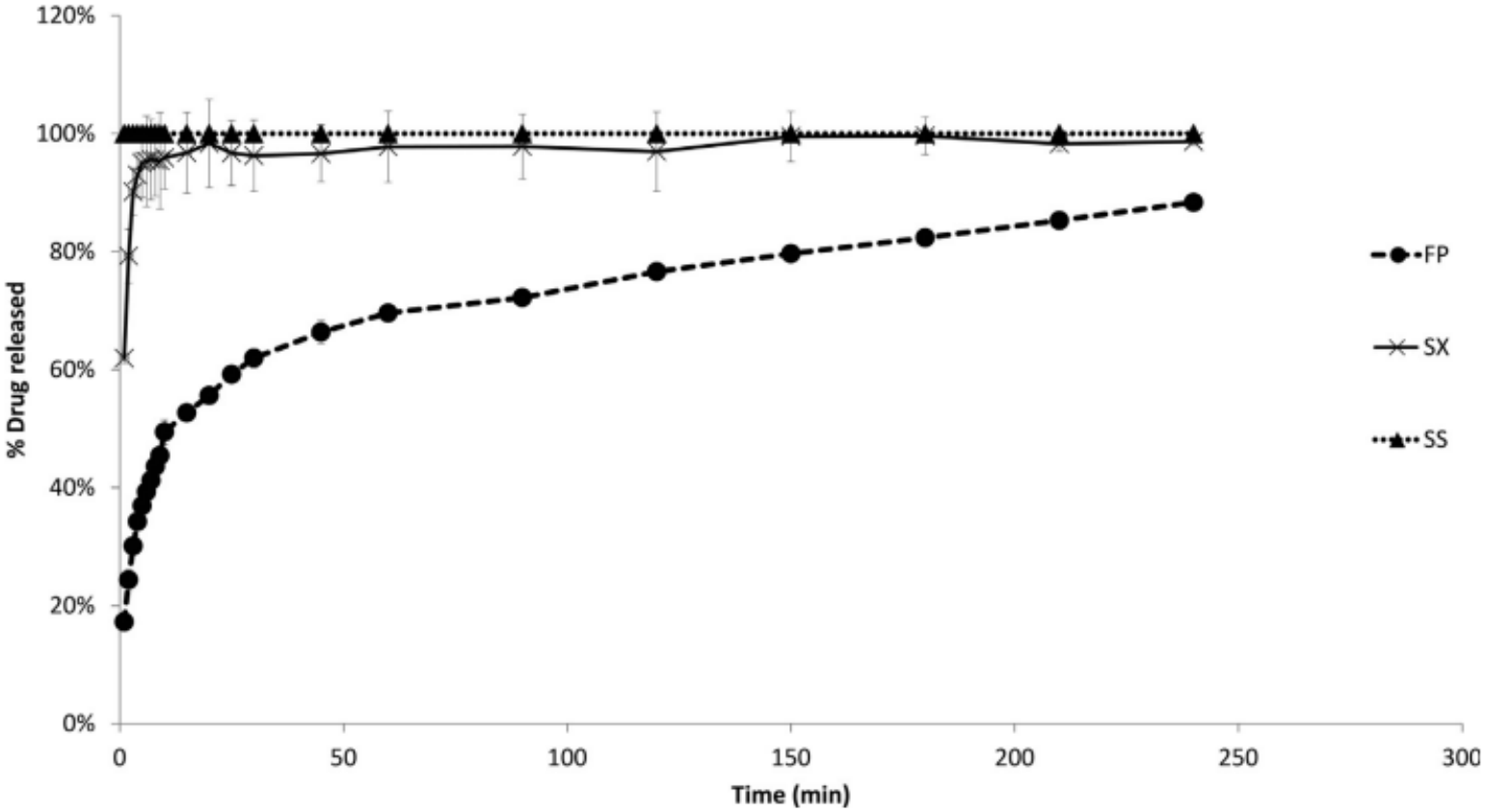


Fig. 4. Dissolution profile of FP (×), SX (●) and SS (▲) in mSLF.

Case Study I: Dissolution of Fine Particle Fraction from Truncated Anderson Cascade Impactor with an Enhancer Cell

SUMMARY:

The Method was able to differentiate between 3 particle formulations successfully.

- SS is BCS Class 1 with high solubility as well as high surface area
- SX which is highly soluble shorted a rapid burst profile
- FP follows a logarithmic function

These were expected given their relative solubilities. In vivo studies support the slower release of glucocorticoids such as FP.

Use of the Enhancer Cell allowed for a discriminatory dissolution method using commercially available equipment already present in the USP, with a slight modification.

Use of this approach could allow for a reproducible means of testing these products and would also be adaptable for automation such as autosamplers and/or online UV-Dissolution analysis.

Case Study II: Evaluation of the coat quality of sustained release pellets by individual pellet dissolution methodology

- Drug Loaded Pellets were made through extrusion-spheronization
- 25% w/w MMC, 25% w/w lactose, and 50% w/w metformin was used
- Drug pellets were then transferred to a fluid bed coated and sustained release pellets with 8% and 10% w/w coat weight gains were created
- Pellets were then dried at 60 C for 12 hours

Table 2
Physicochemical properties of sustained release pellets with 8% and 10% coats.

Coat (%)	D_{50} (μm)	SP_{pel}	Aspect ratio	Roundness	W_s (μg)	Drug content (%)	Coat thickness (μm)
8	813 ± 24	0.35 ± 0.01	1.11 ± 0.05	1.13 ± 0.01	516 ± 10	48.7 ± 4.0	13.9 ± 2.2 (15.7%*)
10	849 ± 56	0.40 ± 0.03	1.10 ± 0.05	1.12 ± 0.01	513 ± 8	49.4 ± 3.5	15.7 ± 0.9 (5.9%*)

* The relative standard deviation of pellet coat thickness.

Case Study II: Evaluation of the coat quality of sustained release pellets by individual pellet dissolution methodology

Initial Studies were performed with USP Apparatus 1 and 2. Data showed high variability and different phases of dissolution release.

This data is explained by floating and clumping behavior of the beads in both apparatus types.

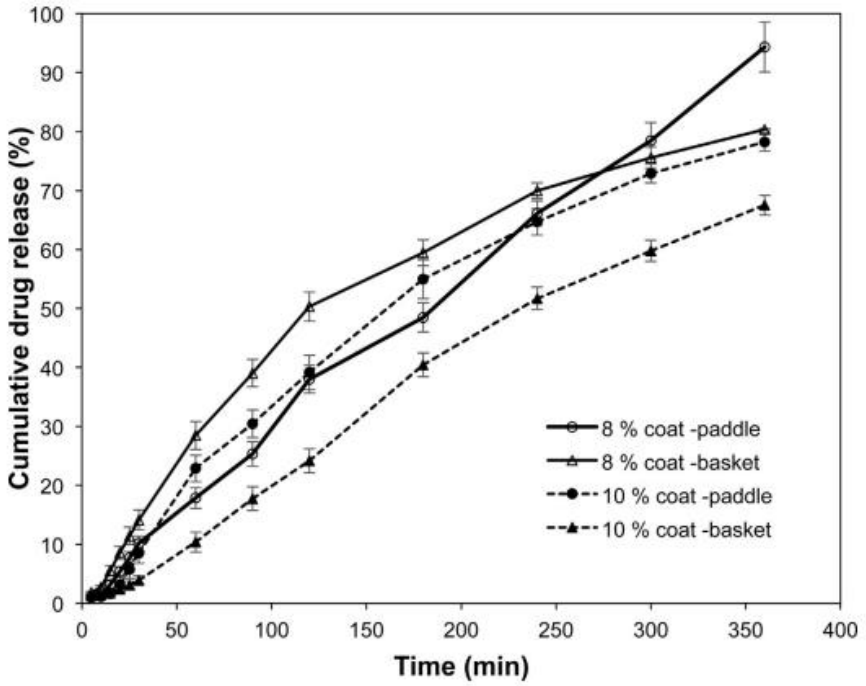


Fig. 3. Cumulative drug release profiles of ensemble of sustained release pellets with 8% and 10% coats using USP dissolution apparatus 1 (basket) and apparatus 2 (paddle).

Case Study II: Evaluation of the coat quality of sustained release pellets by individual pellet dissolution methodology

USP Apparatus 7 – Small Volume – 400-DS

- Originally designed for medical device market
- Low dose, high potency drugs
- Essentially no evaporative loss
- 3 - 12mL test conditions

Case Study II: Evaluation of the coat quality of sustained release pellets by individual pellet dissolution methodology

Small-volume USP App 7: 400-DS

- Sample holder reciprocates 2 cm per USP <724> Drug Release
- Mixing from Reciprocation avoids the challenges of agglomeration of particles as well as the challenges of floating
- Product is completely submerged and free-flowing within the dissolution media

Case Study II: Evaluation of the coat quality of sustained release pellets by individual pellet dissolution methodology

Holder Types for the 400-DS

Products that can work well with this method include:

- Subcutaneous implants
- Stents
- Contact Lenses
- Wire/Tubing/Leads
- Birth Control (IUDs, Implants, etc.)

Product must be **non-disintegrating** due to no filtration.

Case Study II: Evaluation of the coat quality of sustained release pellets by individual pellet dissolution methodology

400-DS Apparatus 7 Study

In this study, particles were separated into various fractions using an Anderson Cascade Impactor as with the previous study.

The fractions were collected onto a filter, and another filter was placed on top. This particle/filter sandwich was then rolled tightly and placed within the 400-DS PEEK basket holder

Case Study II: Evaluation of the coat quality of sustained release pellets by individual pellet dissolution methodology

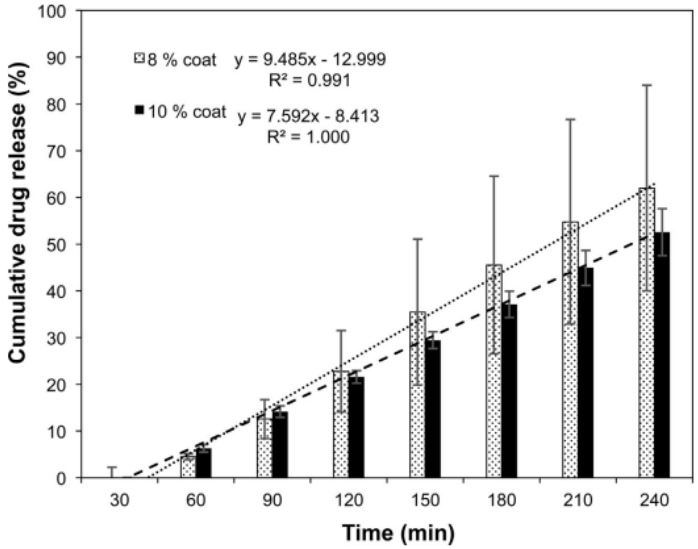


Fig. 4. Cumulative drug release profiles of individual sustained release pellets with 8% and 10% coats and their linear correlation values.

- 400-DS method parameters were optimized with changes to dip speed, dip interval, and dissolution media volume
- Linear dissolution release rates were able to be determined through the optimized methods with R2 values of 0.991 and 1.000 for the 8% and 10% coated products, respectively
- More variability was seen in the 8% v/v and indicates a greater variability of coat quality compared to the 10%.

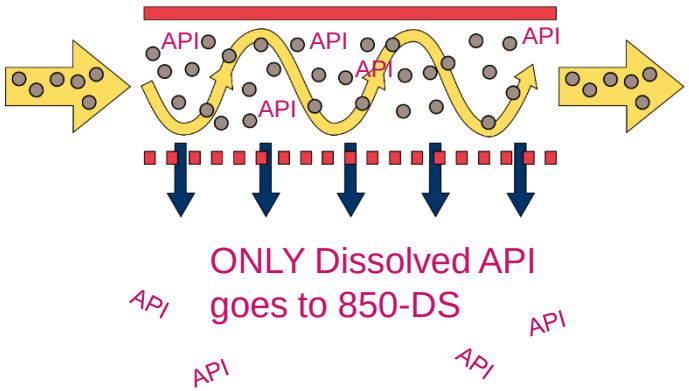
Promising Options Using the NanoDis System

Cross Flow Filtration for Nanoparticles

NanoDis - Hollow Fiber Filters
Cross Flow Filtration for Nanoparticles

- Used for manufacturing for purification and solvent removal
- Tangential flow of the filtration medium “different from the dead-end filtration”
- No filter cake
- No blockage of the filters

Dissolution Media with Dispersed API loaded Nanoparticles + Dissolved (free) API



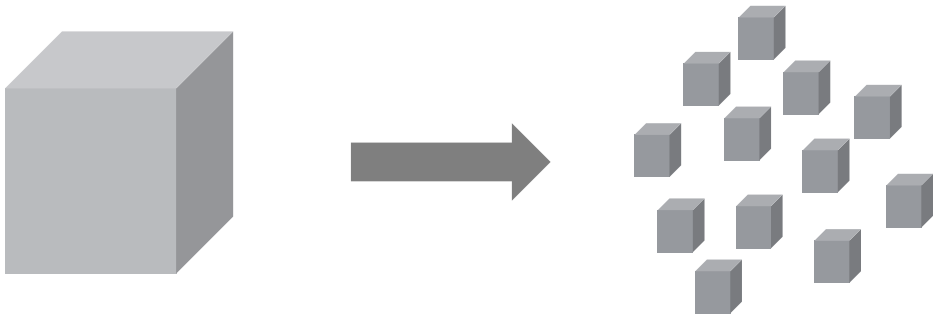
Dissolution Media with Dispersed API loaded Nanoparticles

NanoDis - Hollow Fiber Filters
Cross Flow Filtration for Nanoparticles

- Nanoparticle formulations have great potential for pharmaceutical development
  - especially for low soluble substances

- Small particle size of nanoparticles results in
  - greater surface area
  - greater bioavailability of the Active Pharmaceutical Ingredient (API)

Increase in surface area



Increase in dissolution rate

NanoDis - Hollow Fiber Filters
Cross Flow Filtration for Nanoparticles

However, conventional dissolution techniques present significant challenges:

- difficult to filter using conventional membrane technology, thus the dissolution process continues
- filters may rupture and dispersed nanoparticles pass into the measuring vial
- nanoparticles tend to clump within dialysis membranes which can become blocked and incorrect results are observed
- unsuccessful separation of nanoparticles from the dissolution medium
- negative impact on the ability to accurately predict the true API dissolution profile and selection of the best lead formulation

The NanoDis System – what is it?

A workflow that ensures *in vitro* dissolution of nanoparticle API

NanoDis System

Unique to Agilent, the NanoDis System addresses the pharmaceutical industries need for compliant, semi-automated testing of nanoparticle drug formulations.

The NanoDis System enables formulation scientists to produce accurate release profiles of API's utilizing conventional dissolution apparatus:

- A market first that combines Agilent's conventional USP App 1 & 2 (708-DS) with automated sampling (850-DS), cross-flow filtration, and flexible software
- An automated, compliant solution ideal for regulated environments

The NanoDis System – what is it?

A workflow that ensures *in vitro* dissolution of nanoparticle API

708-DS (USP App 1, 2, 5, 6 and Intrinsic)

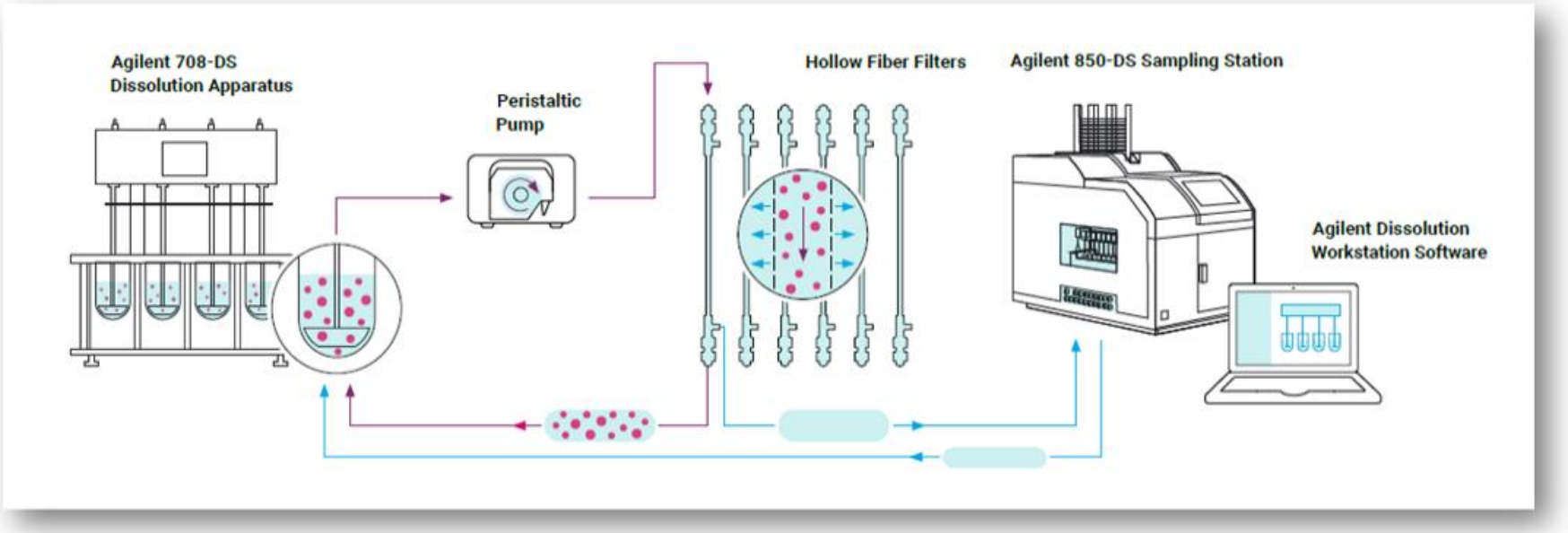
Nanoparticle Filtration

850-DS Dissolution Sampling Station

DWS Dissolution Workstation Software

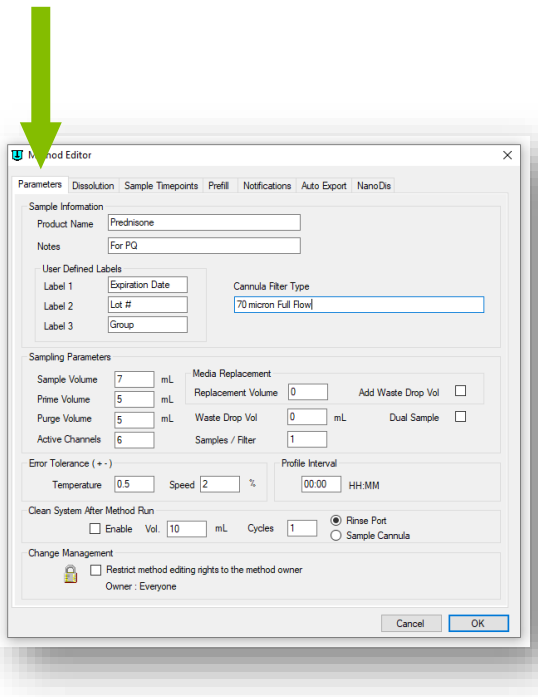
The NanoDis System – what is it?

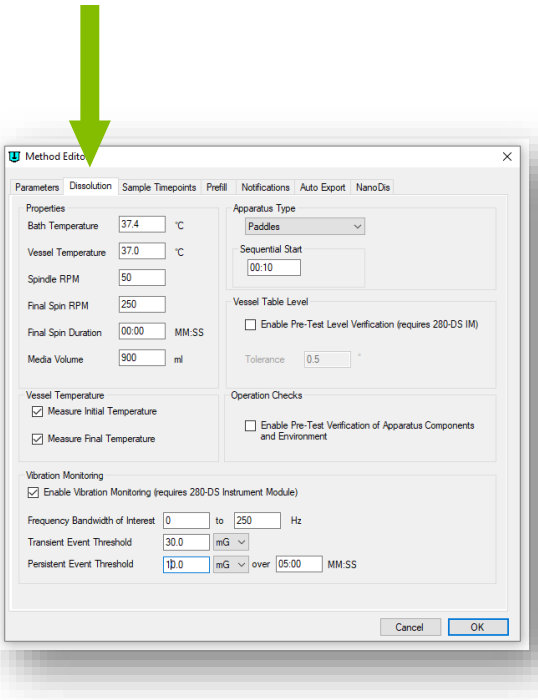
A workflow that ensures *in vitro* dissolution of nanoparticle API

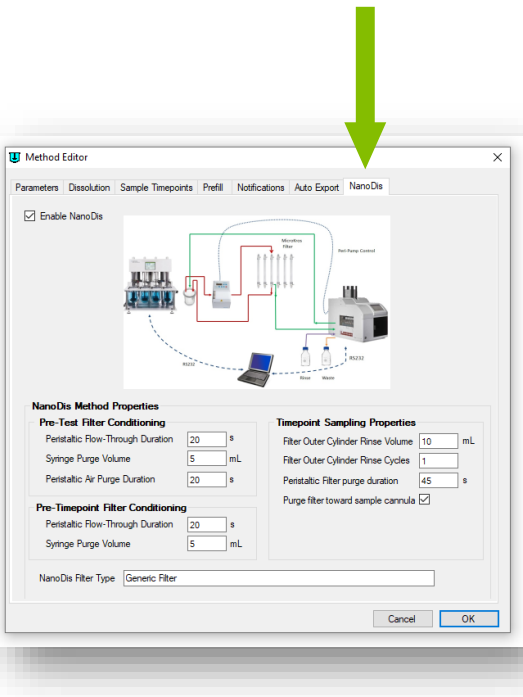


The NanoDis System – what is it?

Powered by flexible, compliant Dissolution Workstation Software







The NanoDis System – what is it?

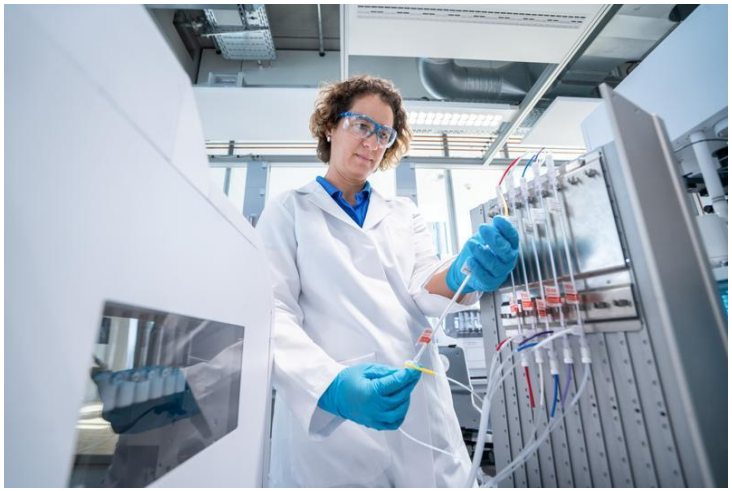
Using the right methodology is critical in drug development and quality control of nanoparticle formulations.

Critical steps:

1. complete separation of API from the nanoparticle
2. a quick separation method - especially for immediate release formulations
3. a blockage & rupture free filtration solution
4. quantification of only the dissolved API

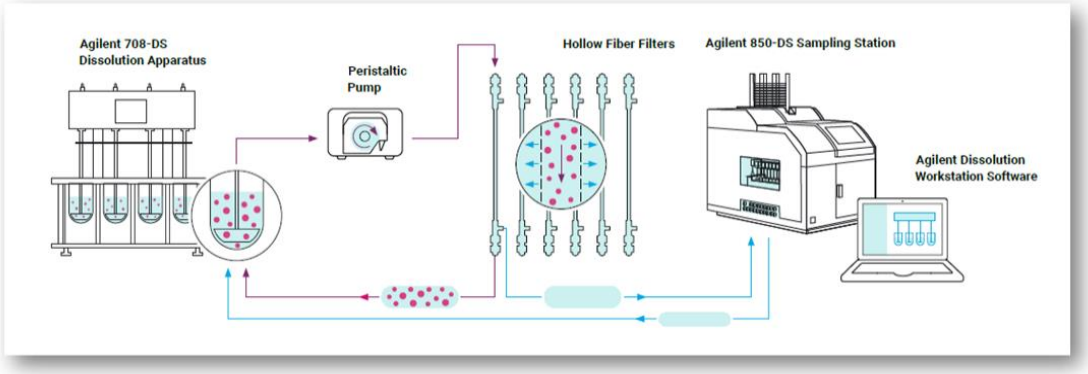
The NanoDis System – what is it?

- **Separation** of nanoparticles from dissolution media independent of particle size
- **Online** and simultaneous particle separation
- **Accurate** *in vitro* dissolution of nanoparticles and quantification of only dissolved API
- Ability to test immediate and extended-release nanoparticle formulations
- A system that is free from blockages and filter ruptures

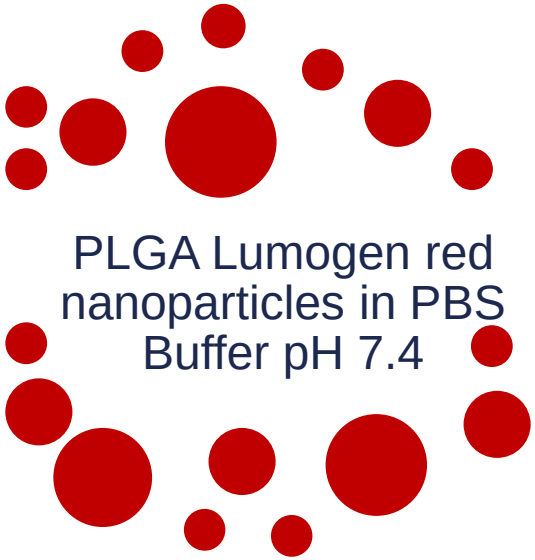


The NanoDis System – what is it?

- An uninterrupted dissolution process as media and any dispersed nanoparticles are recycled back to the 708-DS vessels
- **Rugged and robust** methodology using conventional USP apparatus. Methods are easily transferred to QA/QC.
- **Automatically** maintained and consistent fill-volumes during analysis
- Full **compliance** - all methods are operated, electronically documented and auditable (DWS)
- **Peace of mind** knowing that a fully compliant Dissolution Testing solution manufactured to stringent quality control procedures has been implemented



NanoDis System > Filter Efficiency Test



PLGA Lumogen red nanoparticles in PBS Buffer pH 7.4

0.45 µm Syringe filter

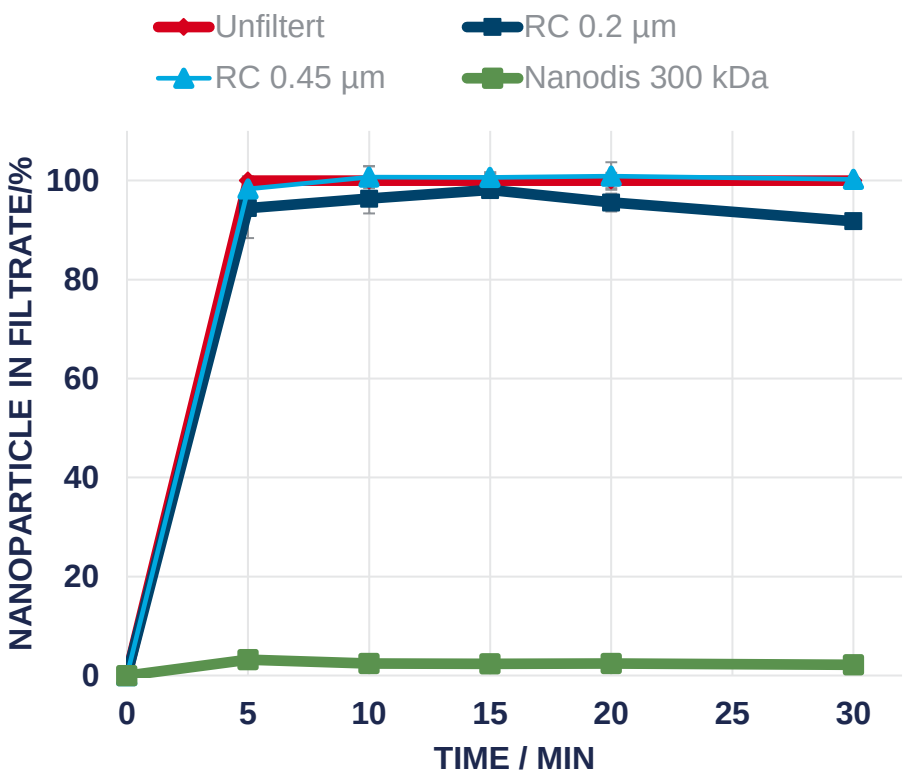
0.22 µm Syringe filter

Nanodis

- Visual inspection of the samples for red color from Lumogen nanoparticles
- Determination of particle concentration with DLS

Separation of nanoparticles from dissolution medium after sampling

NanoDis System > Filter Efficiency Test

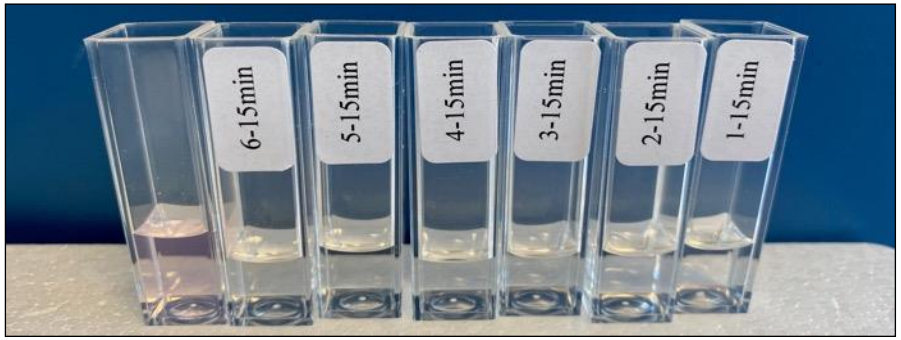


No difference between unfiltered sample, 0.45 µm, 0.2 µm filtered sample

COMPLETE PERMEATION OF NANOPARTICLES THROUGH FILTER

Nanoparticles are absent in Nanodis samples

COMPLETE SEPARATION OF NANOPARTICLES WITH NANODIS

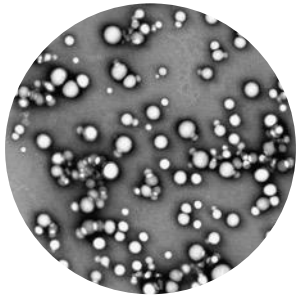


All dissolution samples are colorless with Nanodis

Dissolution of Immediate Release (IR) Nanoparticles

Immediate Release Nanoparticles

Case Study



Ibuprofen nanoparticles

Selection of dissolution medium

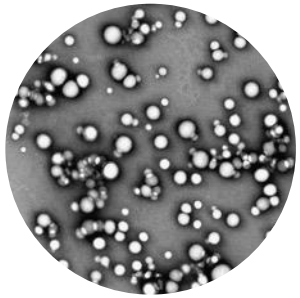
- A dissolution medium in which nanoparticles are 100% dispersible
- A dissolution medium where the API is limited soluble

pH 4.5 Acetate buffer

- Particles do not agglomerate
- Solubility limited in the medium
- The aim of dissolution is to determine
  - ✓ ONLY the dissolved API, and
  - ✓ NOT dispersed nanoparticles

Immediate Release nanoparticles

Case Study



Ibuprofen nanoparticles in pH 4.5 acetate buffer 200 mg in 900 mL

Nanoparticles dispersed in dissolution medium (60%)

Nanoparticles dissolved in dissolution medium (40%)

FAILURE to separate nanoparticles from dissolution medium…

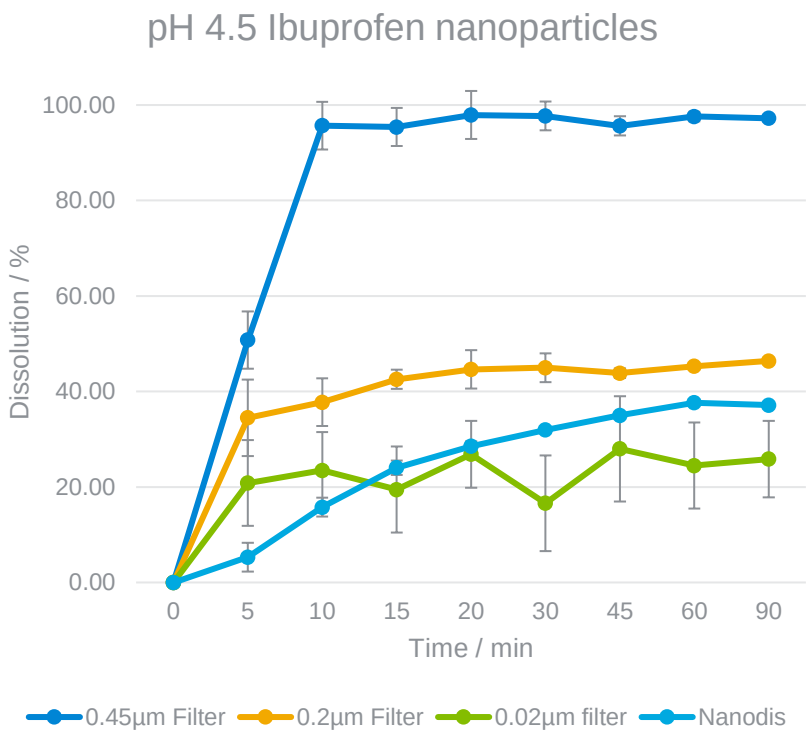
- **post-sampling analysis with HPLC shows 100% dissolution**
- **because dispersed samples dissolve during HPLC analyses**

SUCCESSFUL separation of nanoparticles from dissolution medium…

- **post-sampling analysis with HPLC shows max 40% dissolution**

Immediate Release Nanoparticles

Case Study



- 100% Dissolution is reached with **0.45 µm** filter although the API solubility is limited to 40%. This shows the complete permeation of nanoparticles through the 0.45 µm filter
- Lower dissolution values were observed for **0.2 µm** filter due to the particle size of Ibuprofen where a significant amount of particles are larger than 220 nm
- **0.02 µm** filter was blocked during sampling resulting in lower and inconsistent dissolution profile

NanoDis System

- Only dissolved API was characterized using NanoDis enabling true *in vitro* dissolution testing.
- Nanoparticles were completely retained by the filter

Dissolution of Extended-Release (ER) nanoparticles

Extended-Release Testing
Case Study

Rhodamine PLGA Nanoparticles

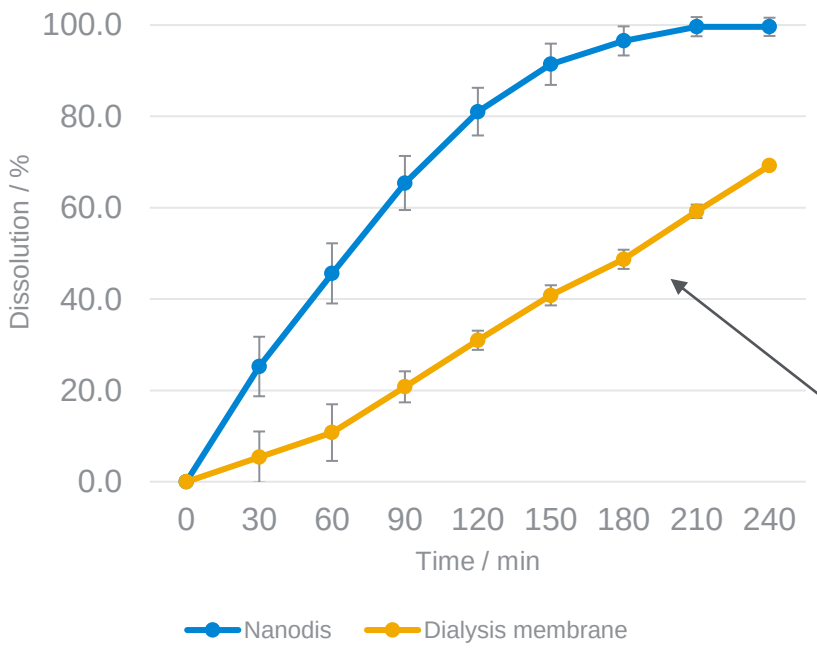
Dialysis bag

Nanodis

Dissolution studies

Quantification of Rhodamine with HPLC

Extended-Release Testing
Case Study



NanoDis System

- quantifies the real dissolution kinetics for the extended-release formulations
- enables true *in vitro* dissolution testing.

Dissolution through dialyses membrane is controlled by

- permeation coefficient, and
- supersaturation in the dialyses membrane

Summary & Key Takeaways

- Currently a lack of clear guidance for Dissolution Testing of Metered Dose Inhalers
- Many attempts with traditional filtration and dialysis techniques have severe challenges associated with them
- There are new promising approaches to these types of products using:
  - NanoDis Cross-Flow Filtration
  - Enhancer Cell Immediate Cell
  - 400-DS Small Volume Apparatus 7

Summary & Key Takeaways
Acceptable Method Requirements

- Low-to-moderate variability
- Complete Release (85%+ or Asymptote)
- Characterizing timepoints below 85%
- Challenged with other formulations
- Evaluated to ensure they are rugged and reproducible enough for repeated testing by multiple people/units

Method Development Resources

- USP <1092>
- FDA Dissolution Method Database (http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm)
- Dissolution Discussion Group (www.dissolution.com)
- Dissolution Technologies (www.dissolutiontech.com)

Questions?

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- or find me on LinkedIn