Applications in area of drug release using the flow through cell

Society of Pharmaceutical Dissolution Science
26-27th July 2016 – Ahmedabad (India)

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SPS Pharma: Who we are?

- CRO offering all analytical services.
- Since 2005, only company in the world specialized in R&D for dissolution and release testing.
- Located in Orleans, 1h South of Paris (France).
- Facility fully cGMP compliant, US FDA inspected, regularly subject to audits.
- 30% of clients in North Am, 40% in Europe and 30% in Asia.

R&D services

- Dissolution feasibility studies (ie innovative dosage forms)
- Dissolution method developments
- Dissolution method transfers to automation
- Content testing method transfer on automated platforms
- Analytical methods development (HPLC/ UPLC & UV)
- Troubleshooting/ investigations/ consulting (failed BE, IVIVC, manufacturing..)

Routine analytical services

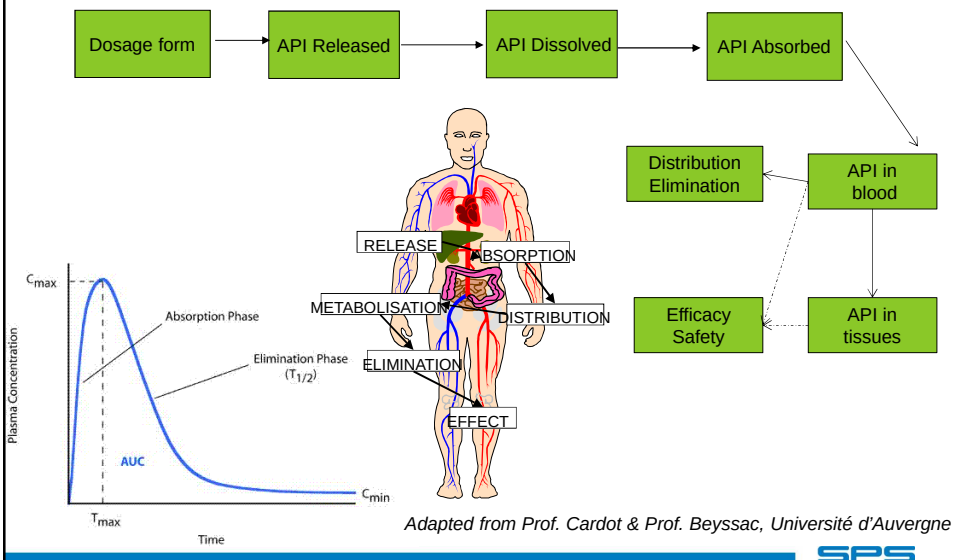
- Method validations
- QA/QC analysis (GMP)
- Stability studies (including samples storage)
- Dissolution (all compendia techniques)
- Automated dissolution
- Automated content
- Loss on drying
- Crushing force
- Friability
- Disintegration

Outline

– Introduction about flow through cell dissolution

– API characterization
  – Intrinsic dissolution rate
  – Apparent dissolution
  – Case studies

– Conclusion



Adapted from Prof. Cardot & Prof. Beyssac, Université d'Auvergne

$$\frac{dW}{dt} = \frac{D}{h} S(C_s - C_b)$$

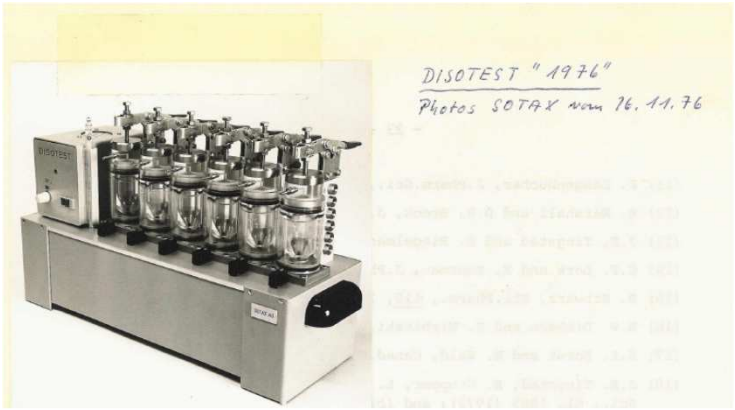
Where
dW/dt = dissolution rate
D = diffusion coefficient
h = thickness of the stagnant layer surrounding the dissolving particle
S = the surface area of the solid
Cs = the concentration of a saturated solution
Cb = the concentration at any given time of the bulk solution

In the early 70‘s

* Only recently we discovered some documents which indicate that about 20 years ago the column method was favoured by the FDA and also considered by USP, for the release from timed-release preparations: a letter dated Aug. 23, 1957, from E.B. Vliet to the members of a Subcommittee on Tablets and a paper by D. J. Campbell and J. G. Theivagt in Drug Standards, 26, 73 (1958).

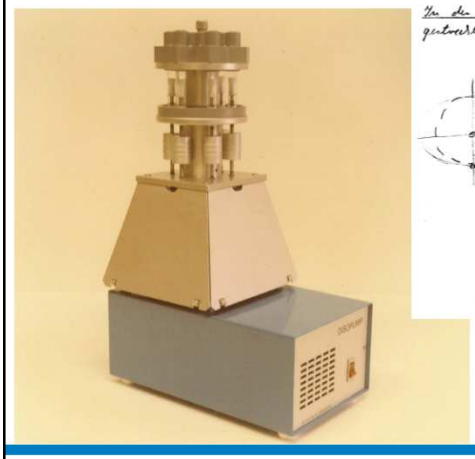
Extract from „Dissolution rate testing with the method column;Methodology and results“ F.Langenbucher, H.Rettig, 1977

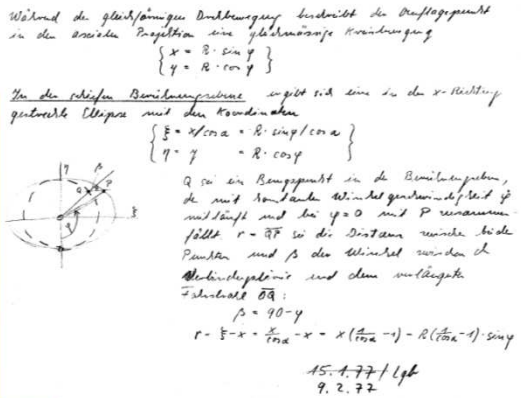
Sotax following request from Dr Langenbucher in Ciba in the 70's…



Slide presented courtesy of Sotax AG

...developed and…





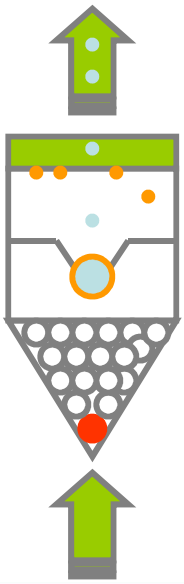
Slide presented courtesy of Sotax AG

…improved continuously the USP 4 instrument

Slide presented courtesy of Sotax AG

Why choose USP4?

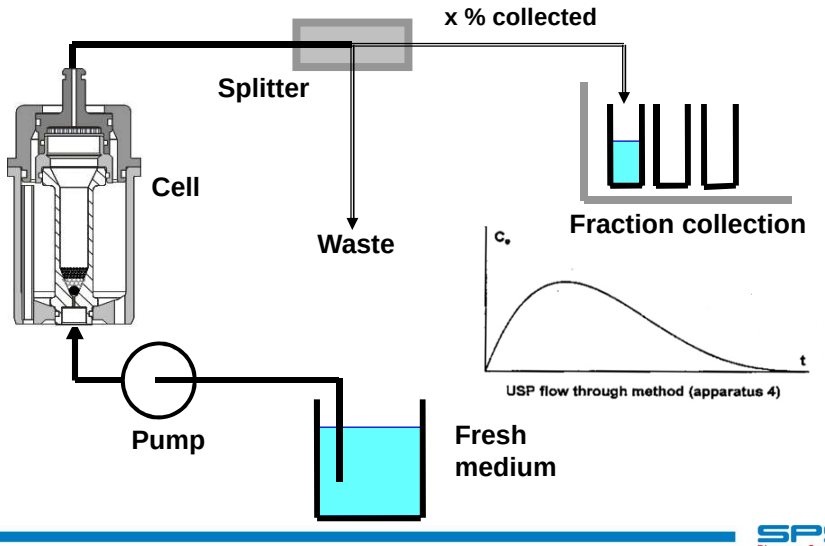
- USP 4 is the method of choice for **poorly soluble compounds** in order to maintain sink conditions
- USP 4 is a **compendial method for low volume** dissolution media
- Specific cells for special/novel dosage forms are available
- **Automated pH changes** can be easily achieved for IVIVC studies
- Solves many challenges of USP 2 such as floating or sticking products, and inherent sampling issues
- USP 4 method is increasingly used for measuring **API characterization** (apparent dissolution in Eur. Ph. § 2.9.43).
- USP 4 is a recommended method for **injectable suspensions**.



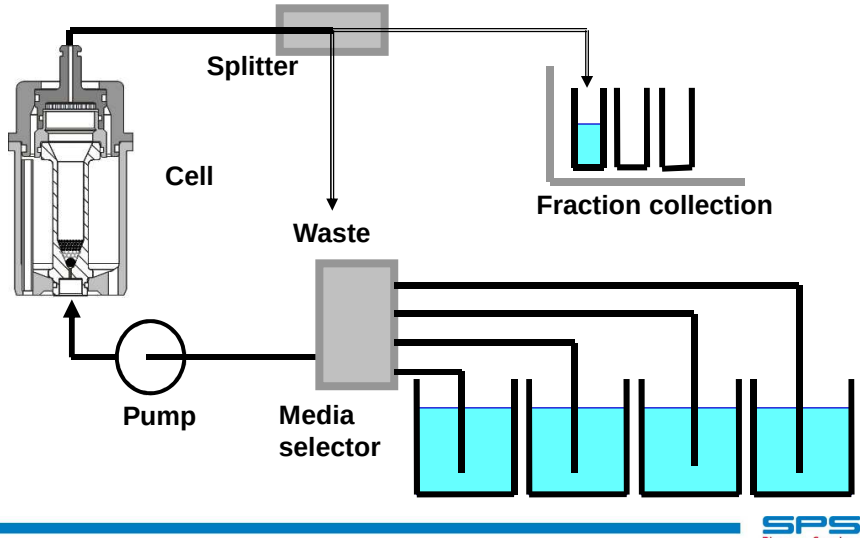
The Flow Through Cell

- The test sample is located in a small-volume cell through which solvent passes
- The eluate is filtered upon leaving the cell
- The eluate is analyzed directly (on-line) with a spectrophotometer and/or collected in a fraction collector (off-line).

Open system



Open system with pH change



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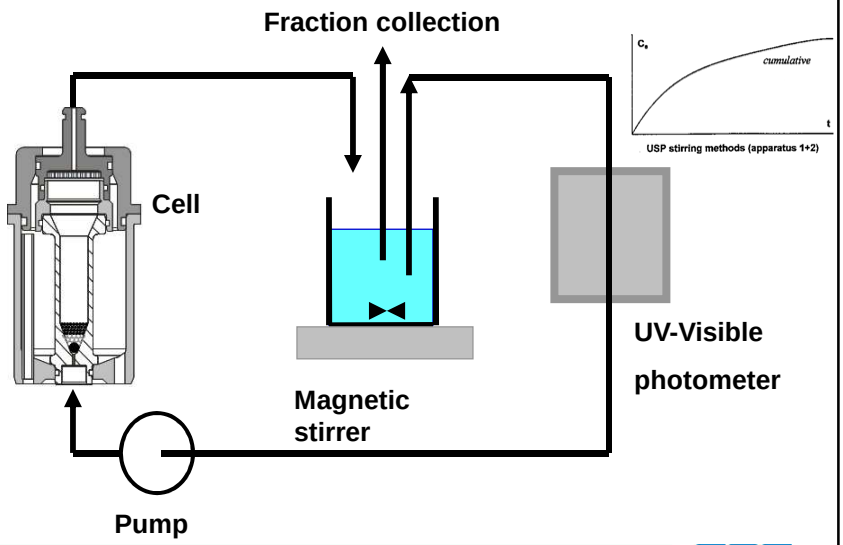
Closed loop system



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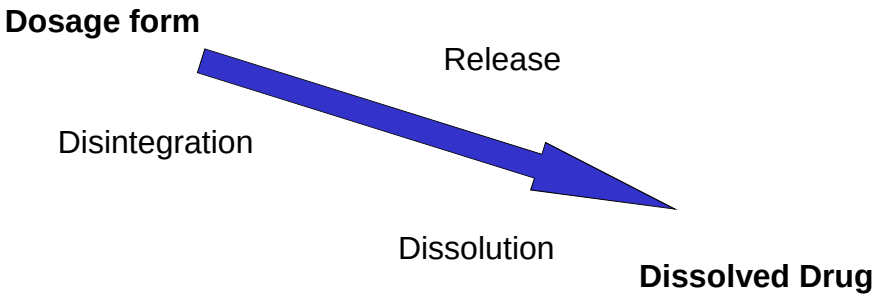
Disintegration → cohesive properties of the formulation
Release → type and proportion of excipients
Dissolution of the drug →API characteristics

Importance of all steps in dissolution test interpretation



Outline

– Introduction about dissolution

– API characterization
  – Intrinsic dissolution rate
  – Apparent dissolution
  – Case studies

– Conclusion

Intrinsic dissolution (1)

The intrinsic dissolution rate is the rate of dissolution of pure pharmaceutical ingredients when conditions such as agitation or stirring speed, pH and ionic strength of the dissolution medium and surface area are held constant .

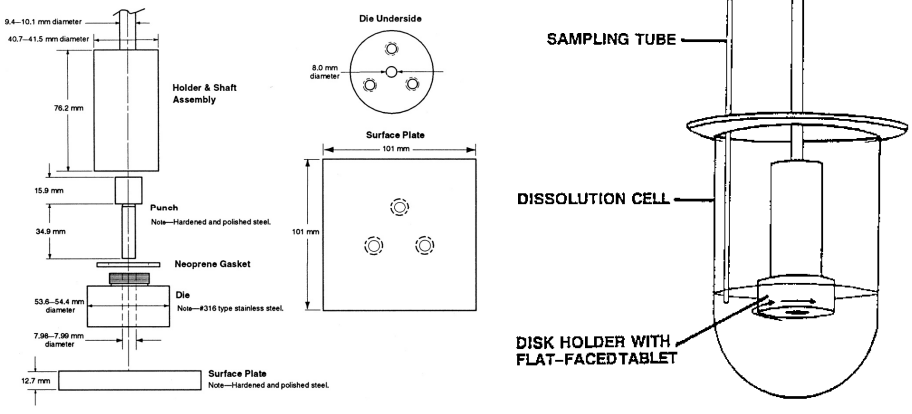
Physical properties effects are minimized or eliminated.

- Determination of the constant k
- Use of a tablet of pure drug
- Expressed as mg/min/cm^2

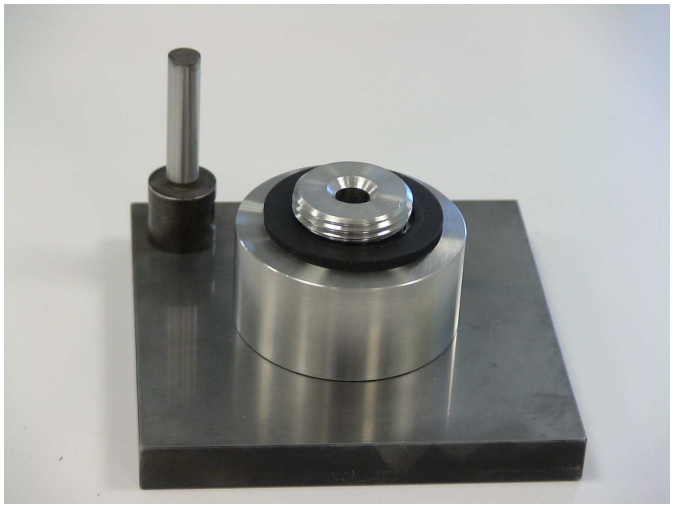
$$\frac{dW}{dt} = \frac{D}{h} S(C_{sat} - C_t)$$

Eur. Ph. § 2.9.29
USP <1087>

Intrinsic dissolution (2)



Intrinsic dissolution (3)



Intrinsic dissolution (4)

Intrinsic dissolution (5)

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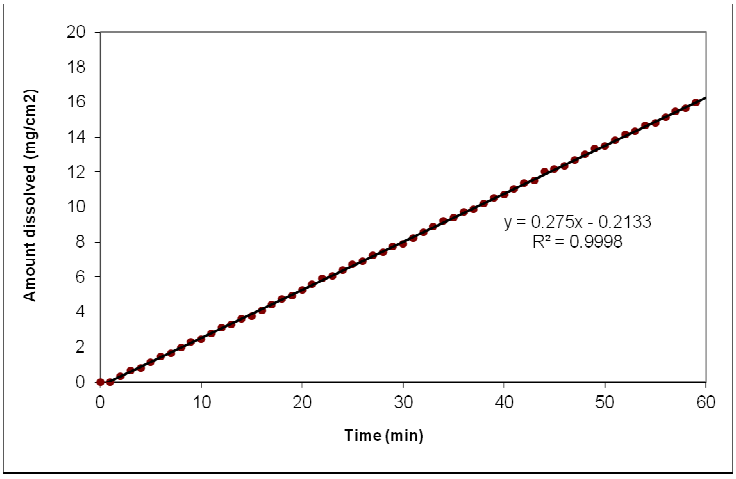
Intrinsic dissolution (6)



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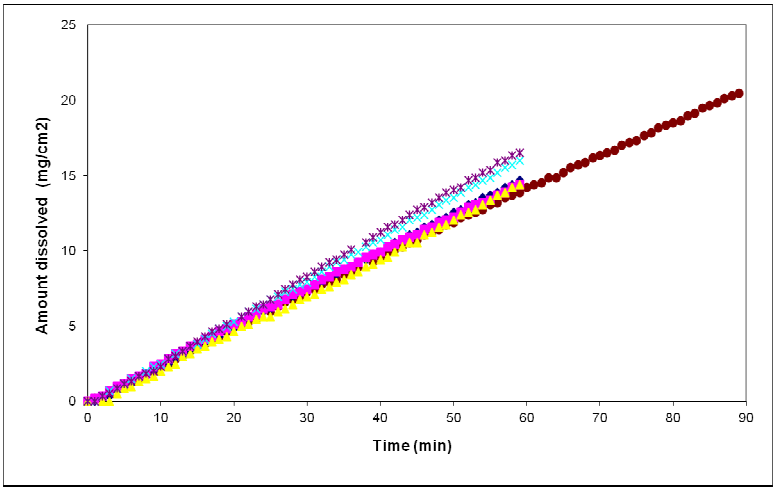
Intrinsic dissolution: comparison



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Apparent dissolution (1)

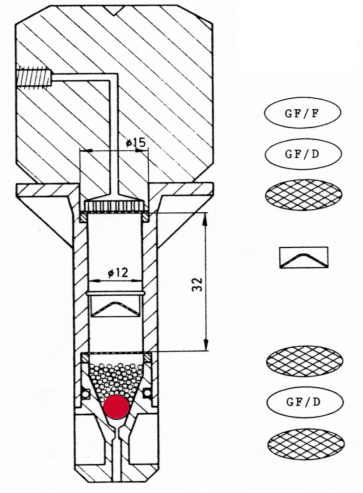
Dissolution studies when applied to powders allow :

- To optimize formulation variables, including particle size.
- To compare batches of active ingredient having different physical properties: surface area and particle size distribution.

The comparison of various polymorphic forms of drug substances can show identical or very different biopharmaceutical properties.

Apparent dissolution (2)

Eur. Ph. § 2.9.43



Apparent dissolution (3)

Outline

– Introduction about dissolution

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  – Apparent dissolution
  – Case studies : Paracetamol

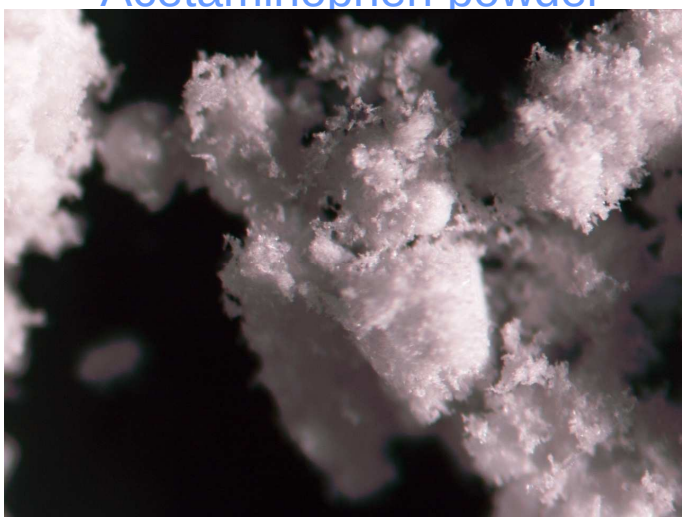
– Conclusion

Powder dissolution : Acetaminophen

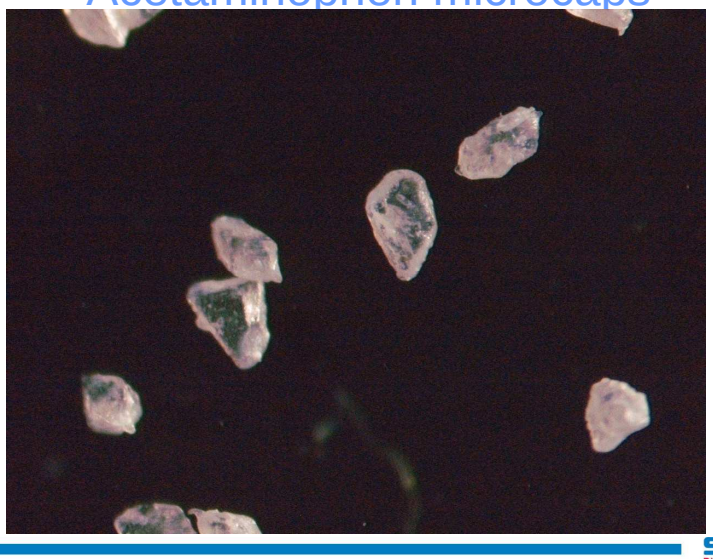
Surface area and particle size

Product	Surface area m^2/g	Mean diameter µm
Powder	0.16	88.45
Capsule grade	0.53	394.4
Crystal grade	0.33	58.86
Fine powder	0.38	48.36
Micronized	0.68	34.82
Microcaps	---	419.8

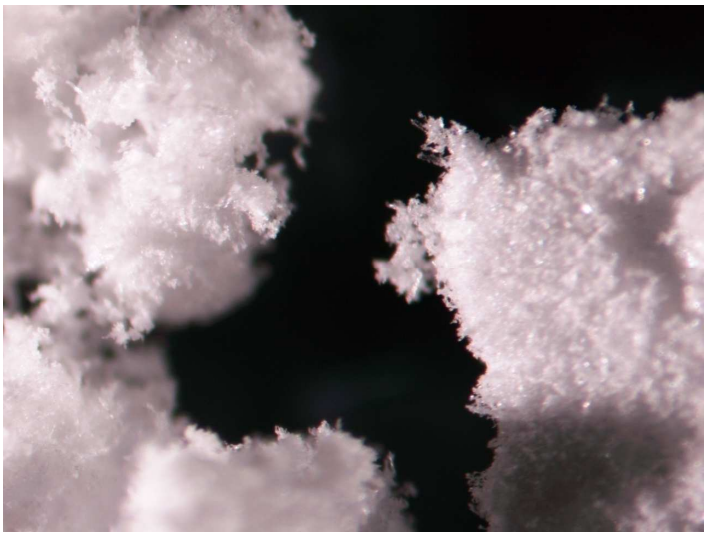
Acetaminophen powder



Acetaminophen microcaps



Acetaminophen Micronized

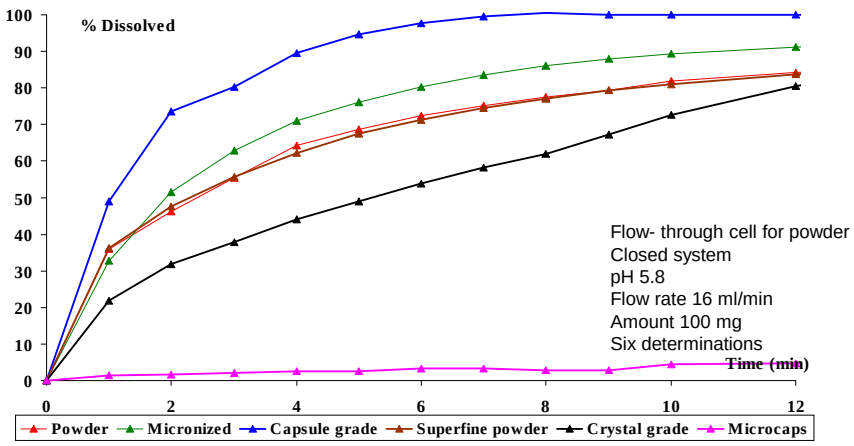


Intrinsic dissolution rate

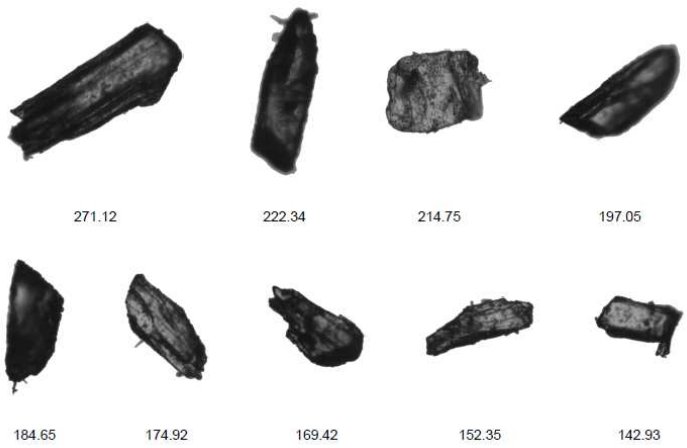
- Amount 100 mg
- pH 5.8
- Mean of three determinations

Product	K h^{-1}
Powder	1.8
Capsule grade	1.7
Crystal grade	1.6
Fine powder	1.8
Micronized	1.8
Microcaps	---

Apparent dissolution



Acetaminophen powder



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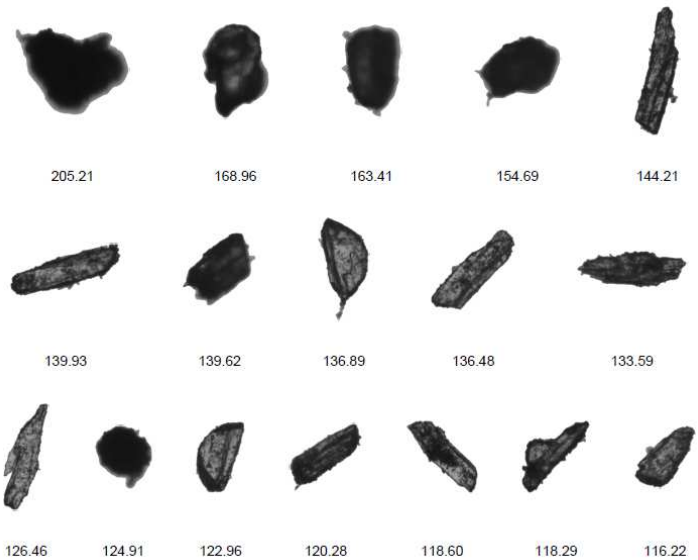
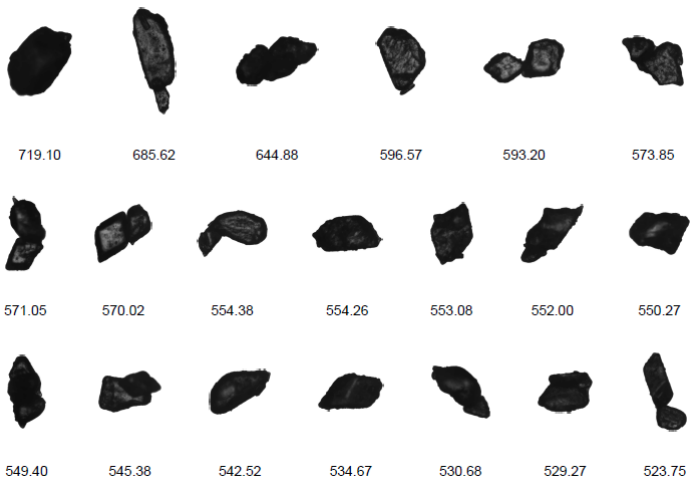
Acetaminophen Micronized



SPS Pharma Services

Acetaminophen microcaps



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Particle morphology

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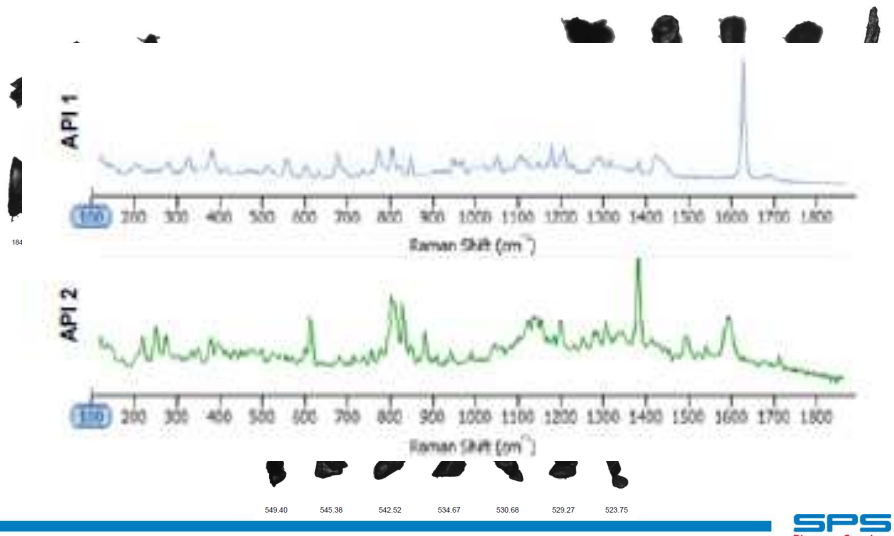
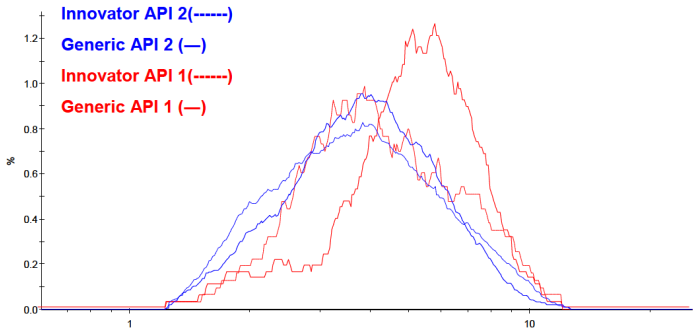
Particle morphology and identification !



What is the added value….

- Deformulation based on a RLD product
- Evaluate the physical properties of API (comparison of sources, etc…)
- Manufacturing troubleshooting (process issues, etc…)
- Many other possibilities…



Outline

– Introduction about dissolution

– API characterization
  – Intrinsic dissolution rate
  – Apparent dissolution
  – Case studies : IR tablets

– Conclusion

Case study: IR tablets

Product already marketed

Developed more than 20 years ago

Class I drug: soluble and good permeation

Background

A paddle dissolution method is in place and validated for QC purposes.

- Paddle 50rpm
- 500mL of HCl 0.1N
- UV online

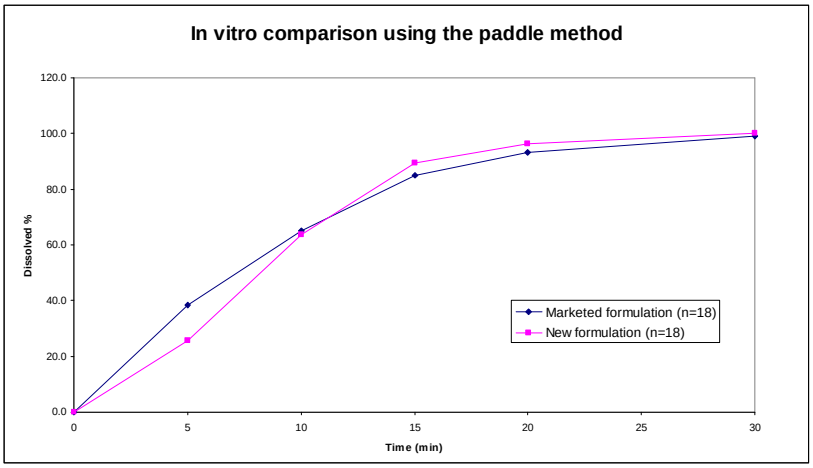
Changes:

- new API supplier
- slightly different quantitative formulation

Both formulations had been tested with the existing paddle method

➔ In vitro equivalence demonstrated

Background



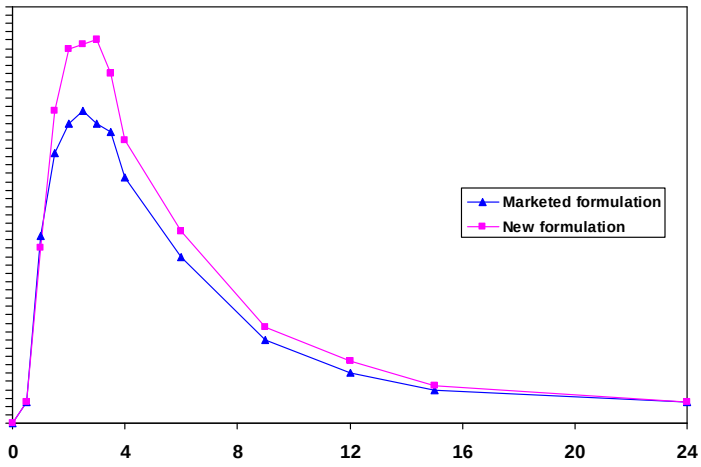
Background

Based on those data, the bioequivalence study was initiated:

- Male and female subjects
- 24 healthy volunteers
- fasted conditions

Results showed **in-equivalence** between both formulations.

Background



Hypothesis

API ?

- Intrinsic dissolution rate
- Apparent dissolution

Formulation ?

- Change the dissolution medium
- Change the dissolution technique

Manufacturing process ?

- Evaluate the product at each step of the process

APIs investigations

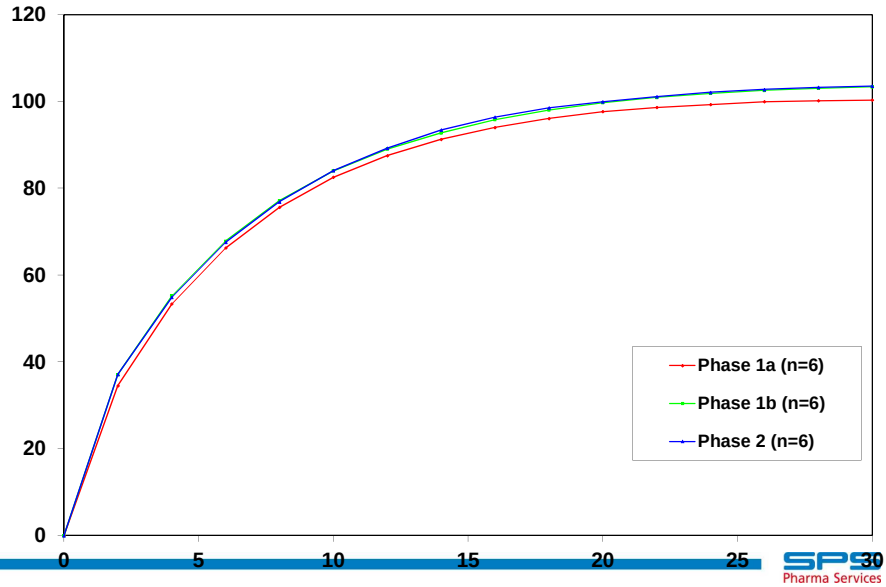
No polymorph (or pseudo-polymorph) known for this drug

➔ no need to go for **intrinsic dissolution rate**.

Apparent dissolution using USP4 flow through cell with the specific powder cell according to EP chapter 2.9.43

Starting from the existing paddle method, a USP4 was developed using a closed system with the same dissolution medium and the same UV quantification method.

APIs investigations



API investigations: conclusion

➔ No difference showed by this technique between both APIs.

➔ Remaining options: Formulation or manufacturing process

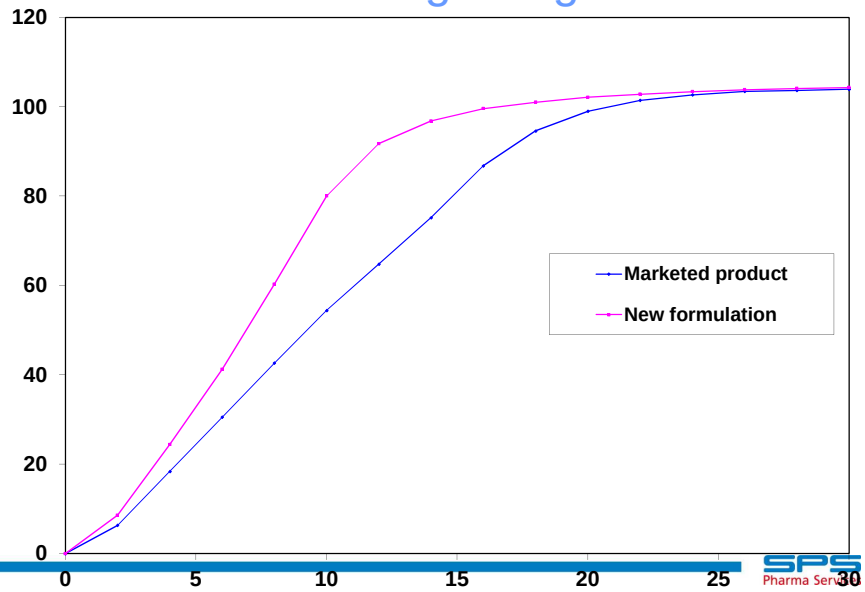
Formulation and process

Apply the USP4 flow through cell method to evaluate its discriminative ability…

- on the finished products (formulation)
- on samples taken at each process steps (process)

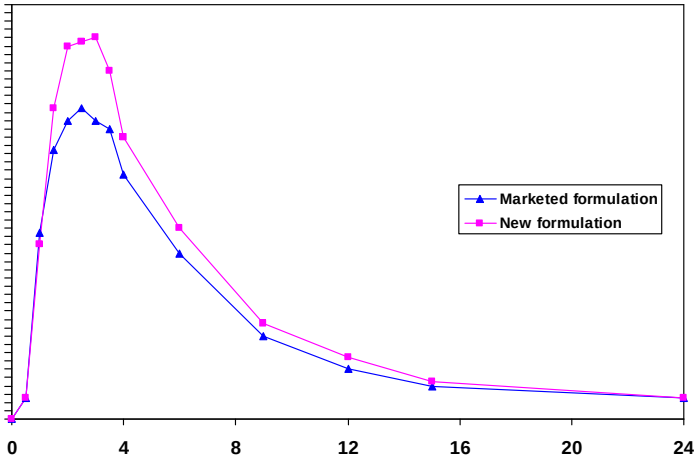
Conditions identical to previously except that the cell is adapted to the tested form (cells for tablet or powder).

Tablets testing using USP4



Background

The rank obtained is identical to the rank observed in vivo.



IR tablets case study

The flow through cell dissolution technique was able to show the difference seen in vivo with the same rank order.
The USP4 dissolution method was used to support a reformulation of the product.

A new formulation was tested with both dissolution methods which showed it to be equivalent in vitro.
Even tough there was no certainty about an IVIVC or IVIVR, using USP4 was a way to minimize the risk of bio in equivalence.

The BE study was repeated and concluded favorably.
The paddle method was maintained as QC method for the release of batches.
And the USP4 method was kept in house as a tool for R&D.

Outline

– Introduction about dissolution

– Dissolution tools

– API characterization
  – Intrinsic dissolution rate
  – Apparent dissolution
  – Case studies

– Conclusion

Take-home message

API biopharmaceutical characterization may be considered as time consuming but…

- In vitro testing is not expensive compared to in vivo studies.
- It can guide and facilitate formulation development.
- These are good tools to derisk biostudies.

Different approaches can be used:

- XRPD, DSC, particle morphology
- intrinsic / apparent dissolution
- evaluation of different dissolution methods than USP1&2
- use of different pHs/ media

Finally, development time can be shorten.

Outline

– Introduction about dissolution

– Dissolution tools

– API characterization
  – Intrinsic dissolution rate
  – Apparent dissolution
  – Case studies

– **Conclusion : Bis repetita ! ☺**

Lipophilic dosage forms

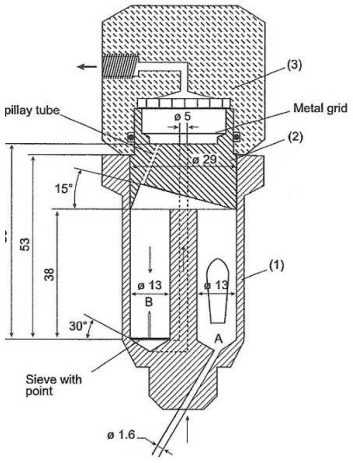
USP <2040>

2.9.42. DISSOLUTION TEST FOR LIPOPHILIC SOLID DOSAGE FORMS

APPARATUS

The apparatus (see Figure 2.9.42.-1) consists of:

– A reservoir for the dissolution medium.
– A pump that forces the dissolution medium upwards through the flow-through cell.
– A flow-through cell shown in Figure 2.9.42.-2 specifically intended for lipophilic solid dosage forms such as suppositories and soft capsules. It consists of 3 transparent parts which fit into each other. The lower part (1) is made up of 2 adjacent chambers connected to an overflow device.

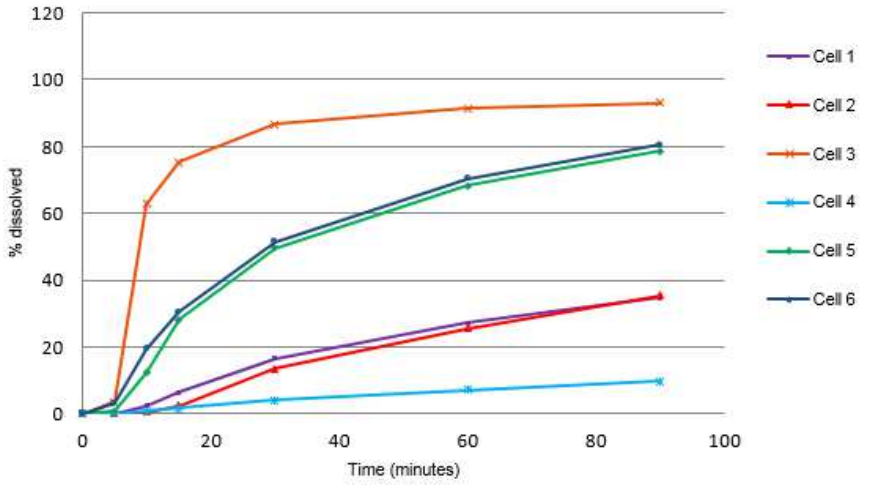


Be science-driven…

- In October 2012 and April 2013, the US FDA issued new draft guidances related to fish oil-based soft gelatin capsules.
- The recommendation to get the approval for a generic formulation is either:
  - Clinical bioequivalence study or
  - In vitro USP4 profiles comparison (using the lipid cell)

Although, the Omega-3 capsules are classified as lipidic formulations, the use of the lipid cell was bringing to highly variable results.

Be science-driven…



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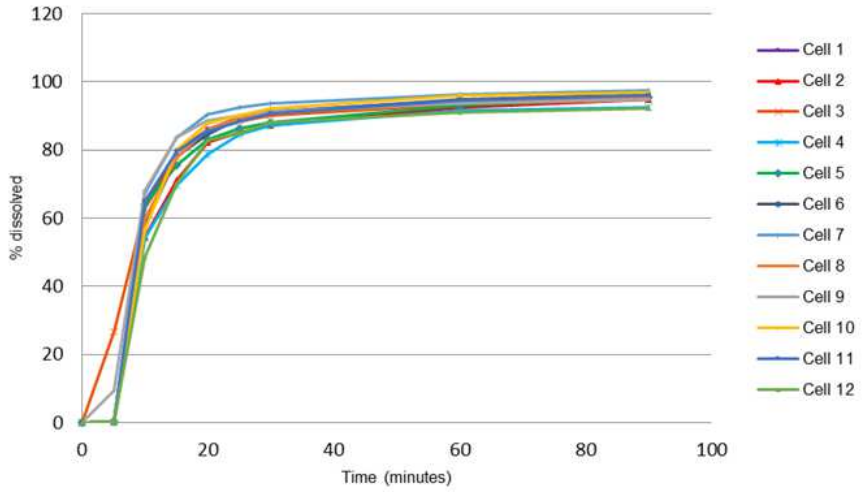
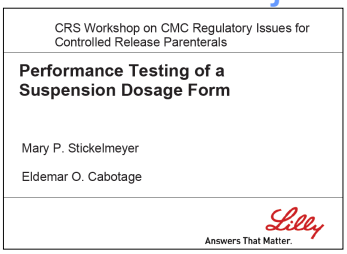
Although, the Omega-3 capsules are classified as lipidic formulations, the use of the lipid cell was bringing to highly variable results.

Bringing a science-sounded justification, we demonstrated that the recommendation from FDA was not suitable and proposed an alternative as switching to a different cell than the recommended one addresses the issue of variability.

Be science-driven…



Injectable suspensions

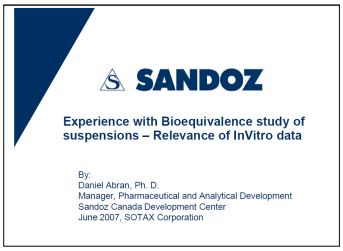

CRS Workshop on CMC Regulatory Issues for Controlled Release Parenterals

Performance Testing of a Suspension Dosage Form

Mary P. Stickelmeyer

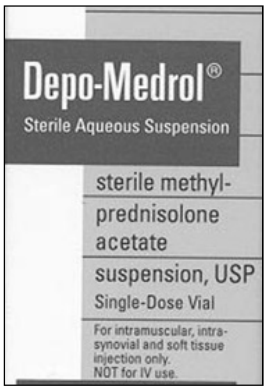
Eldemar O. Cabotage

Lilly
Answers That Matter.


SANDOZ

Experience with Bioequivalence study of suspensions – Relevance of InVitro data

By:
Daniel Abran, Ph. D.
Manager, Pharmaceutical and Analytical Development
Sandoz Canada Development Center
June 2007, SOTAX Corporation



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Injectable suspensions (2)

The authorities published clear statements requiring the use of the flow through cell for injectable suspensions such as:

- Betamethasone Acetate/Betamethasone Sodium Phosphate
- Leuprolide Acetate
- Methylprednisolone Acetate
- Risperidone
- Triamcinolone Acetonide
- Naltrexone
- Octreotide injection

" Develop a dissolution method using USP IV (Flow-Through Cell), and, if applicable, Apparatus II (Paddle) or any other appropriate method, for comparative evaluation by the Agency"

Source:(US FDA website)

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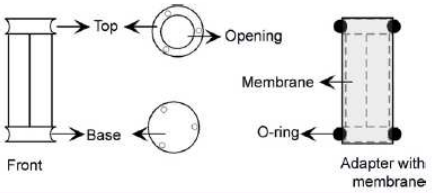
Liposomal formulations

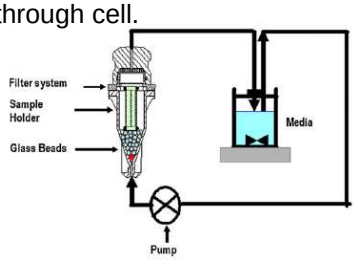
A novel USP apparatus 4 based release testing method for dispersed systems

BHARDWAJ U., BURGESS D.
International Journal of Pharmaceutics 388, 287-294, 2010

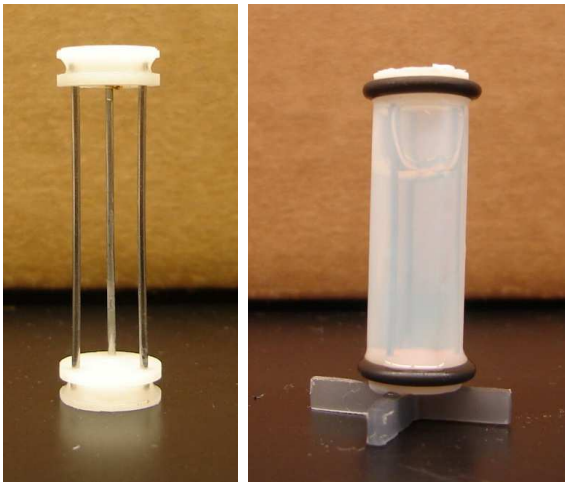
Design of a dialysis adapter

A specific adapter has been designed in order to hold the dialysis membrane within a compendial 22.6mm flow through cell.

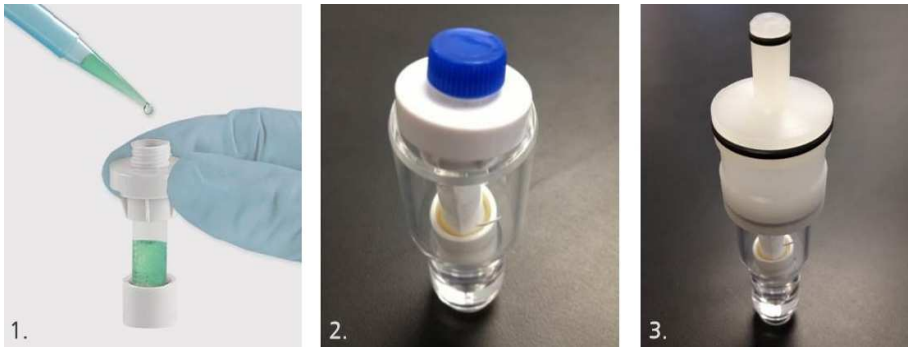




Liposomal formulations (2)



Liposomal formulations (2)



FAL adapter: Float-A-Lyzer Adapter

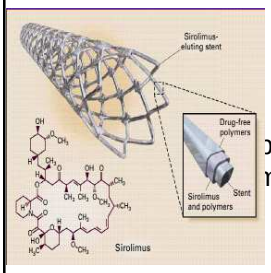
Semi-Solid formulations

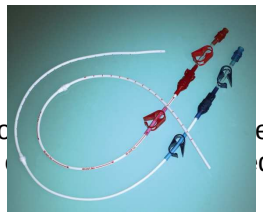
Semi-Solid Adapter (SSA) in USP <1724>
Slide presented courtesy of Sotax AG

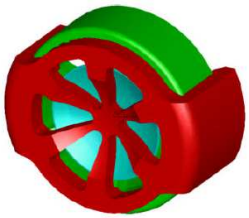
Medical devices

- A product comprised of two or more regulated products that are physically, chemically or otherwise combined mixed and produced as a single entity.
- Sometimes one is used to compensate the side effects of the other…

Medical devices







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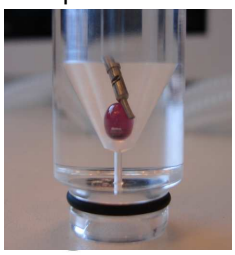
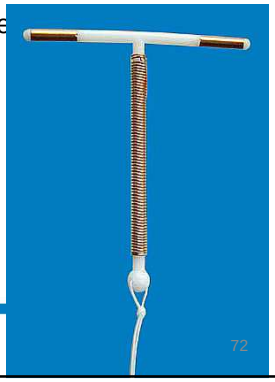
nically d mixed

- Sometimes one is used to compensate the side e

Retrieved prosthesis after being implanted for 38 years





Acknowledgements

- SPDS Scientific Committee
- Organizing team
- All the people behind….

- SPDS 2017:
  ….would you invite me again ???

- If so, I promise that I will not talk about USP4…

Thank you !

Questions?

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