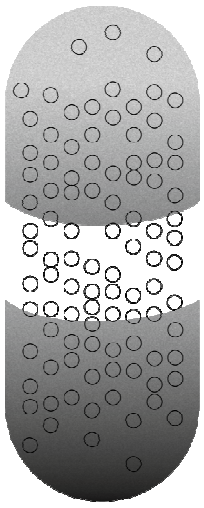
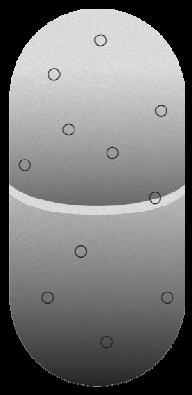


The Flow Through Cell: Principles and Applications.

Disso Europe 2016
20 - 21 October 2016 | Bucuresti, Romania

Samir Haddouchi | samir.haddouchi@sps-pharma.com

SPS Pharma Services.



- Who we are
- R&D Services
- Routine Analytical Services (GMP)
- Support Services

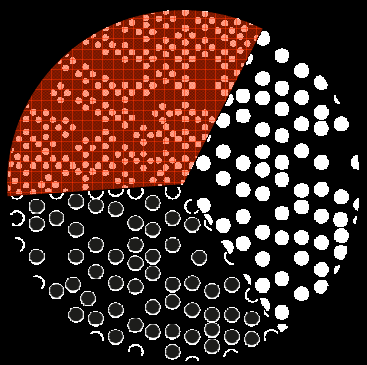
2

SPS Pharma Services: Who we are.

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

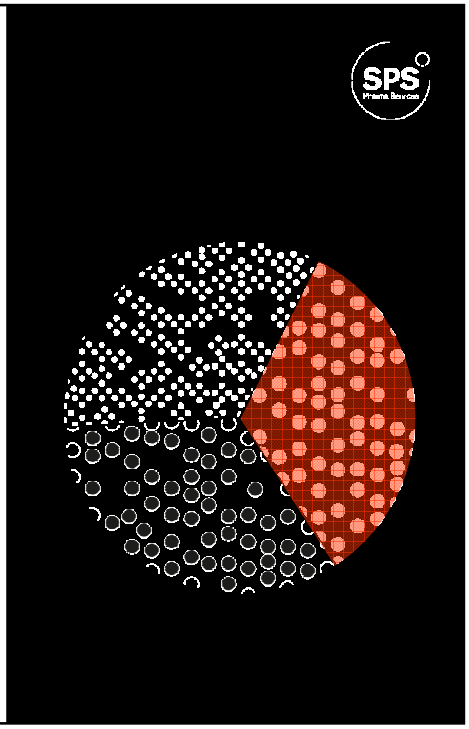
R&D Services.

- API characterization
- Feasibility studies (dosage forms, dissolution techniques…)
- Analytical method development (UV / HPLC / UPLC)
- Dissolution method development
- Method automation (dissolution & sample preparation)
- Method validation & re-validation
- Method transfer



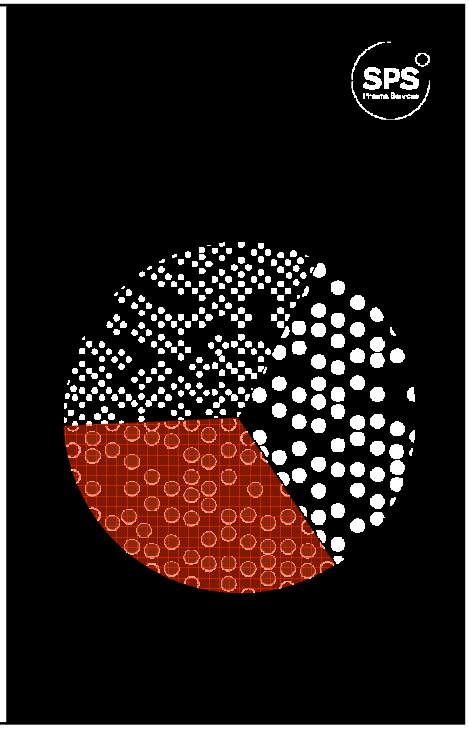
Routine Analytical Services (GMP).

- **QC analysis**
  - Dissolution testing using all compendial techniques
  - Assay and degradation products
  - UV / HPLC / UPLC testing
  - Physical testing (hardness, disintegration, and more…)
- **Stability studies**
  - Secured storage conditions with automatic alarms and backup
  - Supportive or registration stability testing
  - Periodic stability testing of your commercial products
- **Clinical and commercial batch release**
  - GMP certified Pharmaceutical Establishment
  - Commercial batch testing using validated methods
  - Batch release for Europe by our Qualified Person

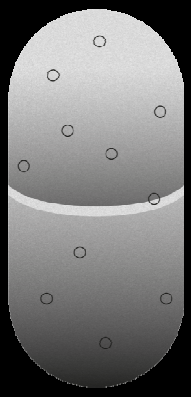


Support Services.

- **Troubleshooting & Investigations**
  - Identification of possible causes and solutions from R&D to manufacturing of commercial batches
- **Consulting**
  - Review of analytical and clinical data from failed bioequivalence
  - Support for the handling of OOS results to identify the root cause
  - Audits of manufacturing and testing contractors
- **Training**
  - Best practices of dissolution testing
  - In-vitro dissolution methods development
  - Dissolution testing for non-conventional dosage forms
  - Dissolution testing using non-conventional dissolution techniques
  - IVIVC (in-vivo in-vitro correlations)
  - GMP implementation



The Flow Through Cell: Principles and Applications



- Introduction on Dissolution
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  - Principles
  - Dissolution for API characterization
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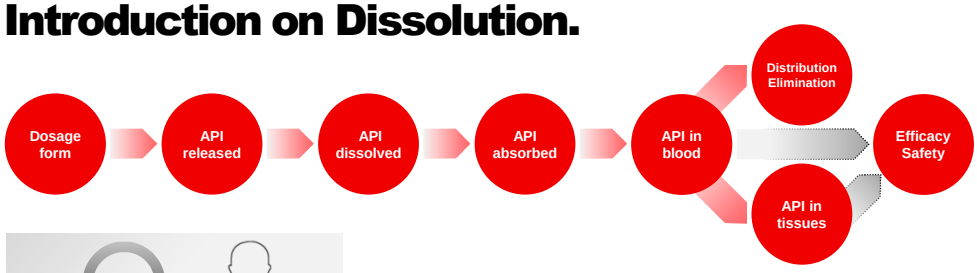
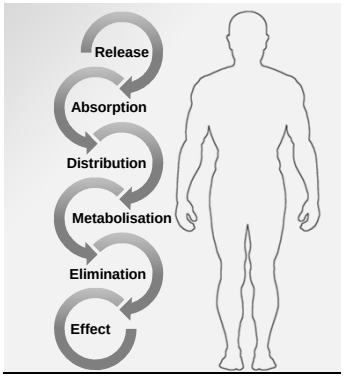
  - Case Studies: Non conventional dosage forms
- Conclusion

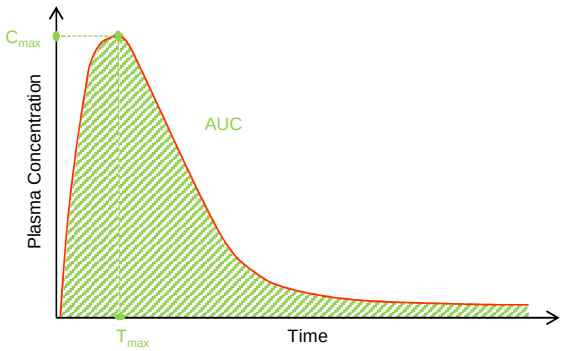
7

Introduction on Dissolution.



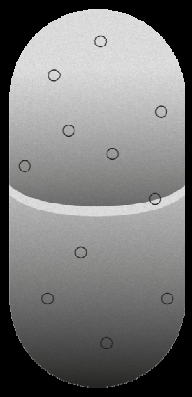


■ *Adapted from Prof. Cardot & Prof. Beyssac (Université d'Auvergne)*



8

The Flow Through Cell: Principles and Applications



- Introduction on Dissolution
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9

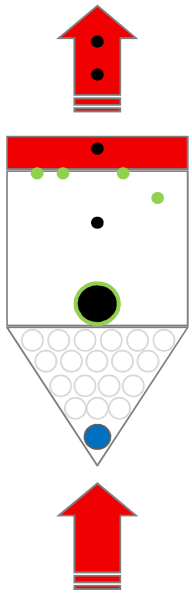
Why Using The Flow Through Cell ?

- 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

10

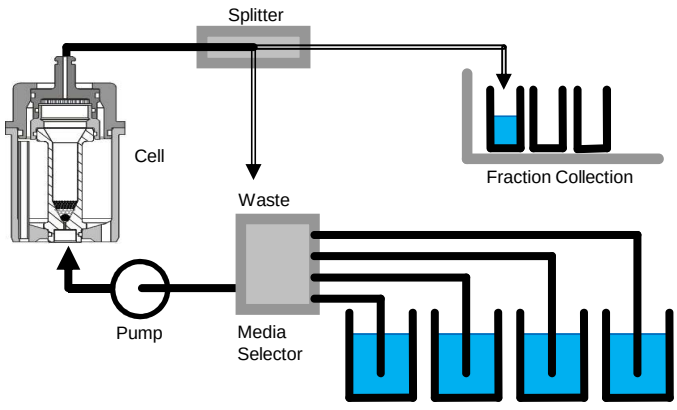
The Flow-Through Cell.

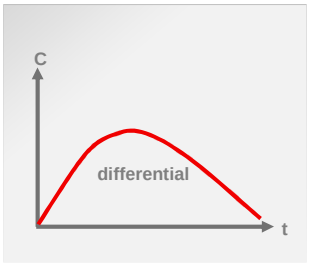
- The test sample is located in a small volume cell through which solvent passes
- The eluate is filtered upon leaving the cell
- The eluate is analyzed directly (on-line) with a spectrophotometer and/or collected in a fraction collector (off-line)



11

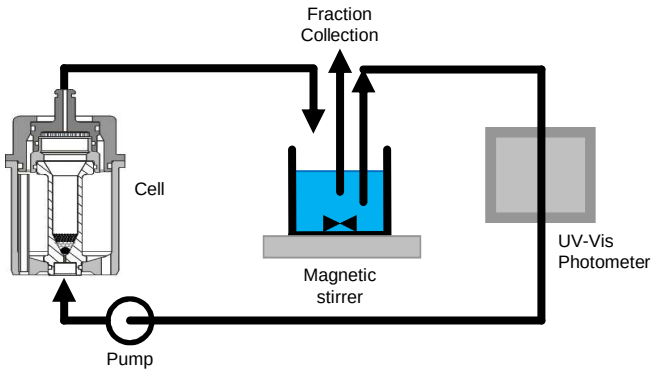
Open System with pH Change.

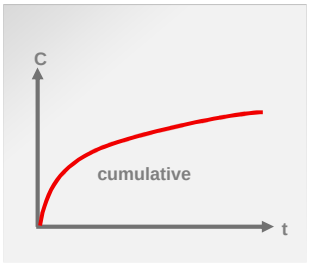




12

Closed Loop System.





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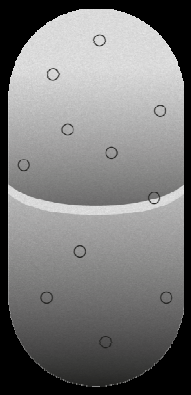

The Flow Through Cell: Principles and Applications

- Introduction on Dissolution
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14

Intrinsic Dissolution. (1)

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

Physical properties' effects are minimized or eliminated.

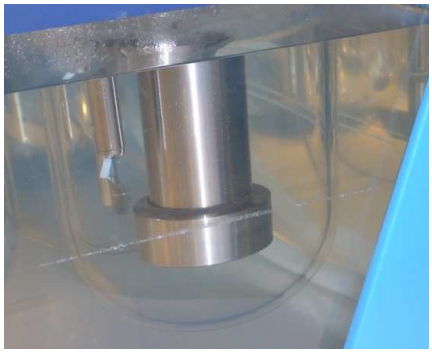
- Determination of the constant k
- Use of a tablet of pure drug
- Expressed as mg/min/cm^2

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

→ *Eur. Ph. § 2.9.29*
→ *USP <1087>*

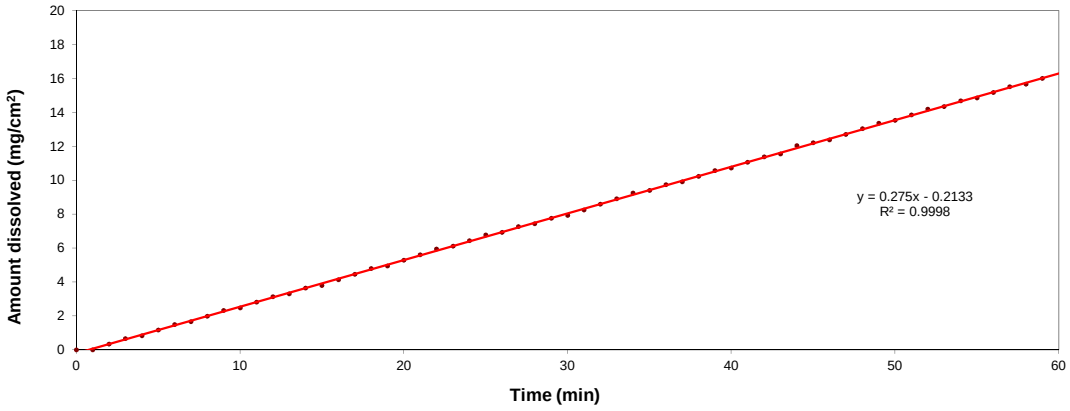
15

Intrinsic Dissolution. (2)



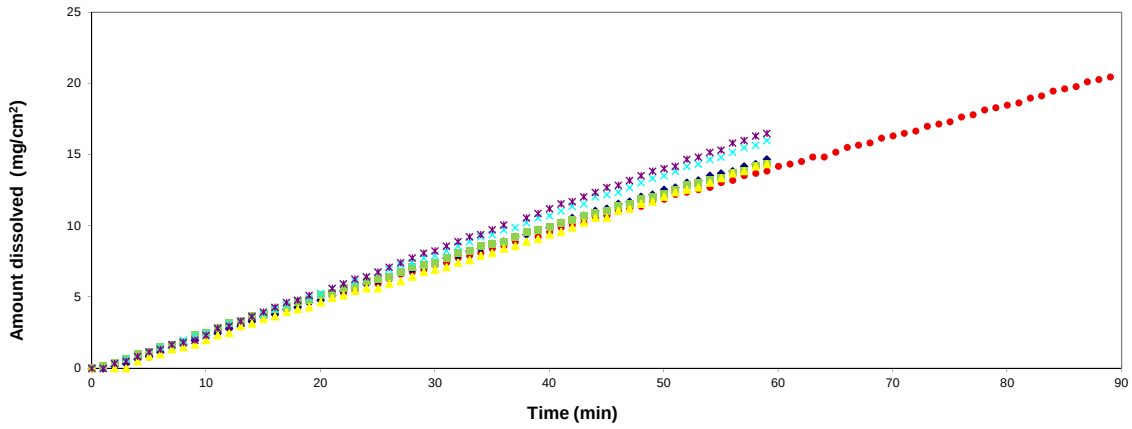
16

Intrinsic Dissolution. (3)



17

Intrinsic Dissolution: Comparison.



18

Apparent Dissolution. (1)

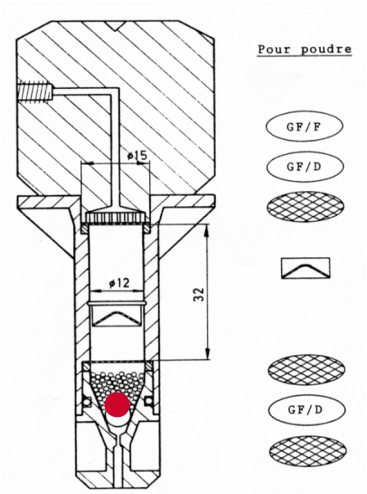
When applied to powders, dissolution studies allow:

- To optimize formulation variables, including particle size.
- To compare batches of active ingredient taking into account their respective 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.

19

Apparent Dissolution. (2)



→ *Eur. Ph. § 2.9.43*

20

Apparent Dissolution. (3)

21

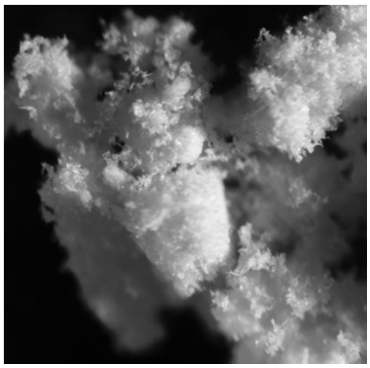
Powder Dissolution: Paracetamol.

Surface Area and Particle Size

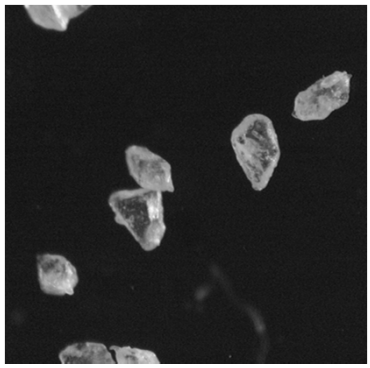
Product	Surface area (m^2/g)	Mean diameter (µm)
Powder	0.16	88.45
Capsule grade	0.53	394.40
Crystal grade	0.33	58.86
Fine powder	0.38	48.36
Micronized	0.68	34.82
Microcaps	---	419.80

22

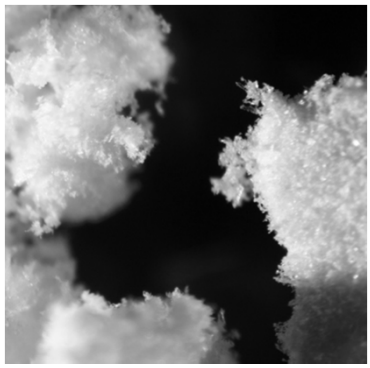
Powder Dissolution: Paracetamol.



■ Paracetamol *Powder*



■ *Paracetamol Microcaps*



■ *Paracetamol Micronized*

23

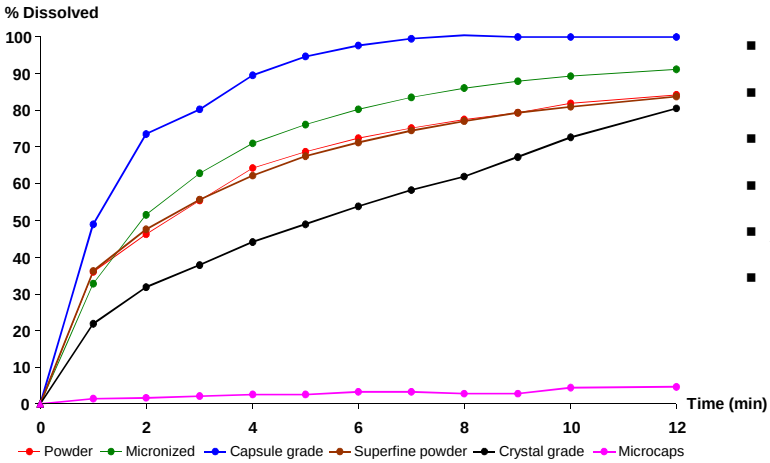
Intrinsic Dissolution Rate.

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

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

24

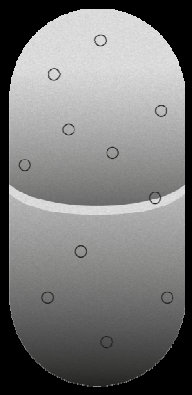
Apparent Dissolution.



- Flow through cell for powder
- Closed system
- pH 5.8
- Flow rate 16 mL/min
- Amount 100 mg
- Six determinations

25

The Flow Through Cell: Principles and Applications



- Introduction on Dissolution
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26

Case Study: IR Tablets.

- Product already marketed
- Developed more than 20 years ago
- Class I drug: soluble and good permeation

27

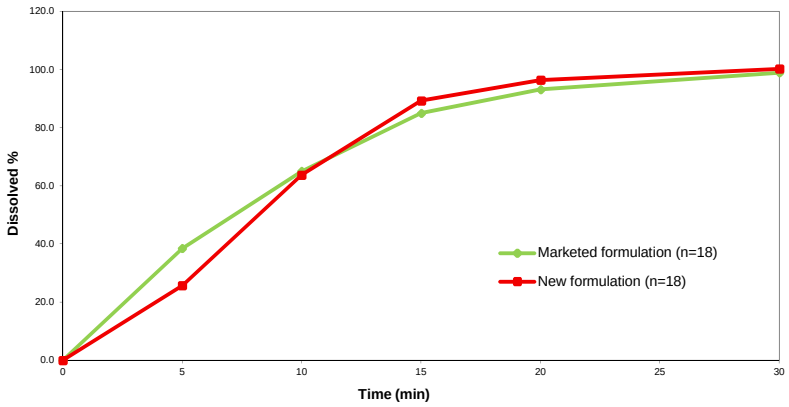
Background.

- **A paddle dissolution method is in place and validated for QC purposes:**
  - Paddle 50 rpm
  - 500 mL 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

28

Background.

In-vitro Comparison Using the Paddle Method



29

Background.

The bioequivalence study was initiated based on that data:

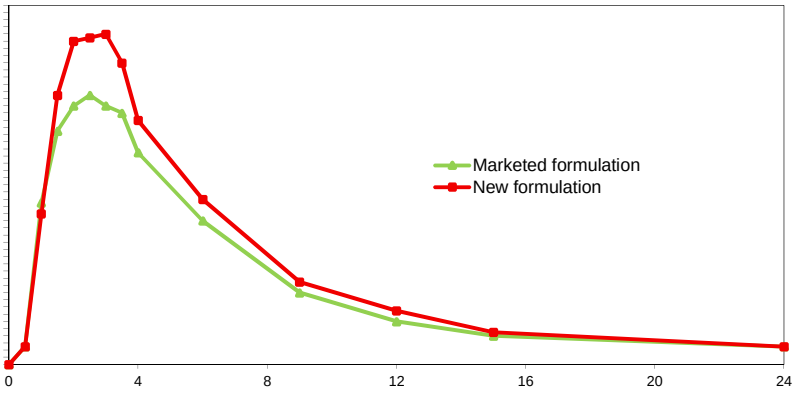
- Male and female subjects
- 24 healthy volunteers
- fasted conditions

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

30

Background.

In-vivo PK profiles



31

Hypothesis.

- **API?**
  - Intrinsic dissolution rate
  - Apparent dissolution
- **Formulation?**
  - Change the dissolution medium
  - Change the dissolution technique

32

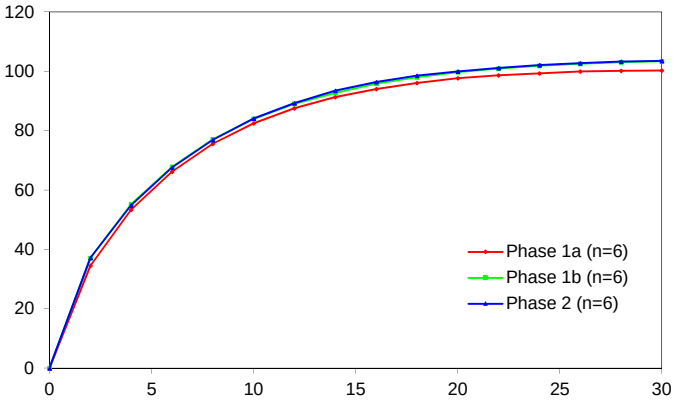
API Investigations.

- No polymorph (or pseudo-polymorph) known for this drug
  → no need to go for **intrinsic dissolution rate**
- **Apparent dissolution** using USP 4 flow through cell with the specific powder cell according to EP chapter 2.9.43
- Starting from the existing paddle method, a USP 4 was developed using a closed system with the same dissolution medium and the same UV quantification method.

33

API Investigations.

Conclusion



- No difference shown with this technique between both APIs
- **Remaining option:**
  → better discrimination to assess the formulations

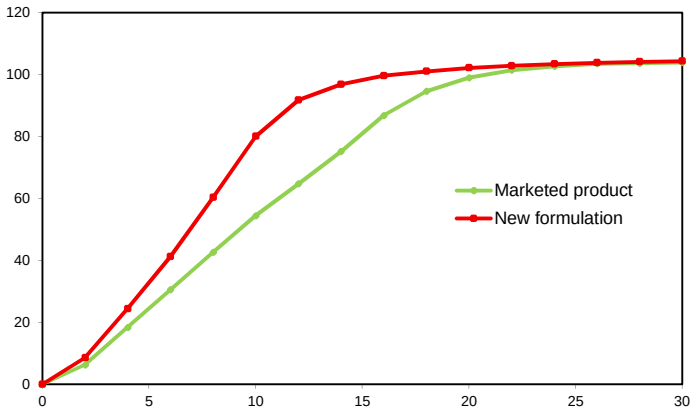
34

Formulation.

- Apply the USP 4 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)

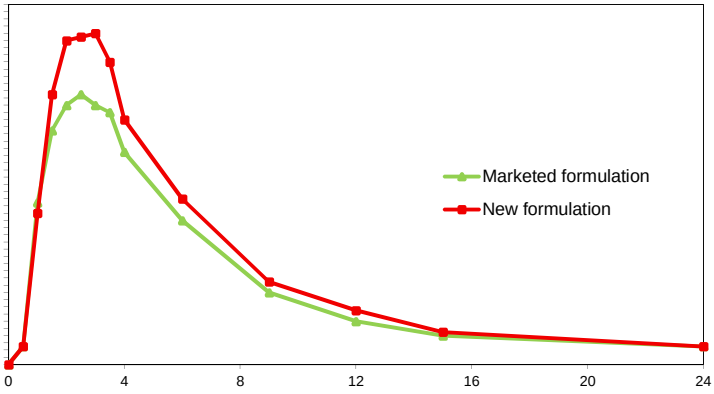
35

Tablet Testing using USP 4.



36

Background.



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

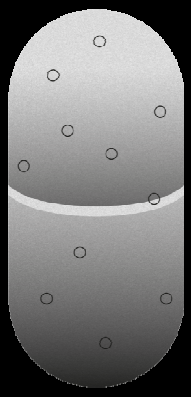
37

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 USP 4 dissolution method was used to support a reformulation of the product.
- A new formulation was tested with both dissolution methods which showed to be equivalent in-vitro.
  Even though there was no certainty about an IVIVC or IVIVR, using USP 4 was a way to minimize the risk of bio-inequivalence.
- The BE study was repeated and concluded favorably.
  The paddle method was maintained as QC method for the release of batches.
  And the USP 4 method was kept in house as a tool for R&D.

38

The Flow Through Cell: Principles and Applications



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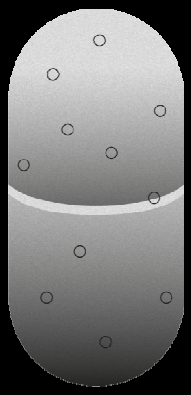
39

The Flow Through Cell: Principles and Applications



- Introduction on Dissolution
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  - Case Studies: Lipophilic dosage forms
- Conclusion

40

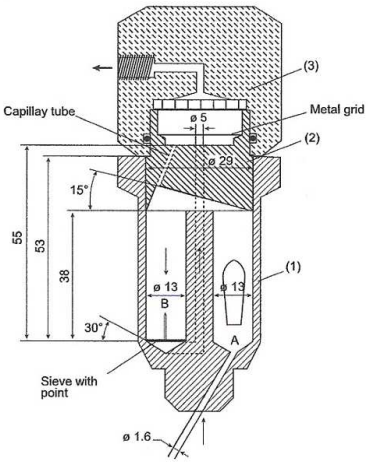
History: European Ph. § 2.9.42

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.



41

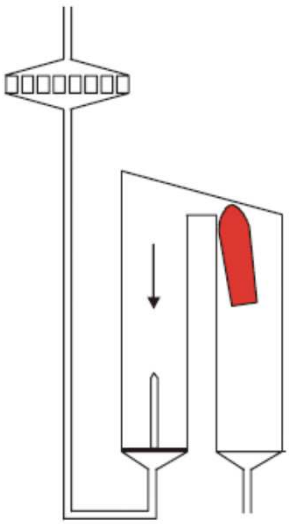
Cell principle

The dissolution medium passes through chamber A and is subjected to an upwards flow. The flow in chamber B is downwards directed to a small-size bore exit which leads upwards to a filter assembly. The middle part (2) of the call has a cavity designed to collect lipophilic excipients which float on the dissolution medium. A metal grill serves as a rough filter. The upper part (3) holds a filter unit for paper, glass fiber or cellulose filters.

Remark:

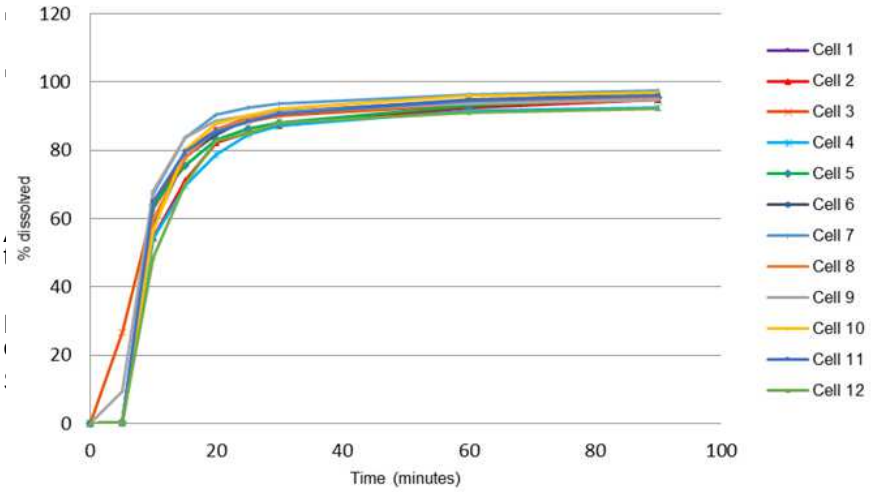
The flow through cell for lipidic formulations is now also described in USP<2040>.

(since December 2011).



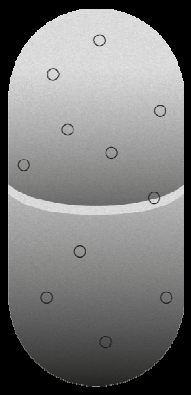
42

Case study: be science-driven…



43

The Flow Through Cell: Principles and Applications



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  - Case Studies: Injectable suspensions
- Conclusion

44

Introduction

What is an injectable product (suspension) ?
Insoluble active ingredient suspended in a suitable medium

Medium ?
Suspending agents
Viscosity modifiers
Surfactants to avoid agglomeration and/or aid in wetting the active

Route of administration ?
Oral
Parenteral

45

CRS Workshop 2006

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.

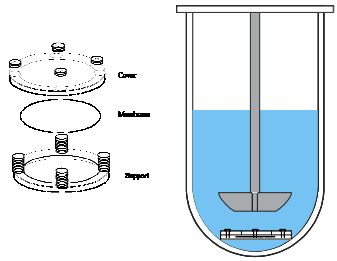
46

Summary ERT study for Depo Medrol

Study carried out in 2006 by Fabien Palmier under the responsbility of Pr Eric Beyssac (Université d'Auvergne – Clermont Ferrand).

Trials have been made using

- USP4
- USP2 with the extraction cell



Conclusion

- **a very fast dissolution with both techniques**
- **an important effect of the membrane in the USP2.**

47

USP4 Workshop 2007

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

48

Case study

Deficiency letter from US authorities

> Your submission lacks the dissolution data for the test product. Dissolution testing is useful for assessing batch to batch manufacturing consistency. Please develop a dissolution testing method for your drug product. Based on the information available to the DBE, the USP apparatus IV (with flow-through-cell) appears to be more appropriate for dosage forms such as suspension, compared to the conventional USP apparatus II (paddle). Therefore, we recommend you explore using USP apparatus IV (flow-through-cell) as well as USP apparatus II (paddle) for dissolution testing of your test product and provide us with the data from both methods for evaluation. Please provide all dissolution method development data showing that your dissolution method has been optimized in the selection of dissolution medium, surfactant (if any), surfactant concentration, and the size of the filter used for sample preparation, where applicable.

49

Background and strategy

Injectable suspension containing two Active Ingredients

Following the request of US FDA, a development strategy has been built to ensure answering all questions

- Evaluation of the test conditions
- Trials with both equipments
- Optimization of the selected method.

50

Preliminary work

A solubility study has been carried out at pH values close to physiological conditions

Defined medium was phosphate buffer pH 7.2 + Tween

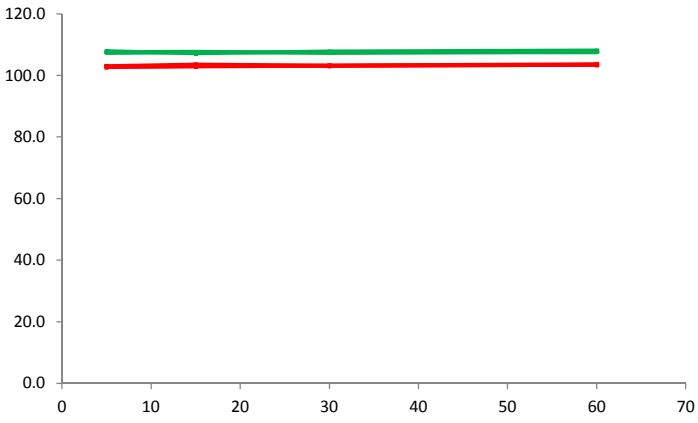
Filter selection has been carried out to satisfy:

- No drug adsorption
- Adapted pore size
- No leachables from the filters.

51

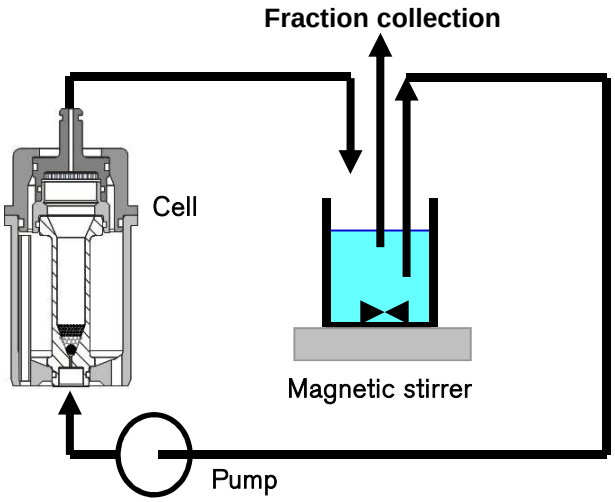
USP2 dissolution test

Trial using USP2: 500ml at 25 rpm



52

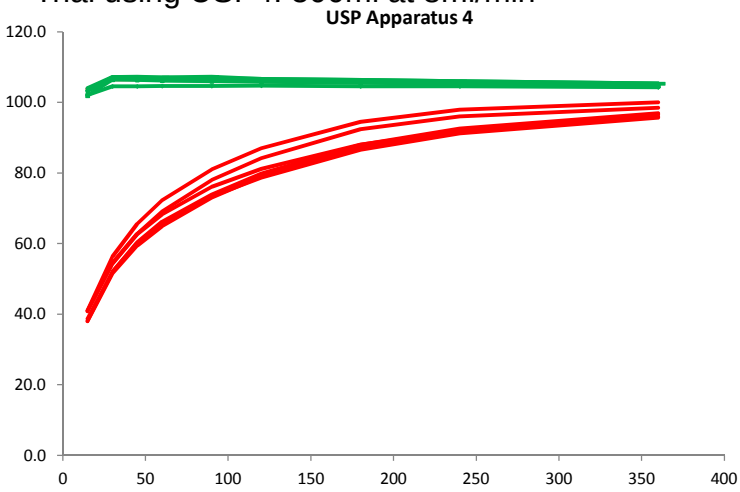
Closed loop system



53

USP4 dissolution test

Trial using USP4: 500ml at 8ml/min

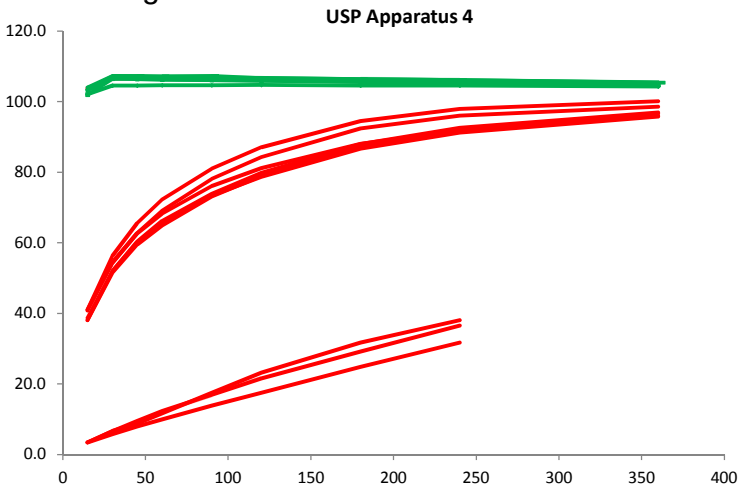


Dissolution profile or release profile ?

54

Better product understanding

Trial using USP4: 500ml at 8ml/min



55

Conclusion for suspensions (1)

- USP4 can have significant advantages compared to other techniques.
- The cell design allows to ensure maintaining the formulation integrity during testing.
- Thus the profile represents the release properties from the formulation and not only the dissolution properties.
- Several products were developed at SPS Pharma and submitted using USP4 mainly for QC purposes.

56

Conclusion for suspensions (2)

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

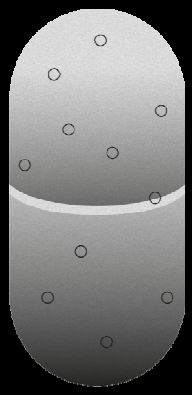
- Betamethasone Acetate/Betamethasone Sodium Phosphate
- Leuprolide Acetate
- Methylprednisolone Acetate
- Risperidone
- Triamcinolone Acetonide
- Naltrexone
- Octreotide injection

" 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)

57

The Flow Through Cell: Principles and Applications



- Introduction on Dissolution
- The flow through cell method
  - Principles
  - Dissolution for API characterization
  - Case Study: IR tablets
  - Case Studies: Liposomes
- Conclusion

58

Reference

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

BHARDWAJ U., BURGESS D.

International Journal of Pharmaceutics 388, 287-294, 2010

59

USP4 for liposome testing

Depending on the different routes (IM, SC or IV), physiological conditions may vary.

The main challenge expected when testing dispersed formulations in USP4 was that they can either block the filter or pass through it.

The aim was to obtain a method able to discriminate between formulation variables to support product development and quality control.

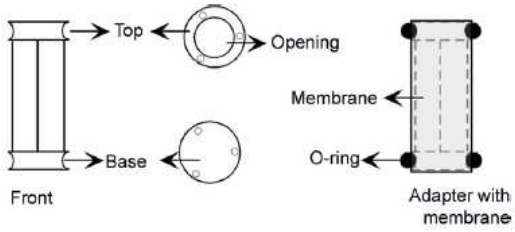
The developed method should be able to offer better results (less variability) than those already existing.

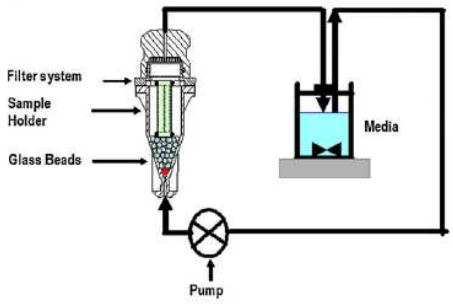
60

Operating conditions

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.





61

Conclusion

•This novel dialysis adapter utilizes the advantages of the compendial USP4.

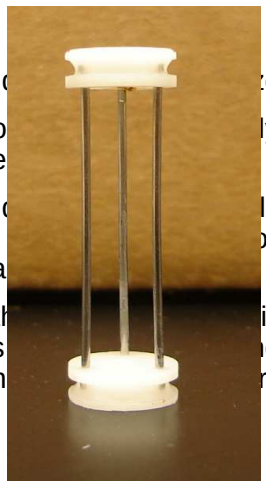
•Release conditions can be easily adapted to provide biorelevant conditions such as use of serum, enzymes, etc…

•This novel dialysis adapter fulfills the need for a method based on a compendial apparatus for in vitro release testing of dispersed systems such as liposomes and nanoparticles.

•Based on the demonstration of its feasibility and discriminatory ability, the adapter has been redesigned and is now available from Sotax: as well as a modification allowing the use of ready-to-use devices.

62

Conclusion



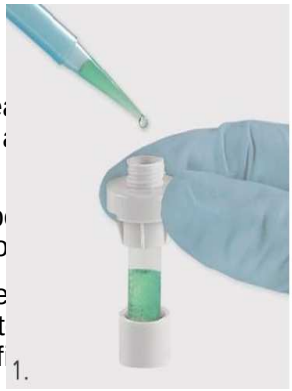
•This novel c ze mpendial USP4.

•Release co ly evant conditions such as use

•This novel c ls sed on a compendial o d systems such as liposomes a

•Based on th it ory ability, the adapter has ac ax: as well as a modification re

Conclusion



•This P4.

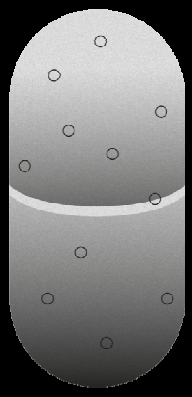
•Relea ns such a

•This comp ch as liposo

•Base adapt a modif

FAL adapter: Float-A-Lyzer Adapter

The Flow Through Cell: Principles and Applications



- Introduction on Dissolution
- The flow through cell method
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  - Case Study: IR tablets
  - Case Studies: Semi-Solid formulations
- Conclusion

65

Introduction

▪In vitro release testing (IVRT) for topical semi-solid preparations is studying skin transfer kinetics and establishing batch-to-batch uniformity of topical preparations.

▪Formulation integrity should not be modified during IVRT.

▪Appropriate **inert** and commercially available synthetic membranes should be used.

▪Appropriate receptor medium such as aqueous buffer for water soluble drugs or a hydro alcoholic medium for sparingly water soluble drugs or another medium with proper justification.

▪A plot of the amount of drug released per unit membrane area (mcg/cm2) versus square root of time should yield a straight line.

The slope of the line (regression) represents the release rate of the product.

66

Regulations

A collaborative study was initiated in 2009 with the USP, different instrumentation suppliers and experts. SPS Pharma was part of this study.

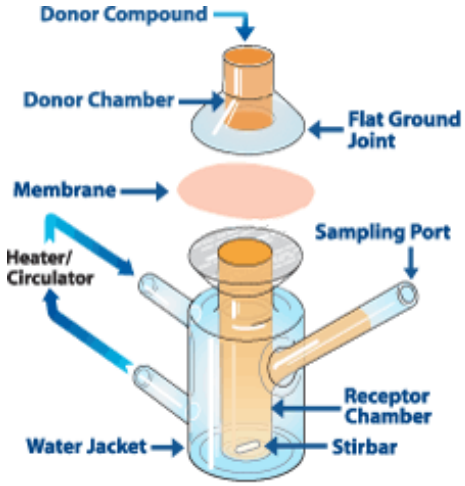
It ended with the publication of USP <1724>.

This chapter refer to 3 different techniques:

- Vertical diffusion cell
- Immersion cell
- Flow through cell

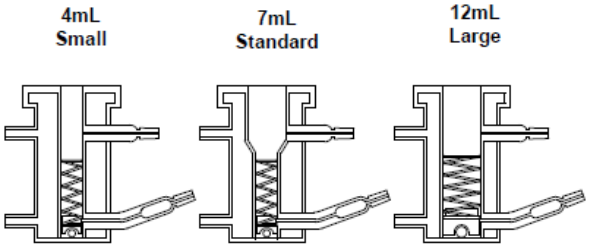
67

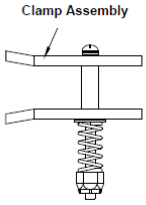
Vertical diffusion cell



68

Different types of cells





7ml standard: Recommended by FDA

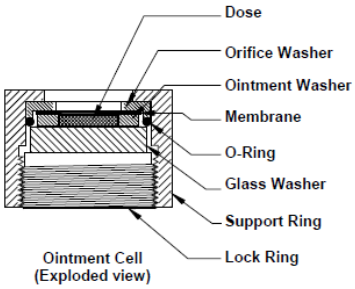
69

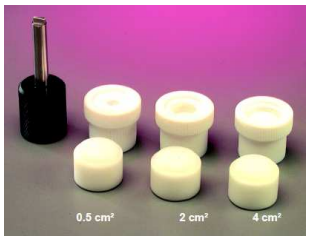
Immersion cell

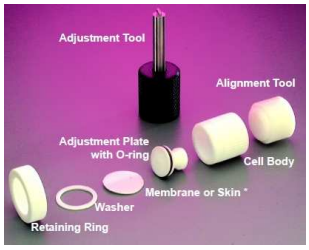
- Use of the rotating paddle (USP2) or a modified paddle and a cell made of Teflon.
- The cell is available with different volume and surface and which used also a membrane to hold the topical form.
- The central part of the cell forms a cavity where the the transdermal product in introduced.

70

Enhancer cell







71

Flow through cell

- Described in all pharmacopeias:
  - USP
  - Eur. Ph.
  - JP

- Different configurations possibles according to properties of both drug substance and drug product:
  - Open: Low solubility, media change
  - Closed: Highly flexible in regards to the volume used

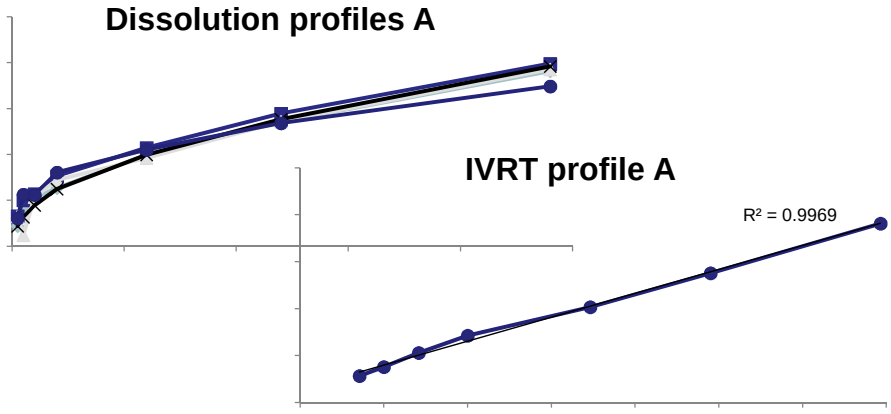
- A specific adapter (SSA) has been created to be used for semi-solids (with a membrane)

72

Semi-Solid Adapter: SSA

73

Case study #1



74

Conclusion

All these techniques may be highly sensitive to the membrane used…

Ideal characteristics for a membrane:

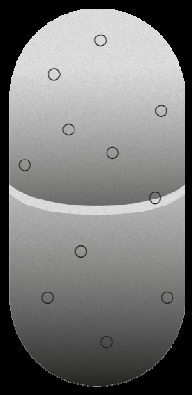
- High pore size
- Minimal thickness
- No interaction with the drug

➔Minimize the resistance to the diffusion

Ex: Cellulose, Cuprophan, Nylon, etc.

75

The Flow Through Cell: Principles and Applications



- Introduction on Dissolution
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  - Principles
  - Dissolution for API characterization
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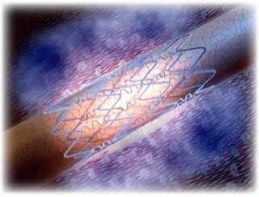
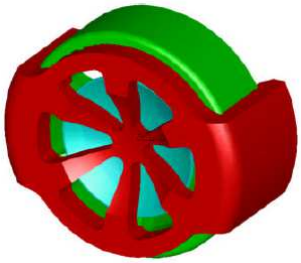
  - Case Studies: Medical devices
- Conclusion

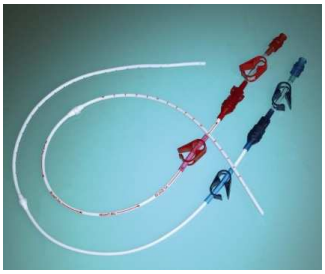
76

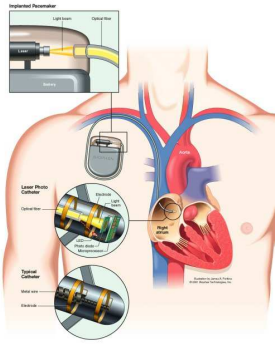
Device…

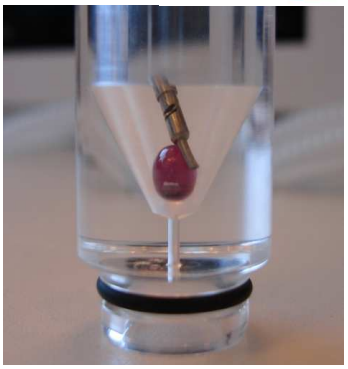


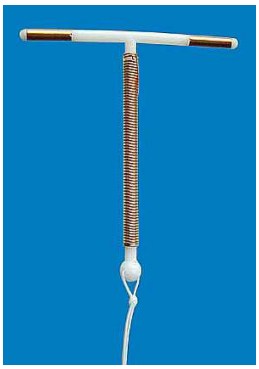


Retrieved prosthesis after being implanted for 38 years









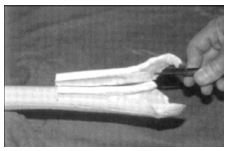
77

Medical device recommendations

- The developed method should be adequately validated to ensure accuracy, precision and reproducible results.
- Manufacturing of defective lots may be necessary to validate the discriminative power of the method.
- Complicated media or non compendial "dissolution" techniques can only be used when classical approaches failed
- Do not try to make it too complicated, search for the best simple method that answers your need…

78

Bone reconstruction



Two possible therapeutic strategies

Allografts Autografts	Synthetic materials ie ceramics
Osteoinduction	Osteoconduction
Morbidity	Biocompatibility
Risk of graft rejection	

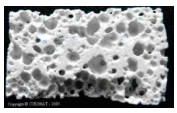
79

Phosphocalcic ceramics

Two types of porosity

Macroporosity :
Bone filling

Microporosity :
Liquids exchanges
Drug loading



Main presentations

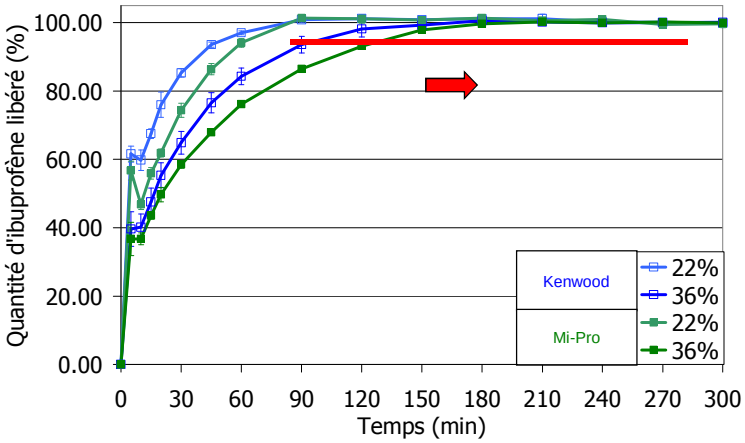
Blocks
Complexe shapes

Cements
Porosity created *in situ*

Spheroïds

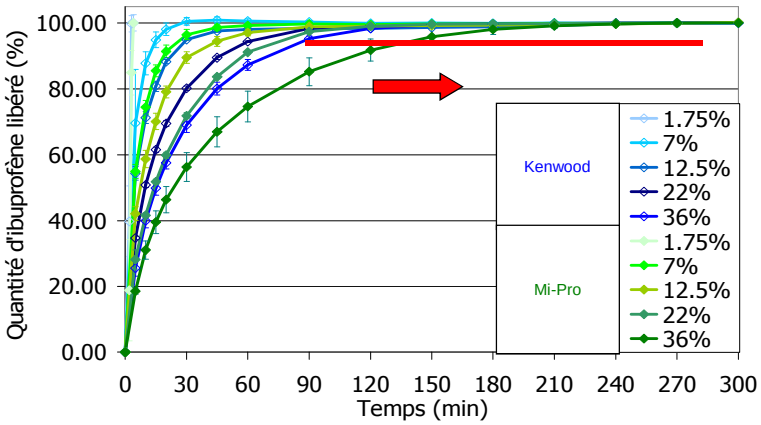
80

Dissolution profiles: USP2 paddle



81

Dissolution profiles: USP4 FTC



82

Bioceramics case study conclusion

- Complete release of the drug

- Increase of the drug content → Increase of dissolution time
Both tested devices were able to exhibit how the dissolution time increased with the ibuprofen content

- The flow through cell (USP4) offers more discriminative ability. The volume of dissolution medium used in the paddle apparatus, even reduced, was too important for testing all drug contents.

- Release kinetics were not greatly influenced by the granulation process, whatever the dissolution apparatus.

83

References

Comparison of three dissolution apparatuses for testing calcium phosphate pellets used as Ibuprofen delivery systems

CHEVALIER E., VIANA M., ARTAUD A., CHOMETTE L., HADDOUCHI S., DEVIDTS G., CHULIA D.

AAPS PharmSciTech, 10 (2), p.597-605, Jan 2009

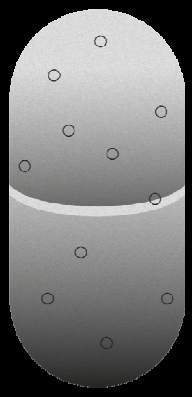
A novel application of the T-cell for flow through dissolution : the case of bioceramics used as ibuprofen carrier

CHEVALIER E., VIANA M., ARTAUD A., HADDOUCHI S., CHULIA D.

Talanta, 77, 1545-1548, 2009

84

The Flow Through Cell: Principles and Applications



- Introduction on Dissolution
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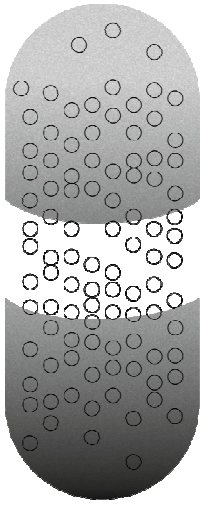
  - Principles
  - Dissolution for API characterization
  - Case Study: IR tablets
  - Case Studies: Injectable suspensions
- Conclusion

85

Take-home messages

- The flow through cell may have significant advantages compared to conventional methods.
- Its high flexibility and versatility make it a great tool for the characterization of complex dosage forms. It allows adapting the operating conditions to the properties of the pharmaceutical product.
- However, it is just another compendial dissolution method following the same principles !

86



Thank you!

Questions?

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