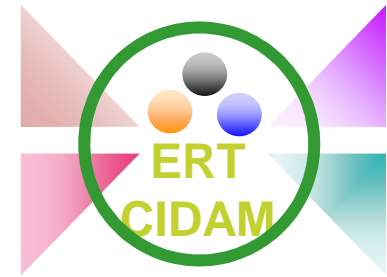


Dissolution testing and in vivo predictability

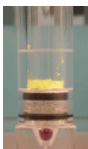


BEYSSAC Eric

**Faculty of Pharmacy
ERT CIDAM**



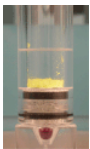
Université d'Auvergne – Clermont-Ferrand - France



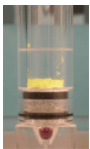
Introduction

□ Key points of the presentation

- Goals of dissolution testing
- Dissolution as a measure of product performance
- Developing a discriminatory method
- USP4
- Early phase development screening of API
- Dissolution in biorelevant media
- Dissolution and in vivo predictability



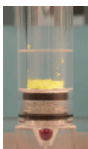
Goals of dissolution testing



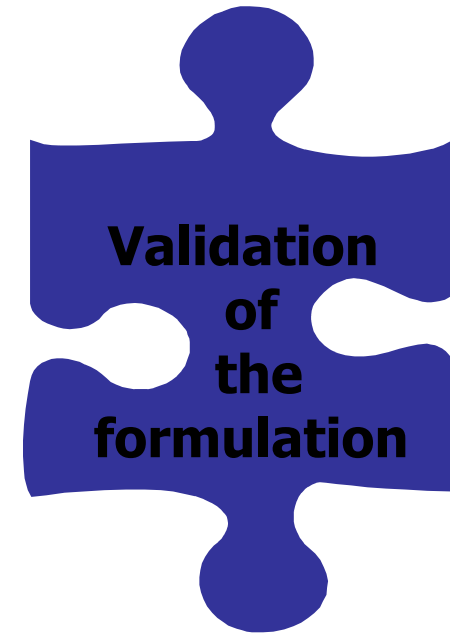
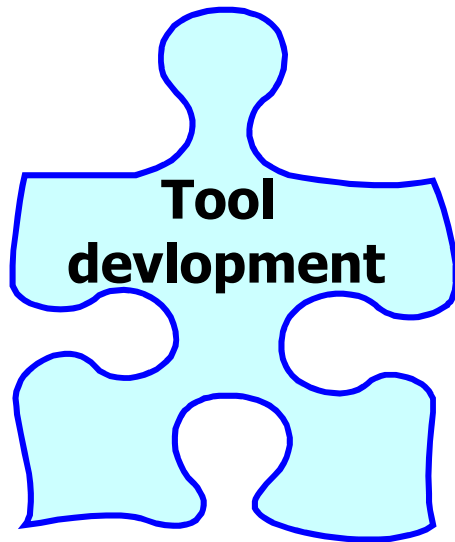
Goals of dissolution testing



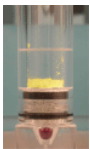
- Discriminant
- Good reproducibility
- Robust
- Validated
- User friendly
- Cost effective
- Transferable
- Automation



Goals of dissolution testing



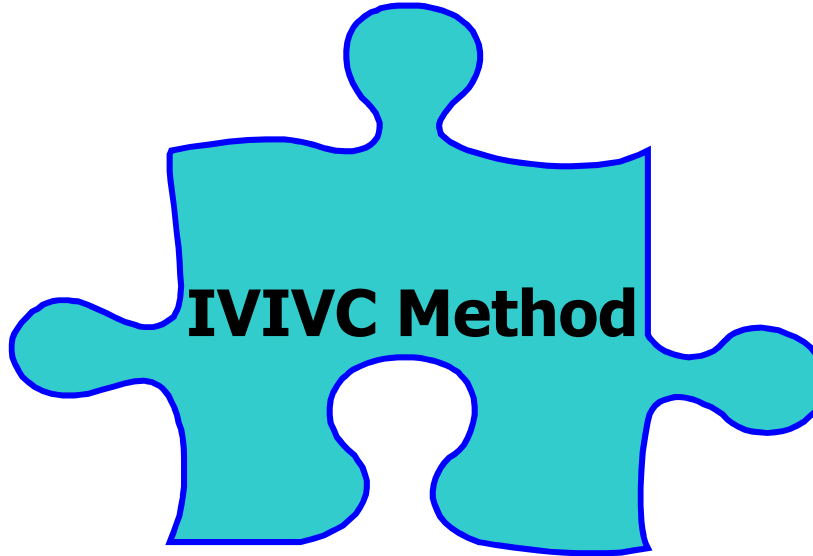
- Understand the release mechanisms (i.e. for modified release formulations)



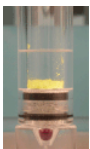
- Minimize influence of physiological factors on drug release

- Discriminative towards critical manufacturing variables
- Validation of scale up

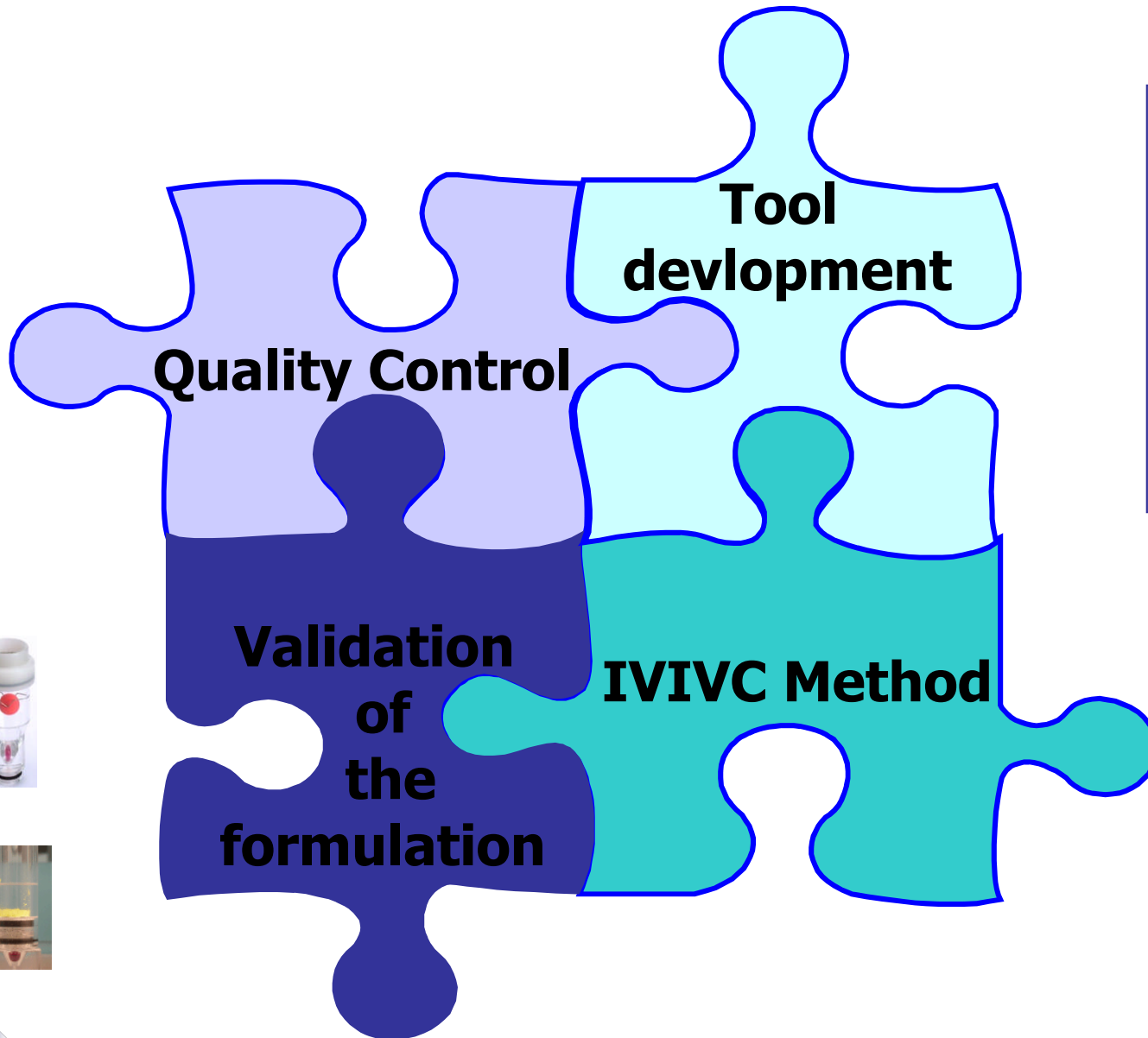
Goals of dissolution testing



- Relationship between in vitro and in vivo data
- Discriminating method that can predict in vivo performance (or signal possible bio-in-equivalence) and control key manufacturing
- Good internal and external predictability
- Reproducible
- Robust

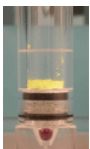


Goals of dissolution testing



Different methods according to the type of study and dosage form

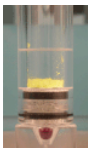
Ideal Case
One method for four cases



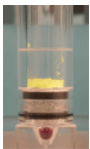
Goals of dissolution testing

□ Limitations

- Traditional role of dissolution → limited scientific knowledge
- Lack of understanding of the factors affecting product performance
- Specification is empirical
(except in case of IVIVC or IVIVR)
- The *in vitro* test may not reflect safety and efficacy
- Relevance to all drug products?



Dissolution as a measure of product performance?



Dissolution as a product performance

Systemic availability

Physico-chemical parameters

The diagram illustrates the relationship between physico-chemical parameters, dissolution, and systemic availability. A red curved arrow points from the 'Physico-chemical parameters' box to the 'Dissolution' box. A blue arrow points from the 'Dissolution' box to the 'Systemic availability' box. A black arrow points from the 'Dissolution' box to a detailed anatomical illustration of the human digestive system, specifically the stomach and intestines, where the drug is shown being absorbed.



Dissolution as a measure of product performance?

i.v.

Distribution-Elimination

p.o.
solution

Absorption

Distribution-Elimination

p.o. solid
form IR

Disintegration
Dissolution

Absorption

Distribution-Elimination

p.o. solid
form ER

Release and dissolution

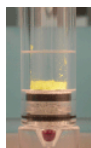
Absorption

Distribution-Elimination

*Biopharmaceutical
phase*

Permeability

Dissolution



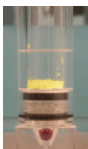
Dissolution as a measure of product performance?

❑ The plasma concentration curve is a global representation ; it depends of :

- Input of the drug within the blood flow, depending of properties of the drug, dosage form, patient, illness

(properties : solubility, dissolution rate, particle size, crystal shape, polymorphism, pKa, stability in GIT, FPE, Pgp, location of absorption, type of absorption, etc...)

- Disposition of the drug afterwards, depending of drug and patient



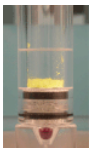
Dissolution as a measure of product performance?

- ❑ The active substance is the core of any formulation, the formulation is constructed around it

- ❑ Two major classical cases:



- Case 1: the drug dosage form disintegrates and disappears rapidly after intake: IR formulation

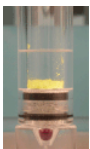


- Case 2: the DDF keeps its integrity during a long part of the G.I.T: ER formulation

Dissolution as a measure of product performance?

□ Case 1

- The behavior of the drug and of the excipients are independent
- Interaction and stability are the two main points
- % of drug substance into solution at the site of absorption and **dissolution rate** is of importance



Dissolution as a measure of product performance?

□ Case 2

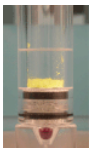
- The excipients are the core of the problem for the behavior of the drug within the body

Exemple of HPMC matrix : Interaction with water : swelling, gel formation, slow diffusion through the formatted gel, final erosion/destruction of the system after complete gel formation

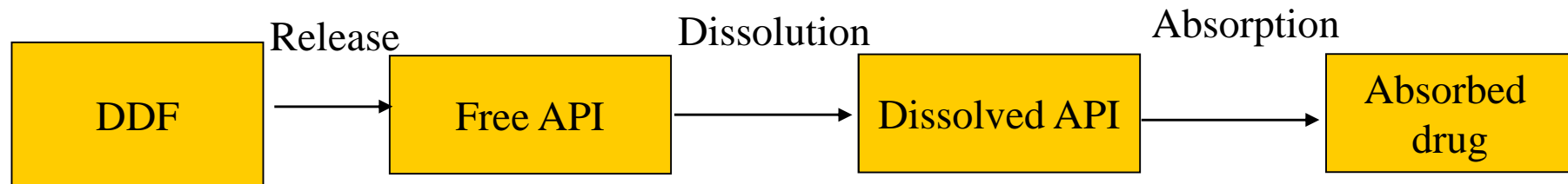
- Slower release of drug substance into solution at the site of absorption
- If GI permeability is not the limited factor and passive absorption

in vivo dissolution to correlate with input (absorption)

***in vitro-in vivo* correlation (IVIVC)**



Dissolution as a measure of product performance?



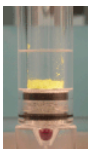
k_d = dissolution rate

→ solubility

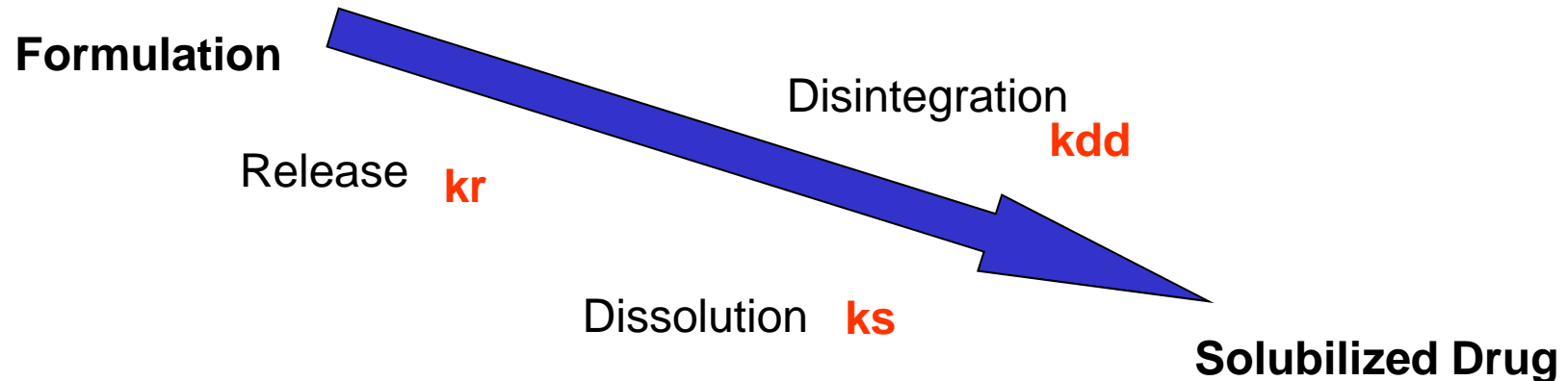
→ including food and formulation

k_p = permeability rate

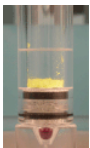
→ API molecular structure



Dissolution as a measure of product performance?



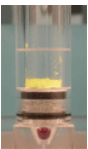
- Release → type and proportion of excipients
- Disintegration → cohesive properties of the formulation
- Dissolution of the drug → API characteristics



Importance of k_r , k_{dd} and k_s in dissolution test interpretation

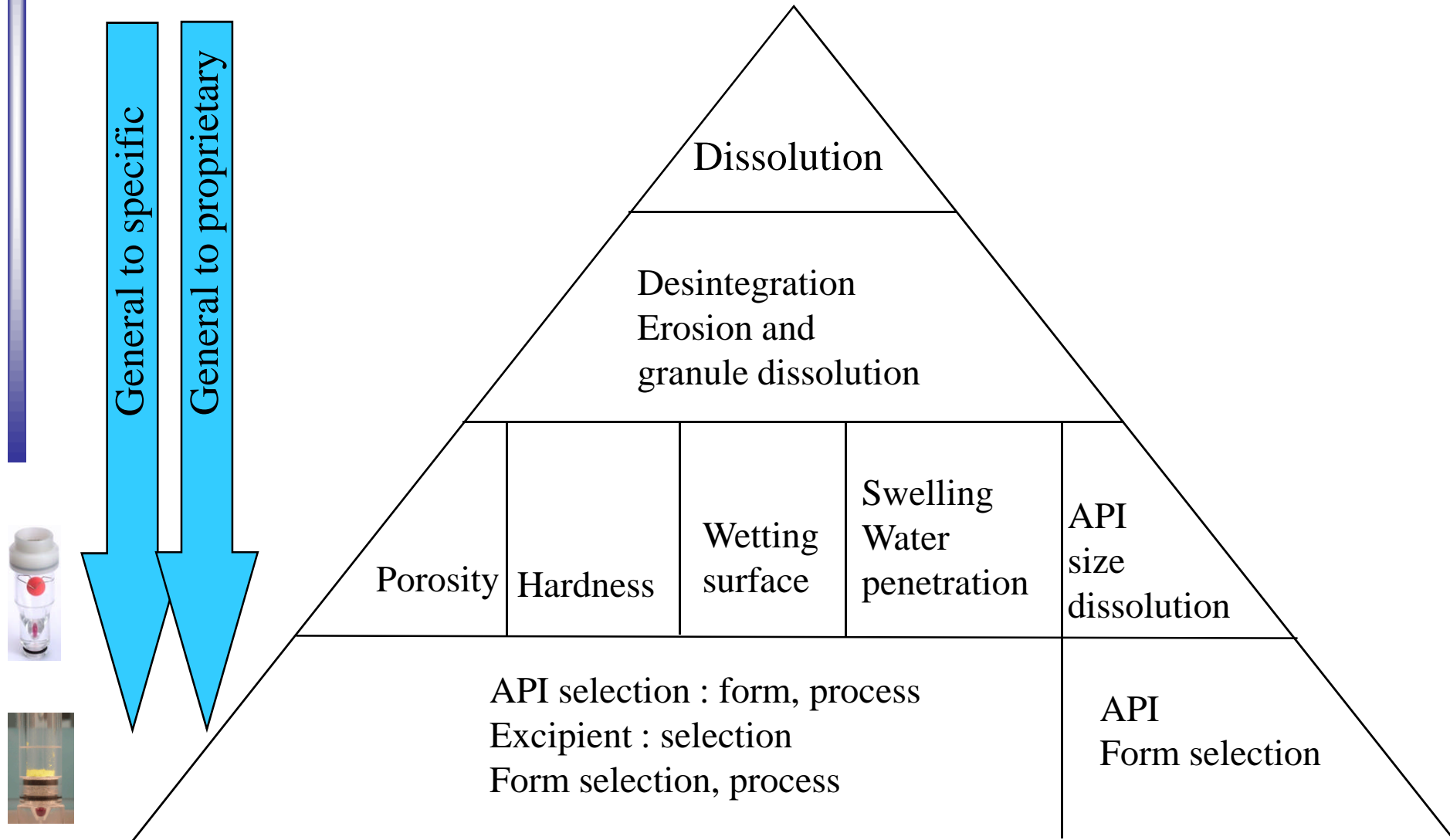
Dissolution as a measure of product performance?

- ❑ Possible sources of bio-inequivalence
 - Incomplete release of drug at site (formulation)
 - Insufficient drug in solution at site (substance)
 - First pass metabolism (variability)
 - Low g.i. permeability (variability)
 - Pgp important (variability)
 - If absorption is not passive (variability)



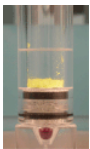
⇒ Study the release/dissolution of the drug as that are the only factors on which you can play

Dissolution as a measure of product performance?



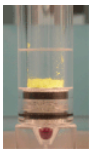
Adapted from A Quality by Design Approach to Dissolution Based on the Biopharmaceutical Classification System, R. Reed

Developing a discriminatory method



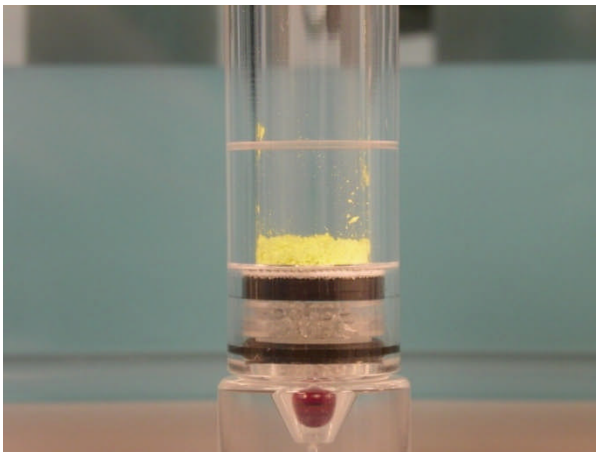
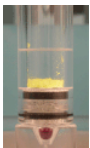
Developing a discriminatory method

- ❑ Selection of a dissolution apparatus
 - Immediate release drug dosage forms
 - Enteric coated dosage forms
 - Extended release dosage forms
 - Concept of release
 - Type of drug dosage form : monolithic, multiparticulate, powder, suspension
- ❑ Selection of a agitation or flow rate
- ❑ Selection of medium
- ❑ Position of the dosage form



Developing a discriminatory method

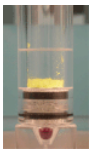
□ EP/ USP apparatus



Developing a discriminatory method

□ Simulating *in vivo* with apparatus design

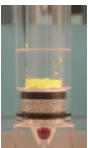
Create a similar kinetic and hydrodynamic test conditions as *in vivo* (apparatus IV and Apparatus III, and slow rotation speed). However, hard to achieve same hydrodynamic



Developing a discriminatory method

□ Dissolution media

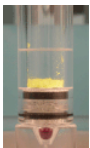
- Water but not recommended by European Pharmacopea
- Buffer solutions
 - pH 1.2
 - pH 4.5
 - pH 6.8
 - pH 7.2
- Surfactant solutions
 - SLS, Tween 80, Brij 35



Developing a discriminatory method

❑ What is Important dependent on the drug in formulation

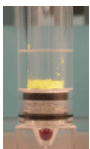
- pH: important for salt, but less important for neutral drug. (test all pH for poor soluble drugs)
- Buffer capacity: If the drug or the excipients react with medium, buffer capacity will be an issue.
- Surface tension/Wetability: Hydrophobic drugs, poorly water-soluble, even buffer can reduce surface tension and results in better dissolution
- Solubilization: Poorly water-soluble drugs dissolve in surfactant media.



Developing a discriminatory method

❑ Biopharmaceutics Classification system

Class	Solubility	Permeability	Dissolution Medium
I	High	High	Aqueous medium
II	Low	High	Tensio active or USP 4
III	High	Low	Aqueous medium
IV	Low	Low	Tensio active or USP 4

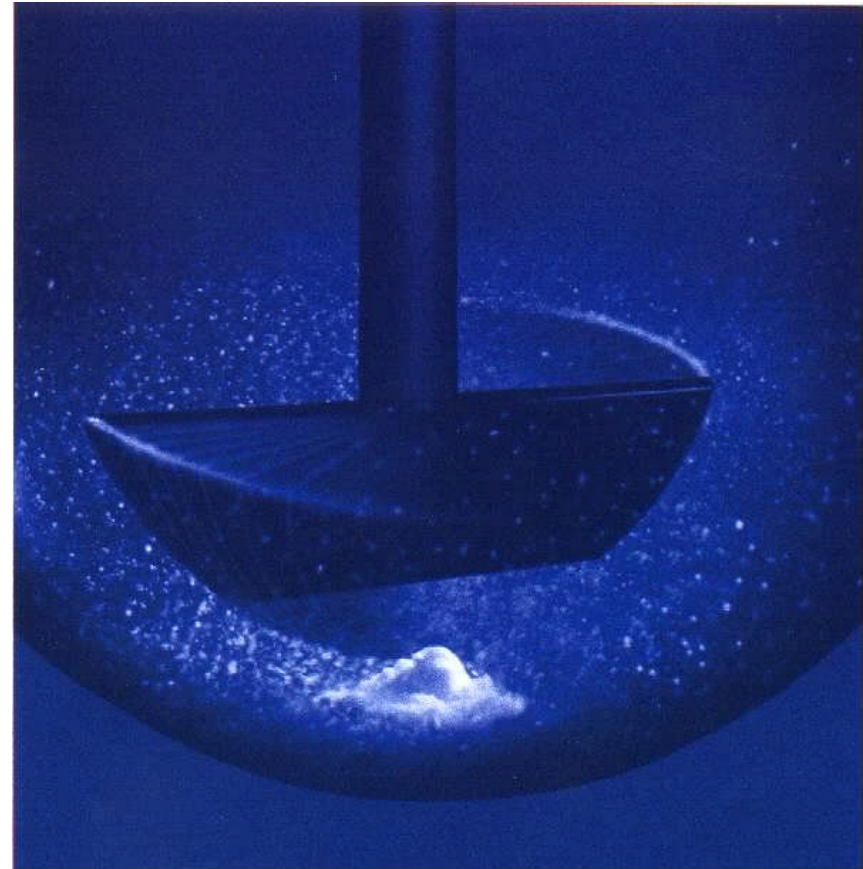
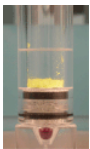


Developing a discriminatory method

Avoid artefact !!

Cross linking

Coning effect



Developing a discriminatory method

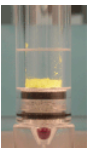
The dissolution method and its acceptance criteria must be established based upon

- Design or type of formulation
- BCS
- Consideration of critical attributes
- Scientific evidence
- Prior knowledge

→ Screen a number of method



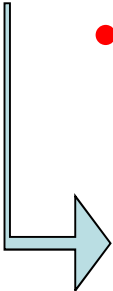
- Classical or biorelevant media (Fassif, Fessif), tensioactive
- Dissolution rate
- Apparatus : USP1, USP2, USP3 or USP4
- Open or close system

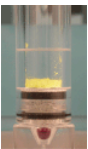


Identification of variables with significant effect on release

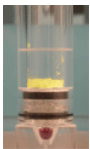
Developing a discriminatory method

❑ Use batches which are likely to exhibit differences in performance

- 
- Distinguish the good from the bad products with intentional change
 - Ensure good knowledge of batches (formulation, processing, API characteristics, Excipients...etc)
 - Use characterisation technique in combination
 - Know what you are measuring
 - Link dissolution results with other characterisation data
 - Know your method variability and batch to batch variability



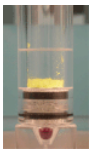
USP 4



❑ Challenges and issues

Pharmaceutical development increased dramatically the complexity of formulations over the past decades...

- Poor solubility drug
- Active substances from biotechnology
- Modified/extended release
- Highly potent drug with low dose
- Patent protection, etc...



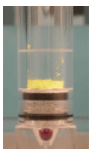
❑ Challenges and issues

- Problem of solubility and dissolution rate

More and more active ingredients are poorly soluble. In addition to the difficulty for the formulation, dissolution testing could be an issue with conventional techniques (rotating paddle and basket) due to the limited volume of dissolution.



Solubility is important but the dissolution rate is also to be considered and must be evaluated during development even with small amounts of product.

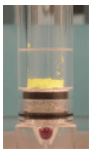


❑ Challenges and issues

- Problem of sensitivity

The dosage strengths could be very low (for example a drug eluting stent contains 80 to 400 μg of drug).

Need to decrease the dissolution volume to maintain accuracy in analytical measurements.



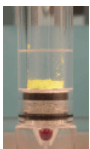
❑ Challenges and issues

- Route of administration and new dosage forms

Parenteral delivery systems are becoming increasingly utilized by the pharmaceutical industry:

- Improved therapeutic response, patient comfort & treatment compliance
- Reduced adverse reactions
- Targeted drug release

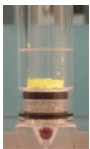
Due to the route of administration, these forms contain often low doses of drug.

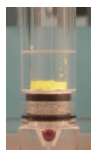


❑ Challenges and issues

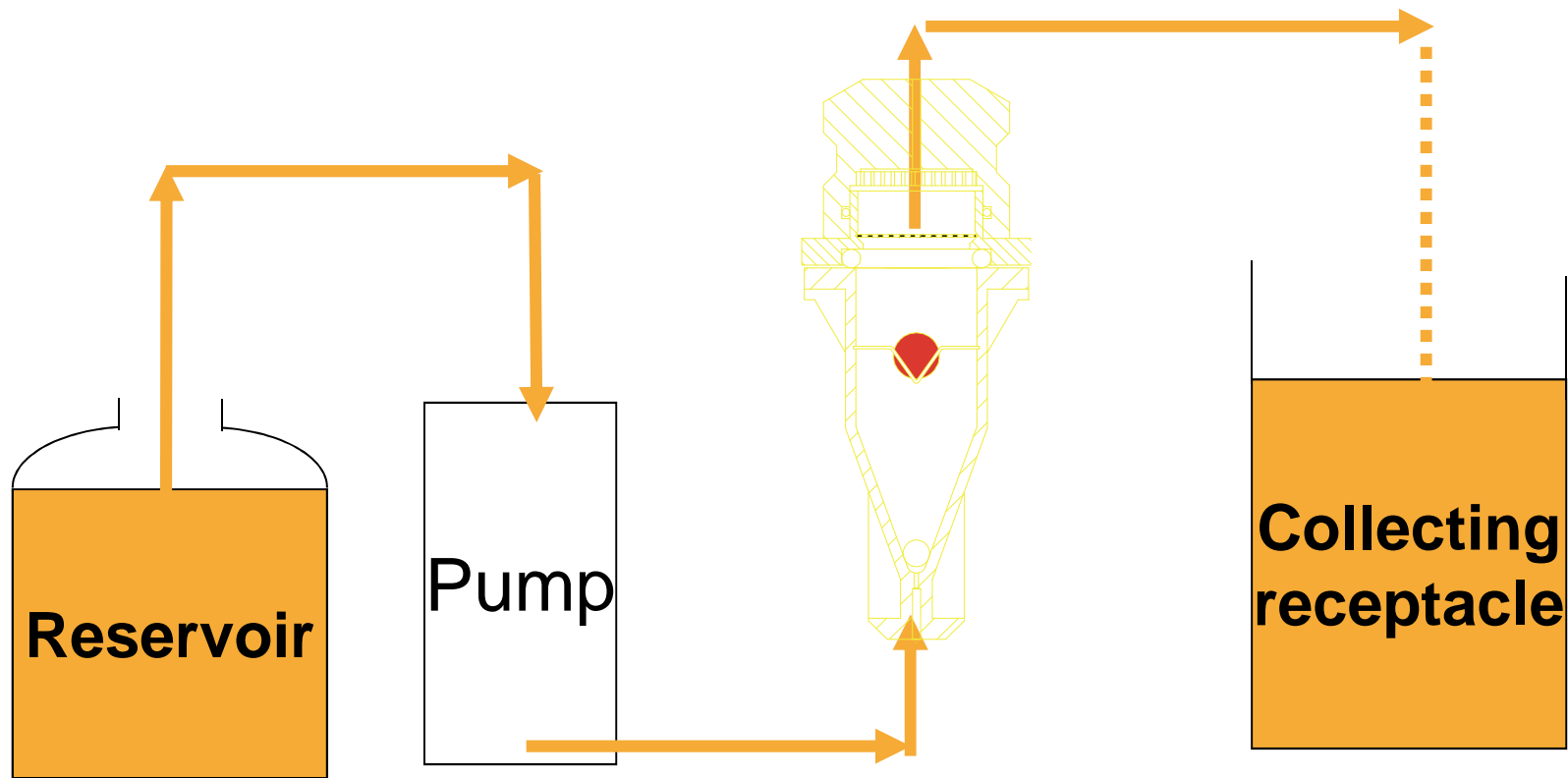
Because of its flexibility, flow through cell method may help to overcome these challenges especially for:

- API specifications
- Low soluble products
- Extended release dosage forms
- Specific dosage forms
- CR parenteral forms
- Implants
- Drug eluting stents





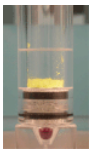
□ Flow-through apparatus open system



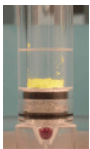
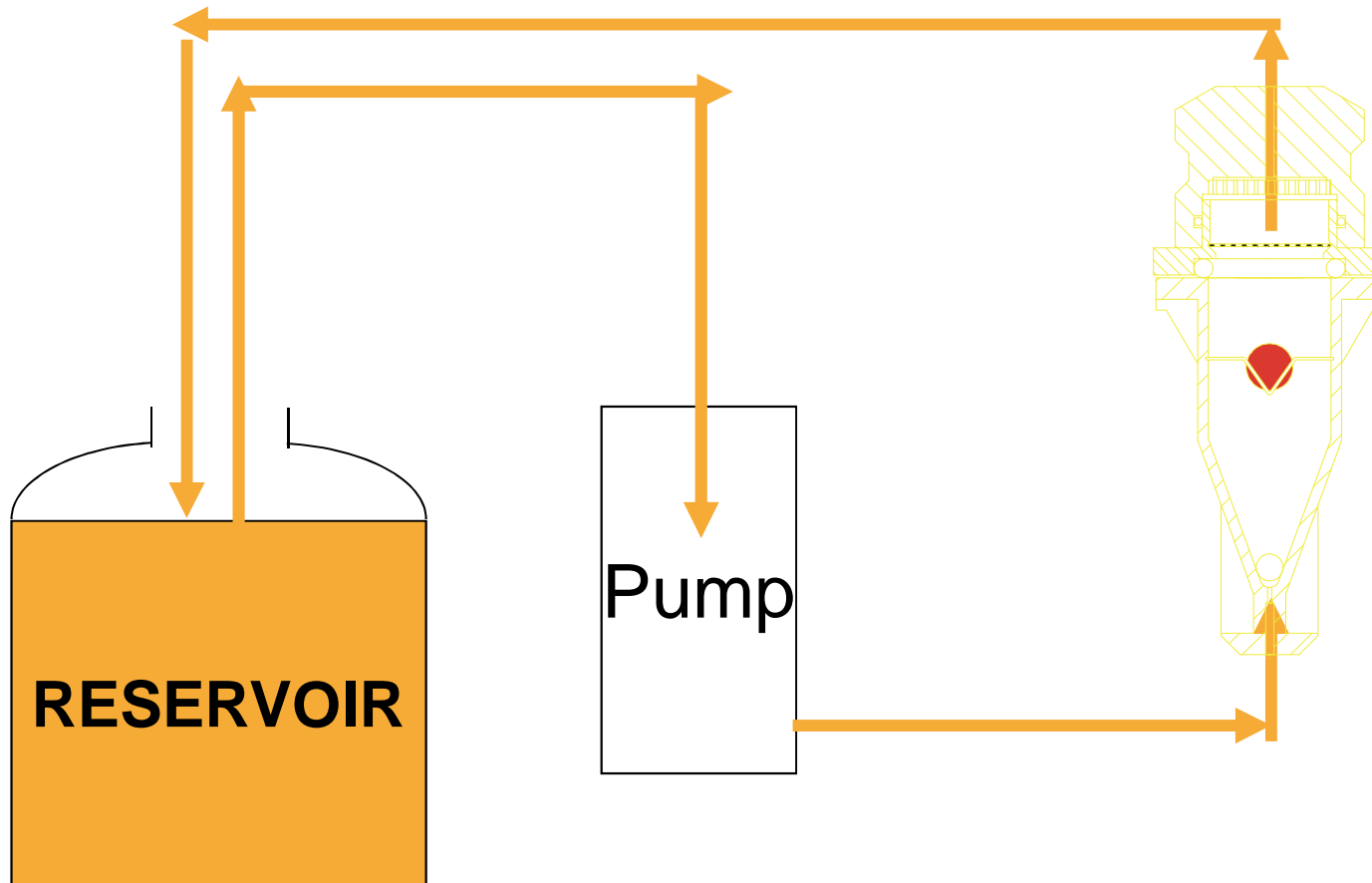
A reservoir for the dissolution medium

A pump that forces the dissolution medium upwards through the flow-through cell

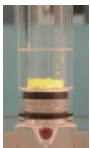
A flow through cell mounted vertically with a filter system preventing escape of undissolved particles



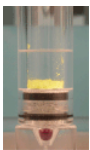
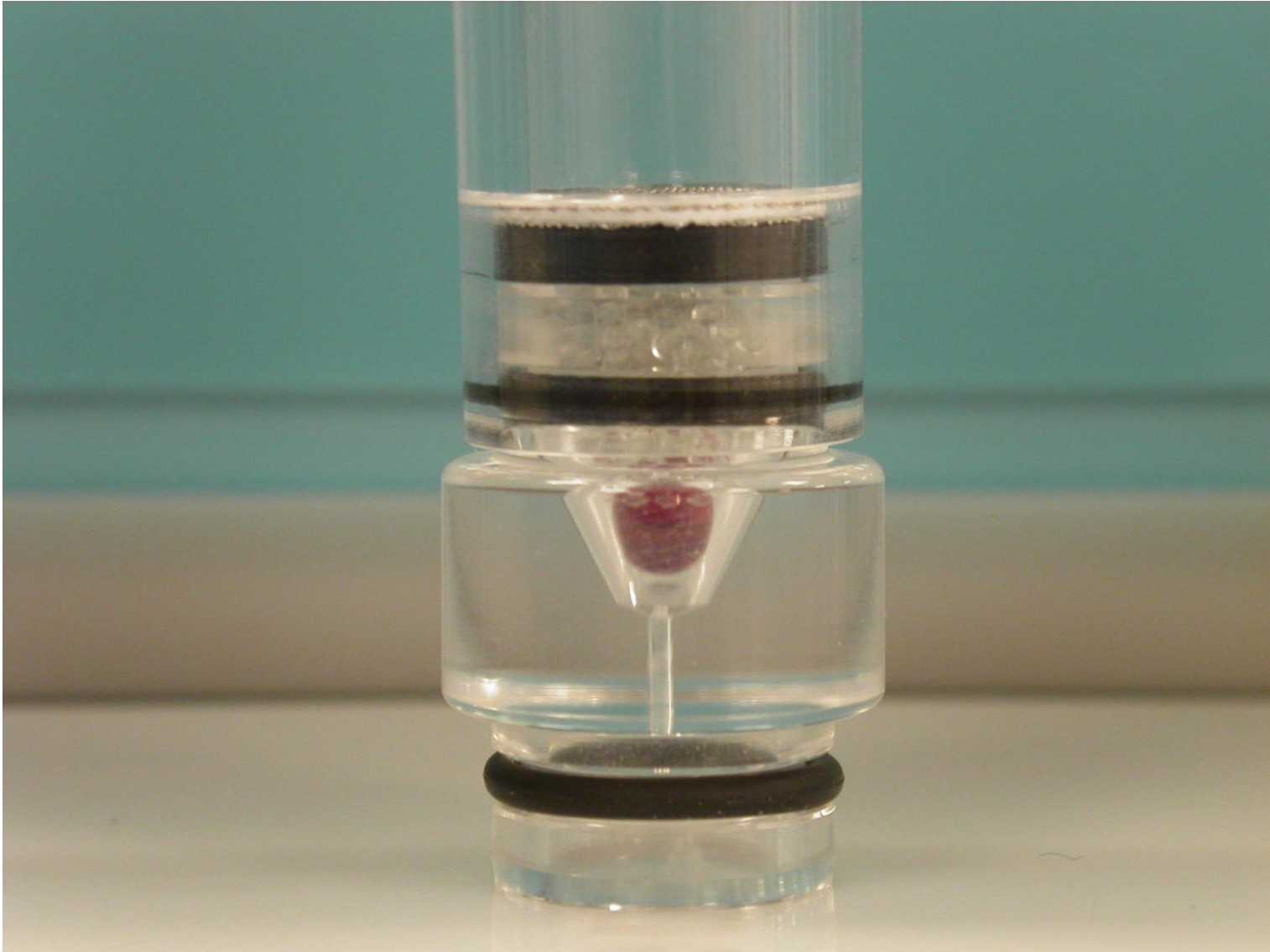
□ Flow-through apparatus : close system



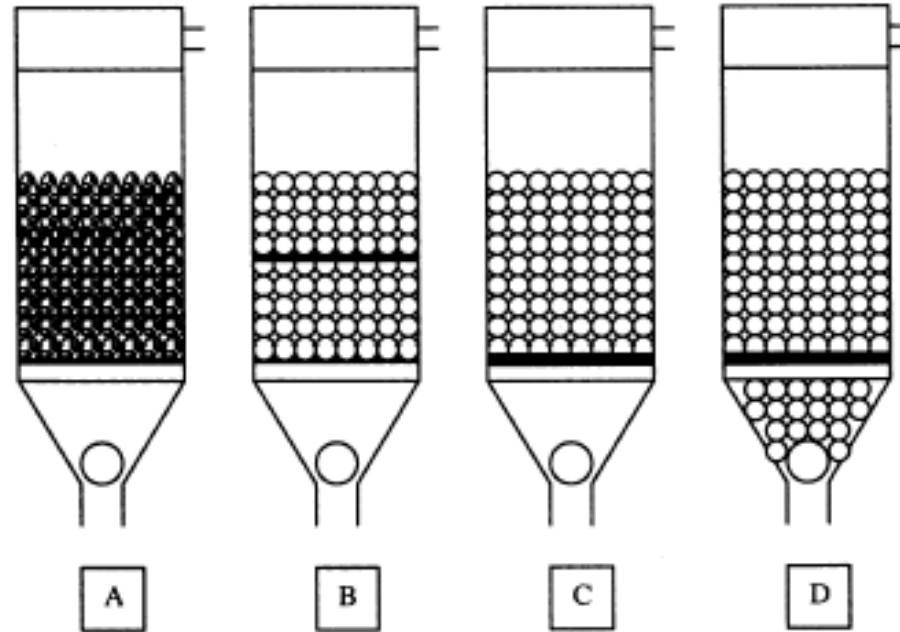
□ Position of the dosage form



❑ Position of the dosage form



Position of the dosage form: Powder



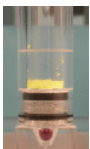
Pattern A : drug homogeneously mixed with glass beads

Pattern B : drug layered midway across the bed of glass beads

Pattern C : Drug layered on the bottom of the cylindrical portion below the bed of glass beads

Pattern D : same C with lower cone filled with glass beads

S.N. Bhattachar et al. / International Journal of Pharmaceutics 236 (2002) 135–143



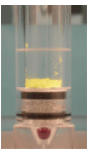
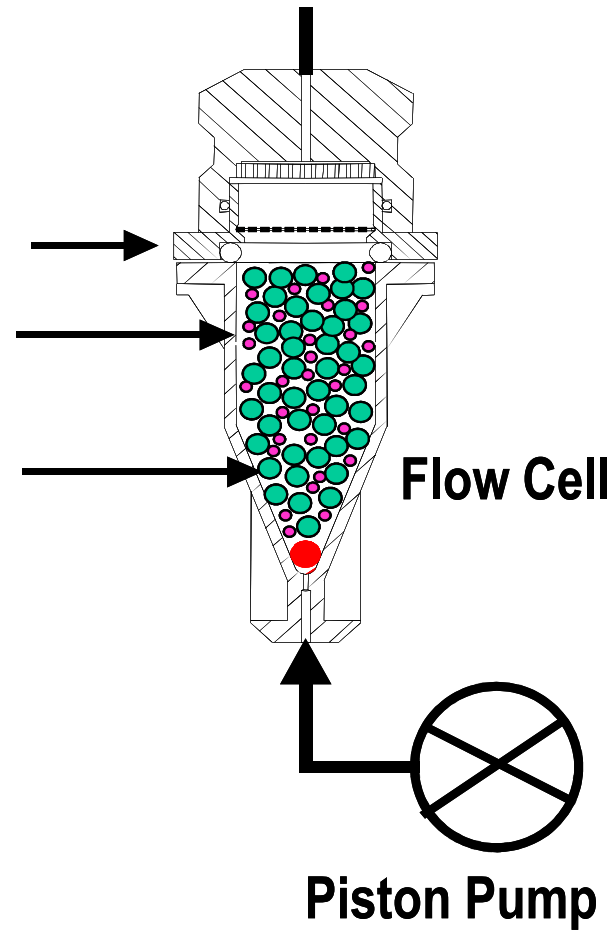
□ Position of the dosage form



Filter system

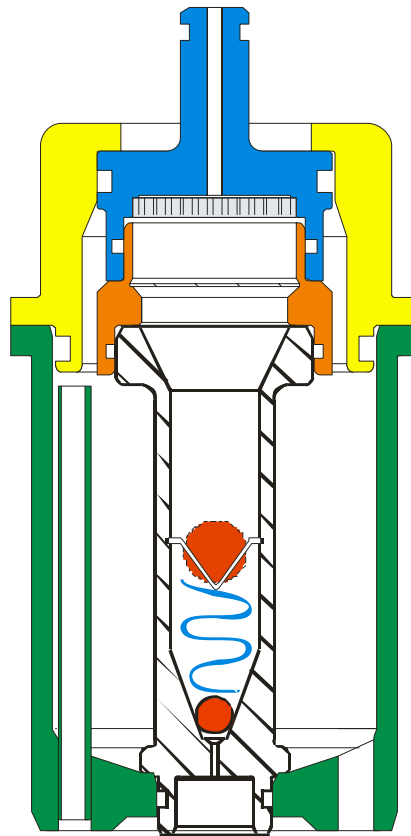
Drug Product

Glass Beads

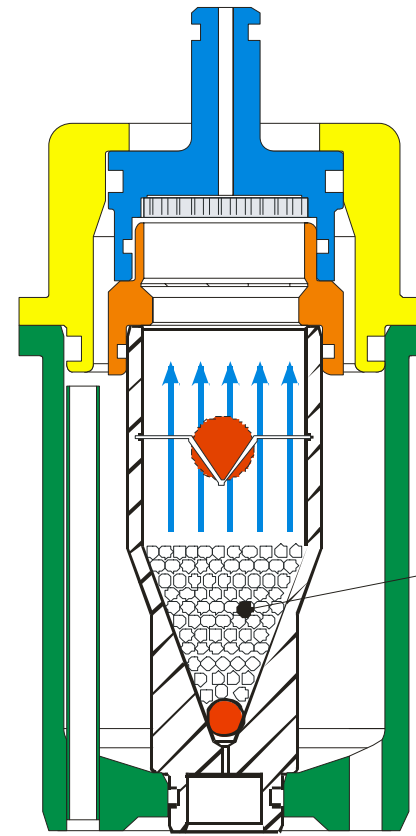


□ Laminar and turbulent flow

- Glass beads reduce variability caused by turbulent flow
- Glass beads allow for “positioning” of the tablet in the cell to prevent tablet from sticking to sides of the cell

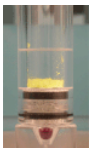


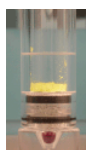
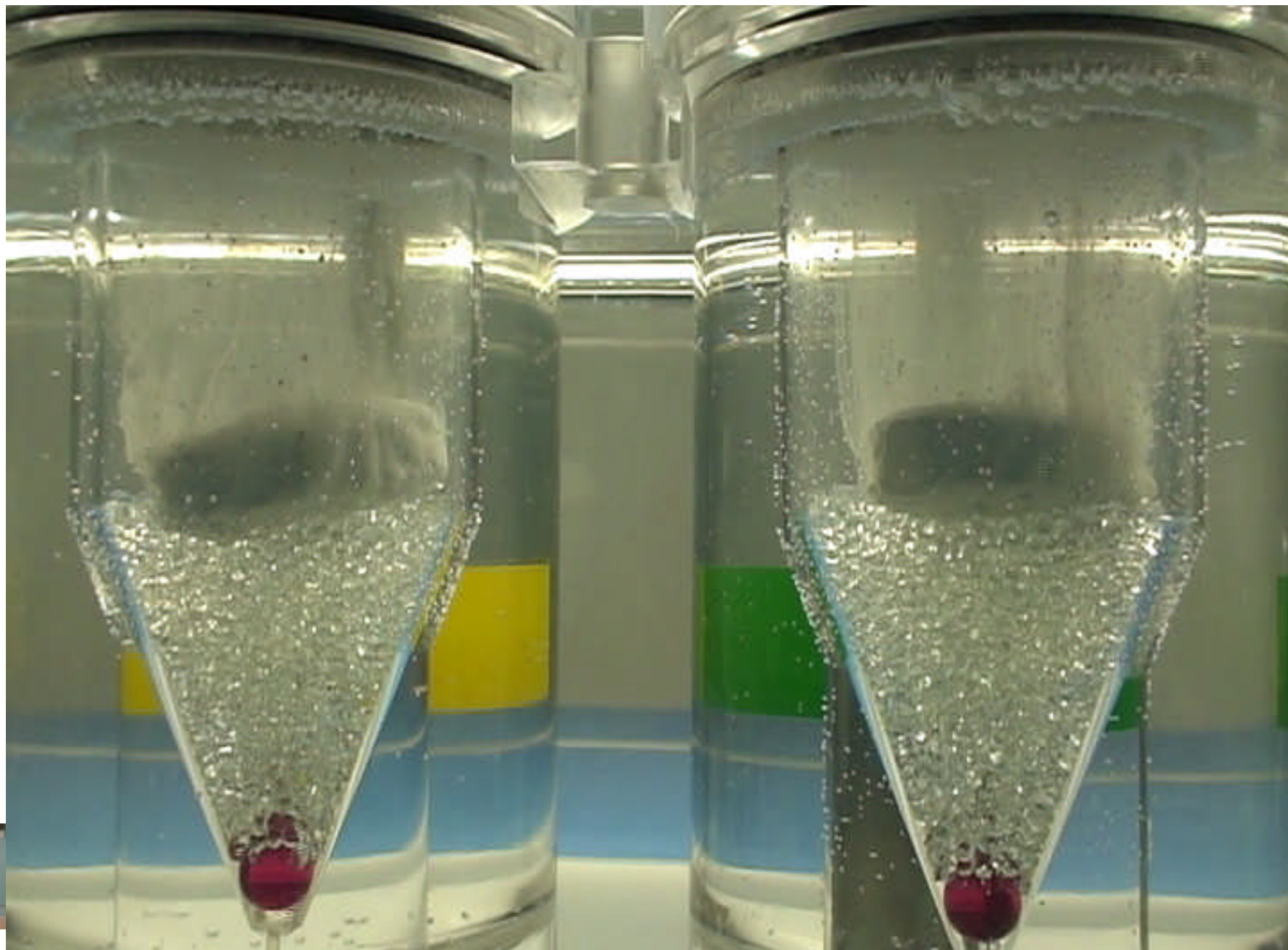
Turbulent

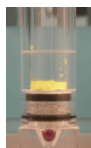
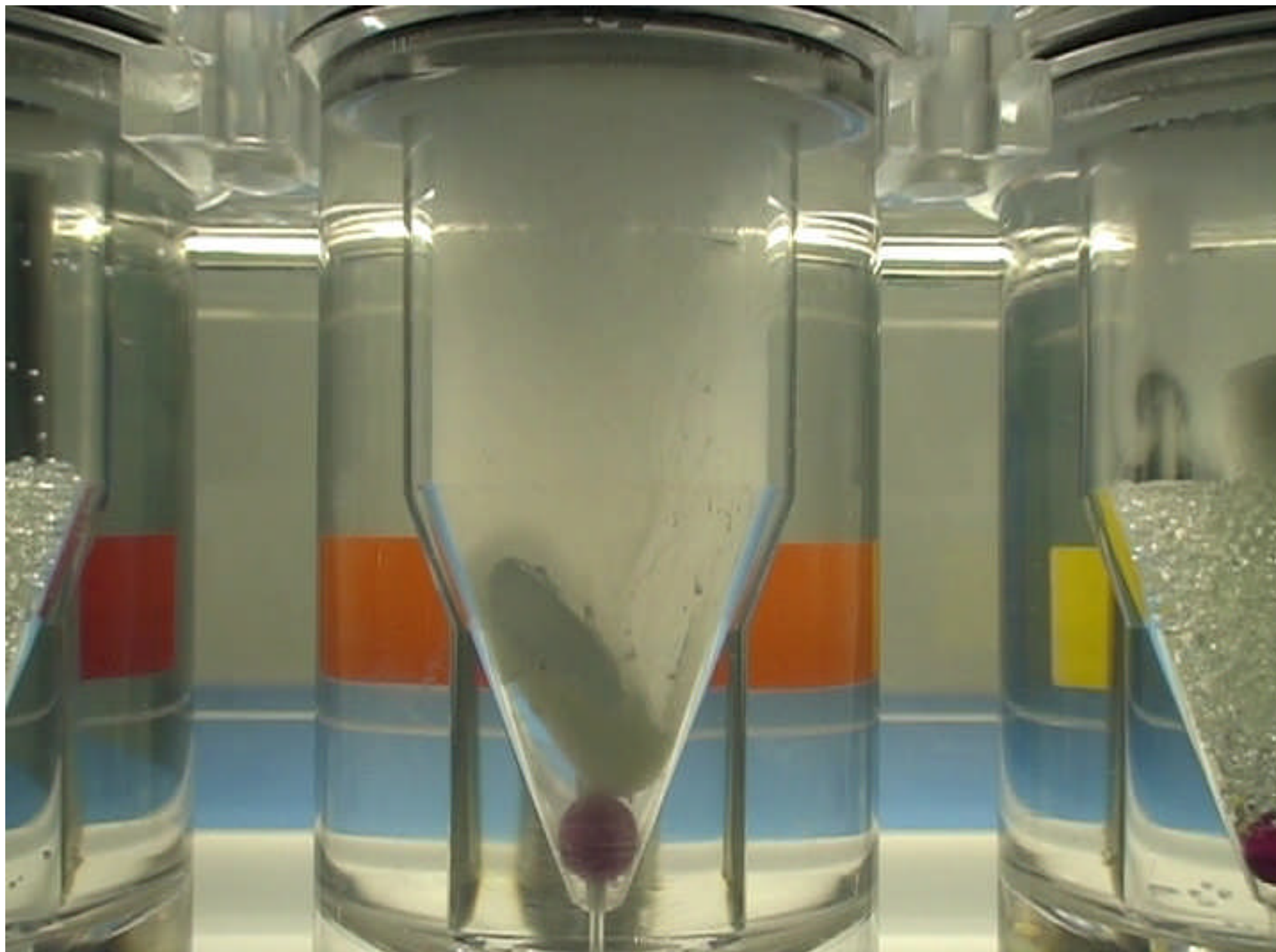


Glass beads

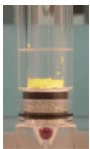
Laminar







Early phase development screening of API



Early phase development screening of API

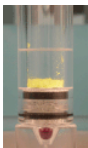
☐ Solubility affects

- Classification in BCS,
- Choice of formulation,
- Choice of the analytical method,
- Possibility of IVIVC.

Link always solubility to the dose administered and to the dissolution rate



❖ Fast dissolution rate : good point even if solubility is low as in GIT “sink” condition are existing



❖ Slow dissolution rate : physical (micronisation, etc.), or chemical modification (co precipitation, solid solution, etc.) to change BCS class

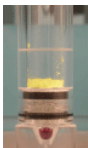
Early phase development screening of API

□ API

- Different batches
- Different salts
- Modified crystals
- Different polymorphs
- Different particle size and/or morphology
- Different specific surface areas

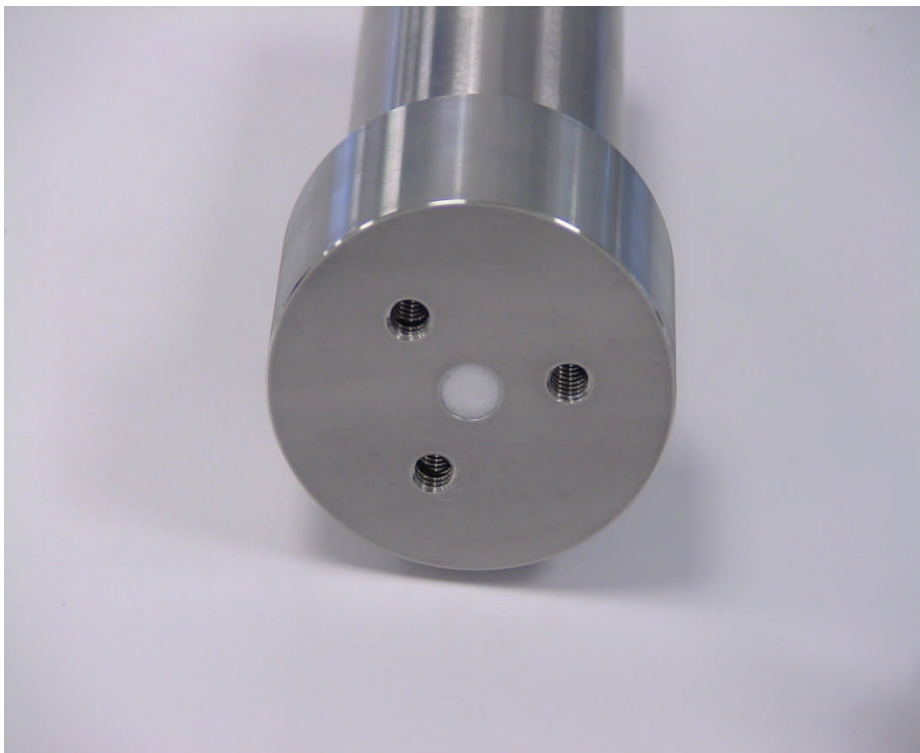
□ Intermediate drug product

- Spray-dried material
- Freeze-fried material
- Capsule powder blends
- Tablet powder blends

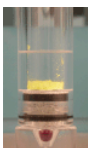
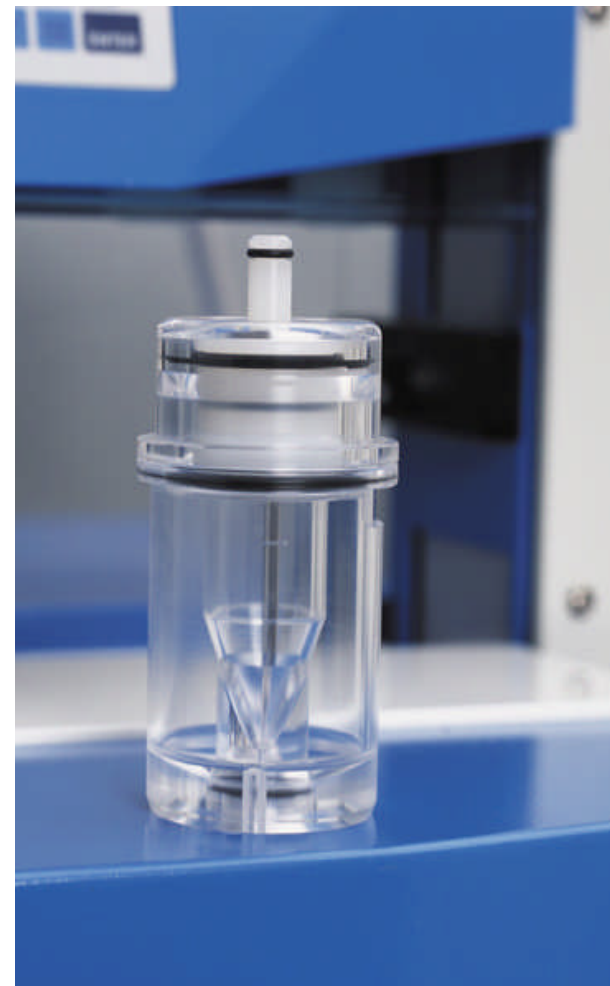


Early phase development screening of API

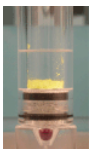
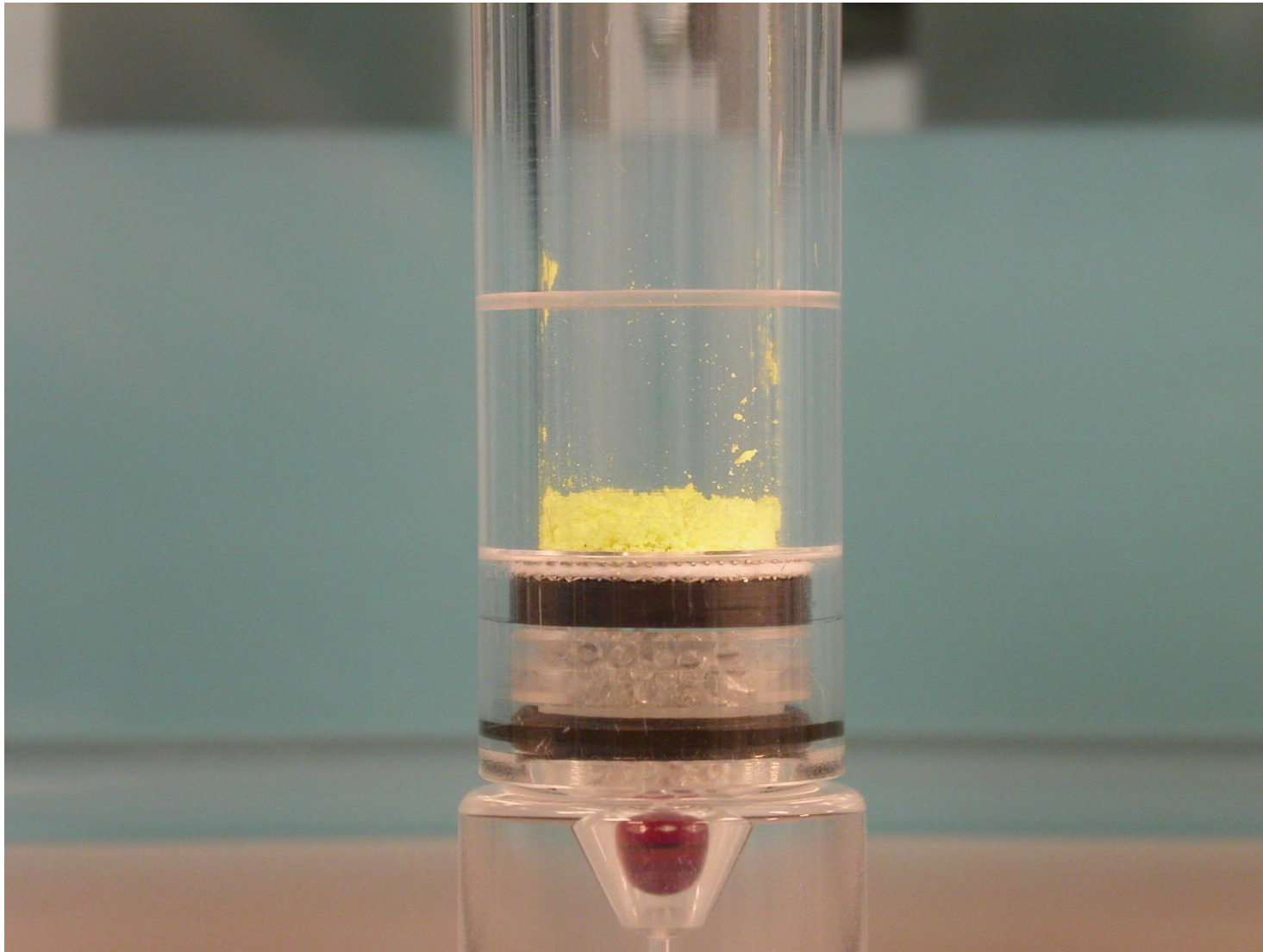
Intrinsic dissolution



Apparent dissolution



Early phase development screening of API



Early phase development screening of API

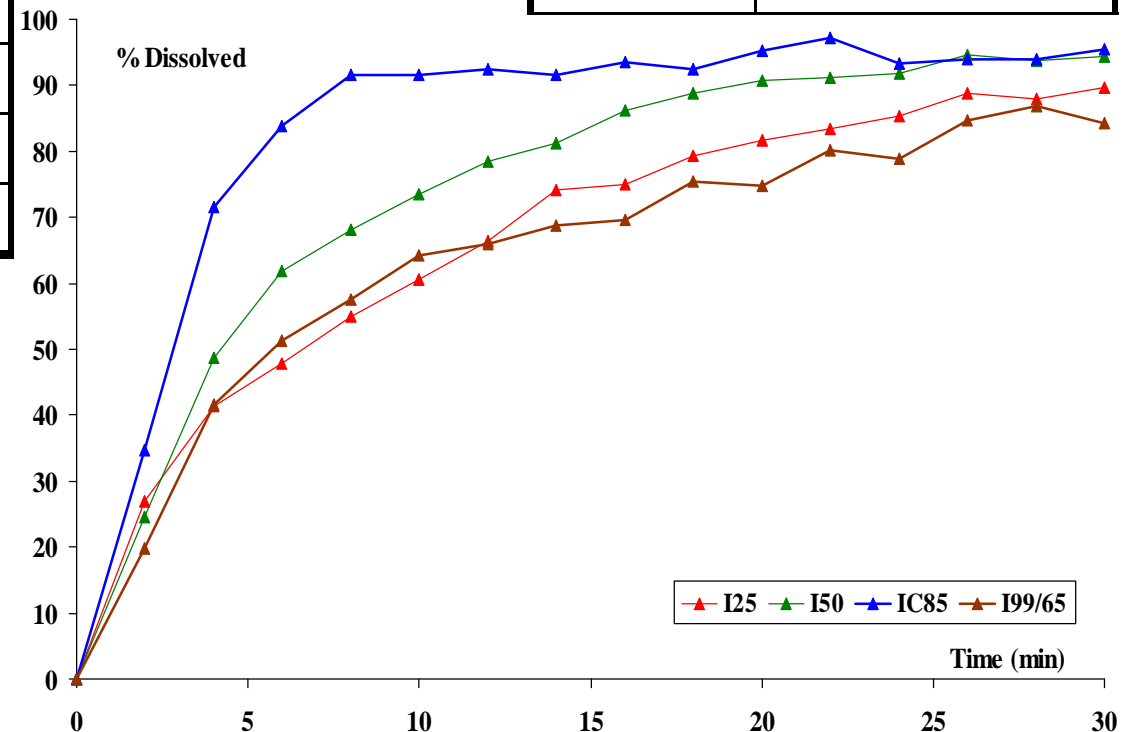
□ Example : Drug Class I

4 different batches with different characteristics

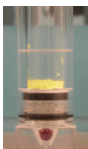
Product	Surface area m ² /g	Mean diameter μm
I25	0.92	122.2
I50	0.45	74.5
IC85	4.36	206.9
I99/65	---	165.4

Product	K h ⁻¹
I125	3.77
I150	3.81
IC185	Fast disintegration of the tablet
I99/65	4.13

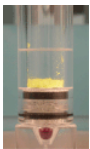
Intrinsic dissolution



Apparent dissolution



Dissolution in biorelevant media



□ Interest

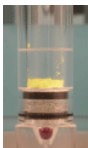
Estimation of intraluminal dissolution kinetics

Intragastric dissolution

- For prediction of the plasma profile of a weak base in the fasted state
- For prediction of the plasma profile in fed state
- For confirming rapid dissolution of the dose during gastric residence

Intraintestinal dissolution

- For prediction of the plasma profile of lipophilic compounds
- For confirming rapid dissolution in the small intestine



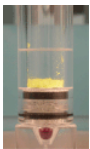
□ True biofluid

- Human aspirates
(human intestinal fluid, human gastric juice)

- Gastric fluid: about 300 mL, pH 1-3, surface tension lower than water.

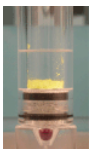
- Intestinal fluid: about 500 mL, pH 3-8, surface tension lower than water

- Animal aspirates : Canine fluid



❑ **Simulated biofluids (Biorelevant media) containing enzymes/proteins**

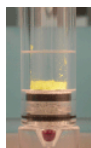
- Simulated Gastric Fluid (pH 1.2, with pepsin)
- Simulated Intestinal Fluid (pH 6.8, with pancreatin)
- Modified simulated gastric fluid (same as above with 0.1% Triton X100)
- Milk (fed) (bovine milk, 3.5% fat)
- Fasted intestinal fluid (FaSSIF) pH 6.5, containing lecithin.
- Fed intestinal fluid (FeSSIF) pH 5.0, containing sodium taurocholate and lecithin



□ Bio relevant media

Fasted state simulated intestinal fluid (FaSSIF)		
pH		6.5
osmolality		270 ± 10 mOsmol
Sodium taurocholate		3 mM
Lecithin		0.75 mM
KH ₂ PO ₄		3.9 g
KCl		7.7 g
NaOH	qs	pH 6.5
Deionized water	qs	1 liter

Fed state simulated intestinal fluid (FeSSIF)		
pH		5.0
osmolality		635 ± 10 mOsmol
Sodium taurocholate		15 mM
Lecithin		3.75 mM
Acetic acid		8.65 g
KCl		15.2 g
NaOH	qs	pH 5.0
Deionized water	qs	1 liter



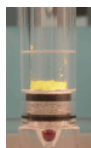
From Pharma Research Vol
15, N°5, 1998,698-705

□ Biorelevant media

From Dissolution Technologies August 2009 21-25

Table 1. Composition of the Medium to Simulate the Fasted-State Stomach: Fasted-State Simulated Gastric Fluid (FaSSGF)

Composition	
Sodium taurocholate (μM)	80
Lecithin (μM)	20
Pepsin (mg/mL)	0.1
Sodium chloride (mM)	34.2
Hydrochloric acid q.s.	pH 1.6
Properties	
pH	1.6
Osmolality (mOsm/kg)	120.7 ± 2.5
Buffer capacity (mmol/L/pH)	–
Surface tension (mN/m)	42.6

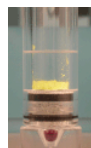


□ Biorelevant media

From Dissolution Technologies August 2009 21-25

Table 2. Composition of the Media to Simulate the Fed-State Stomach, Including Fed-State Simulated Gastric Fluid (FeSSGF)

Composition	Early	Middle (FeSSGF)	Late
Sodium chloride (mM)	148	237.02	122.6
Acetic acid (mM)	–	17.12	–
Sodium acetate (mM)	–	29.75	–
Ortho-phosphoric acid (mM)	–	–	5.5
Sodium dihydrogen phosphate (mM)	–	–	32
Milk/buffer	1:0	1:1	1:3
Hydrochloric acid/sodium hydroxide q.s.	pH 6.4	pH 5	pH 3
Properties			
pH	6.4	5	3
Osmolality (mOsm/kg)	559	400	300
Buffer capacity (mmol/L/pH)	21.33	25	25
Surface tension (mN/m)	49.7 ± 0.3	52.3 ± 0.3	58.1 ± 0.2

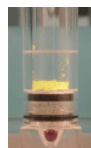


□ Biorelevant media

From Dissolution Technologies August 2009 21-25

Table 3. Composition of the Medium to Simulate the Fasted-State Upper Small Intestine: Fasted-State Simulated Intestinal Fluid, Updated Version (FaSSIF-V2)

Composition (mM)	
Sodium taurocholate	3
Lecithin	0.2
Maleic acid	19.12
Sodium hydroxide	34.8
Sodium chloride	68.62
Properties	
pH	6.5
Osmolality (mOsm/kg)	180 ± 10
Buffer capacity (mmol/L/pH)	10
Surface tension (mN/m)	54.3

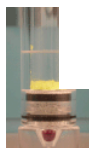


□ Biorelevant media

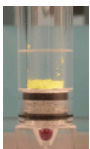
From Dissolution Technologies August 2009 21-25

Table 4. Composition of the Media to Simulate the Fed-State Upper Small Intestine, Including Fed-State Simulated Intestinal Fluid, Updated Version (FeSSIF-V2)

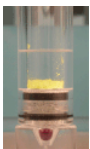
Composition (mM)	Early FeSSIF	Middle FeSSIF	Late FeSSIF	FeSSIF-V2
Sodium taurocholate	10	7.5	4.5	10
Lecithin	3	2	0.5	2
Glycerol monooleate	6.5	5	1	5
Sodium oleate	40	30	0.8	0.8
Maleic acid	28.6	44	58.09	55.02
Sodium hydroxide	52.5	65.3	72	81.65
Sodium chloride	145.2	122.8	51	125.5
Properties				
pH	6.5	5.8	5.4	5.8
Osmolality (mOsm/kg)	400 ± 10	390 ± 10	240 ± 10	390 ± 10
Buffer capacity (mmol/L/pH)	25	25	15	25
Surface tension (mN/m)	30.1 ± 0.2	32.7 ± 0.5	46.0 ± 0.2	40.5 ± 0.2



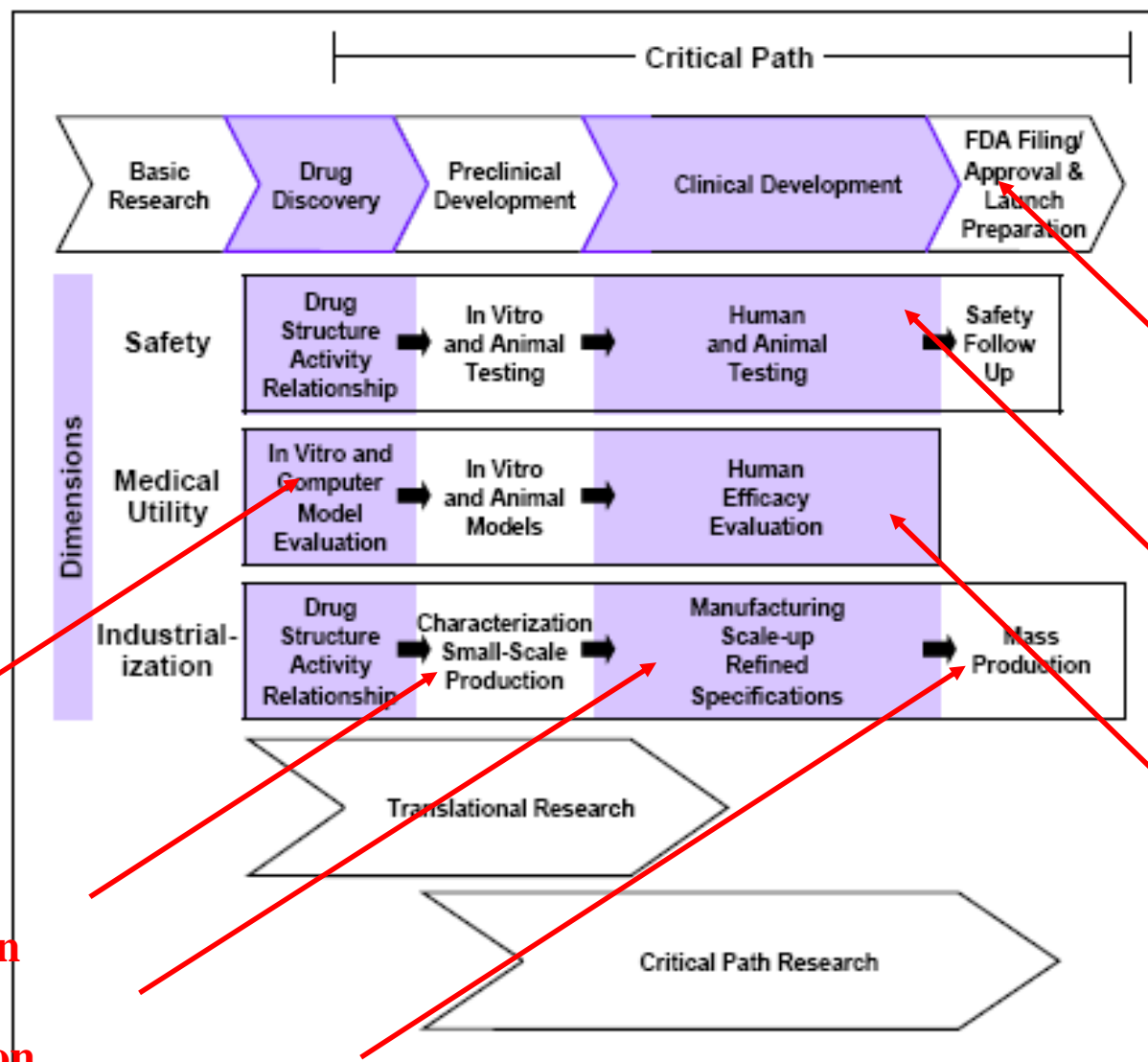
□ Bicarbonates



Dissolution and in vivo predictability



Dissolution and in vivo predictability

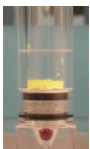
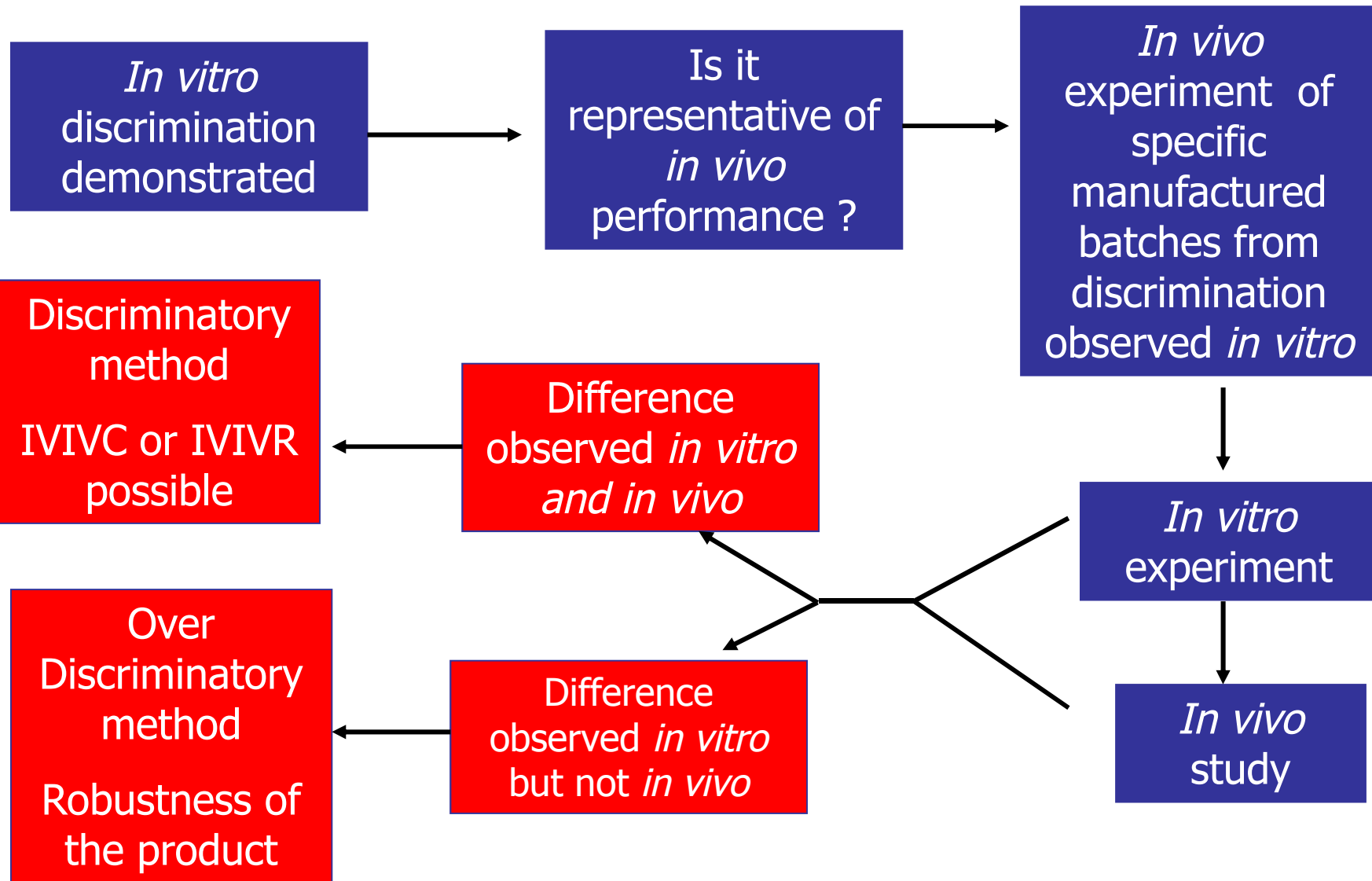


Biowaiver

Prediction

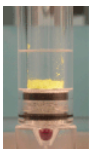
Formulation
-design
-optimization

Dissolution and in vivo predictability



Dissolution and in vivo predictability

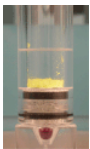
- ❑ **IVIVC**: “**quantitative**” linear mathematical model that is used to simulate in vivo data and for regulatory purposes like **biowaivers** (Ex level A In **vitro** **dissolution** vs **absorption curve**)
- ❑ **IVIVR**: more a “**qualitative**” ranking between in vitro and in vivo data that indicates qualitative tendencies and help in the identification of **key factors**. Ex quantity dissolved at xx minutes (linked with **coating thickness**) vs **Cmax**



Dissolution and in vivo predictability

□ Once relevance of dissolution test to clinical performance has been established

- Use to develop a specification which is meaningful versus safety and efficacy
- Use to guide further product development
- Use to test limits of design space
- Use to demonstrate bioequivalence

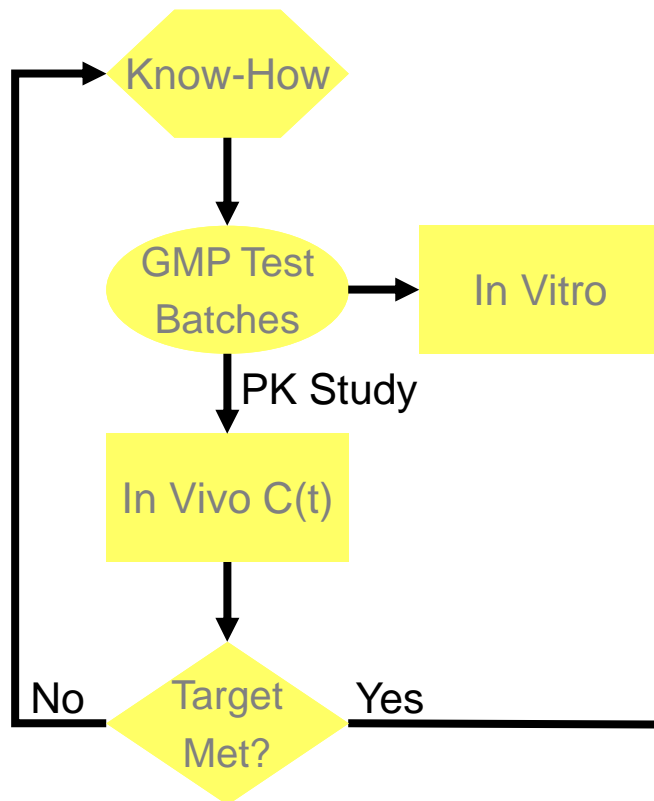


Quality by design and dissolution improve know how about formulation and critical points and optimize development

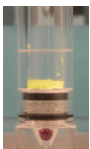
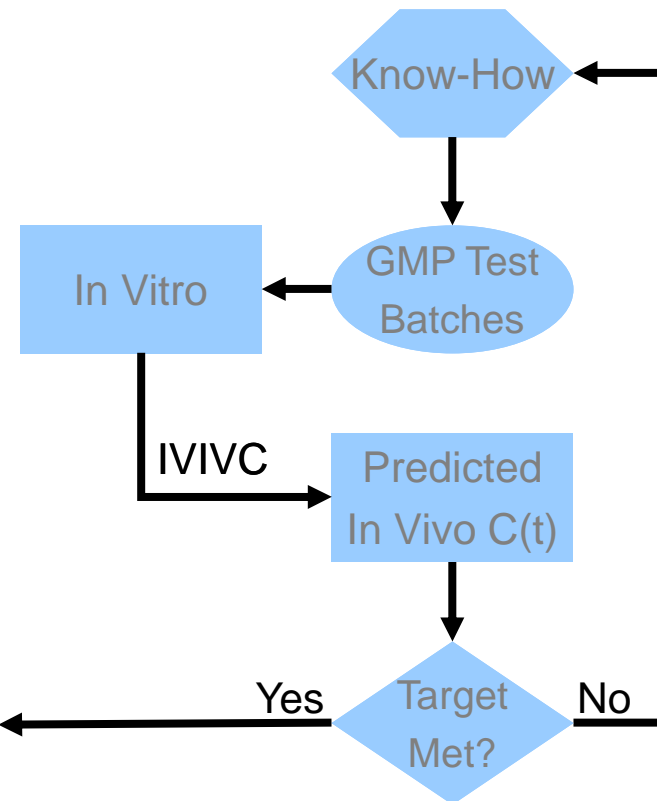
Dissolution and in vivo predictability

Pre- and Post-Approval Changes With and Without an IVIVC

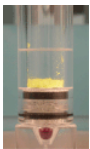
Without IVIVC



With IVIVC



CONCLUSION



❑ In vitro dissolution is one of the most powerful test method for development and quality control

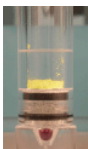
- Characterisation and selection of API
- Batch to batch consistency

❑ In vitro dissolution is one of the most important test method when developing a new dosage form.

- Investigation of drug release mechanism
- Establishment of in vitro in vivo correlation



❑ In vitro dissolution is a multivariate and quality by design approach should be made



Special Thanks to

❑ Research Team ERT CIDAM – Faculty of Pharmacy – Auvergne University – Clermont-Ferrand

❑ **sotax**



❑ **SPS**

Pharma Services

