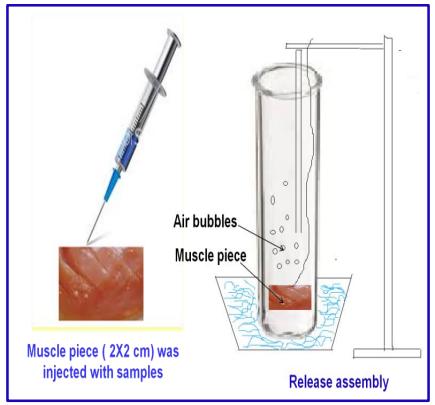
DISSOLUTION TESTING IN PRODUCT DEVELOPMENT



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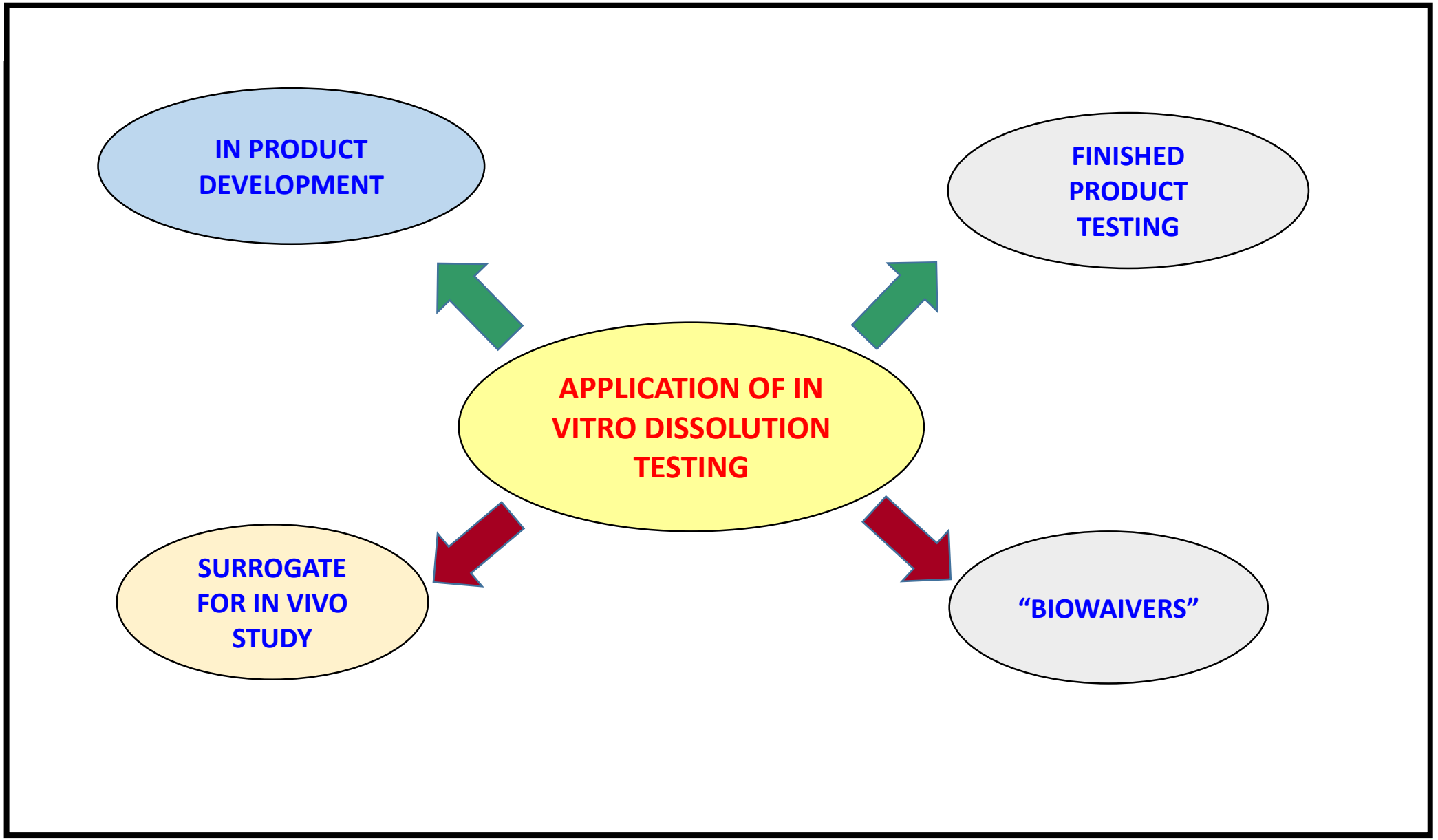
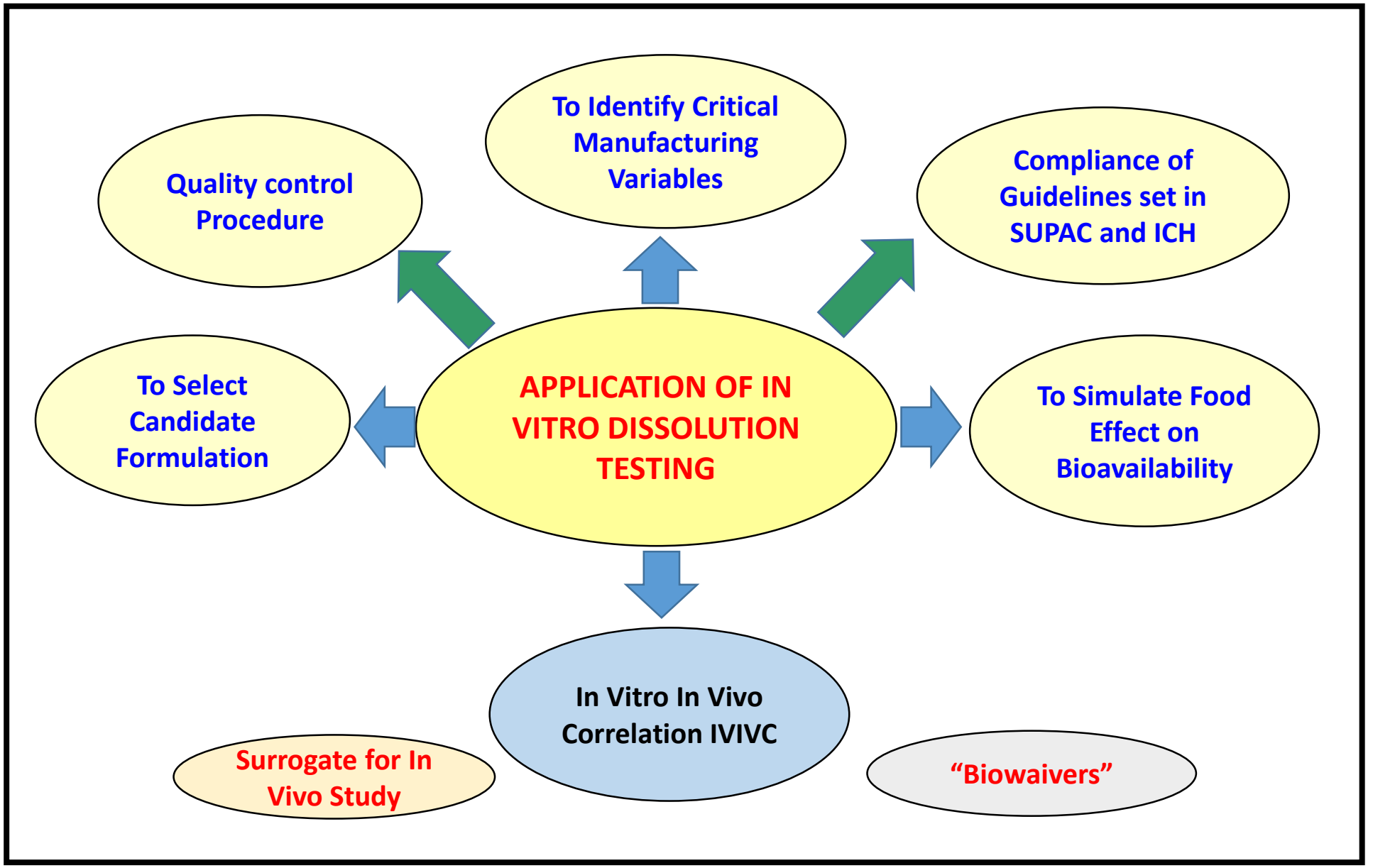
DISSO INDIA AHMEDABAD 2016- JULY 26-27


IN PRODUCT DEVELOPMENT
FINISHED PRODUCT TESTING
APPLICATION OF IN VITRO DISSOLUTION TESTING
SURROGATE FOR IN VIVO STUDY
“BIOWAIVERS”


To Identify Critical Manufacturing Variables
Quality control Procedure
Compliance of Guidelines set in SUPAC and ICH
To Select Candidate Formulation
APPLICATION OF IN VITRO DISSOLUTION TESTING
To Simulate Food Effect on Bioavailability
In Vitro In Vivo Correlation IVIVC
Surrogate for In Vivo Study
“Biowaivers”

GUIDING PRINCIPLES

Avoid unnecessary

- Proliferation of equipment
- Complex method design
- Modifications of compendial equipment
- Development or use of alternative equipment

PRODUCT DEVELOPMENT VS QUALITY CONTROL

Product Development

- Discriminating
- Focus on elucidating the release mechanism
- Attempt to simulate in vivo environment
- May be impractical for routine Quality control

Quality control

- Test the key performance indicators of the formulation
- Robust
- Reproducible

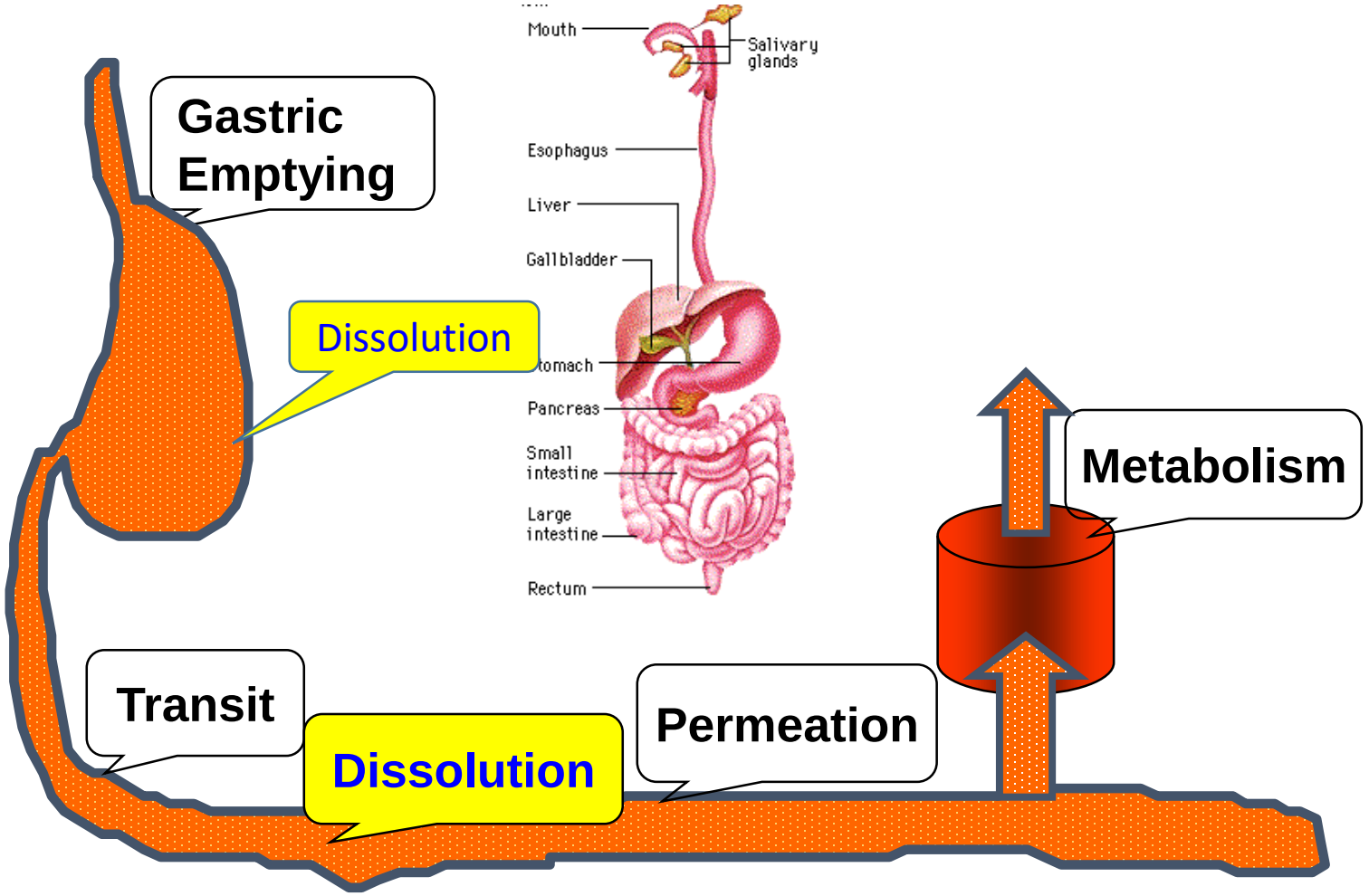
DISSOLUTION TEST CONSIDERATIONS

- Apparatus selection
- Agitation (HYDRODYNAMICS)
- Composition of the dissolution medium
- Temperature

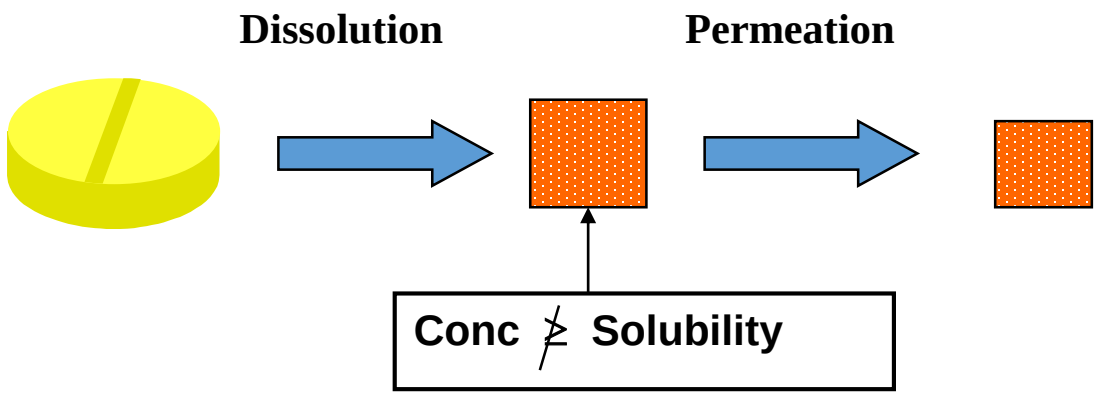
SUMMARY OF THE PRESENTATION

- Dissolution test Apparatus - Why so many
- Dissolution media - and test objective
- Release Kinetics Analysis
- Dosage Forms- Selection of optimal apparatus and conditions
- Case studies

ORAL DRUG ABSORPTION



IN VIVO AND *IN VITRO* RELATIONSHIP



LIMITS TO ORAL DRUG ABSORPTION

- **DISSOLUTION LIMITED**
- SOLUBILITY LIMITED
- PERMEABILITY LIMITED

LIMITS TO ORAL DRUG ABSORPTION

Rate-limiting Steps	Conditions	Comments
Dissolution limiting	T_{diss} > 199 min P_{eff} > 2 × 10^{-4} cm/sec D_{abs} >> Dose	The absolute amount of absorbed drug increases with the increased dose.
Permeability limiting	T_{diss} < 50 min P_{eff} < 2 × 10^{-4} cm/sec D_{abs} >> Dose	The absolute amount of absorbed drug increases with the increased dose.
Solubility limiting	T_{diss} < 50 min P_{eff} > 2 × 10^{-4} cm/sec D_{abs} < Dose	The absolute amount of absorbed drug does not increase with the increased dose.

(Yu, Pharm. Res. 16:1884-1888 (1999))

USP APPARATUS I & II

USP APPARATUS I

USP APPARATUS II

SINKERS

DRAWBACKS of USP APPARATUS I & II

USP Apparatus I

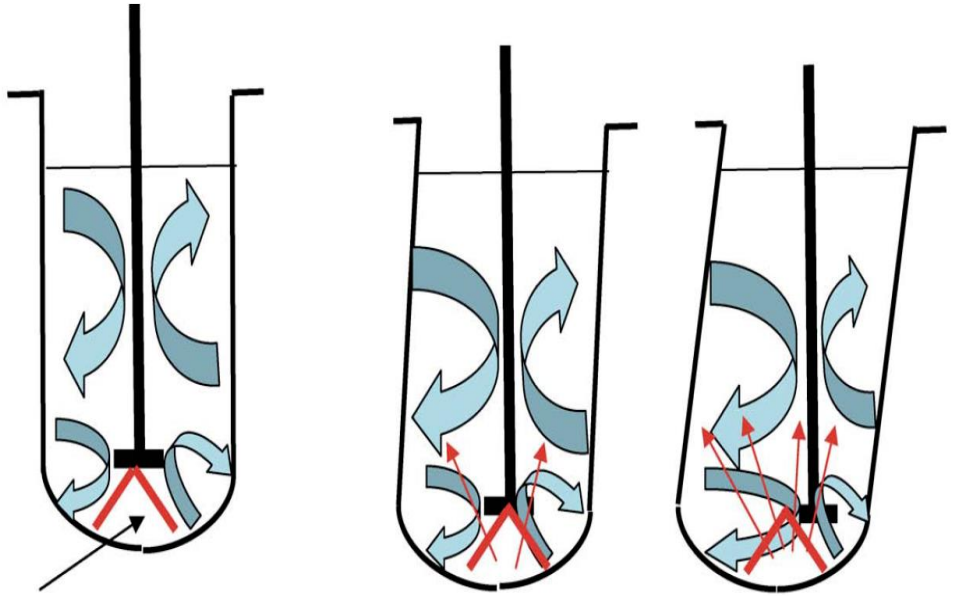
- Gummy substances clog basket screen
- Very sensitive to dissolved gases
- Inadequate flow characteristics for low and high density particles

USP Apparatus II

- Coning results in non homogeneity
- Tablet location in vessel affects dissolution results
  Hydrodynamic variability
- Size and shape of sinkers can disturb the cone – erratic results

Maintain Sink Condition ?????

OVERCOMING CONING



Schematic of perturbation study demonstrating the existence of dead zone at the bottom of the USP vessel

Peak Vessel

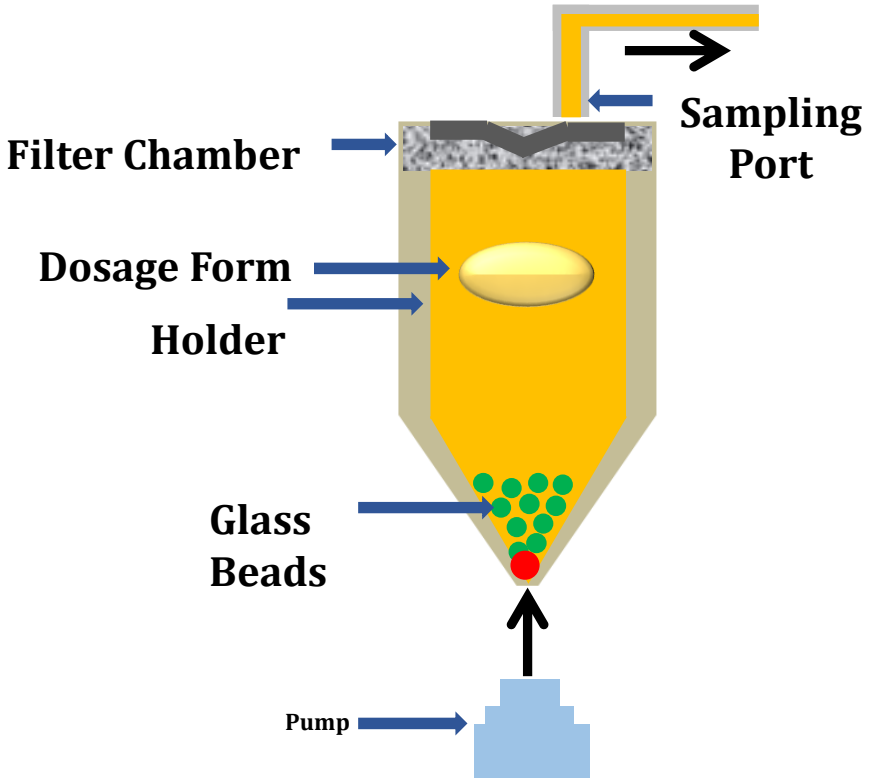
MAINTAINING SINK CONDITIONS

Ct <<<0.15Cs

STRATEGIES TO INCREASE DISSOLUTION MEDIUM VOLUME

MAINTAINING SINK CONDITIONS
USP APPARATUS-IV - *FLOW THROUGH*

MECHANISM OF FLOW THROUGH CELL



IDEAL FOR DRUGS EXHIBITING POOR SOLUBILITY

HYDRODYNAMIC VARIABILITY

- Hydrodynamics in the USP apparatus II shows that the device is highly vulnerable to mixing problems that can affect testing performance and consistency.

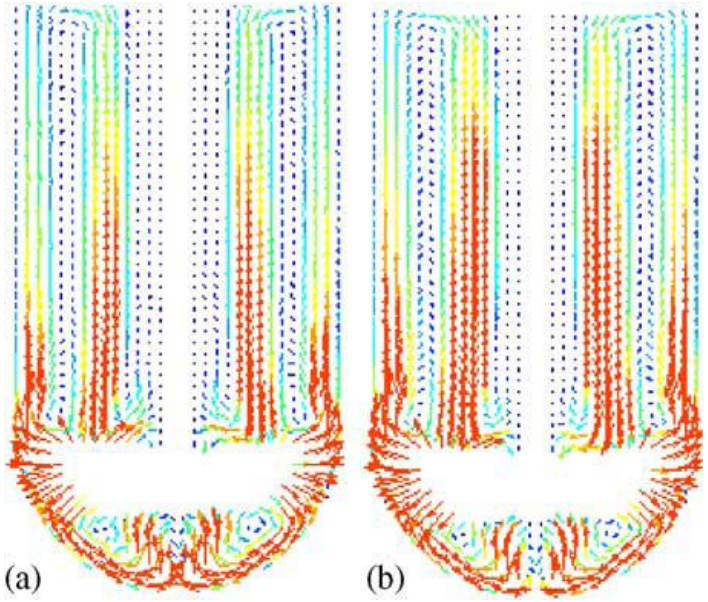


Fig. 1. Two-dimensional, time-averaged CFD velocity fields for (a) *Re = 4688, and (b) Re = 9375.*

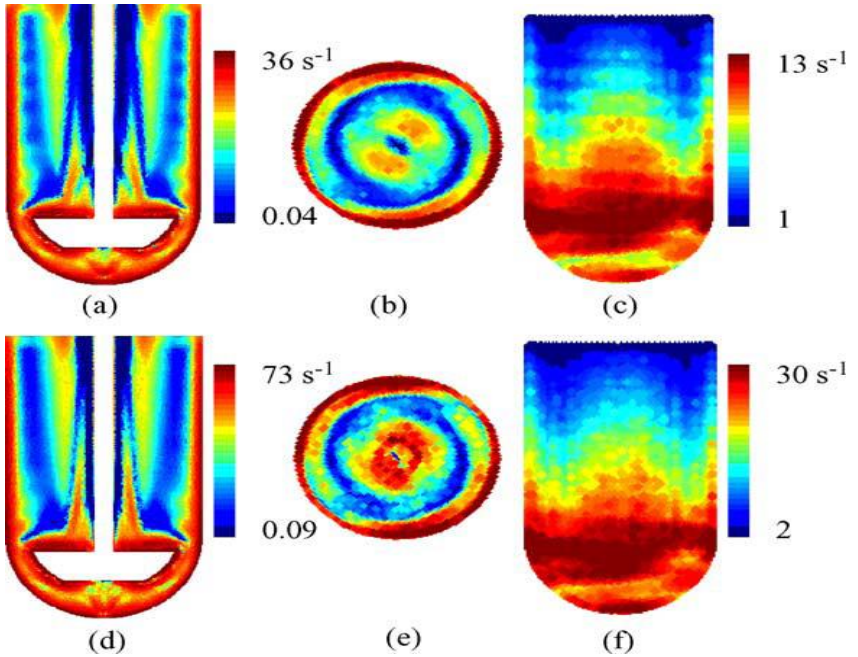
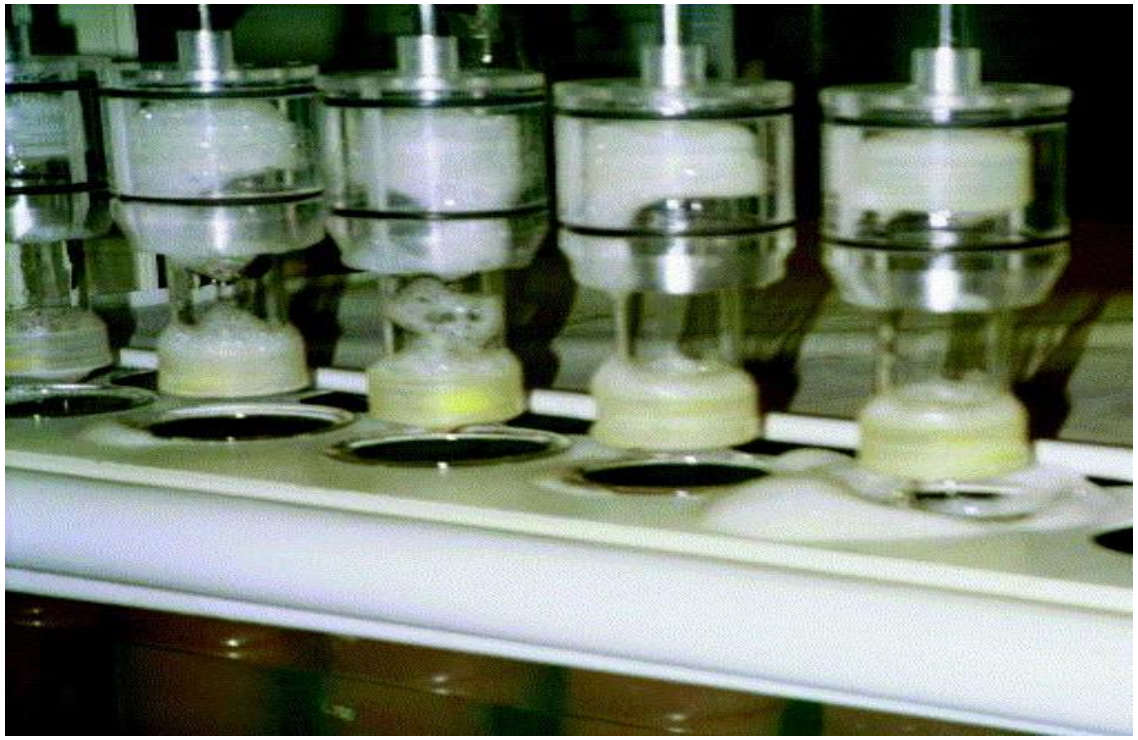


Fig. 2. Distribution of strain rates for *Re = 4688 (a) in the fluid, (b)* along the wall, depicted from a bottom view of the dish, (c) along thewall, depicted from a side viewof the entire vessel; and for *Re = 9375,*(d) in the fluid, (e) along the wall, depicted from a bottom view ofthe dish, (f) along the wall, depicted from a side view of the entire
vessel.

USP APPARATUS-III
RECIPROCATING CYLINDER



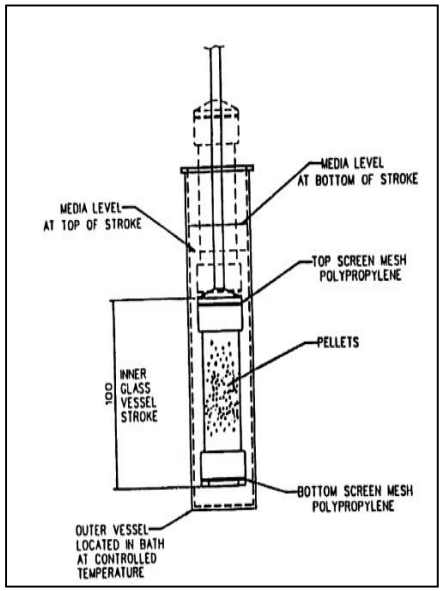
ALTERING HYDRODYNAMICS

USP DISSOLUTION APPARATUS VII

THE NEED FOR USP APPARATUS III & VII

HYDRODYNAMICS

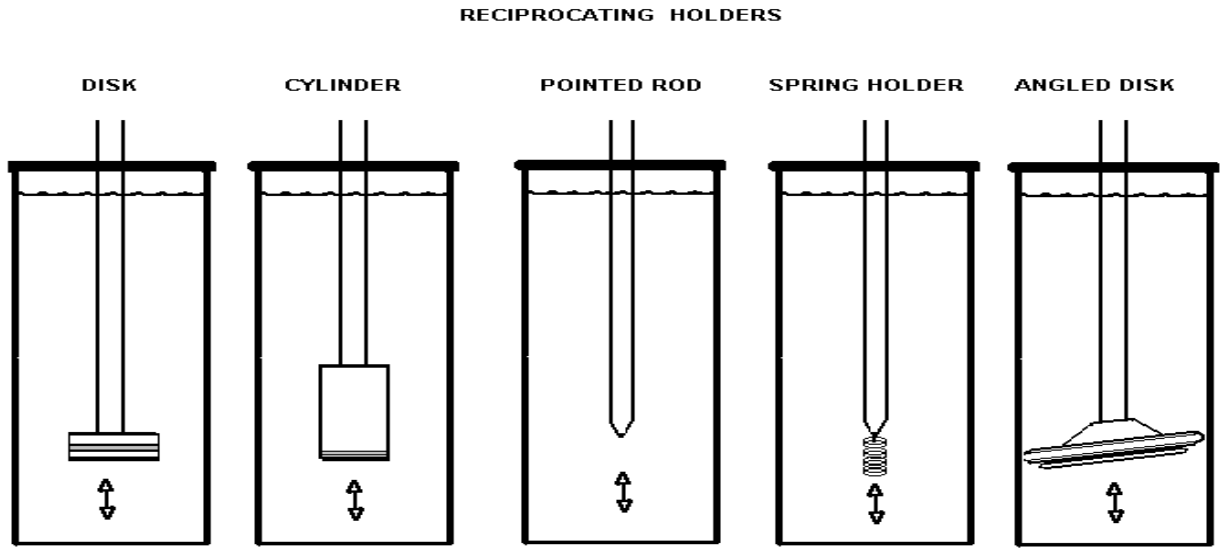
USP APPARATUS-III
RECIPROCATING CYLINDER



USP Apparatus 7
Reciprocating Holder

Useful for:
Transdermal Patches
Solid Dosage
pH Profile
Small Volume

Modifications:
Volume 20 - 200ml
Dosage Form Holder



Mimics changes in physiochemical conditions and mechanical forces experienced by products in the GIT

USP APPARATUS-III & VII

Also facilitate sequential alteration of

- pH
- Osmolarity
- Anions, cations
- Viscosity
- Buffers
- Surface active agents
- Degree of agitation

TO HELP ACHIEVE THE GOAL OF IVIVC

DISSOLUTION MEDIUM

MEDIA TO SIMULATE THE FASTED AND FED STATE

- **Water**
- **Compendial Dissolution Media**
- **Simulated Gastric Fluid**
- **Simulated Intestinal Fluid**
- **Compendial Media Simulating the Fed State**

AQUEOUS BUFFERS

SIMULATE

pH conditions in the stomach or small intestine

DO NOT REPRESENT

Composition of the GI contents

Osmolarity, Ionic strength, Viscosity, Surface tension

CANNOT SIMULATE

The influence of food ingestion on drug release

BIORELEVANT MEDIA

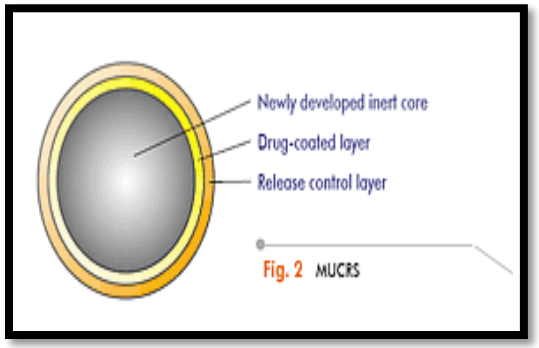
- ✓Useful for qualitative forecasting of formulation and food effects
- ✓Can provide a more accurate simulation of pharmacokinetic profiles
- ✓Have a great impact on the pharmacokinetic studies performed to optimize dosing conditions and product formulation
- ✓Could be used to assess bioequivalence of post-approval formulation changes in certain kinds of formulations

BIORELAVANT MEDIA FOR GASTRIC FLUID

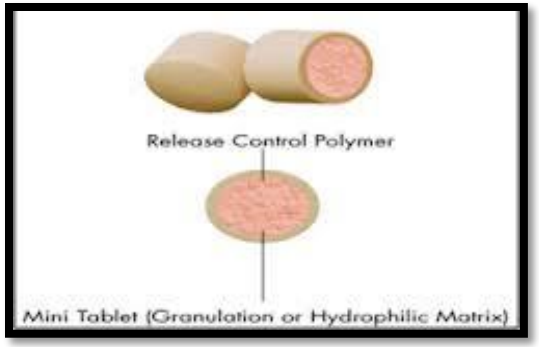
FaSSGF pH 1.6		FeSSGF pH 5	
Sodium taurocholate	80 µM	NaCl	237.02 mM
Lecithin	20 µM	Acetic acid	17.12 mM
Pepsin	0.1 mg/ml	Sodium acetate	29.75 mM
NaCl	34.2 mM	Milk / acetate buffer	1:1
HCl conc. qs ad	pH 1.6	HCl conc. qs ad	pH 5.0
Deionized water ad	1 l	Deionized water ad	1 l
pH	1.6	pH	5.0
Osmolality (mOsmol/kg)	120.7 ± 2.5	Osmolality (mOsmol/kg)	400
Buffer capacity (mEq/pH/L) –		Buffer capacity (mEq/pH/L)	25
Surface tension (mN/m)	42.6		

BIORELAVANT MEDIA INTESTINAL FLUID

FeSSIF		FaSSIF	
Sodium taurocholate	3 mM	Sodium taurocholate	15 mM
Lecithin	0.75 mM	Lecithin	3 mM
NaH_2PO_4	3.438 g	Acetic acid	8.65 g
NaCl	6.186 g	NaCl	11.874 g
NaOH pellets	qs ad pH 6.5	NaOH pellets	4.04 g
Deionized water	qs ad 1 litre	Deionized water	qs ad 1 litre
pH	6.5	pH	5.0
Osmolality [mOsmol/kg]	~ 270	Osmolality [mOsmol/kg]	~ 670
Buffer capacity [mEq/pH/L]	~ 12	Buffer capacity [mEq/pH/L]	~ 72
Surface tension [mN/m]	54	Surface tension [mN/m]	48

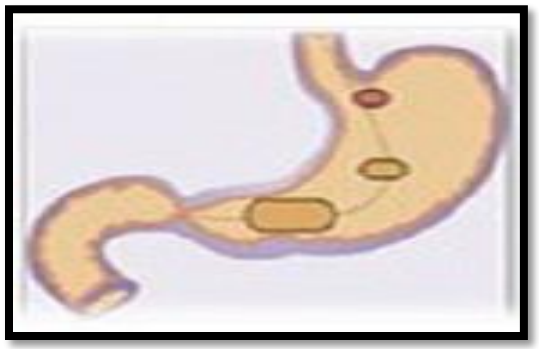


MUCRS

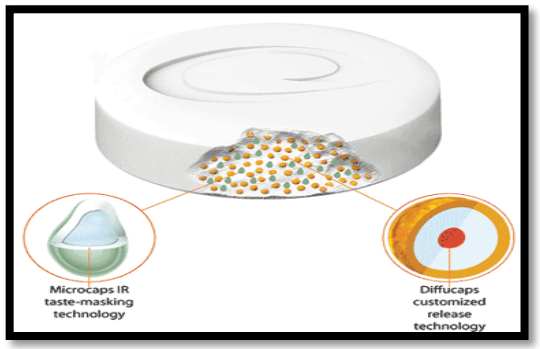


Minitab®

RINGCAP TECHNOLOGY

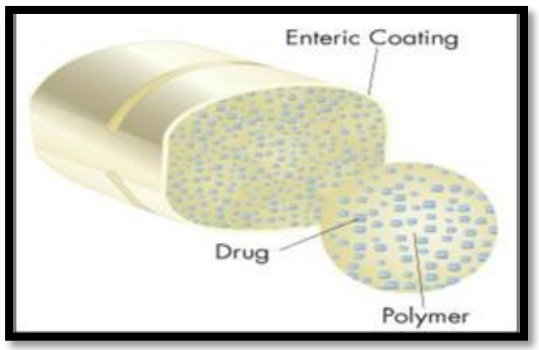


ADVANCED ORAL DDS



AdvaTab® (ODT)

OSDRC® OptiDose™



Diffutab™

NOYES-WHITNEY EQUATION

$$\frac{dC}{dt} = \frac{DS}{Vh}(Cs\text{-}Ct) \quad \text{.....} \quad \text{Noyes \& Whitney equation}$$

- ✓ dC/dt — Rate of dissolution
- ✓ S — Surface area
- ✓ (Cs-Ct) — Concentration driving force.
- ✓ Cs — Equilibrium solubility of the solute at the experimental temperature.
- ✓ Ct — Concentration at time t
- ✓ V — Volume of the dissolution medium
- ✓ D — Diffusion coefficient
- ✓ h — Diffusion layer thickness

KINETICS OF DRUG RELEASE FROM CONTROLLED RELEASE FORMULATION

- **Statistical methods** :

1. Exploratory data analysis method
2. Repeated measures design
3. Multivariate approach [MANOVA: multivariate analysis of variance]

- **Model dependent methods:**

1. Zero order
2. First order
3. Higuchi
4. Korsmeyer – Peppas
5. Hixson Crowell
6. Baker-Lonsdale
7. Weibull
8. Gompertz
9. Hopfenberg

- **Model independent methods:**

1. Difference factor(f_1)
2. Similarity factor (f_2)

APPLICATION ZERO-ORDER MODEL

- ✓This relationship can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs in coated forms, osmotic systems, etc.

FIRST ORDER MODEL

This is used to describe absorption and/or elimination of some drugs.

$$dC/dt = -Kc$$

Where;

K is first order rate constant expressed in units of time-1.

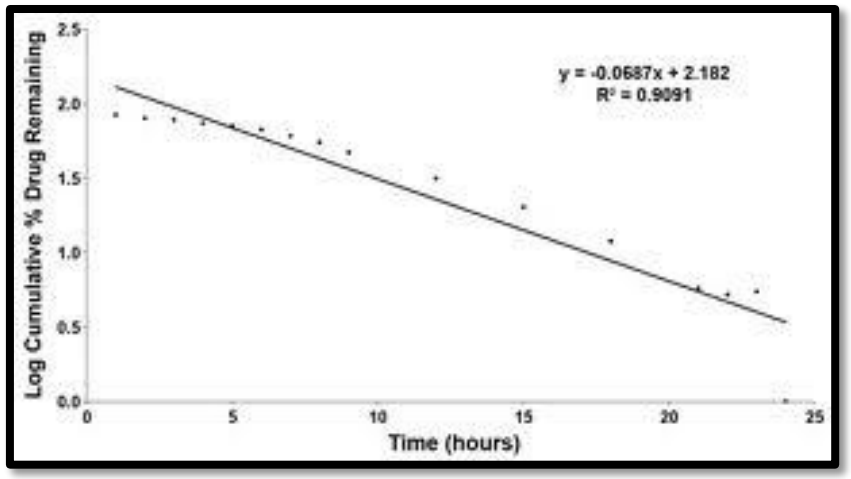
Equation can be expressed as:

$$\log C = \log C_0 - Kt / 2.303$$

Where;

C_0 is the initial concentration of drug,

k is the first order rate constant, and **t** is the time .



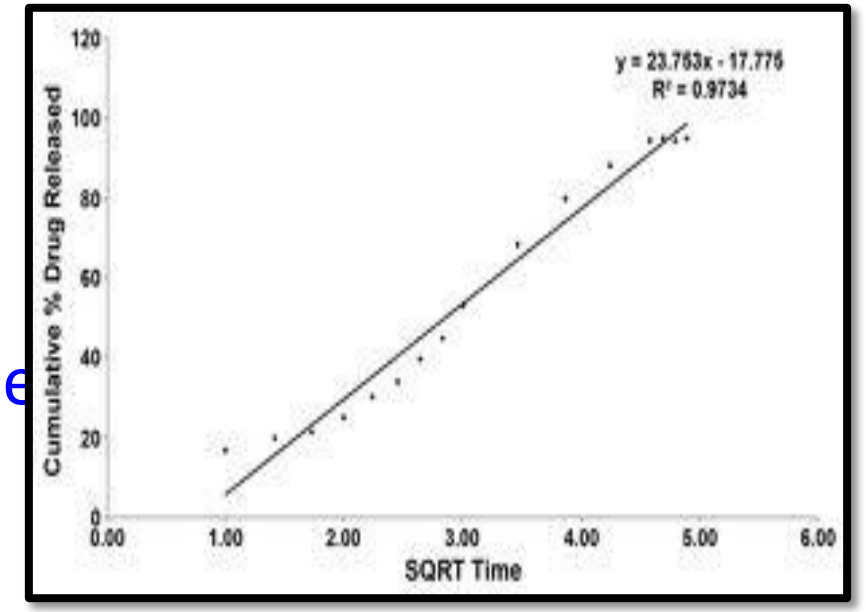
- **Note:**

  The data obtained are plotted as log cumulative percentage of drug remaining *vs. time which would yield a* straight line with a slope of -K/2.303.

This relationship can be used to describe the drug dissolution in pharmaceutical dosage forms such as those containing water-soluble drugs in porous matrices.

HIGUCHI MODEL

$$f_t = Q = \sqrt{D\delta/\tau(2C - \delta Cs)\, Cs\, t}$$



Where,

- ✓D is the diffusion coefficient of the drug molecule the solvent.
- ✓δ is the porosity of the matrix.
- ✓τ is the tortuousity of the matrix.

To study the dissolution from a planar heterogeneous matrix system, where the drug concentration in the matrix is lower than its solubility and the release occurs through pores in the matrix, the expression is given by equation.

KORSMEYER- PEPPAS MODEL

Korsmeyer et al. (1983) derived a simple relationship which described drug release from a polymeric system equation.

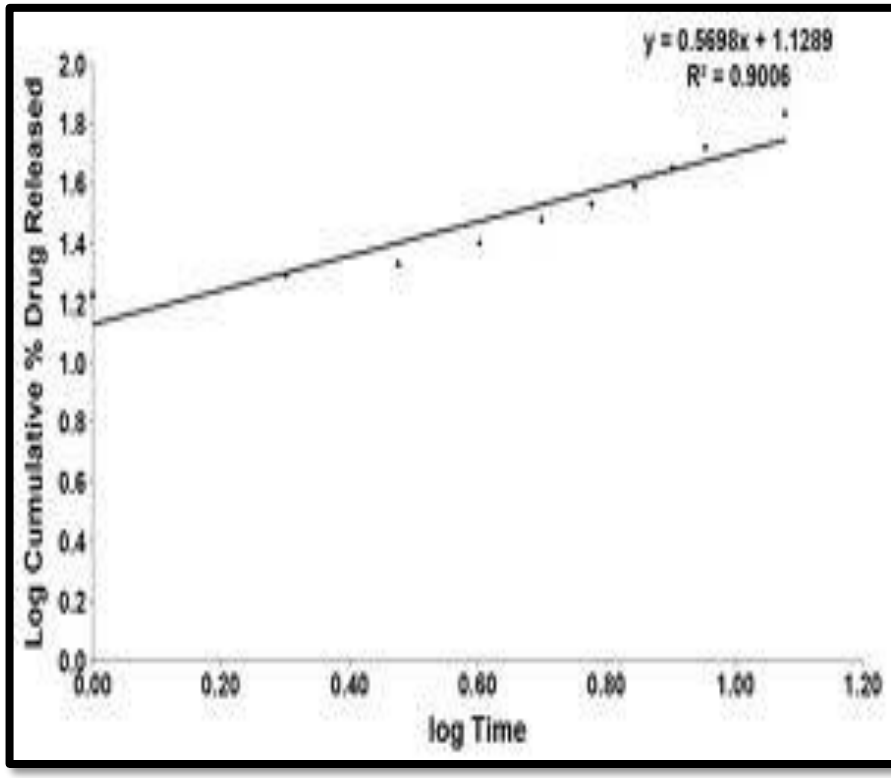
$$M_t / M_\infty = Kt^n$$

where;

M_t / M_∞ is a fraction of drug released at time t,

k is the release rate constant and n is the release exponent.

n value is used to characterize different release for cylindrical shaped matrices



- ✓ 0.45 ≤ n corresponds to a Fickian diffusion mechanism.
- ✓ 0.45 < n <0.89 to non-Fickian transport.
- ✓ n = 0.89 to Case II (relaxational) transport.
- ✓ n > 0.89 to super case II transport.

This equation has been used to the linearization of release data from several formulations of microcapsules or microspheres.

MODEL INDEPENDENT APPROACH

For comparison of in vitro dissolution profiles, similarity and difference factors are emphasized by US FDA.

➢ Similarity Factor (f_2):

- ✓ The similarity factor should be between 0 and 100.
- ✓ It is 100 when two comparative groups of reference and test are identical and approaches 0 as the dissimilarity increases
- ✓ Similarity factor $\geq$ 50 indicates comparable profiles

➢ Difference factor (f1)

- ✓ F1$\leq$ 15 indicates similarity in profiles

- ☑ The dissolution profiles can be compared only when number of dissolution units used are equal to or greater than 12. The similarity factor should be computed from the average mean dissolution data of 12 units. The mean data for comparison can be used only if the coefficient of variation at the first time point is NMT 20%, and NLT 10% at the rest of time intervals.
- ☑ For accurate calculation of similarity factor, statistical approach of establishment of confidence intervals, to determine whether the reference and test are statistically significant or not may be used.

DISSOLUTION TESTING FOR VARIOUS FORMULATIONS

- Suspensions
- Orally disintegrating tablets
- Chewable tablets, Chewing gums
- Transdermal patches
- Semisolid topical preparations
- Suppositories
- Implants

ORAL SUSPENSIONS

- APPARATUS -USP II
- Method
- Shaking or mixing.
- Sample introduction-
  - accurate, precise, and reproducible
- Agitation Rate
  - on the basis of the viscosity and composition of the suspension matrix.
  - should facilitate discrimination between batches with different release properties.
  - For low-viscosity suspensions, A slow agitation rate of 25 rpm is generally
  - for high-viscosity samples faster agitation rate such as 50 or 75 rpm to prevent sample mounding at the bottom of the vessel

Ideally, sample weight/volume should reflect a typical dose of the product. However, testing a partial dose— for instance, ≥10% to 20% of the usual product dose—is recommended rather than using a surfactant TO MAINTAIN SINK

ODT

- **APPARATUS -USP II**
- **Method**
- **Agitation Rate**
  - Should facilitate discrimination between batches with different release properties.
  - 50RPM
  - Higher agitation rates may be necessary in the case of sample mounding.

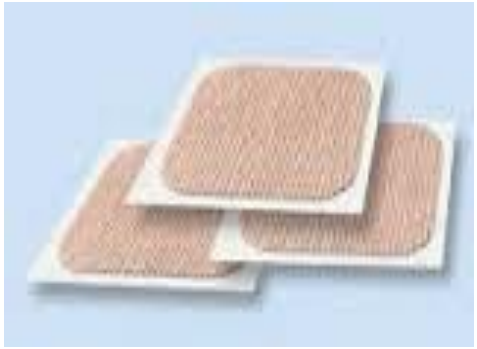
- **Disintegration test as substitute- Discriminating**
- **Taste Masking**
  - A dissolution criterion (typical example: ≤10% dissolved in 5 minutes) would largely depend on the taste intensity of the drug and may enable the in vitro evaluation of the taste-masking properties while avoiding organoleptic measurements.
  - Multipoint profile in neutral medium
- **Challenge**
  - Floating particles/granules

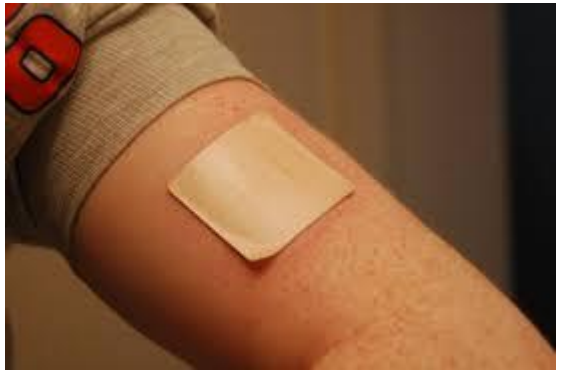
CHEWABLE TABLETS

- Same as that used for regular tablets.
- Based on the possibility that a patient might swallow the dosage form without proper chewing,
- The nondisintegrating nature of the dosage form, it may be necessary to increase the agitation rate and increase the test duration
- The reciprocating cylinder (USP apparatus 3) with the addition of glass beads may also provide more "intensive" agitation
- Mechanical breaking of chewable tablets prior to exposing the specimen to dissolution testing could be considered

TRANSDERMAL

Transdermal Patches

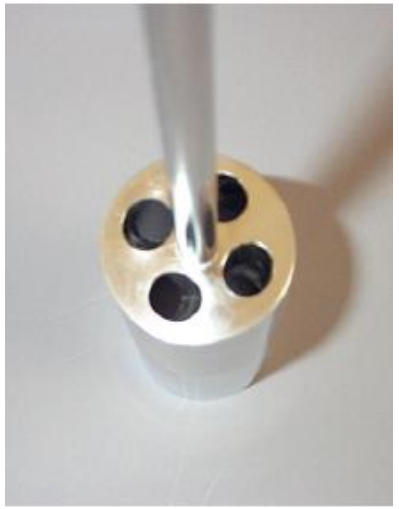


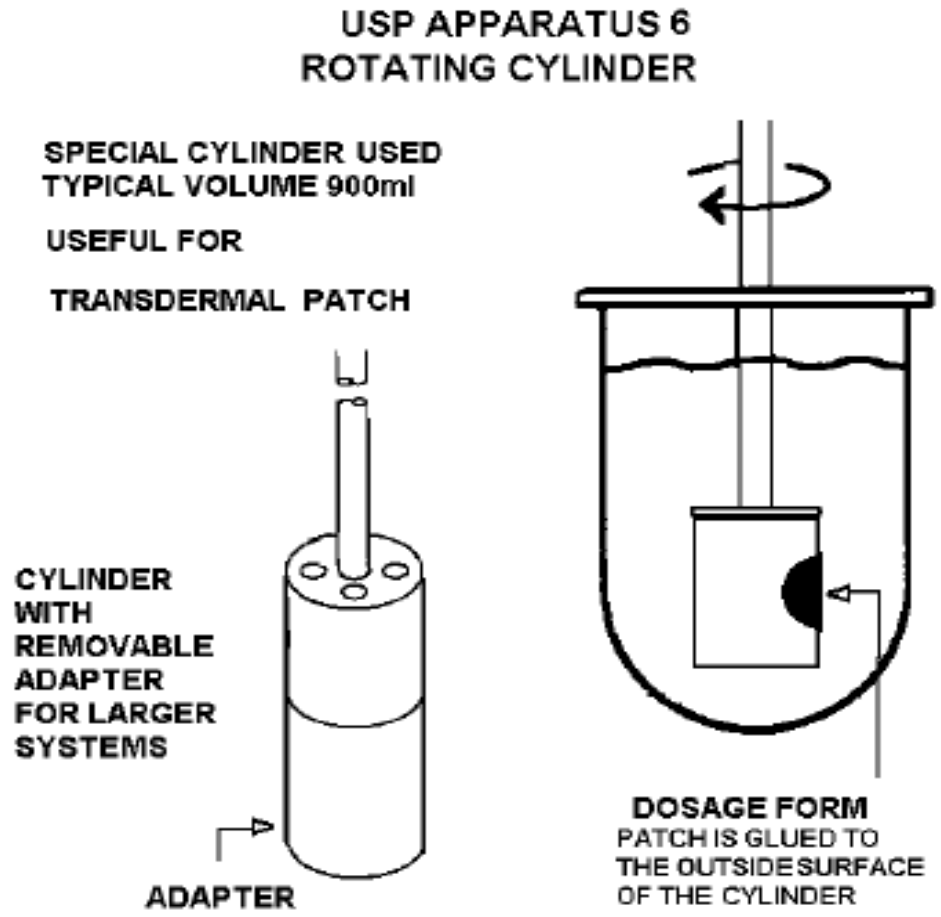


USP APPARATUS V
PADDLE OVER DISK

A distance of 25 ± 2mm between the paddle blade and the surface of the disc assembly is maintained during the test.
Temperature: 32+0.5^{o}C

USP APPARATUS-VI
ROTATING CYLINDER





APPARATUS –VI

ROTATING CYLINDER

Carefully apply the adhesive-coated side of the system to the exterior of the cylinder with the long axis of the system fitting around the circumference of the cylinder.

USP APPARATUS-V
PADDLE OVER DISK

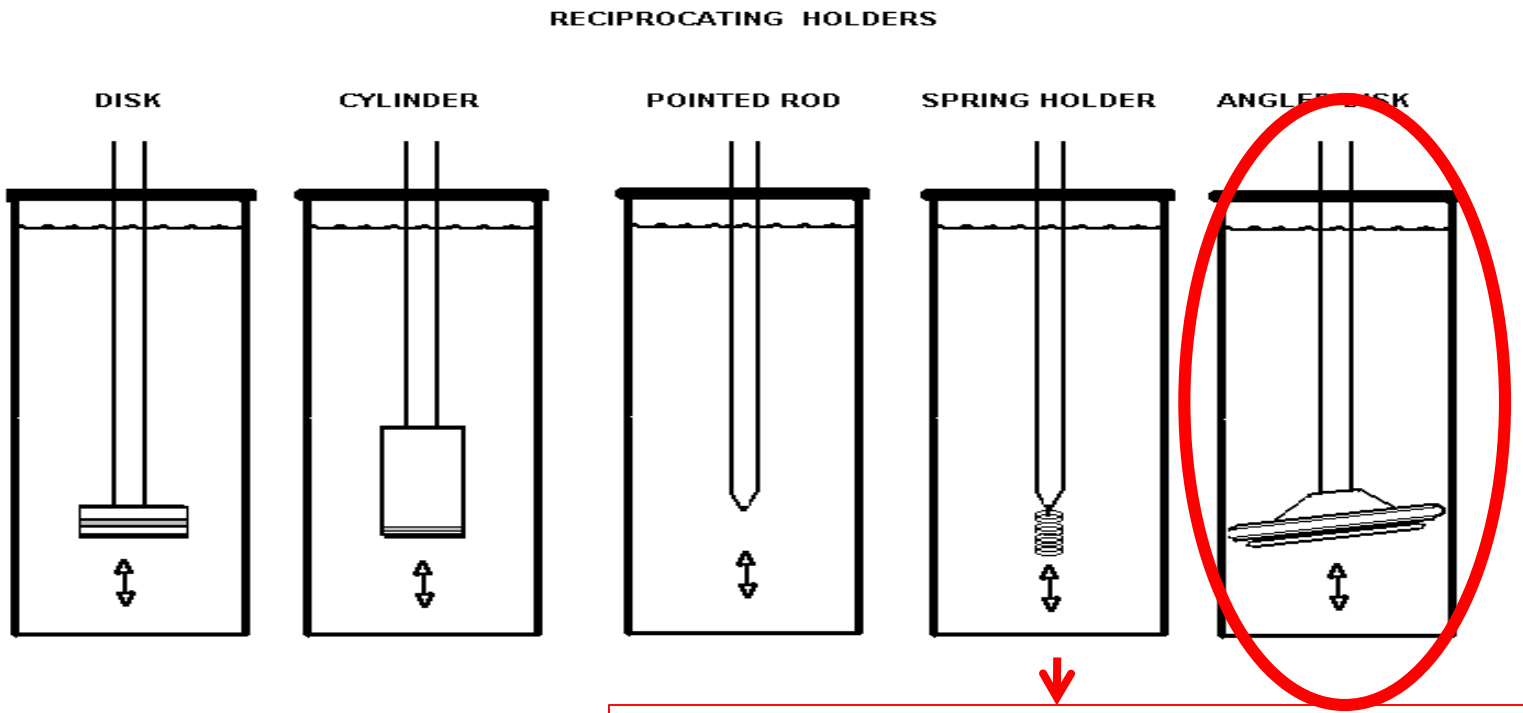
- Method of choice for transdermal patches
- Reproducible
- Patch is prevented from floating
- Proper positioning of the patch so that the drug-loaded surface is exposed to the medium.
- The medium pH 5 to 6, reflects physiological skin conditions
- Temperature is typically set at 32°C
- PhEur considers 100 rpm a typical agitation rate
- Also allows for testing an aliquot patch section (sink condition)
- Provided that cutting a piece of the patch is validated to have no impact on the release mechanism

APPARATUS VII
RECIPROCATING HOLDER

USP Apparatus 7
Reciprocating Holder

Useful for:
Transdermal Patches
Solid Dosage
pH Profile
Small Volume

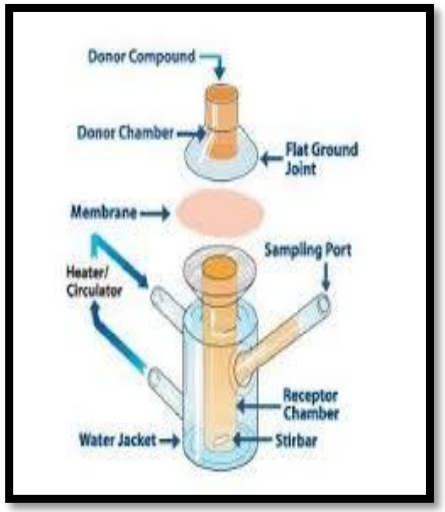
Modifications:
Volume 20 - 200ml
Dosage Form Holder

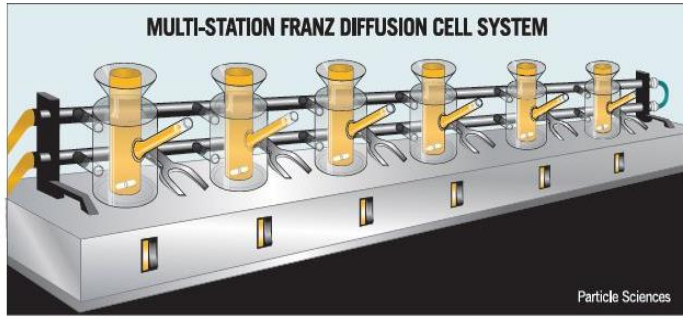


Spring may be replaced with a nylon mesh cloth

TOPICAL

- Creams, ointments, and gels.
- Franz cell diffusion system with a synthetic membrane with optional support membrane
- Receptor medium may need to contain alcohol and/or surfactant
- Deaeration is critical to avoid bubble formation at the interface with the membrane
- The test temperature is typically set at 32°C to reflect the usual skin temperature.
- Vaginal creams may be tested at 37°C.
- Full or partial dose rather than adding a surfactant or alcohol to the receptor medium in order to obtain sink conditions.
- No compendial apparatus, procedures, or requirements for in vitro release





SUPPOSITORIES

- For hydrophilic suppositories that release the drug by dissolving in the rectal fluids, the basket, paddle, or flow-through cell can all be used.
- For lipophilic suppositories
  - a modified basket method
  - a paddle method with a wired screen and a sinker
  - a modified flow-through cell with a specific dual chamber suppository cell have all been recommended.
  - No single test method will be suitable for all suppository formulations.
  - However, when starting development of an in vitro dissolution/release test, it might be advantageous to begin with the basket or paddle in the case of hydrophilic and with the modified flow-through cell in the case of lipophilic suppositories.

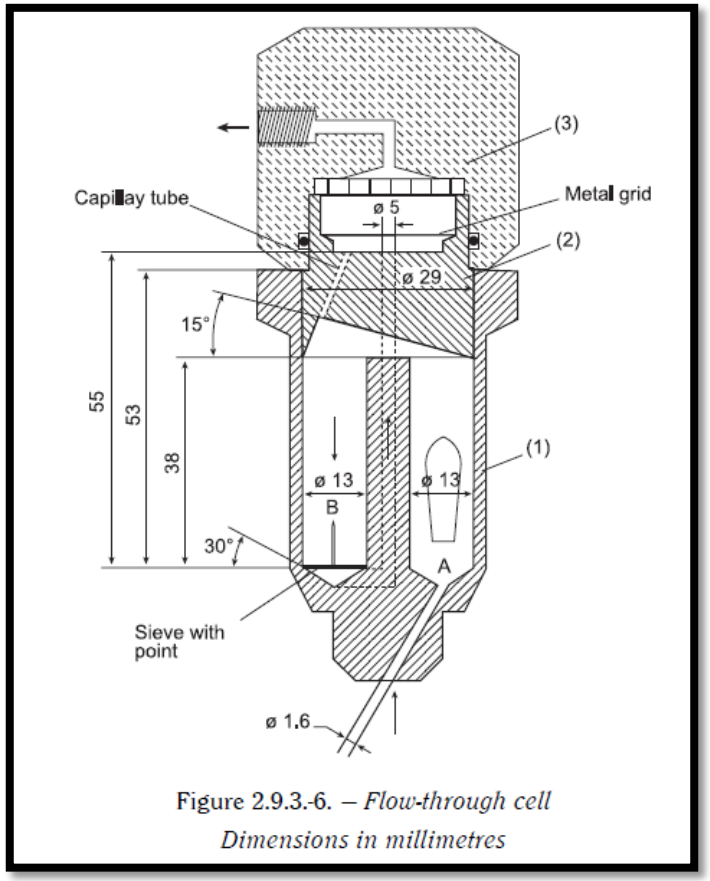
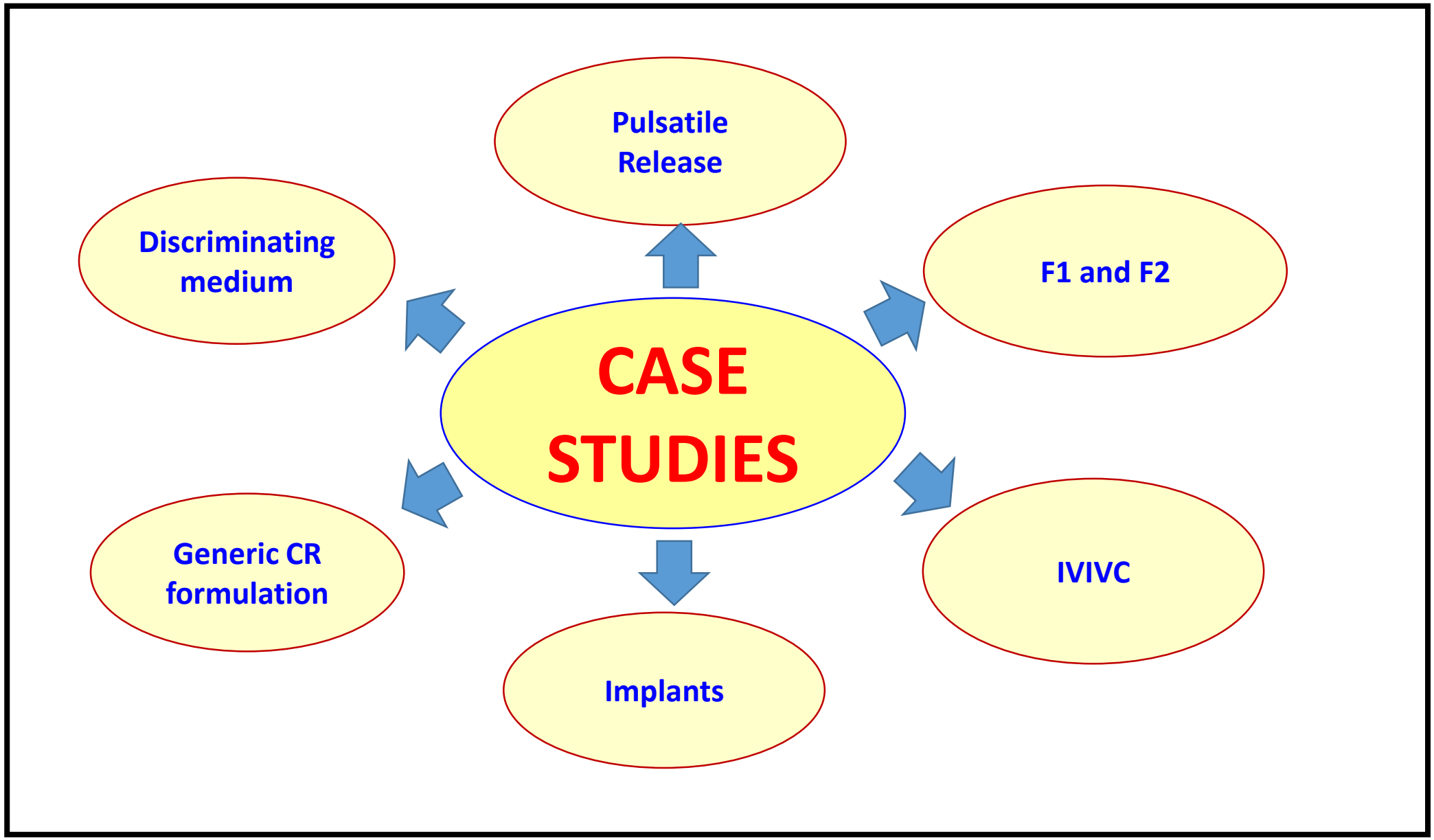


Figure 2.9.3.-6. – *Flow-through cell*
Dimensions in millimetres

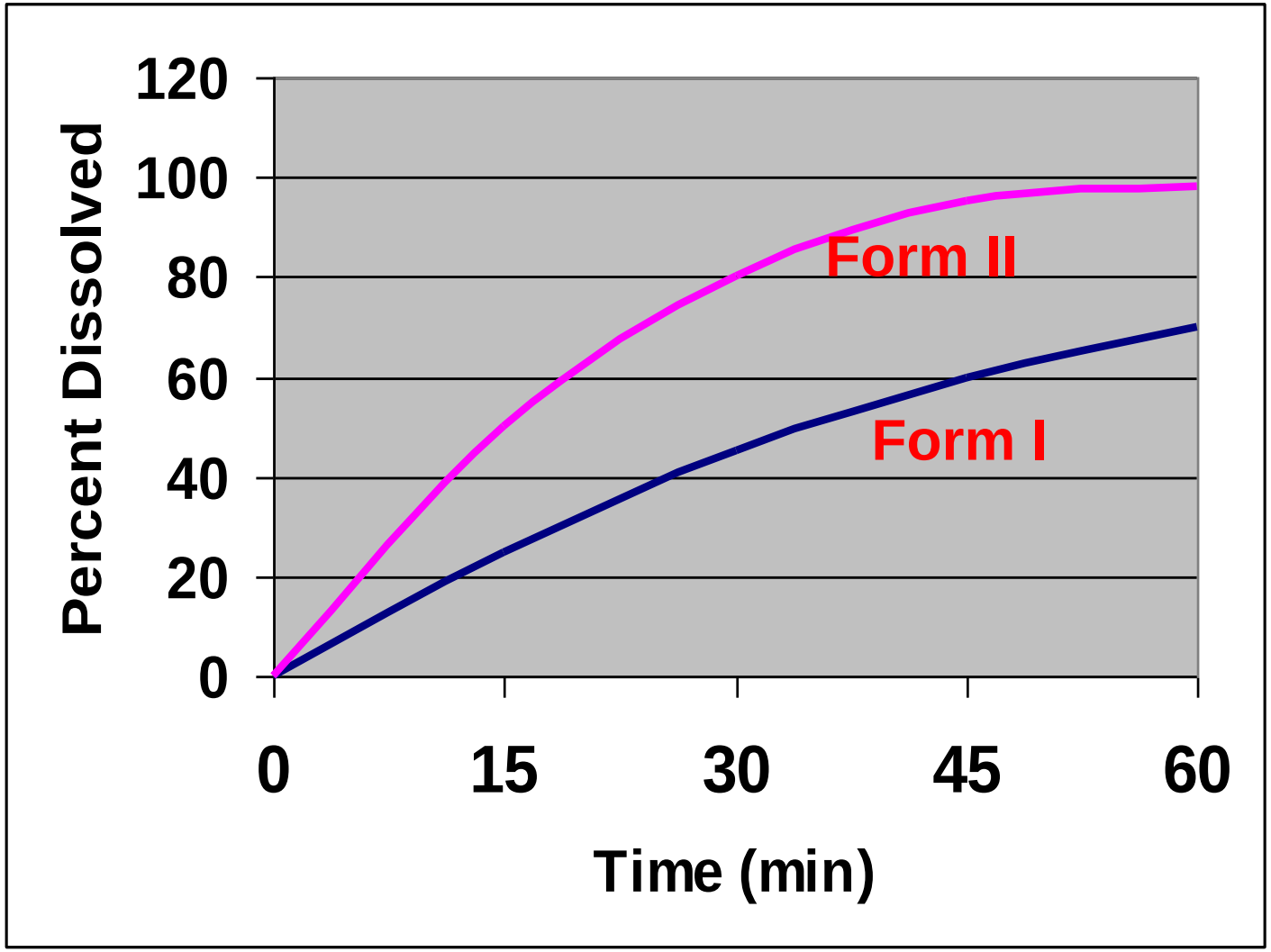
IMPLANTS

- The compendial and the modified flow-through cell have been used successfully for implants
- Static or rotating bottles have also been used for in vitro release testing.
- Flow-through apparatus with low volume of fluid , slow flow rate
- Intermittent flow might also be an option.
- As tests are often run over a long time period (eg, several weeks to months), measures have to be taken to compensate against evaporation.
- Suitable preservatives may be added to prevent microbial contamination
- The osmolarity, pH, and buffer capacity of the with lower buffer capacity.
- **Main challenges**
  - to determine the appropriate duration of the test
  - times at which samples are to be drawn
  - The possibility of running the test under accelerated conditions (temperatures even above glass transition temperatures of the polymers involved) and at pH values offering faster drug release

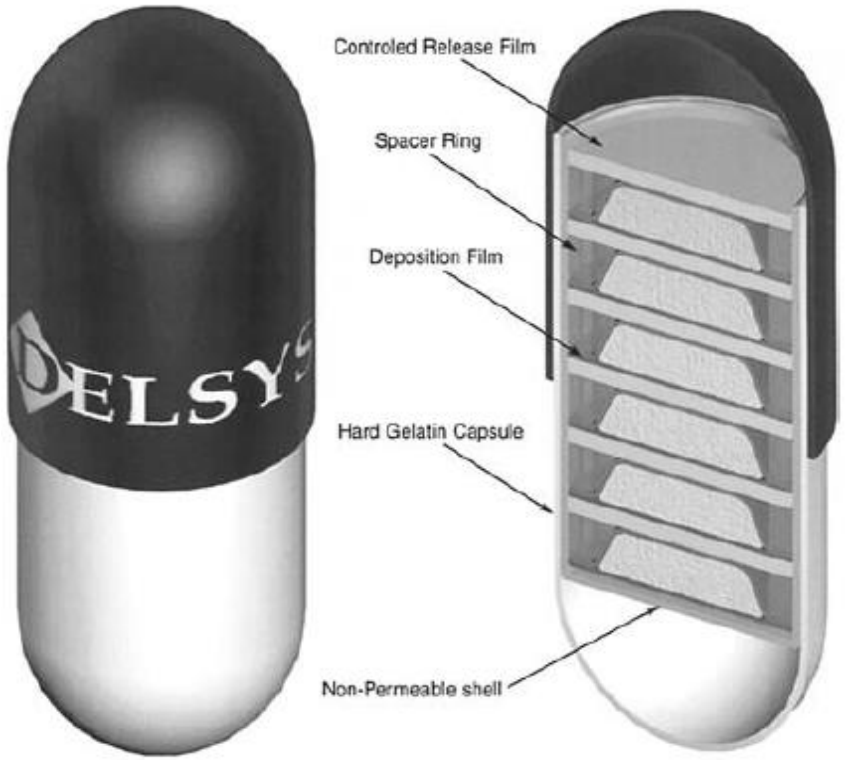

Pulsatile Release
Discriminating medium
F1 and F2
CASE STUDIES
Generic CR formulation
IVIVC
Implants

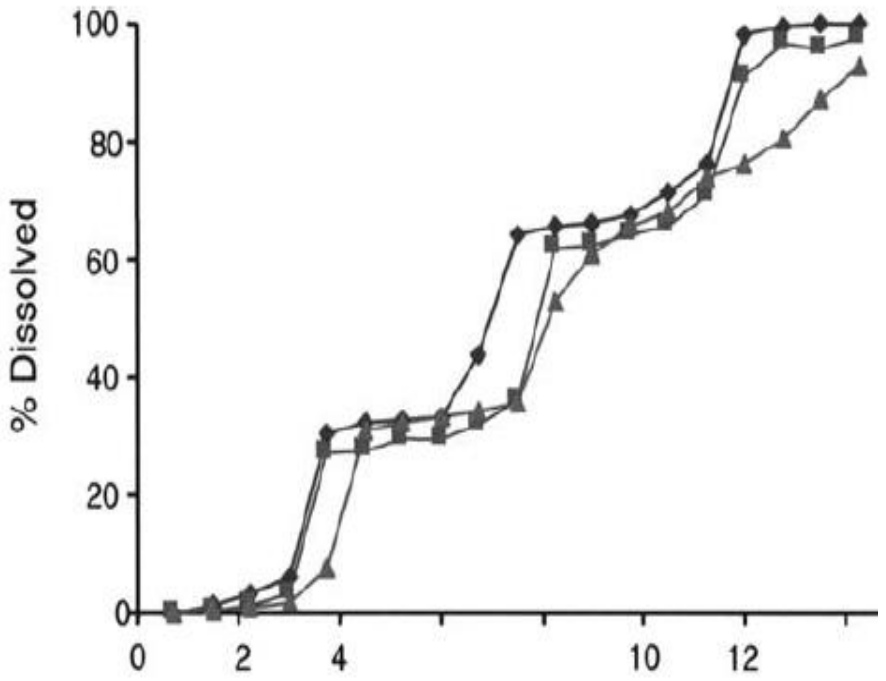
DISCRIMINATING MEDIUM

POLYMORPHS

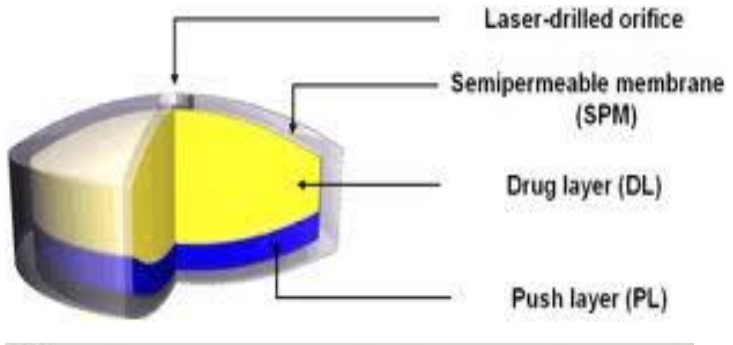


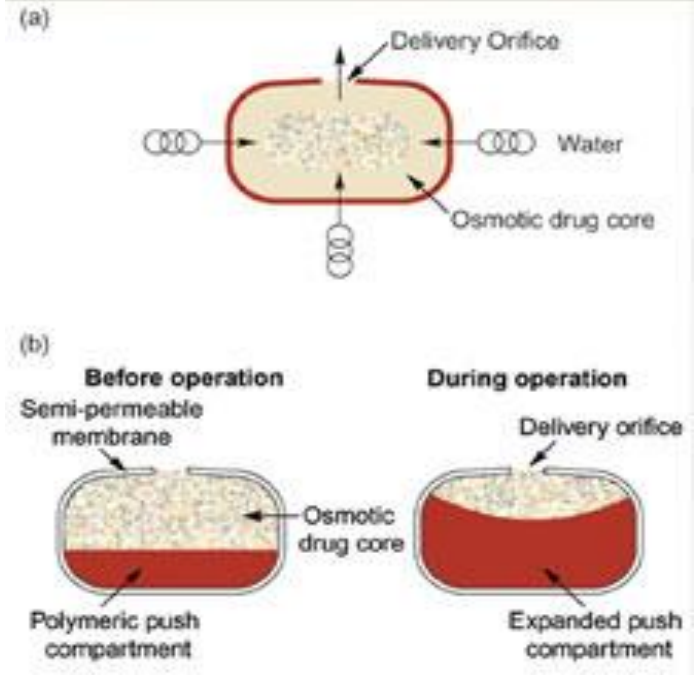
ACCUDEP - PULSATILE

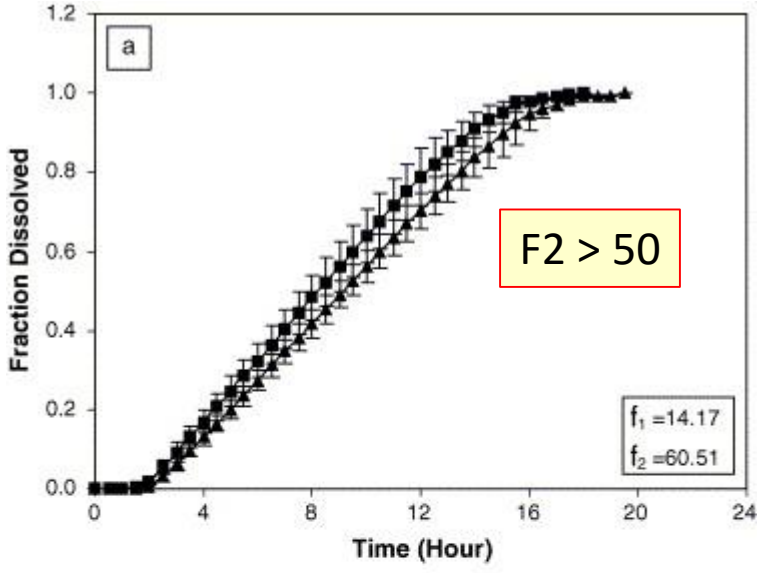


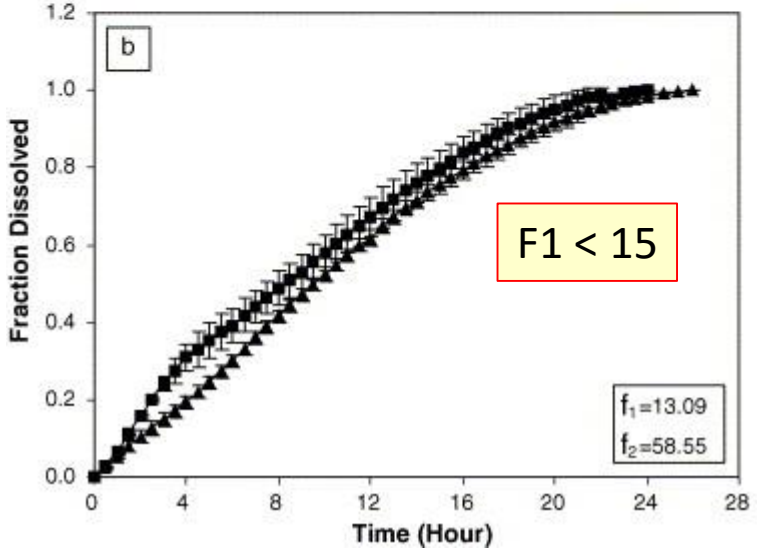


OSMOTIC DRUG DELIVERY SYSTEMS F1 AND F2



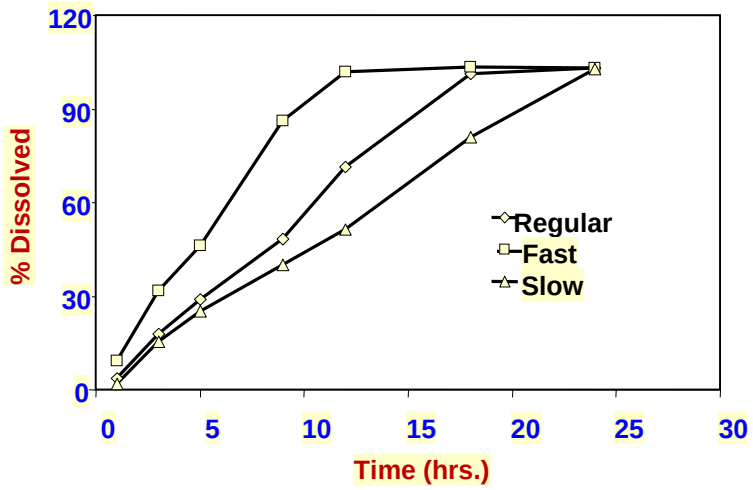




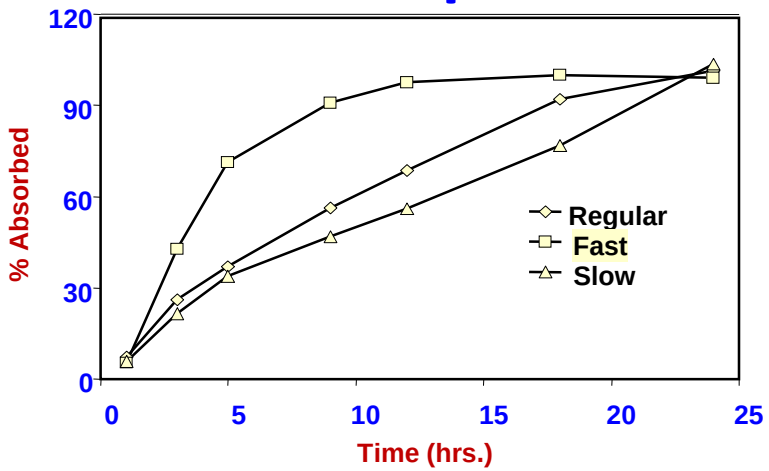


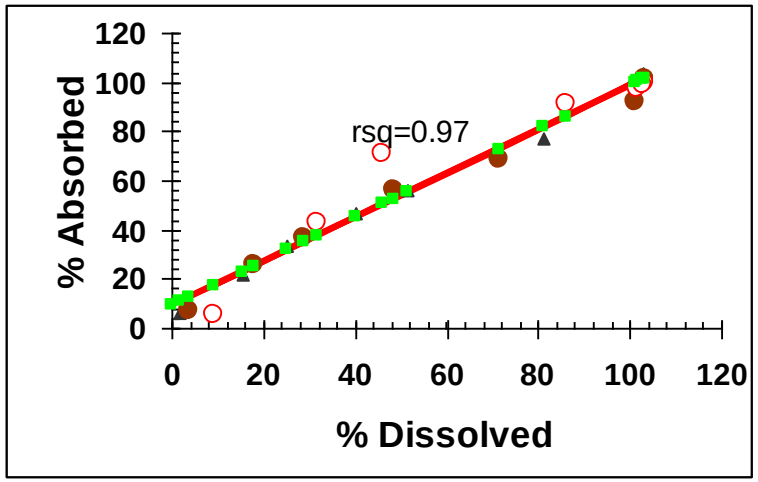
IN VIVO BIOEQUIVALENCE: IVIVC

Dissolution Profiles



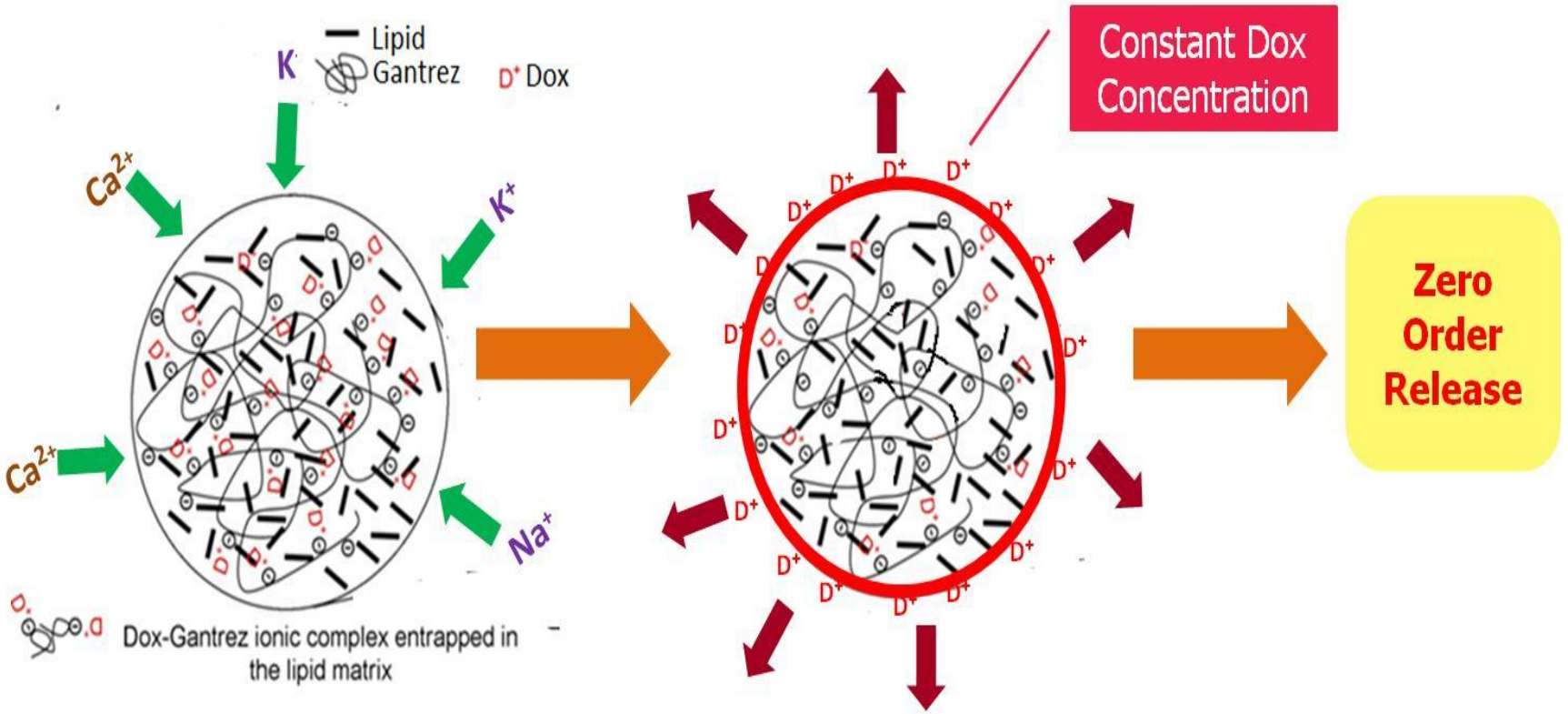
Fraction Absorption Profiles





DOX LIPOMER

ZERO ORDER RELEASE



KINETIC MODEL PREDICTION

ZERO ORDER RELEASE

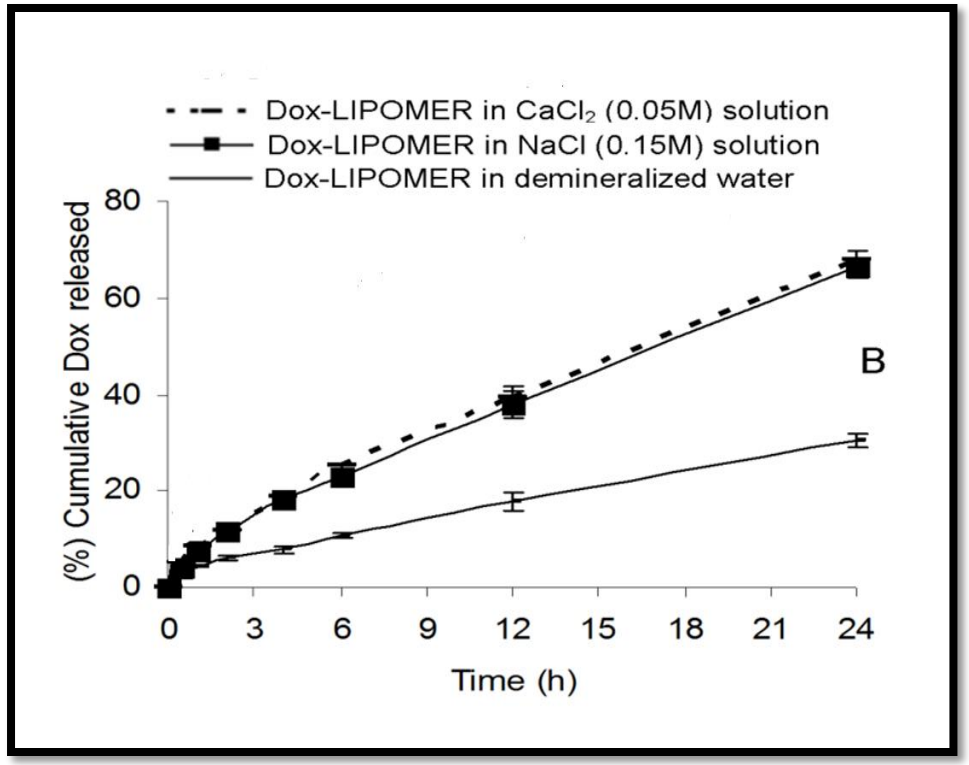
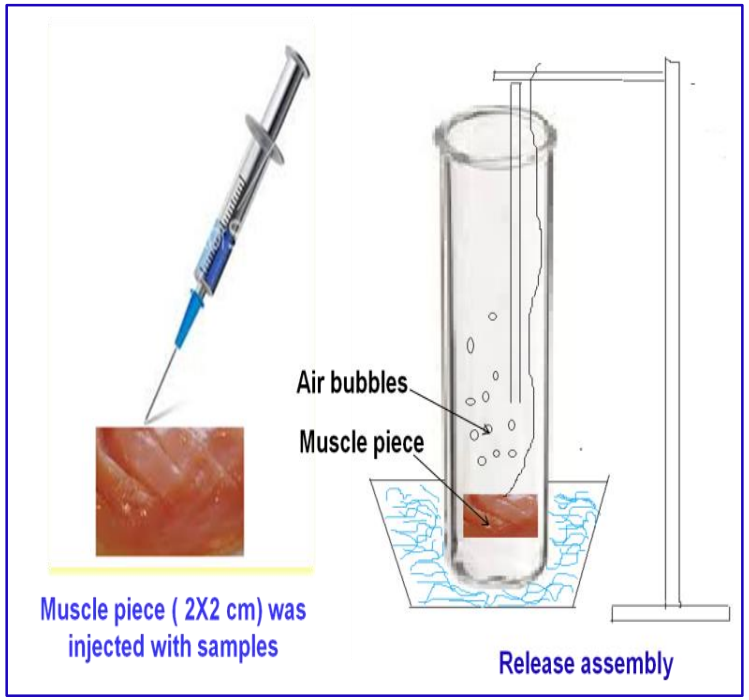


Fig. 1. In vitro release profile of Dox solution, Dox-Gantrez ionic complex and PGDS (Polyglyceryl -6 Distearate) based Dox-LIPOMER in (A) acetate buffer pH 4.5 and (B) demineralized water, NaCl (0.15M) solution and CaCl2 (0.05M) solution (mean ± S.D.; n = 3)

Dox formulation	Model	Zero order			First order			Higuchi			Korsmeyer-Peppas		
	Release media	r^2	Slope	Intercept	r^2	Slope	Intercept	r^2	Slope	Intercept	r^2	Slope	Intercept
Dox-Gantrez ionic complex	Acetate buffer (pH 4.5)	0.621	2.764	33.325	0.469	0.027	1.441	0.815	17.995	11.909	0.895	0.535	1.340
Dox-LIPOMER	Water	0.994	1.146	3.249	0.841	0.039	0.648	0.974	6.448	-3.319	0.987	0.606	0.593
	Acetate buffer (pH 4.5)	0.990	3.226	5.853	0.793	0.046	0.949	0.980	18.24	-12.84	0.997	0.741	0.872
	NaCl (0.15M) solution	0.992	2.565	5.970	0.790	0.043	0.921	0.979	14.479	-8.845	0.997	0.689	0.848
	$CaCl_2$ (0.05M) solution	0.991	2.615	6.653	0.808	0.041	0.958	0.981	14.786	-8.508	0.997	0.661	0.892

IMPLANT – DEVELOPMENT VS QC

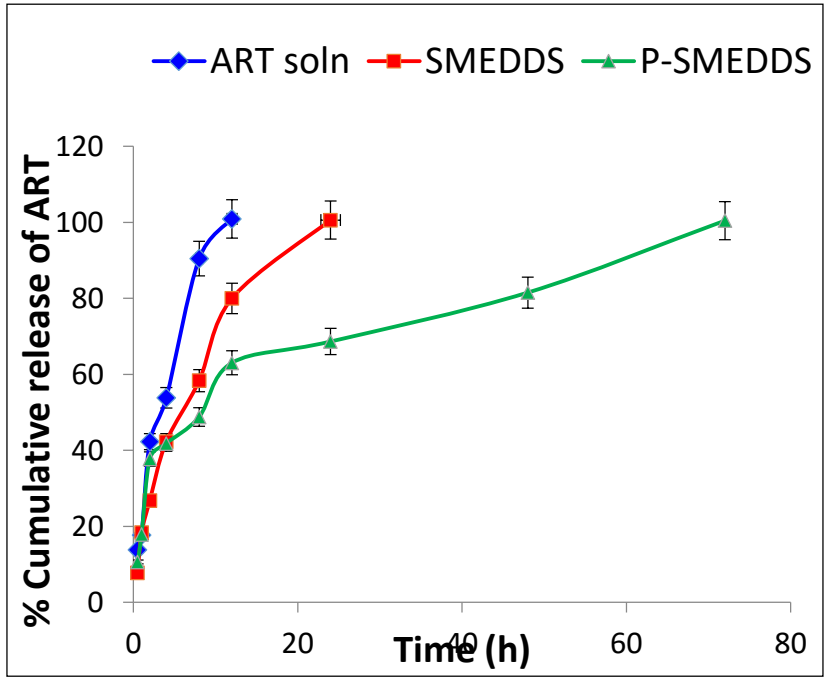
IN HOUSE METHOD



extensor digitorum muscle of *gallus gallus domesticus*

DISSOLUTION PARAMETERS	
Dissolution Medium	Phosphate Buffer pH 7.4 with 0.5% SLS
Dose	5mg
Temperature	37 º C
Time points	0.5, 1, 2,4, 8, 12, 24, 48, 72h
Aliquot sample	1mL

IMPLANT – DEVELOPMENT VS QC



- ✓ P-SMEDDS showed sustain release of ART as compare to SMEDDS and ART solution
- ✓ However method not adaptable for QC

CONCLUSION

- COMPREHENDING THE PURPOSE OF A DISSOLUTION TEST AND IDENTIFYING THE RIGHT APPARATUS AND METHOD CONTINUES TO BE AN AREA OF INTENSE RESEARCH PARTICULARLY FOR NEW DELIVERY SYSTEMS

- CUSTOMIZING NEEDS FOR DEVELOPMENT COULD POSE NUMEROUS CHALLENGES

MY RESEARCH GROUP


THANK YOU