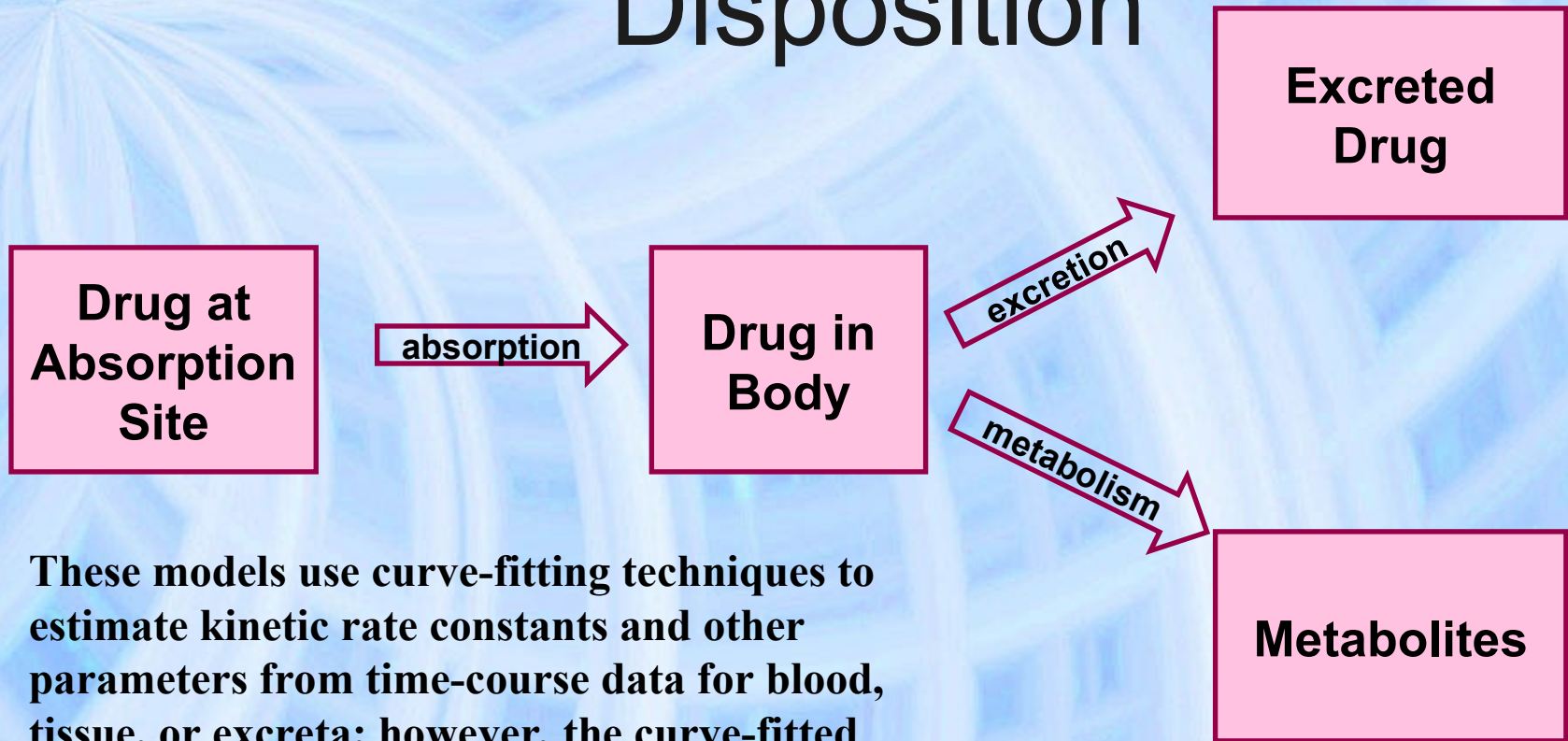




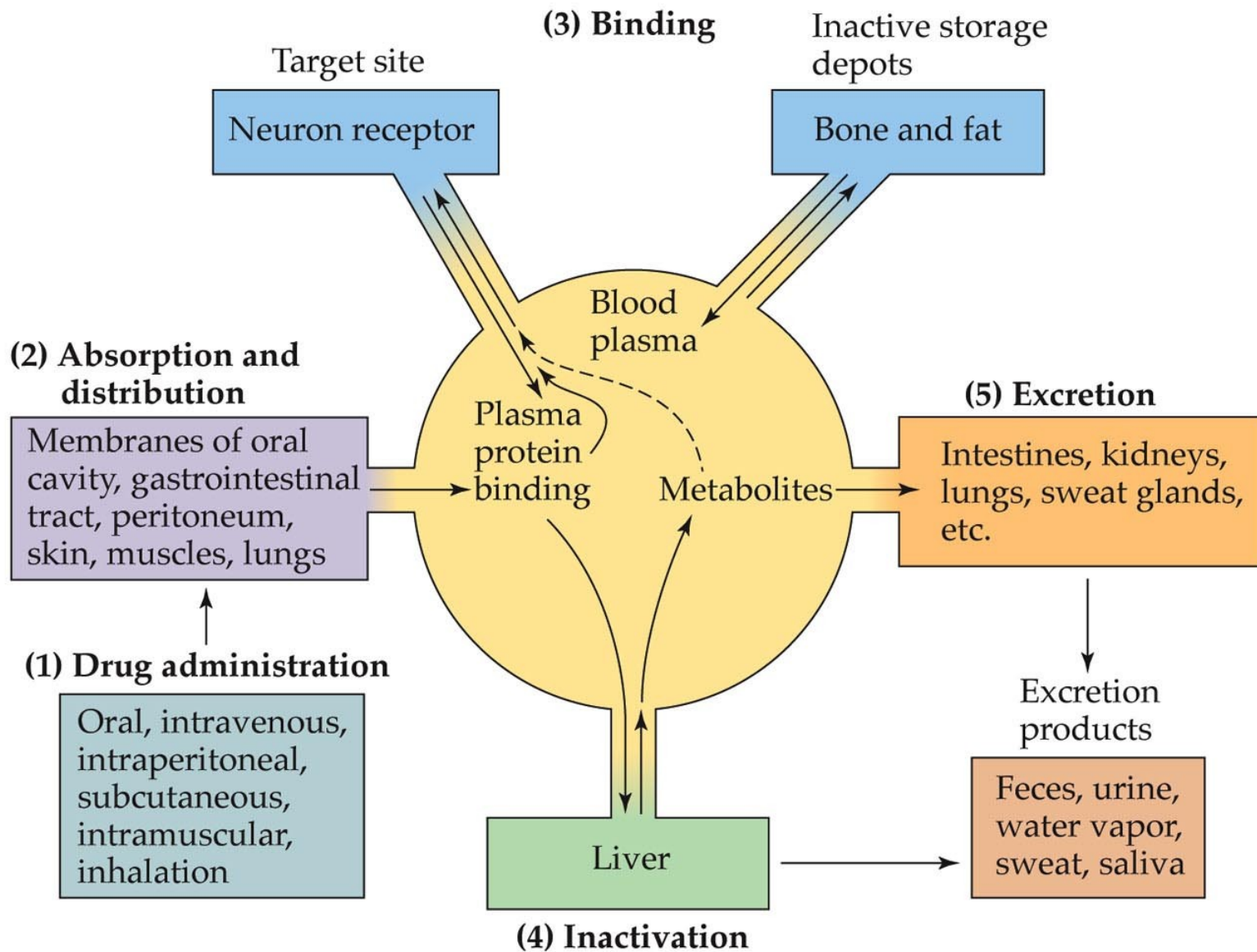
BIOPHARMACEUTICS CLASSIFICATION SYSTEM

Basic Absorption and Disposition

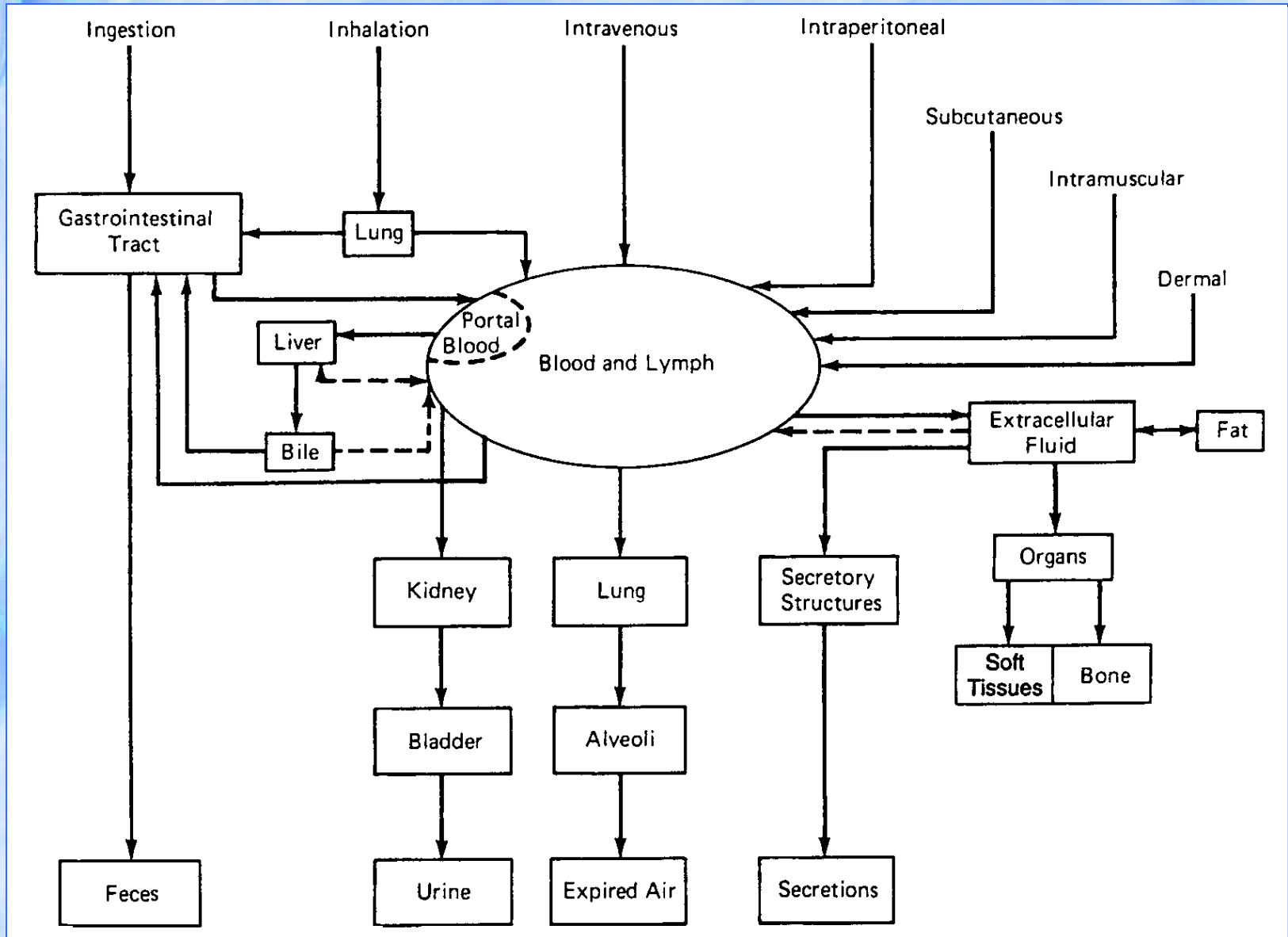


These models use curve-fitting techniques to estimate kinetic rate constants and other parameters from time-course data for blood, tissue, or excreta; however, the curve-fitted parameters lack biological meaning.

Pharmacokinetics



DISPOSITION OF DRUGS



The disposition of chemicals entering the body (from C.D. Klaassen, *Casarett and Doull's Toxicology*, 5th ed., New York: McGraw-Hill, 1996).

Introduction

Biopharmaceutics Classification System (BCS)

♥ **Scientific framework** for classifying drug substances based on their *aqueous solubility* and *intestinal permeability*

□ ***What is the need for a classification based on biopharmaceutics of the drug?***

- **Ans. Its importance in determining bioavailability**

ORAL ROUTE

♠ *Route of choice for the formulators*

▮ *Continues to dominate the area of drug delivery technologies.*

❖ LIMITATIONS

➤ **Absorption and Bioavailability** in the milieu of gastrointestinal tract.

➤ **Limitations more prominent**

✓ with the advent of **protein and peptide drugs**

✓ compounds emerging as a result of *combinatorial chemistry and the technique of high throughput screening*

Drug dissolution and absorption

API structure
Salt form and
excipients

*Bioavailability of drug
is determined by*

*extent of drug solubility
and
permeability*

formulated
drug
product

dissolution

absorbed
drug

excipients
contributes

Biopharmaceutics Classification System

- Guidance provided by the **U.S. Food and Drug Administration** for predicting the **intestinal drug absorption**



🌱 The fundamental basis established by
Dr. Gordon Amidon

🏆 Distinguished Science Award (Aug '06 ,FIP)

- ❖ First introduced into regulatory decision-making process in the guidance document on Immediate Release Solid Oral Dosage Forms: **Scale Up And Post Approval Changes**

- Drug development tool that allows *estimation of the contributions of **3** major factors*, that affect ***oral drug absorption** from **immediate release solid oral dosage forms***

- **Dissolution**

- **Solubility**

- **Intestinal permeability.**

The Biopharmaceutics Classification System (BCS)

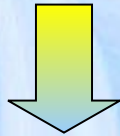
(as defined by the FDA after Amidon)



		High Solubility	Low Solubility
Permeability	High	Class 1 High Solubility High Permeability (Rapid Dissolution for Biowaiver)	Class 2 Low Solubility High Permeability
	Low	Class 3 High Solubility Low Permeability	Class 4 Low Solubility Low Permeability

Basis of BCS

Dissolution of drug *in vivo*



determines

Drug Concentration in
the Membrane Domain



proportional

Intestinal Absorption

**SIMILAR IN VIVO
DISSOLUTION**



SIMILAR IN VIVO ABSORPTION



**SIMILAR SYSTEMIC
AVAILABILITY**

SOLUBILITY DETERMINATION

(37±10°C in aqueous medium with pH range of 1-7.5.)

- ❁ A sufficient number of pH conditions
 - ionization characteristics of the test drug substance
- ❁ A minimum of **three** replicate determinations of solubility in each pH condition
- ❁ **Standard buffer solutions** described in pharmacopoeias
- ★ Methods other than shake flask method (with *Justification*). *e.g. acid or base titration methods*

Determination of permeability

♣ Not just based on lipophilicity (encompass *in vivo* effects of efflux and uptake transporters)

A. Human studies

- *Mass balance studies*
- *Absolute bioavailability studies*
- *Intestinal perfusion methods*

B. In vivo or **in situ intestinal perfusion** in a suitable animal model

C. **In vitro permeability** methods using excised intestinal tissues

D. In vitro permeation studies across a monolayer of cultured epithelial cells.e.g. **Caco-2 cells or TC-7 cells**

DISSOLUTION DETERMINATION

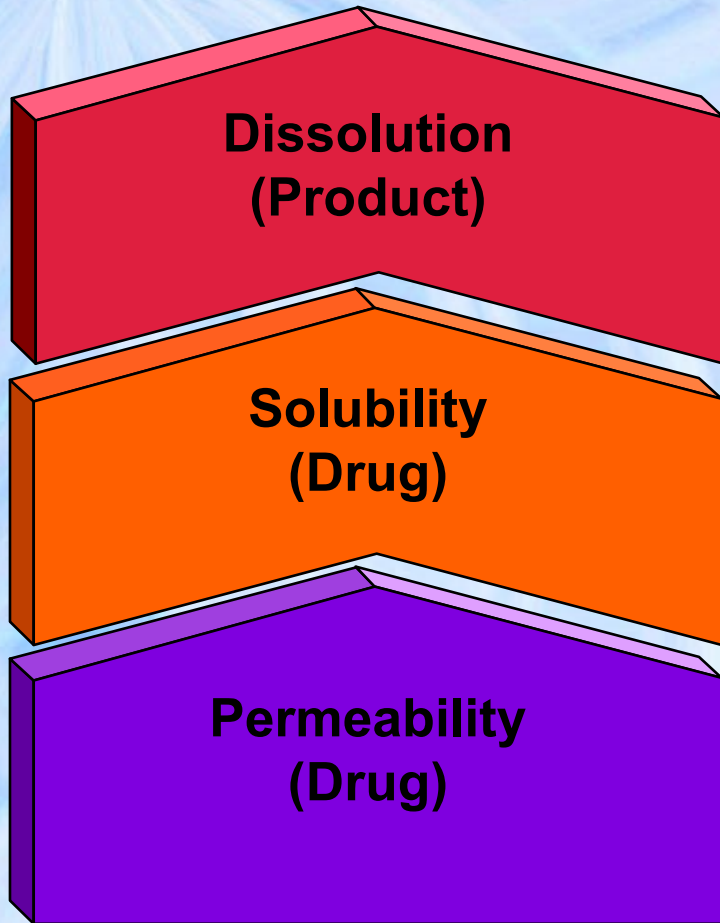
- USP apparatus I (basket) at 100 rpm or USP apparatus II (paddle) at 50 rpm.
- Dissolution media (**900 ml**): *0.1 N HCl or simulated gastric fluid, pH 4.5 buffer, and pH 6.8 buffer or simulated intestinal fluid.*
- Compare dissolution profiles of test and reference products using a *similarity factor (f₂)*.

$$f_2 = 50 \text{Log} \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \right\} \times 100$$

CLASS BOUNDARIES

- Ⓢ **HIGHLY SOLUBLE** *the highest dose strength is soluble in ≤ 250 ml water over a pH range of 1 to 7.5.*
 - Ⓢ The volume estimate-a glassful (8 ounce)
- Ⓢ **HIGHLY PERMEABLE** *when the extent of absorption in humans is determined to be $\geq 90\%$ of an administered dose*
- Ⓢ **RAPIDLY DISSOLVING** *when $\geq 85\%$ of the labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of ≤ 900 ml buffer solutions.*

BCS Class Boundaries: Objectives

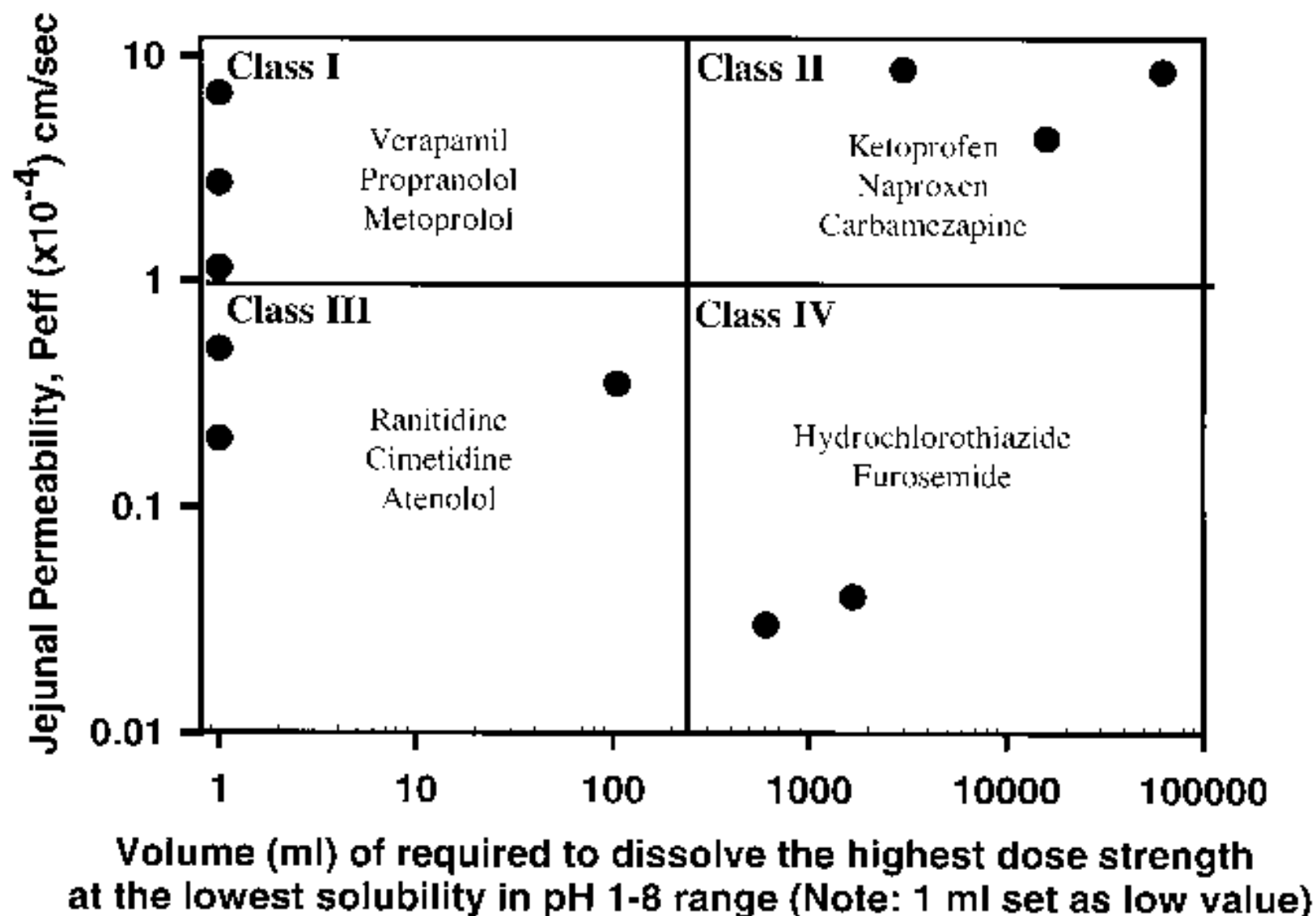


Rapid dissolution - ensure that in vivo dissolution is not likely to be the “rate determining” step

High solubility- ensure that solubility is not likely to limit dissolution and, therefore, absorption

High permeability - ensure that drug is completely absorbed during the limited transit time through the small intestine

BCS Class Membership of Selected Model Drugs



BCS -Implications for drug development

- Ж Application in early drug development and then in the *management of product change through its life cycle*
- Ж Aids fundamental understanding of the biopharmaceutical and physical *properties of the drug*
- Ж Aids discriminatory *dissolution method development*
- Ж Can help guide the development of *in-vitro/in-vivo correlations*
- Ж Can be used to obtain a *biowaiver*
- Ж Development of *poorly soluble drugs*

This classification is associated with drug dissolution and absorption model, which identifies the key parameters controlling drug absorption as a set of dimensionless numbers viz

BCS defines 3 numbers (no units)

- ❖ $A_n \sim$ absorption number
- ❖ $D_o \sim$ dose number
- ❖ $D_n \sim$ dissolution number

Absorption Number

A function of GI *Permeability* to Drug Substance

$$An = \left(\frac{P_{eff}}{R} \right) (T_{GI}) = \frac{T_{GI}}{T_{ABS}}$$

Effective permeability → P_{eff}

Residence time in GI → T_{GI}

Radius of GI → R

T_{ABS} → *Time required for complete absorption*

Dose Number

A function of solubility of drug substance

Highest Dose Unit → D

$D_o = \left(\frac{D}{\frac{V_{\text{Water}}}{C_s}} \right)$

250 mL → V_{Water}

C_s → Solubility

Dissolution Number

A function of drug release from formulation

$$Dn = \left(\frac{3D}{r^2} \right) \left(\frac{C_s}{\rho} \right) (T_{GI}) = \left(\frac{T_{GI}}{T_{DISS}} \right)$$

Diffusivity
 $5 \times 10^{-6} \text{ cm}^2/\text{s}$

Solubility
 mg/mL

Residence time in GI
 180 min

Particle Radius
 $25 \text{ } \mu\text{m}$

Density
 1.2 mg/cm^3

Time required for complete dissolution

Summary - BCS

High Permeability

Low Permeability

Test Drug

High An
Class I or II

Low An
Class III or IV

BE
Variability

High Dn
Class I

Low Dn
Class II

High Dn
Class III

Low Dn
Class IV

BE

High Do

Low Do
IV/VC >

High Do
IV/VC >

Low Do
IV/VC >

IVIVC expectations for immediate release products based on BCS

Class	Solubility	Permeability	Absorption rate control	IVIVC expectations for Immediate release product
I	High	High	Gastric emptying	IVIVC expected, if dissolution rate is slower than gastric emptying rate, otherwise limited or no correlations
II	Low	High	Dissolution	IVIVC expected, if in vitro dissolution rate is similar to in vivo dissolution rate, unless dose is very high.
III	High	Low	Permeability	Absorption (permeability) is rate determining and limited or no IVIVC with dissolution.
IV	Low	Low	Case by case	Limited or no IVIVC is expected.

High Solubility

Class 1

Abacavir
 Acetaminophen
Acyclovir^b
Amiloride^{S,I}
 Amitriptyline^{S,I}
 Antipyrine
Atropine
Buspirone^c
 Caffeine
Captopril
 Chloroquine^{S,I}
Chlorpheniramine
 Cyclophosphamide
 Desipramine
Diazepam
Diltiazem^{S,I}
Diphenhydramine
 Disopyramide
Doxepin
 Doxycycline
 Enalapril
 Ephedrine
 Ergonovine
 Ethambutol
 Ethinyl Estradiol
 Fluoxetine^I
 Glucose

Imipramine^I
Ketorolac
 Ketoprofen
 Labetolol
 Levodopa^S
 Levofloxacin^S
Lidocaine^I
 Lomefloxacin
Meperidine
 Metoprolol
 Metronidazole
Midazolam^{S,I}
Minocycline
 Misoprostol
Nifedipine^S
 Phenobarbital
 Phenylalanine
 Prednisolone
Primaquine^S
 Promazine
 Propranolol^I
Quinidine^{S,I}
 Rosiglitazone
 Salicylic acid
 Theophylline
 Valproic acid
Verapamil^I
 Zidovudine

Low Solubility

Class 2

Amiodarone^I
Atorvastatin^{S, I}
Azithromycin^{S, I}
Carbamazepine^{S, I}
Carvedilol
 Chlorpromazine^I
Cisapride^S
Ciprofloxacin^S
Cyclosporine^{S, I}
Danazol
Dapsone
 Diclofenac
 Diflunisal
 Digoxin^S
Erythromycin^{S, I}
 Flurbiprofen
Glipizide
Glyburide^{S, I}
 Griseofulvin
 Ibuprofen
Indinavir^S
 Indomethacin

Itraconazole^{S, I}
Ketoconazole^I
Lansoprazole^I
Lovastatin^{S, I}
Mebendazole
 Naproxen
 Nelfinavir^{S, I}
 Ofloxacin
 Oxaprozin
 Phenazopyridine
 Phenytoin^S
 Piroxicam
 Raloxifene^S
Ritonavir^{S, I}
Saquinavir^{S, I}
Sirolimus^S
 Spironolactone^I
Tacrolimus^{S, I}
 Talinolol^S
Tamoxifen^I
Terfenadine^I
 Warfarin

	High Solubility	Low Solubility
Low Permeability	<u>Class 3</u>	<u>Class 4</u>
	<div> <i>Acyclovir</i> <i>Amiloride</i>^{S,I} <i>Amoxicillin</i>^{S,I} <i>Atenolol</i> <i>Atropine</i> Bisphosphonates Bidisomide <i>Captopril</i> Cefazolin Cetirizine Cimetidine^S <i>Ciprofloxacin</i>^S Cloxacillin Dicloxacillin^S <i>Erythromycin</i>^{S,I} Famotidine </div> <div> Fexofenadine^S Folinic acid <i>Furosemide</i> Ganciclovir <i>Hydrochlorothiazide</i> Lisinopril Metformin <i>Methotrexate</i> Nadolol Pravastatin^S Penicillins Ranitidine^S Tetracycline Trimethoprim^S Valsartan Zalcitabine </div>	<div> Amphotericin B Chlorthalidone Chlorothiazide Colistin <i>Ciprofloxacin</i>^S <i>Furosemide</i> <i>Hydrochlorothiazide</i> <i>Mebendazole</i> <i>Methotrexate</i> Neomycin </div>

Applications of BCS in oral drug delivery technology

**Class I - High Permeability,
High Solubility**

- Achieve a target release profile associated with a particular pharmacokinetic and/or pharmacodynamic profile.
- Formulation approaches include both control of release rate and certain physicochemical properties of drugs like pH-solubility profile of drug.

Class II - High Permeability, Low Solubility

- + Micronisation,
- + Addition of surfactants,
- + Formulation as emulsions and microemulsions systems,
- + Use of complexing agents like cyclodextrins

Class III - Low Permeability, High Solubility

- Require the technologies that address to fundamental limitations of absolute or regional permeability.
- Peptides and proteins constitute the part of class III and the technologies handling such materials are on rise now days

Class IV - Low Permeability, Low Solubility

- ♪ Major challenge for development of drug delivery system and the route of choice for administering such drugs is parenteral (solubility enhancers.)
- ♪ Fortunately, extreme examples are the exception rather than the rule and are rarely developed and reach the market

Biowaiver

- A biowaiver is an exemption from conducting human bioequivalence studies when the active ingredient(s) meet certain solubility and permeability criteria in vitro and when the dissolution profile of the dosage form meets the requirements for an "immediate" release dosage form.

Waiver of In Vivo Bioequivalence Study based on

- **Pharmaceutical Dosage Form (Solutions)**
- **Biopharmaceutics Classification
System**
- **Dose.** (Highest Strength should be tested)

BCS BIOWAIVER

- Biowaiver for
 - **Rapid and similar dissolution.**
 - **High solubility & High permeability.**
 - **Wide therapeutic window.**
 - **Excipients used in dosage form used previously in approved IR solid dosage forms.**

REQUEST FOR BIOWAIVERS

Data Supporting :-

- ☐ **Rapid and Similar Dissolution**
 - ☐ **High Permeability**
 - ☐ **High Solubility**

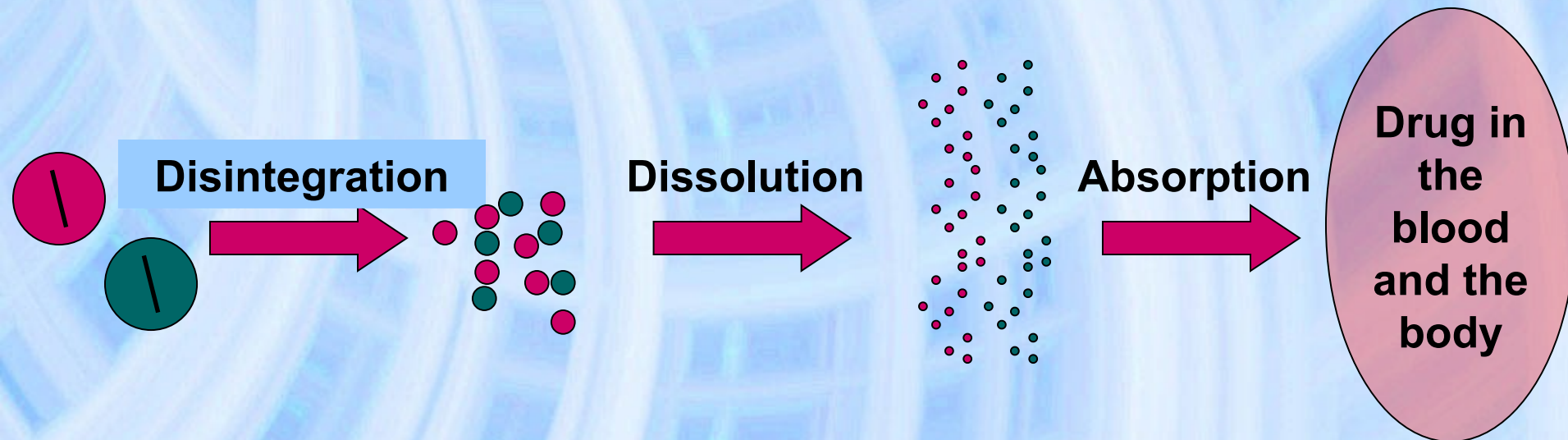
Limitations of BCS as a Predictor of Drug Disposition

- Ω Permeability (90% absorption) is difficult to determine, and difficult to convince the regulatory agency .
- Ω There is little predictability for BCS classification drugs beyond Class 1 primarily due to the difficulty of determining and proving 90% absorption.
 - many drugs are misclassified (e.g. HIV protease inhibitors as Class 4 compounds) .

Conclusion

- BCS aims to provide a **regulatory tool** for **replacing certain BE studies by accurate in-vitro dissolution tests..**
- This increased awareness of a proper biopharmaceutical characterization of new drugs may in the future result in **drug molecules with a sufficiently high permeability, solubility and dissolution rate**, and that will automatically increase the importance of the BCS as a regulatory **tool over time**

Why do we study dissolution?



Dissolution and drug release tests

- Dissolution and drug release tests are *in-vitro* tests that measure the rate and extent of dissolution or release of the drug substance from a drug product, usually in an aqueous medium under specified conditions
- The dissolution test is an important quality control procedure for the drug product and is often linked to product performance *in vivo*.
- *In-vitro* drug dissolution studies are most often used for monitoring drug product stability and manufacturing process

Conditions that May Affect Drug Dissolution and Release: Drug and formulation related

– Drug substance

- Particle size
- Polymorph
- Surface area
- Chemical stability in dissolution media

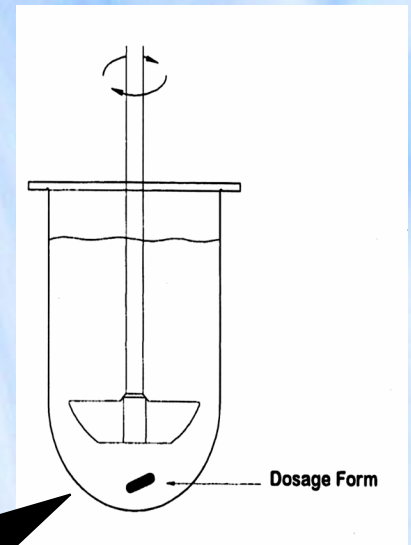
– Formulation of drug product

- Excipients (lubricants, suspending agents, etc)

Conditions that May Affect Drug Dissolution and Release: methodology related

- Medium
 - Volume
 - pH
 - Molarity
 - Co-solvents, added enzymes/surfactants
- Temperature of medium
- Apparatus
- Hydrodynamics
 - Agitation rate
 - Shape of dissolution vessel
 - Placement of tablet in vessel
 - Sinkers (for floating products and products that stick to side of vessel)

Dissolution Apparatus

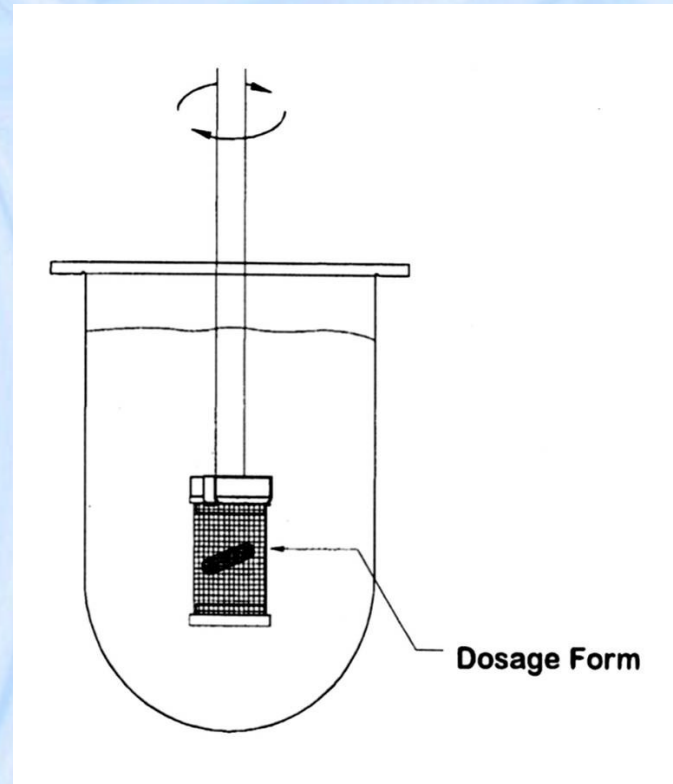


Dissolution Apparatus

Apparatus ^a	Name	Drug Product
Apparatus 1	Rotating basket	Tablets
Apparatus 2	Paddle	Tablets, capsules, modified drug products, suspensions
Apparatus 3	Reciprocating cylinder	Extended-release drug products
Apparatus 4	Flow cell	Drug products containing low-water-soluble drugs
Apparatus 5	Paddle over disk	Transdermal drug products
Apparatus 6	Cylinder	Transdermal drug products
Apparatus 7	Reciprocating disk	Transdermal drug products
Rotating bottle	(Non-USP-NF)	Extended-release drug products (beads)
Diffusion cell (Franz)	(Non-USP-NF)	Ointments, creams, transdermal drug products

^aApparatus 1–7 refer to compendial dissolution apparatus in USP-NF (United States Pharmacopeia)

Rotating basket (Apparatus 1)



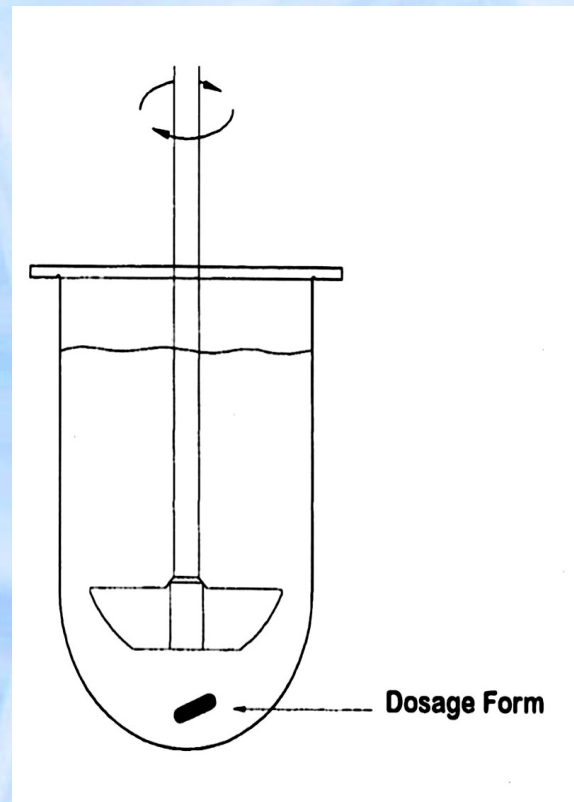
Rotating basket (Apparatus 1)

- In case of none-disintegrating dosage forms this apparatus is superior to apparatus 2 since it constraints the dosage form in a steady state fluid flow
- It is inferior for testing dosage forms which contains gums due to clogging of screen matrix

Rotating basket (Apparatus 1)

- In the case of floating dosage forms this method performs well, but care should be taken that excipients do not clog the basket mesh

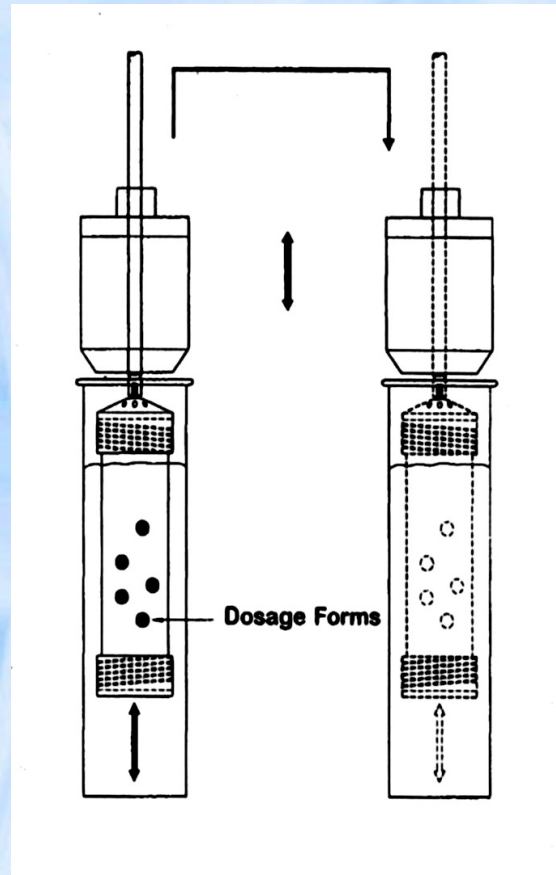
Rotating Paddle (Apparatus 2)



Rotating Paddle (Apparatus 2)

- This apparatus is identical to apparatus 1 except that the paddle is substituted for the rotating basket
- Frequently used for both disintegrating and non-disintegrating dosage forms

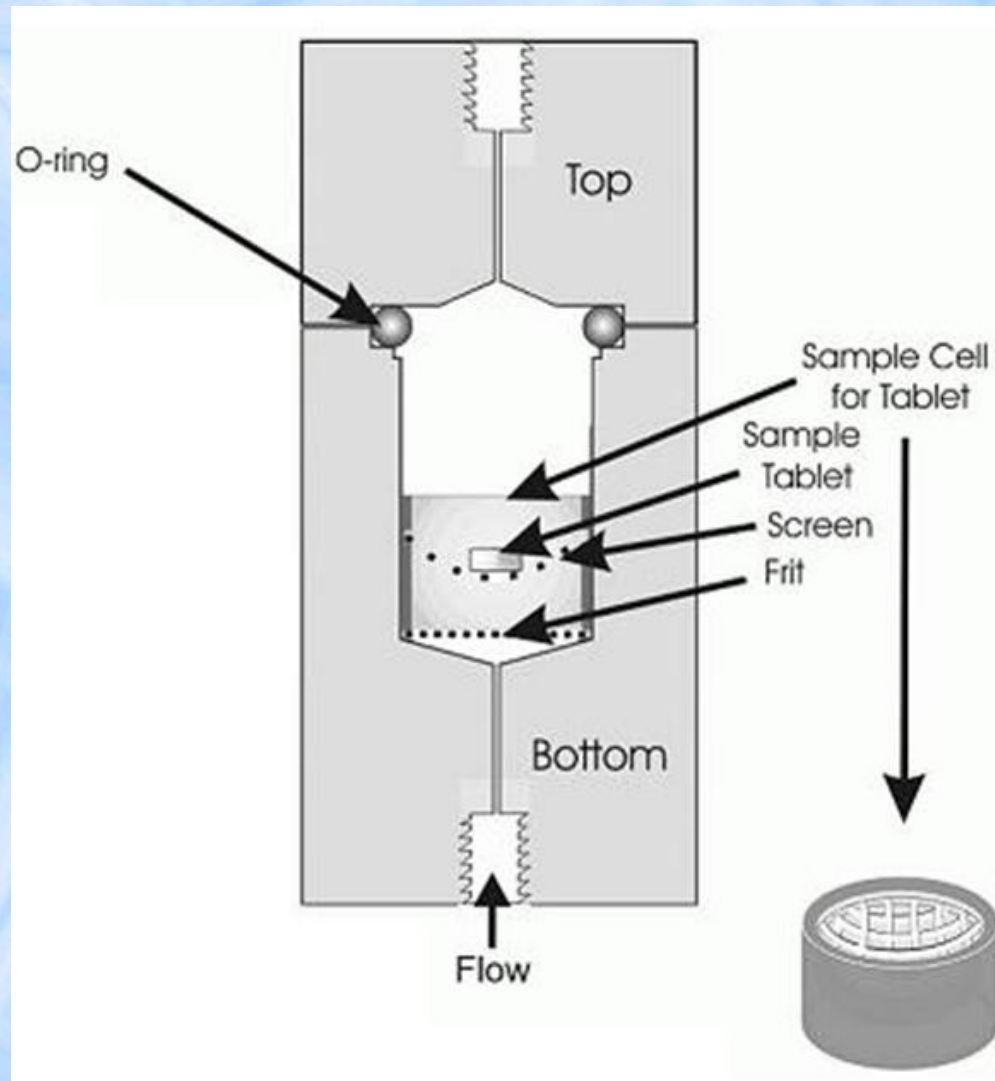
Reciprocating cylinder (Apparatus 3)



Reciprocating cylinder (Apparatus 3)

- One advantage of the reciprocating cylinder is that the gastrointestinal tract conditions can be easily simulated, as it is easy to make time dependent pH changes
- This apparatus is most suitable for nondisintegrating (extended release) or delayed release (enteric coated) dosage forms

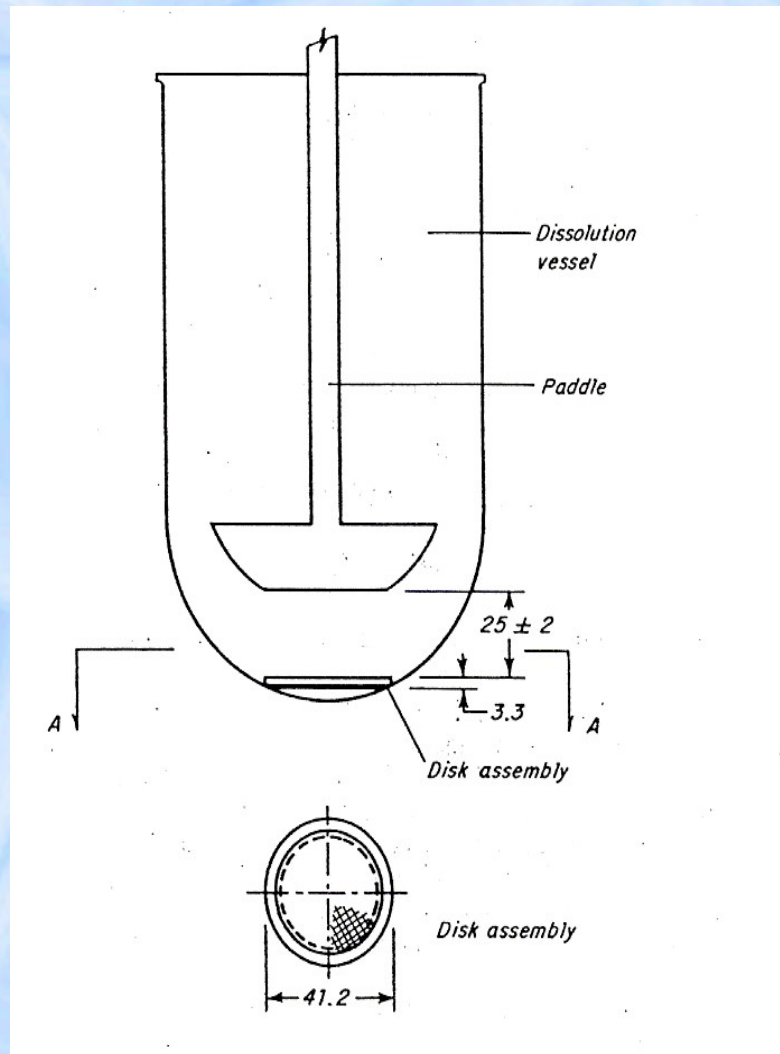
Flow cell (Apparatus 4)



Flow cell (Apparatus 4)

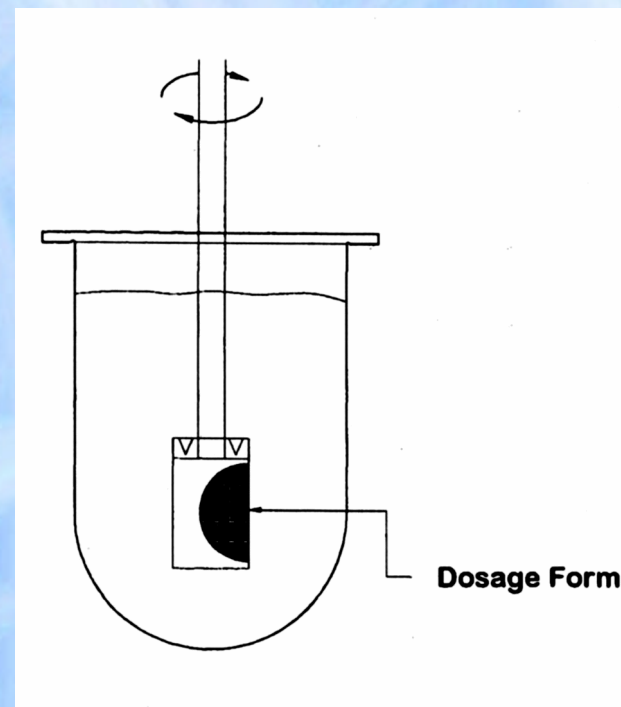
- The advantage of flow through cell apparatus is the ability to test drugs of very low aqueous solubility and the ability to change the pH conveniently during the test

Paddle over disk (Apparatus 5)



Cylinder (Apparatus 6)

- The cylinder method (Apparatus 6) for testing transdermal preparation is modified from the basket method (Apparatus 1). In place of the basket, a stainless steel cylinder is used to hold the sample.



Reciprocating Disk Method (Apparatus 7)

- In the reciprocating disk method for testing transdermal products, a motor drive assembly (Apparatus 7) is used to reciprocate the system vertically, and the samples are placed on disk-shaped holders using cuprophan supports



Reciprocating Disk

Dissolution Testing of Immediate Release Products

- The goal of dissolution testing is to assure the pharmaceutical quality:
 - The ability to manufacture the product reproducibly and ensure that it maintains its release properties throughout the shelf life
 - The ability to rely on stability of the biopharmaceutical properties of the dosage form (rate and extent of absorption)

Dissolution Testing of Immediate Release Products

- A. Quality Control Tests:
 - Current compendial dissolution tests were for the most part developed with the aim of studying the physical properties of the dosage form.
 - The concerns of dissolution testing from a quality control point of view is:
 - To use conditions under which 100% of the drug can be released
 - Reliability and reproducibility of the test
 - The possibility of automating the test (especially for high volume products) Leading to a preference towards simplest medium possible !!!!!!!!!!!

Dissolution Testing of Immediate Release Products

- B. Biopharmaceutical Studies:
 - As a result of the high cost of the pharmacokinetic studies and the inadequacies of the substitute studies (e.g. animal studies etc.) an increasing recent interest in developing dissolution tests to establish IVIVC's.
 - When the dissolution test is designed to indicate the biopharmaceutical properties of the dosage form, it is important that the test simulate the environment in the GIT than necessarily produce sink conditions for release.
 - As a result, it is not always possible to meet the needs of both quality assurance and biopharmaceutical aspects with one dissolution test.

Dissolution Testing of Immediate Release Products

- A variety of factors can determine the rate and extent of drug absorption following oral administration:
 - Slow release of the drug from the dosage form
 - Instability of the drug in the GIT
 - Poor permeability of the GI mucosa to the drug
 - First pass metabolism of the drug in the gut wall or the liver

Dissolution Testing of Immediate Release Products

- As a result, the dissolution test can be used to predict the in vivo performance of the dosage form when the release of the drug is the limiting factor in the absorption process:
 - Controlled release dosage forms
 - Immediate release dosage forms containing drugs that are poorly soluble.

Dissolution Testing of Immediate Release Products

- Selection of dissolution test media based on the BCS:
 - Class 1: High Solubility – High Permeability
 - Class 2: Low Solubility – High Permeability
 - Class 3: High Solubility – Low Permeability
 - Class 4: Low Solubility – Low Permeability

Dissolution Testing of Immediate Release Products

- Class I substances:
 - These are substances with good aqueous solubility and easy transport properties through the GI mucosa.
 - Their bioavailability after oral dose is usually close to 100% provided they are not decomposed in the GI tract and do not undergo extensive first pass metabolism.
 - Acetaminophen and metoprolol are typical examples of class I drugs.

Dissolution Testing of Immediate Release Products

- Because the absorption rate of class I substances is usually limited by non-dosage form related factors, it is rarely possible to achieve an IVIVC for an immediate release dosage form of a class I drug.
- Dissolution testing of a dosage form of a class I drug can be used mainly as a quality control test in addition it can be used to verify that the dosage form functions sufficiently well to ensure that the absorption is not dissolution-controlled.

Dissolution Testing of Immediate Release Products

- Consequently, the FDA recommends a one point test in a simple medium, with 85% or more of the drug to be released within 30 minutes for immediate release dosage forms of class I drugs.
- Since class I drugs have high solubility throughout the physiological pH range, the first choice for a dissolution medium is the **simulated gastric fluid without enzymes**.
- **Pepsin** may be added in case of drugs formulated into **hard gelatin capsules** to ensure a timely dissolution of the shell.

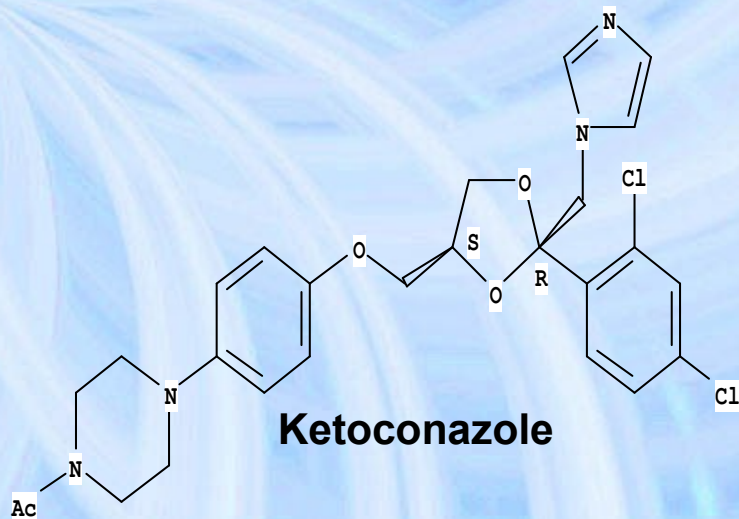
Dissolution Testing of Immediate Release Products

- In some cases, the simulated intestinal fluid USP without enzymes can be used for drugs that are weakly acidic in nature whose dissolution may be hampered by the low pH of the SGF.
- Water is the least suitable medium for the dissolution of class I drugs as it has nominal buffer capacity of zero (i.e. can not resist changes in pH caused by the dissolution and subsequent ionization of an acidic or basic drug).
- More complex biorelevant media are not necessary for class I drugs.

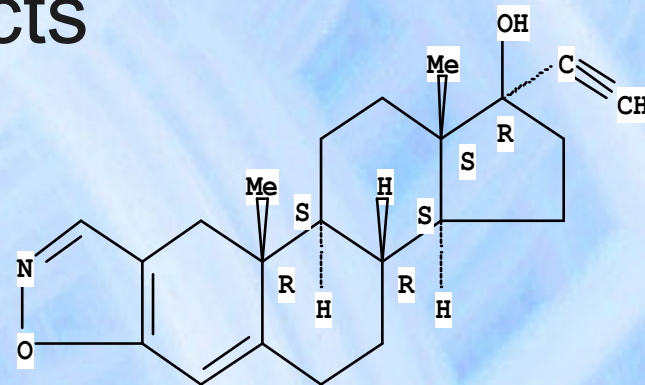
Dissolution Testing of Immediate Release Products

- Class II drugs are characterized with low solubility, however they are easily transported across the GI mucosal membrane.
- An aqueous solubility less than 100 $\mu\text{g/ml}$ or a dose number more than 1 is often a signal that the dissolution of the drug will control the rate of its introduction to the general circulation.
- The FDA uses a D/S value of 250 in the SUPAC guidance as the cutoff value for compounds with good solubility.

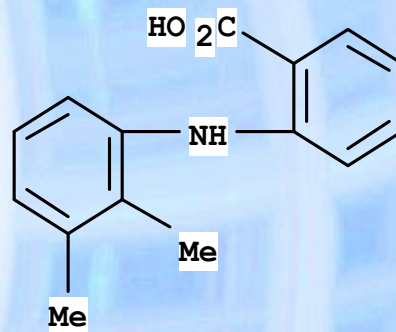
Dissolution Testing of Immediate Release Products



Ketoconazole



Danazol



Mefenamic Acid

Dissolution Testing of Immediate Release Products

- Biorelevant media are usually recommended for class II drugs including:
 - SGF plus surfactant to simulate fasted state in the stomach
 - Ensure or milk 3.5% fat to simulate fed state in the stomach\
 - FaSSIF to simulate fasted state in the small intestine
 - FeSSIF to simulate fed state in the small intestine

Dissolution Testing of Immediate Release Products

- SGF plus surfactant is particularly suitable for weak bases because they are most soluble under acidic conditions.
- The surfactant added must be able to reduce the surface tension to an appropriate value (35-40 mNm⁻¹)
- The volume of the gastric fluid is an important issue in developing a bio-relevant dissolution testing since the volume of the gastric fluid in the fasting state is 30-50 ml. Adding the contribution which reaches about 250-300 ml results in a total volume of 300-500 ml (still practical in USP apparatus 1 or II)

HCl	0.01-0.05 M
Triton X-100	0.01%
SLS	8.67 mM
NaCl	0.2%
Water	qs. ad 1 L

CC(C)(C)C[C@H](C)Cc1ccc(OCCO)n1

Dissolution Testing of Immediate Release Products

- Ensure and milk can be used during the drug development process to approximate conditions in the postprandial stomach.
- Both media contain similar ratios of protein/fat/carbohydrate to that found in a typical western diet.
- Mechanisms by which Ensure and milk can improve drug solubility include:
 - Solubilization of the drug in the fatty part of the fluid
 - Solubilization in casein micelles
 - Favorably high pH values (for weakly acidic drugs)

Dissolution Testing of Immediate Release Products

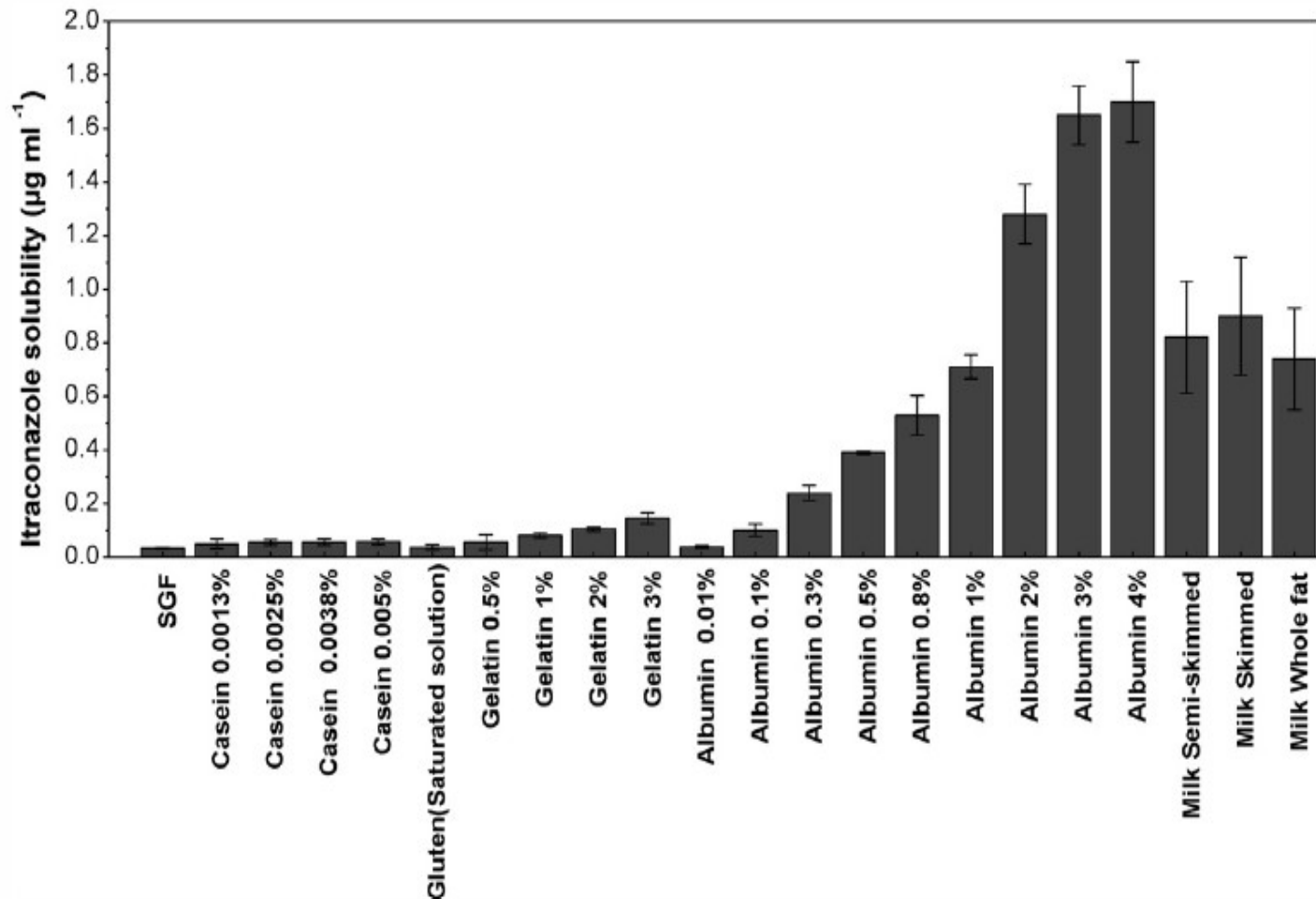


Fig. 4. Solubility of itraconazole in simulated gastric fluid (SGF) pH 3, SGF containing 50% milk (semi-skimmed, skimmed, whole fat) and (SGF) containing different concentrations of albumin, casein, gelatin and gluten. pH of each medium was 3. Each data point represents the mean \pm S.D. of 3 measurements.

Dissolution Testing of Immediate Release Products

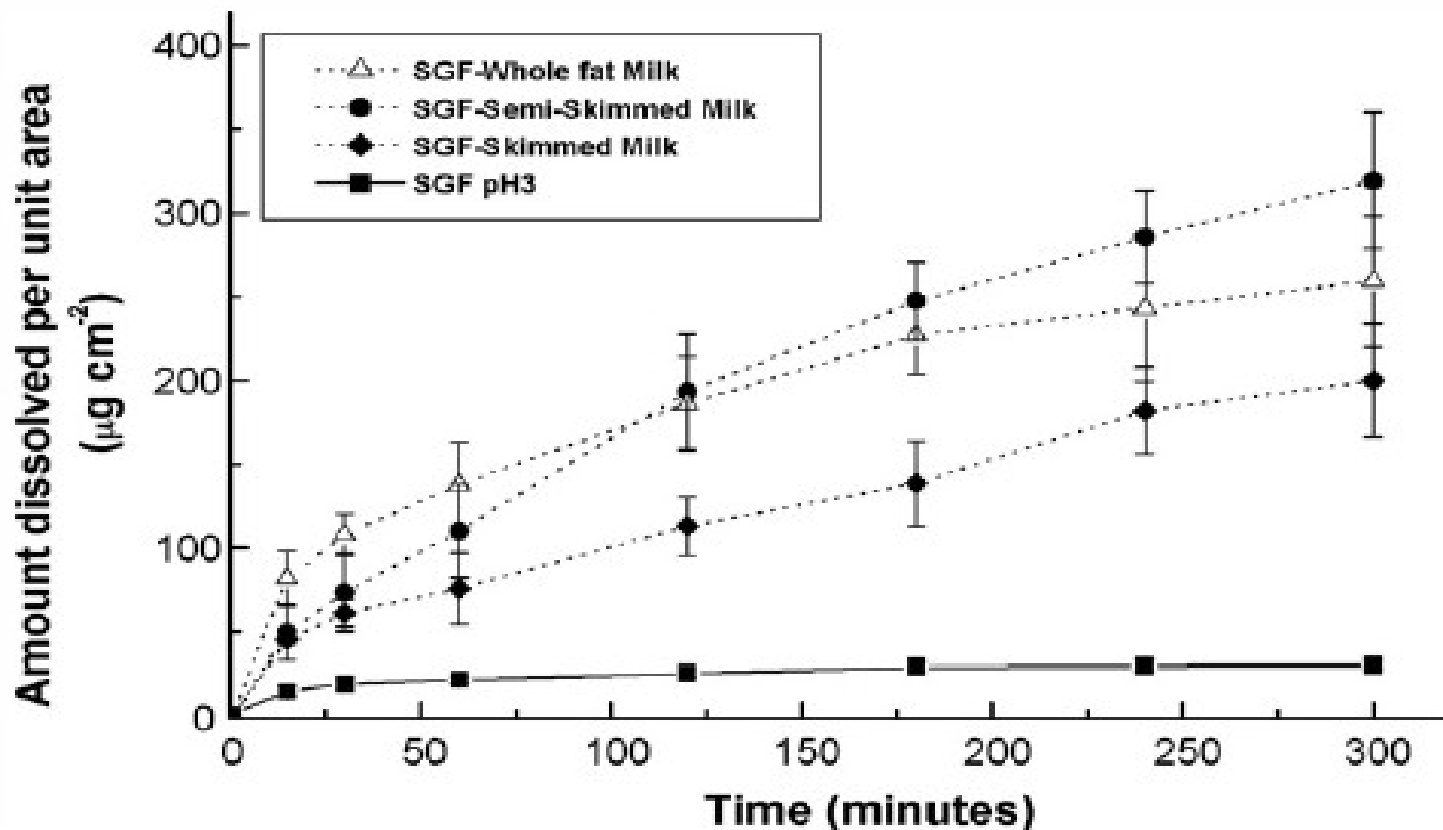


Fig. 3. The intrinsic dissolution profile of itraconazole in simulated gastric fluid (SGF) (■) and SGF containing 50% milk (whole fat (Δ), semi-skimmed (\bullet), or skimmed (\blacklozenge)). The pH of each media was 3. Each data point represents the mean \pm S.D. of at least 4 measurements.

Dissolution Testing of Immediate Release Products

- Ensure and milk are suitable only for IVIVC purposes since difficulties in filtering and separation of the drug from the medium make these media unsuitable for routine quality testing.

Dissolution Testing of Immediate Release Products

- FaSSIF and FeSSIF are two dissolution media that were developed in order to simulate the fed and fasting conditions in the intestinal content.
- The two media are particularly useful for forecasting the in vivo performance of poorly soluble drugs from different formulations and assessing the food effects on the in vivo dissolution.
- They are more useful for IVIVC than the regular compendial media.
- Intended for development rather than QC applications.

Dissolution Testing of Immediate Release Products

- The dissolution rate in FaSSIF and FeSSIF is usually better than that in simple aqueous buffers because of the increased wetting of the surface of the solid particles and micellar solubilization of the drug by the bile components.

Dissolution Testing of Immediate Release Products

Composition of FaSSIF

KH ₂ PO ₄	3.9 g
Na Taurocholate	3 mM
Lecithin	0.75 mM
KCl	7.7 g
NaOH	qs pH 6.5
Distilled Water	qs 1 L

Composition of FeSSIF

Acetic acid	8.65 g
Na Taurocholate	15 mM
Lecithin	3.75 mM
KCl	7.7 g
NaOH	qs pH 5
Distilled Water	qs 1 L

Dissolution Testing of Immediate Release Products

- Drug lipophilicity plays a role in the ability of bile salts to improve drug solubility:
 - At low P values below about 1.5 - 2, the presence of bile salts appears to exert little effect on drug solubility.
 - For more lipophilic compounds. however, there is a very close, log-log correlation between the partition coefficient and solubilization capacity of the bile salts for the drug.

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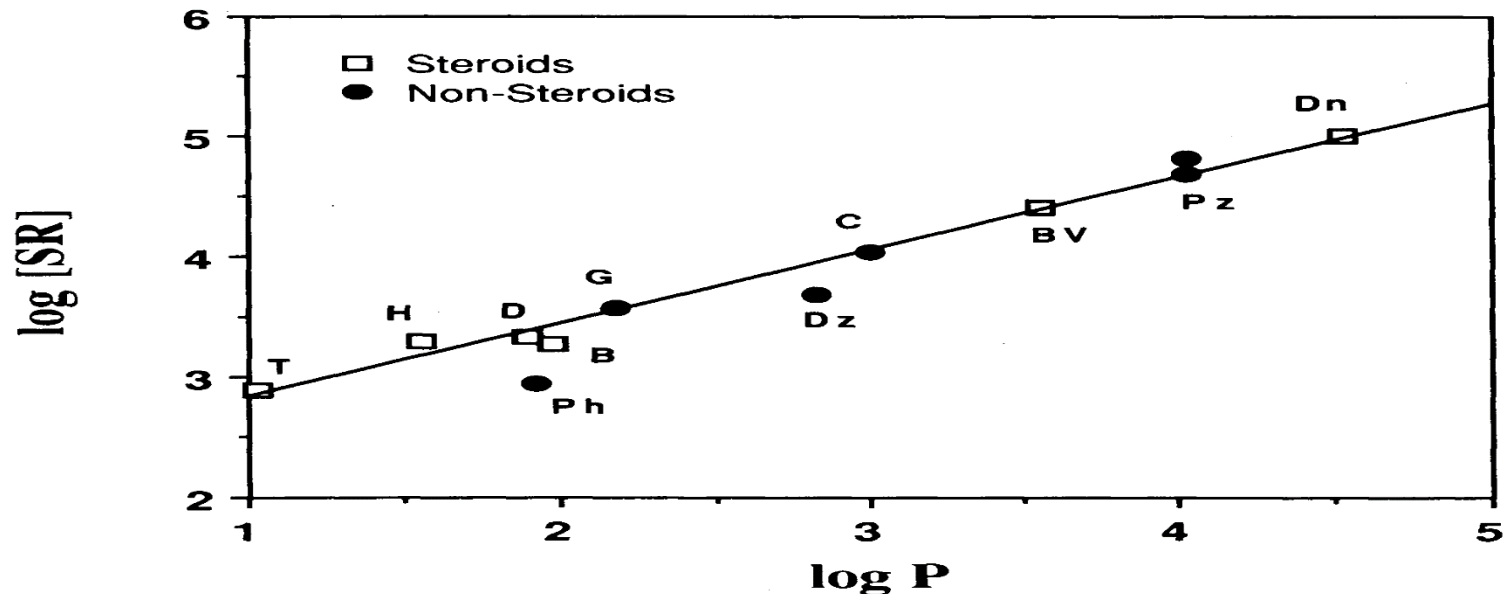


Fig. 1. Log [Solubilization Ratio] in aqueous solution taurocholate solutions as a function of log [octanol/water partition coefficient] for the non-steroidal compounds (circles; Ph = phenytoin, G = griseofulvin, Dz = diazepam, C = cyclosporin A, Pz = pentazocine), along with the prediction line based on steroid data (squares; T = triamcinolone, H = hydrocortisone, D = dexamethasone, B = betamethasone, BV = betamethasone 17-valerate, Dn = danazol); $\log [SR] = 2.23 + 0.60 \log [P]$.

Dependence of the solubilization capacity ($SR = C_{s_{bs}} / C_{s_{aq}}$) of Na taurocholate for a drug on its lipophilicity

Dissolution Testing of Immediate Release Products

- Because FaSSIF and FeSSIF combine a higher pH value with the possibility of micellar solubilization, they are especially suitable for studying the dissolution of poorly soluble weak acids.
- For example, many NSAIDs are weak acids, with pK_a values in the range 3.5-4.5. These drugs tend to dissolve very slowly under gastric conditions, but at intestinal pH and buffer capacity values, their dissolution rates can be several orders of magnitude higher.

Dissolution Testing of Immediate Release Products

- The appropriate volume of medium to use depends on the conditions of administration:
 - In the fasted state the intestine contains relatively little fluid, because the para-intestinal organs are secreting at essentially baseline rates.
 - When a drug is administered in the fed state, the volume of co-administered fluid is supplemented by the volume of fluid ingested with the meal and by secretions of the stomach, pancreas, and bile, all of which can easily achieve near maximal rates in response to meal intake.
 - In addition, depending on whether the meal is hypo- or hypertonic, there may be net absorption or secretion of water across the intestinal wall. As a result, postprandial volumes in the upper Small intestine as high as 1.5 L have been reported.
 - These differences between fasted and fed state are particularly important when designing tests to assess the potential for food effects on in vivo release and absorption.

Dissolution Testing of Immediate Release Products

- Results with danazol in FaSSIF and FeSSIF were in excellent agreement with those of pharmacokinetic studies, which showed a threefold increase in C_{max} and area under the concentration time curve (AUC) when danazol was administered with food.
- By contrast, dissolution results in SIF incorrectly predicted a total lack of bioavailability for danazol.

Dissolution Testing of Immediate Release Products

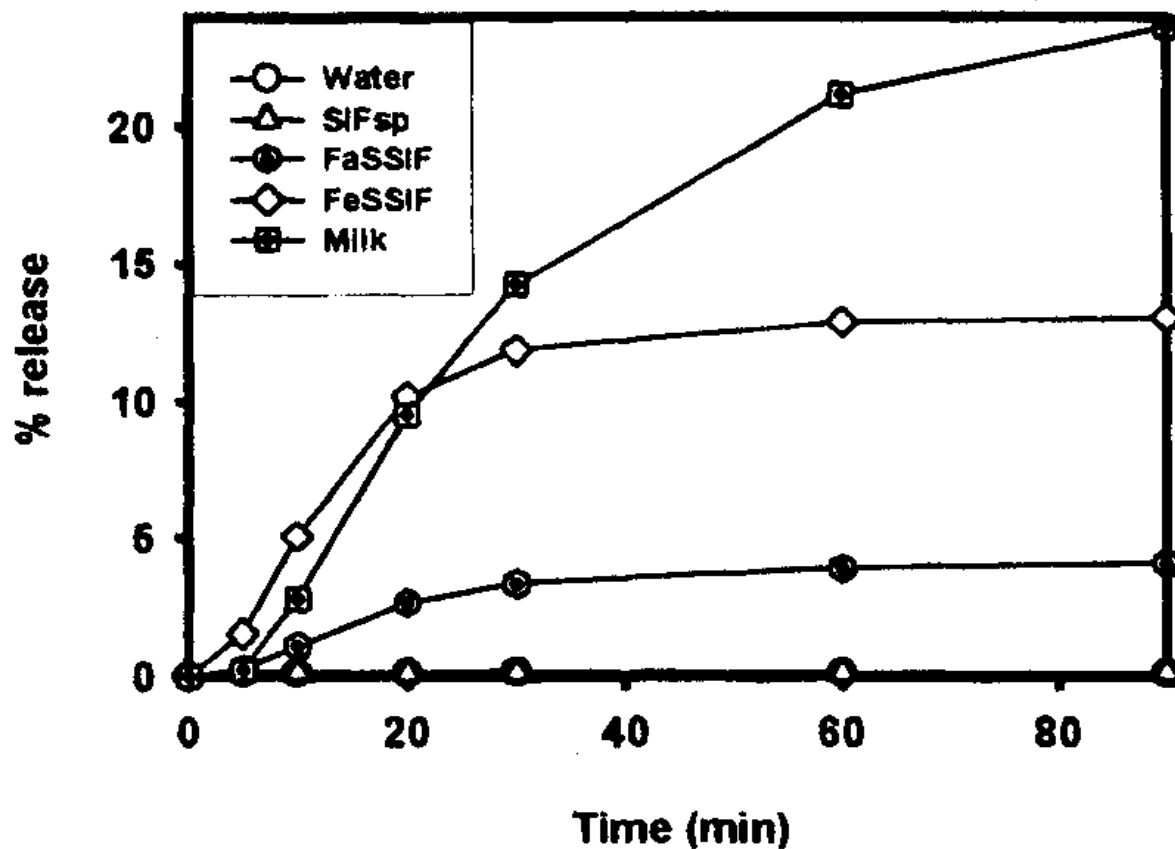
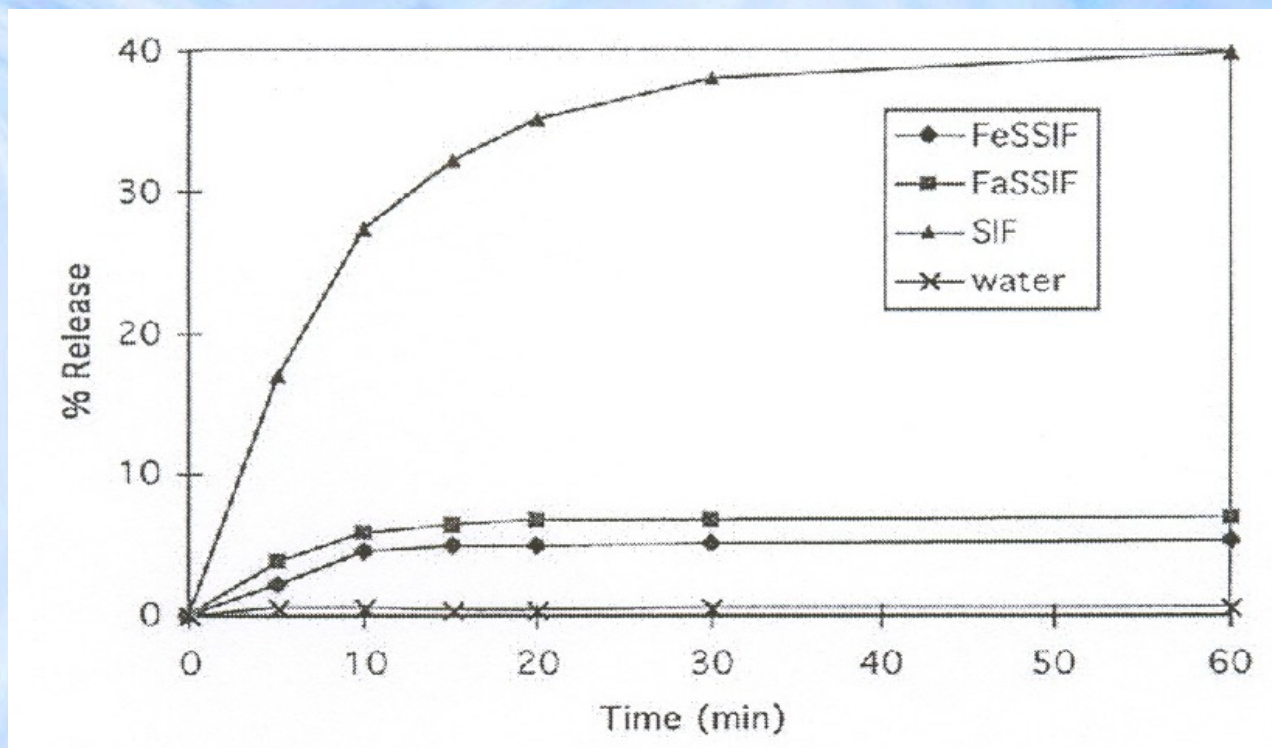


Fig. 3. Mean dissolution profiles of danazol from Danatrol® capsules in various media at 100 rpm.

Dissolution Testing of Immediate Release Products

- Dissolution results in FaSSIF and FeSSIF for mefenamic acid ($pK_a = 4.21$) were similar and agreed with the lack of influence of food on the absorption of this NSAID.
- In SIF (pH 7.5)

Dissolution Testing of Immediate Release Products

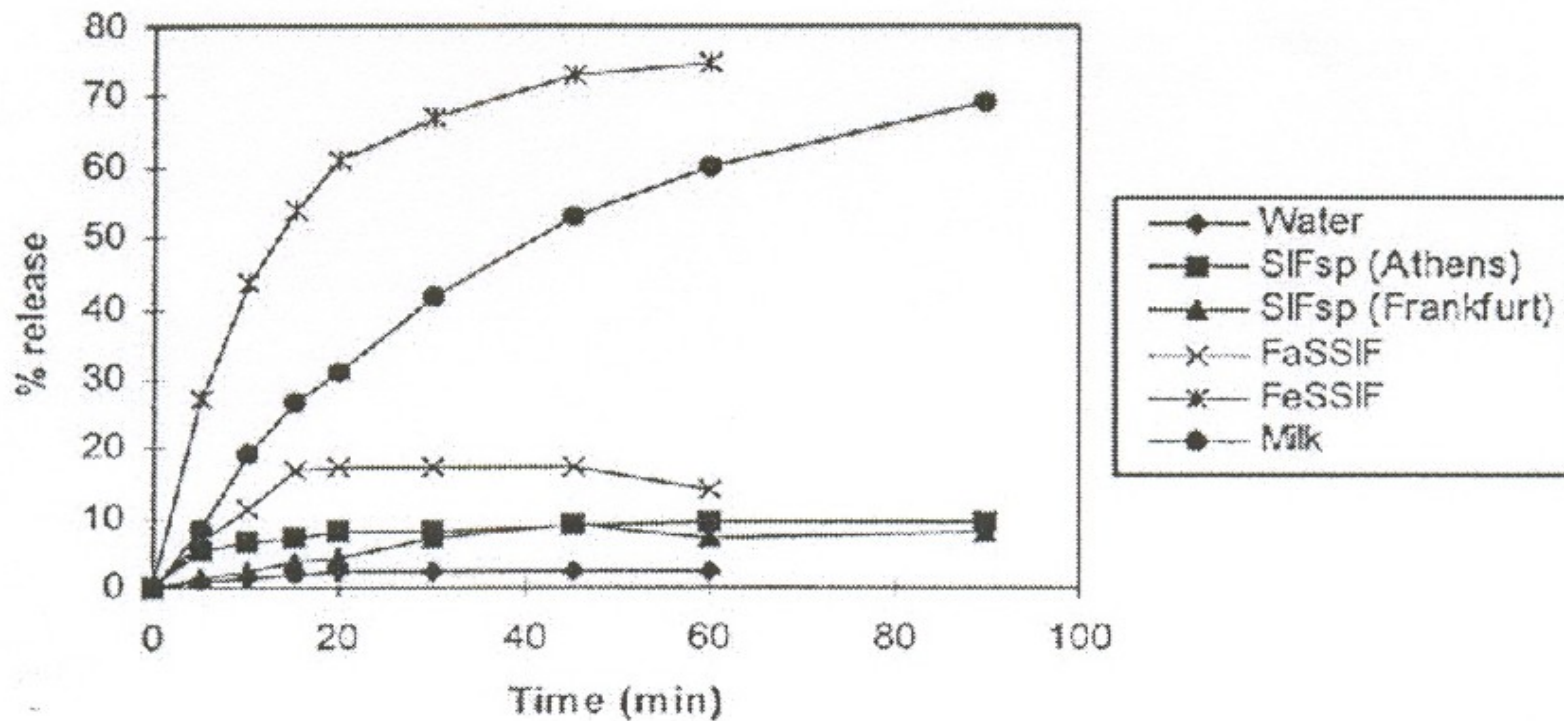


Dissolution of Mefenamic Acid

Dissolution Testing of Immediate Release Products

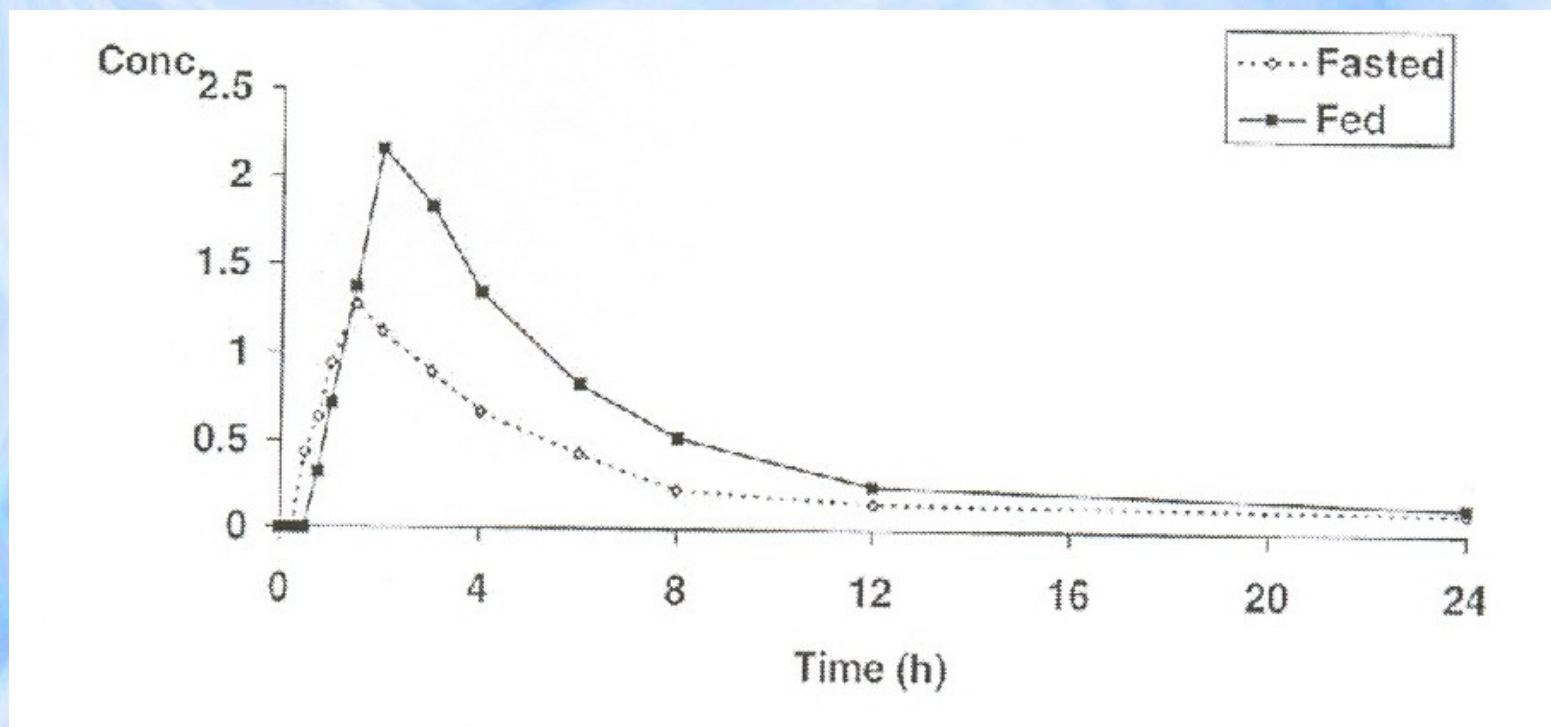
- By contrast, troglitazone dissolution was dramatically enhanced in FeSSIF compared with FaSSIF. These results were in accordance with the higher bioavailability of the antidiabetic agent when given with food.
- Because of its higher pK values ($pK_{a1}=6.1$, $pK_{a2}= 12.0$), the change in bile salt concentration from fasted to fed state conditions more than outweighed the unfavorable decrease in pH value.

Dissolution Testing of Immediate Release Products



Dissolution of Troglitazone

Dissolution Testing of Immediate Release Products



Troglitazone pharmacokinetic profile

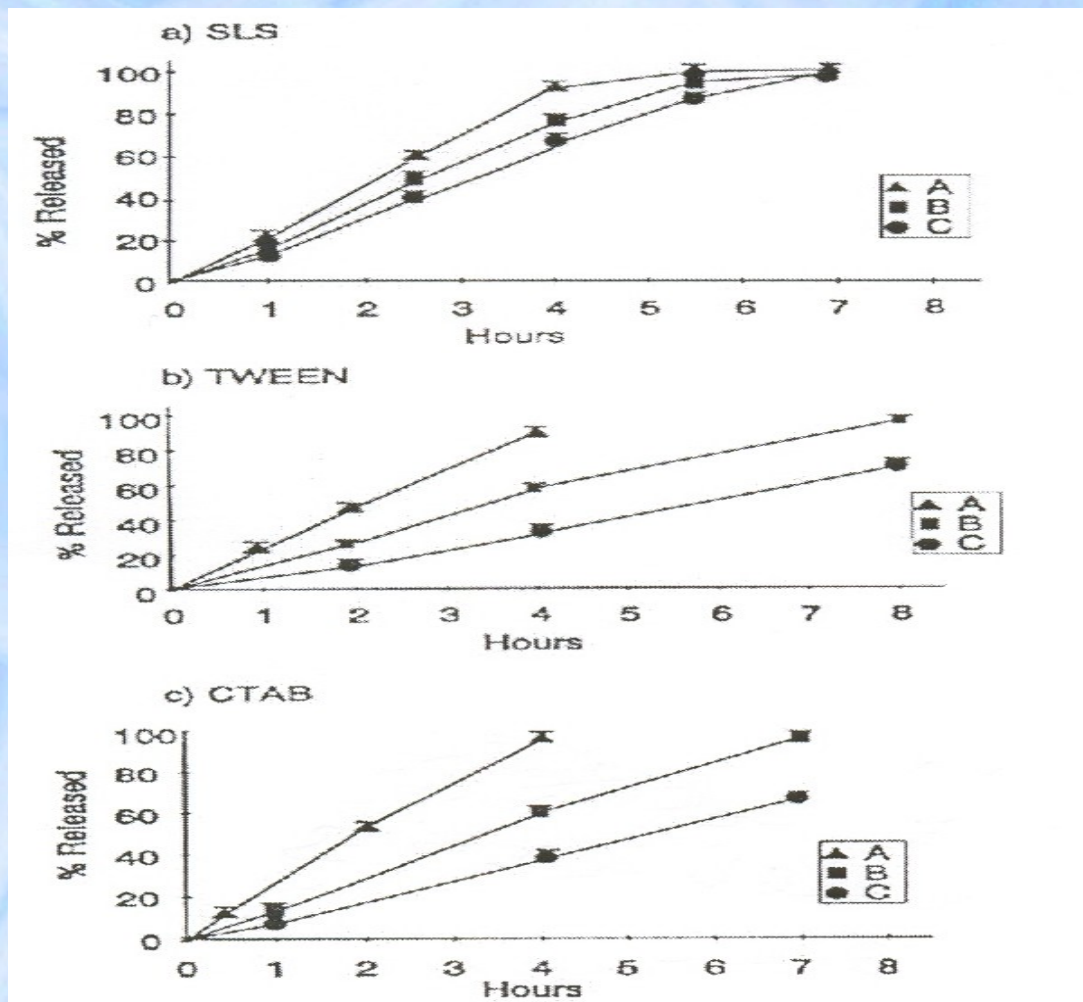
Dissolution Testing of Immediate Release Products

- The bile components (lecithin and bile salts) present some practical problems in terms of their purity and the time and effort required to prepare the medium and analyze the samples, not to mention their cost.
- For routine quality assurance, it would be far more practical to use a synthetic surfactant system that could match the surface tension lowering and solubilization properties of the bile components.
- The bile components lower the surface tension to about 45-50 mN/m which is some what higher than the gastric surface tension.
- Therefore, no single surfactant -concentration combination can be applied for the simulation of both gastric and intestinal conditions.

Dissolution Testing of Immediate Release Products

- Furthermore, it is uncertain that the usual surfactants (SLS, Tweens, or other) can solubilize drugs similarly to the bile components.
- The use of the wrong surfactant could lead either to over- or under discrimination among formulations.
- An example from the controlled-release literature is one in which results in CTAB or TWEEN correctly predicted differences among three formulations in vivo, but SLS falsely predicted similarity among the three formulations.
- Not only the type, but also the concentration of surfactant could play a role here, and much work still needs to be done to identify a synthetic surfactant system that could be used as a general substitute for bile components.

Dissolution Testing of Immediate Release Products



Dissolution of Felodipine in different surfactant solutions



Dissolution Tests for Extended Release Products

General Concepts

- In principle, considerations for testing conditions for extended release (ER) formulations are similar to those for immediate release (IR) ones.
- Ranges of performance are more important for ER products than for IR products to achieve special pharmacokinetic target profiles, especially for drug substances with a narrow therapeutic range.
- Because of the different concepts of slow release formulations and the various therapeutic indications, “standard” specifications for extended release formulations can not be set.

Test Medium

- An aqueous system as a test medium is preferred.
- The instructions on pH differ slightly between the various pharmacopeias

Volume	500-1000 ml
pH	pH 1-6.8 (8), water (justification)
Additives	Enzymes, salts, surfactants
Deaeration	Product by product validation
	Mandatory for flow through cell (Ph.Eur.)

pH of The Test Medium

- For quality control purposes, only one pH is usually used for dissolution testing.
- Exceptions are made only for delayed release formulations.
- Different pH values are preferred in comparison to a pH gradient method.

Apparatus

- The most common types of apparatus used for ER formulations are the paddle and the basket methods.
- Other methods including the flow through systems and the reciprocating cylinder testers can also be used.
- Automation of the process, including technical modifications (sampling valves), is possible, but must be validated on a product by product basis.
- Other methods may also be used, however, their superiority to pharmacopeia methods must be documented.

Agitation

- Different agitation speeds are specified in various pharmacopeia and guidances.
- For basket and paddle, 50-150 rpm are used.
- A scientifically based decision on the velocity of rotation does not exist and the rotational speed is set on a product by product basis.

Sinkers

- The Japanese Pharmacopeia provides specifications for sinkers.
- The FIP requires a justification of their use.
- The USP does not provide any specifications on this.

Test duration

- At least 80% dissolution must be reached within the test period.
- A direct determination of test duration from the dosage interval is scientifically justified only when the time axes in vitro and in vivo have a 1:1 relation.
- In special cases, an in vitro dissolution of less than 80% may be accepted if the test duration is at least 24 hours.
- In these cases a recovery control has to be performed during development using dissolution established under other test conditions.

Setting of Specifications

- For ER formulations, it is generally required that at least three specifications points are determined (USP may accept 2).
 - The first one after 1-2 hours (about 20-30% drug release) to provide assurance against premature drug release.
 - The second specification point has to be close to 50% (definition of dissolution pattern).
 - The last point, the dissolution at this point must be at least 80% to ensure almost quantitative release.
- Dissolution of less than 80% of the last point has to be justified and should be supported by results obtained over a test duration of at least 24 hours.

Setting of Specifications

- The purpose of establishing dissolution specifications is:
 - To ensure batch-to-batch consistency within a range that guarantees acceptable biopharmaceutical performance in vivo
 - To distinguish between good and "bad" batches.

Verification of Specifications

- For extended release formulation development, the relation between the in vitro drug release and the in vivo biopharmaceutical performance needs to be confirmed as a valid and therapeutically relevant acceptance criterion.
- The application of in vitro dissolution tests to the control of critical production parameters, without establishing their relation with the in vivo data, would represent a misunderstanding.
- Deduction of specification limits requires IVIVC studies.

Absorption intestinal-computer simulation-tube model: The drug flow in the gastrointestinal tract (GIT) was simulated with a biased random walk model in the heterogeneous tube model, while probability concepts were used to describe the dissolution and absorption processes. A certain amount of the drug was placed into the input end of the tube and allowed to flow, dissolve, and absorb along the tube. Various drugs with a diversity in dissolution and permeability characteristics were considered. The fraction of dose absorbed (F_{abs}) was monitored as a function of time measured in Monte Carlo steps (MCS). The absorption number, An , was calculated from the mean intestinal transit time and the absorption rate constant adhering to each of the drugs was examined. A fully computerized approach, which describes the flow, dissolution, and absorption of drug in the GIT in terms of probability concepts was developed. This approach can be used to predict F_{abs} for drugs with various solubility and permeability characteristics provided that probability factors for dissolution and absorption are available.

Biopharmaceutics Classification System (BCS)-high throughput (HT)-parallel artificial membrane permeation assay (PAMPA)-permeability: Solubility and permeability were measured by high-throughput solubility assay (HTSA) and PAMPA, respectively. HTSA was performed using simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid without bile acid (SIF, pH 6.8). We categorize 18 drugs based on the BCS using HTSA and PAMPA. Fourteen out of 18 drugs were correctly classified (78% success rate). The result of the present study showed that HTSA could predict BCS class with a high success rate, and PAMPA could also be useful to predict the permeation of drugs.

BCS-profiling permeability-charge state: About 30% of the drug candidate molecules are rejected due to pharmacokinetic-related failures. When poor pharmaceutical properties are discovered in development, the costs of bringing a potent but poorly absorbable molecule to a product stage by "formulation" can become very high. Fast and reliable in vitro prediction strategies are needed to filter out problematic molecules at the earliest stages of discovery. This review will consider recent developments in physico-chemical profiling used to identify candidate molecules with physical properties related to good oral absorption. Poor solubility and poor permeability account for many pharmacokinetic failures. The Food and Drug Administration's (FDA) BCS is an attempt to rationalize the critical components related to oral absorption. The core idea in the BCS is an in vitro transport model, centrally embracing permeability and solubility, with qualifications related to pH and dissolution. The objective of the BCS is to predict in vivo performance of drug products from in vitro measurements of permeability and solubility. In principle, the framework of the BCS could serve the interests of the earliest stages of discovery research. The BCS can be rationalized by considering Fick's first law, applied to membranes. When molecules are introduced on one side of a lipid membrane barrier (e.g., epithelial cell wall) and no such molecules are on the other side, passive diffusion will drive the molecules across the membrane. When certain simplifying assumptions are made, the flux equation in Fick's law reduces simply to a product of permeability and solubility. Many other measurable properties are closely related to permeability and solubility. Permeability (Pe) is a kinetic parameter related to lipophilicity (as indicated by the partition and distribution coefficients, $\log P$ and $\log D$). Retention (R) of lipophilic molecules by the membrane (which is related to lipophilicity and may predict pharmacokinetic