# Delivering the Best Formulation to the Right Patient

**George Kirk, 16th May 2012**

# Introduction

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- Dr George Kirk:
  - Current role: Global Project Manager in Oncology;
  - 15 years in AstraZeneca;
  - 10 years in Pharmaceutical Development;
  - 2 years as Pharmaceutical Development Project Manager;
  - 2 years as a Lean Sigma Black Belt;
  - PhD in Organometallic Synthetic Chemistry;
  - Scottish (and proud!)

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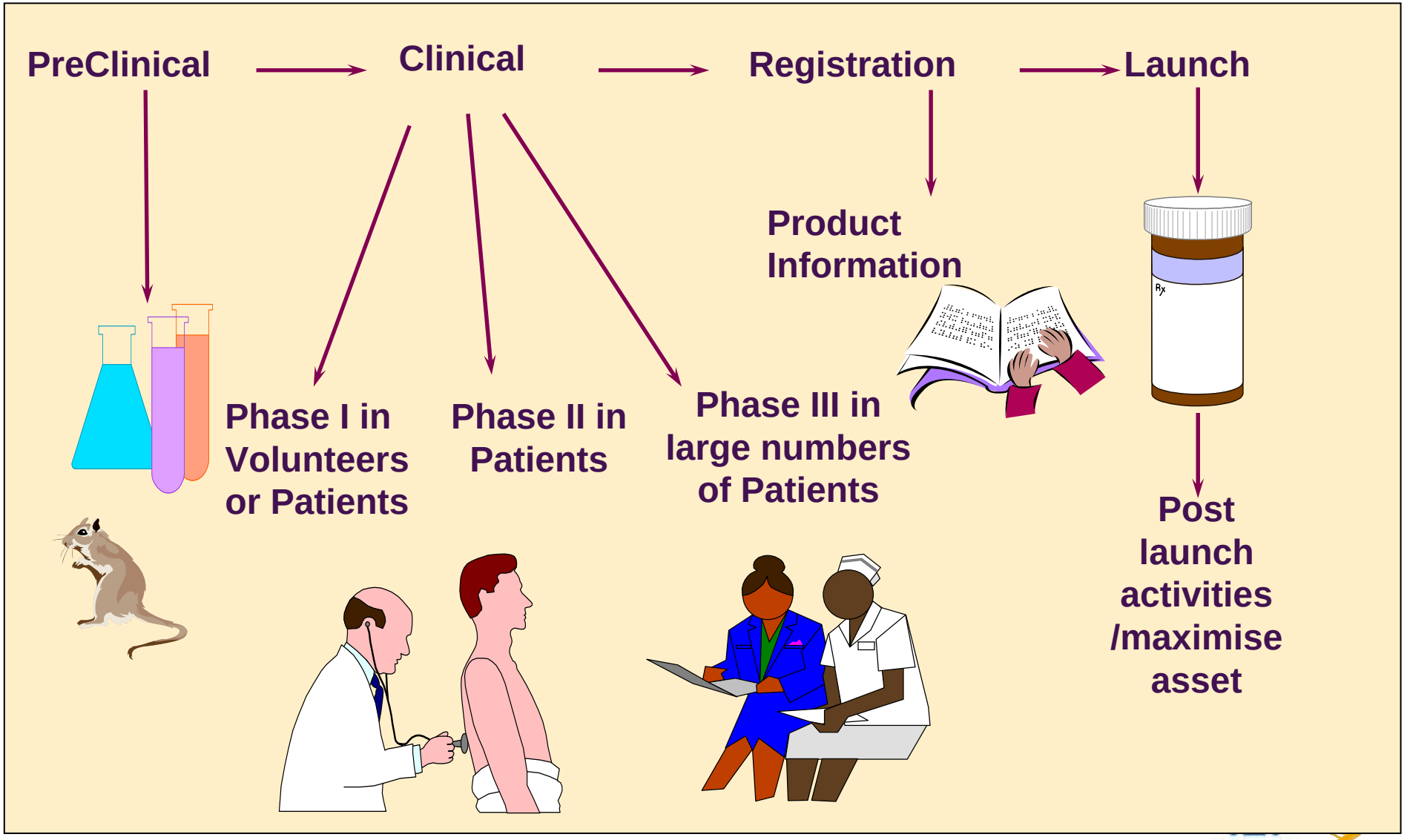
# Introduction: Phases of Development



# Introduction: Principles of Drug Development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# Why is Formulation so Important?

- Personalised medicines are becoming more important, particularly in Oncology;
- Targeted therapies are becoming more commonplace and are of increased interest to Payers and Regulators;
- Understanding how a drug is delivered to a patient and how it gets to its target is critical;
- Choosing the right dose is still a challenge;
- Targeted formulations can increase the chances of success of hitting the right target

# Routes of Administration

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# Routes of Administration

**Via oral route – most common**

| Site of Administration | Region | Dosage Form |
|---|---|---|
| Gastrointestinal Tract | Stomach | }solution, suspension, |
| | Intestine | }tablet, capsule |
| | Rectum | suppository, enema. |
| Buccal Cavity | Mouth | lozenge, solution, |
| | Nose | powder, aerosol |
| Skin | Most areas | solution, lotion, cream, ointment, transdermal devices. |
| Lung | | inhaler, aerosol |
| Vagina | | pessary, cream |
| Eye and Ear | | drops, cream, inserts |
| Parenteral | Intravenous | solution, emulsion |
| | Intramuscular | |
| | Intraperitoneal | } |
| | Intrathecal | } solution, suspension, |
| | Intraarticular | } emulsion and biodegradable |
| | Subcutaneous | } depots. |

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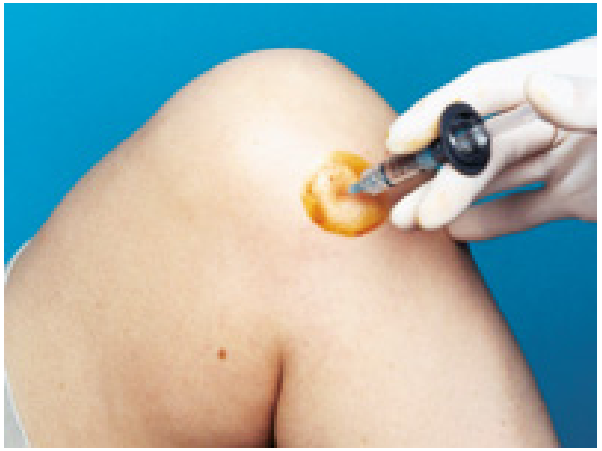
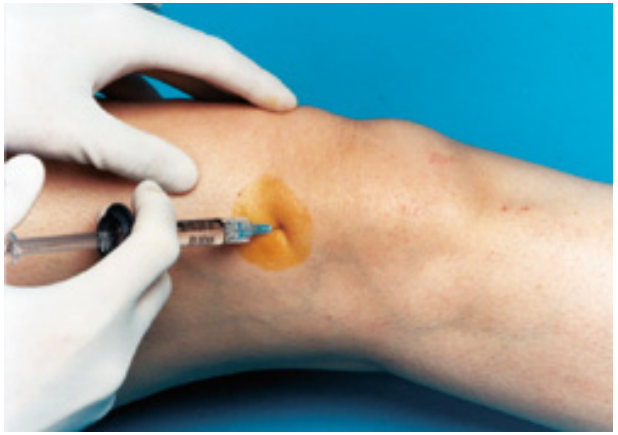
# Example – Intra-Articular Delivery

**Current intra-articular clinical practice**





- Previously accurate delivery to the intra-articular space - 10-20% of injections are not correctly placed
- Improvements with ultrasonic guidance and outpatient techniques such as "back-flow" claim virtually 100% correct IA placement

*(Jones et al., 1993, Bliddall  1999, Jackson, 2002, Luc et al., 2006)*

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# Biopharmaceutical Risk

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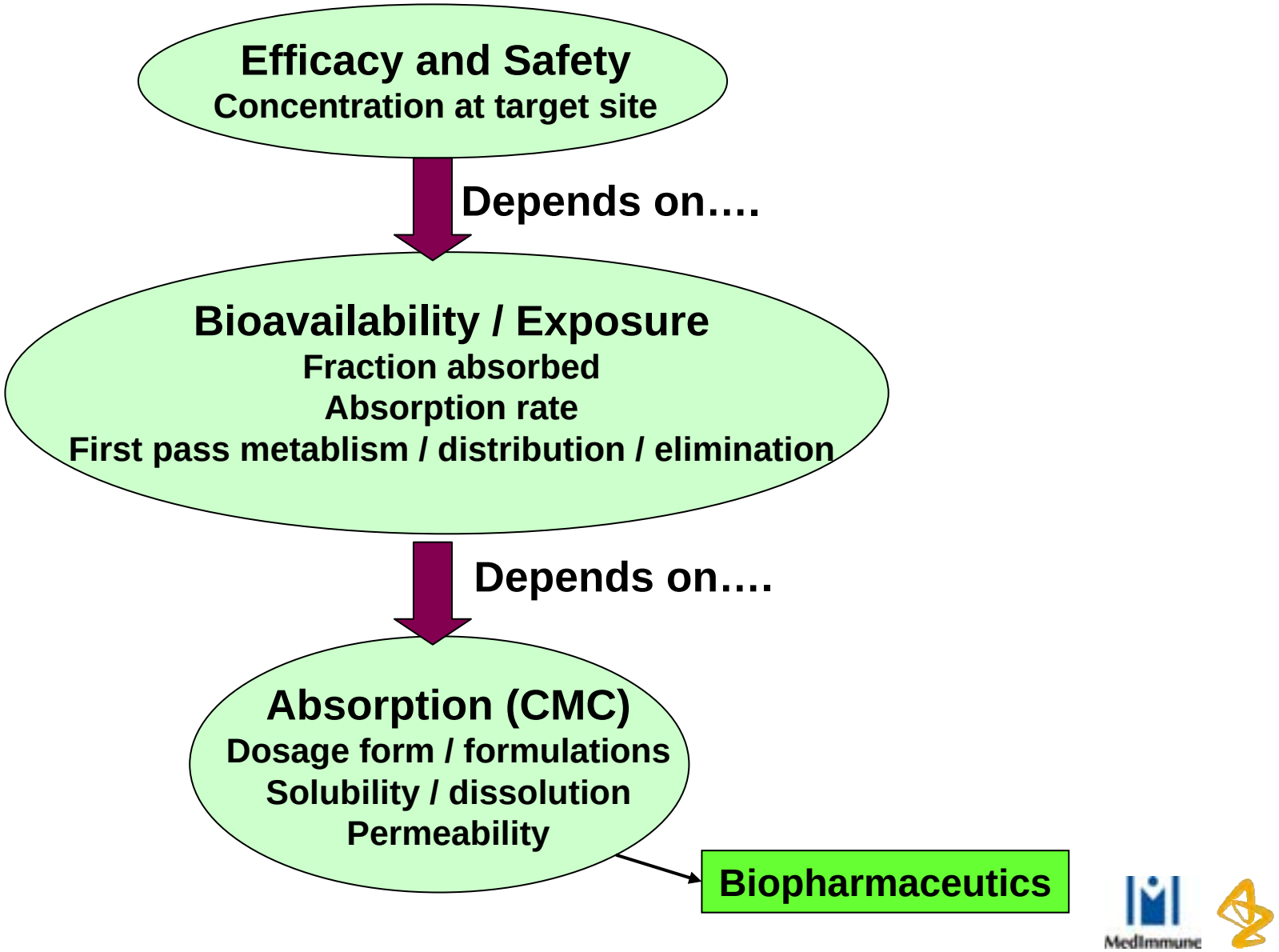
# Biopharmaceutics *versus* drug *in vivo* performance

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# First a slight aside – time for you to work!

- Let's think about solubility and dissolution?

- **What's this building?**
- **Taj Mahal is an integrated symmetric complex of structures that was completed around 1648**
- **What's it made of?**
- **While the white domed marble and tile mausoleum is most familiar**

- **What is the solubility of marble (calcium carbonate)?**
- **47 mcg/mL (normalised 100 mcM) at normal atmospheric $CO_2$ partial pressure, pH 8.3.**
- **At pH 5.3 >1 mg /mL**

**Wikipedia**

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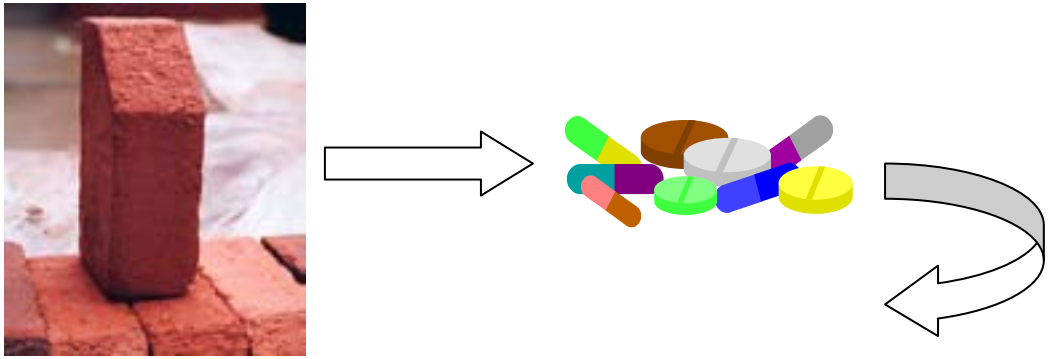
# Why is Solubility so Important in Pharmaceutical Development?



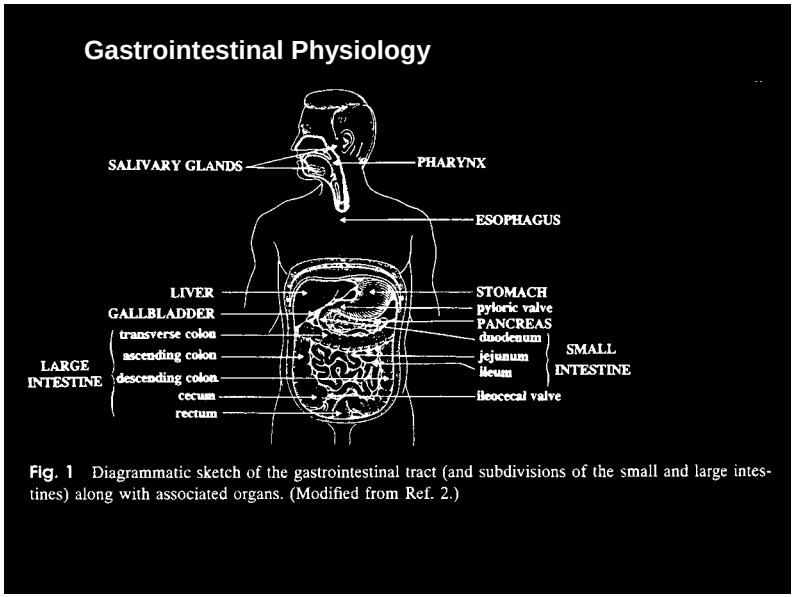



Fig. 1 Diagrammatic sketch of the gastrointestinal tract (and subdivisions of the small and large intestines) along with associated organs. (Modified from Ref. 2.)

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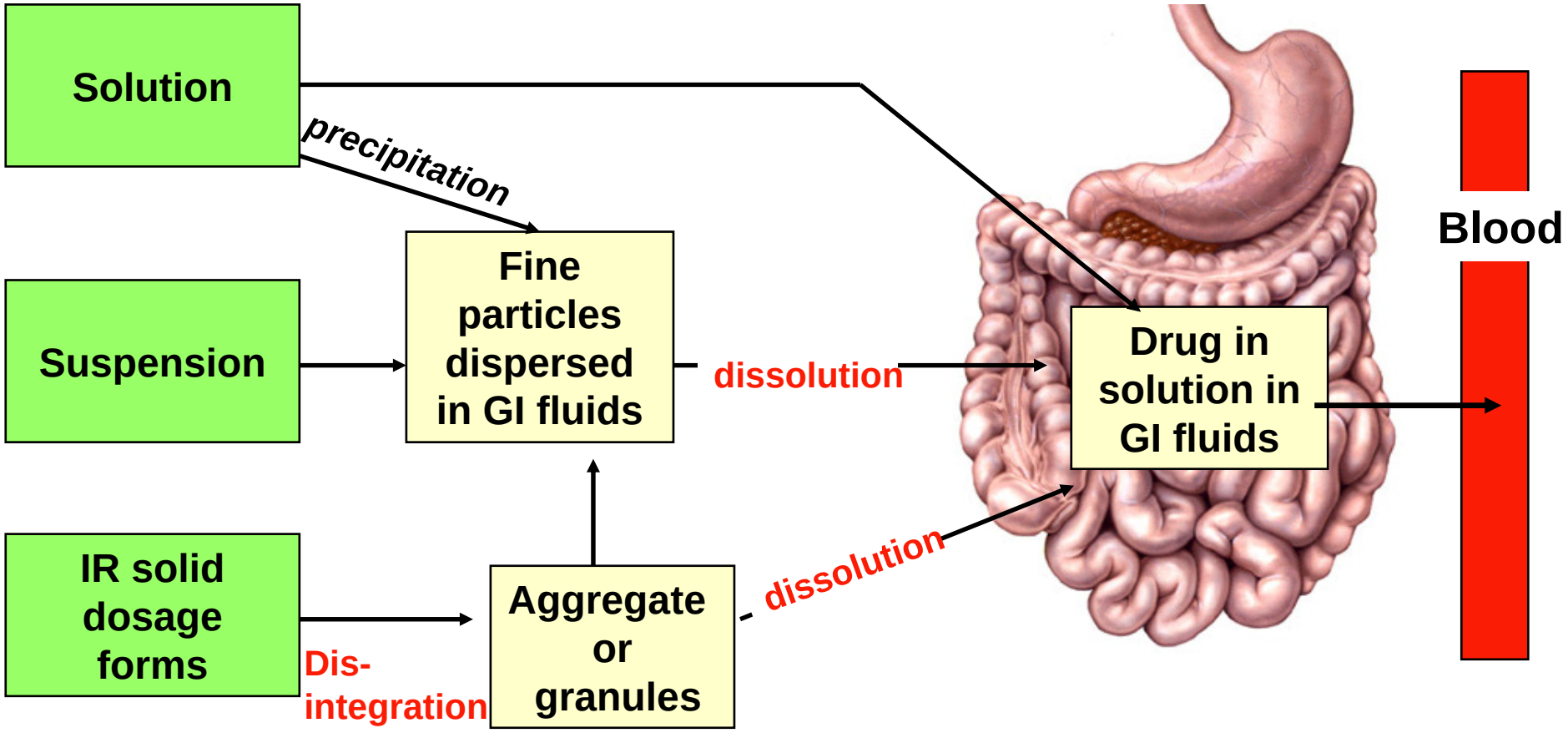
# Formulations for PO administration




**Best if compound dependent inherent dissolution properties not the limiting factor**

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# Physiological aspects on solubility - pH

***pH affects solubility of compounds with ionizing groups.***

| Site | | Fasted pH | Fed pH |
|---|---|---|---|
| Stomach | | 1.4 – 2.1 | 4.3 – 5.4 |
| Small intestine | duodenum | 4.9 – 6.4 | 4.2 – 6.1 |
| | jejunum | 4.4 – 6.6 | 5.2 – 6.2 |
| | ileum | 6.5 – 7.4 | 6.8 – 7.5 |
| Large intestine | caecum | 6.4 | |
| | colon (upper) | 6.0 | |
| | colon (lower) | 7.5 | |

From: Dressman and Hörter (2001). Adv. Drug Del. Rev 46, 75-87

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# So insufficient solubility may mean:

- Insufficient exposure in preclinical species to support safety margins;
- Insufficient exposure in FTiM to confirm good margin in controlled environment;
- Conventional technology not appropriate for commercial product

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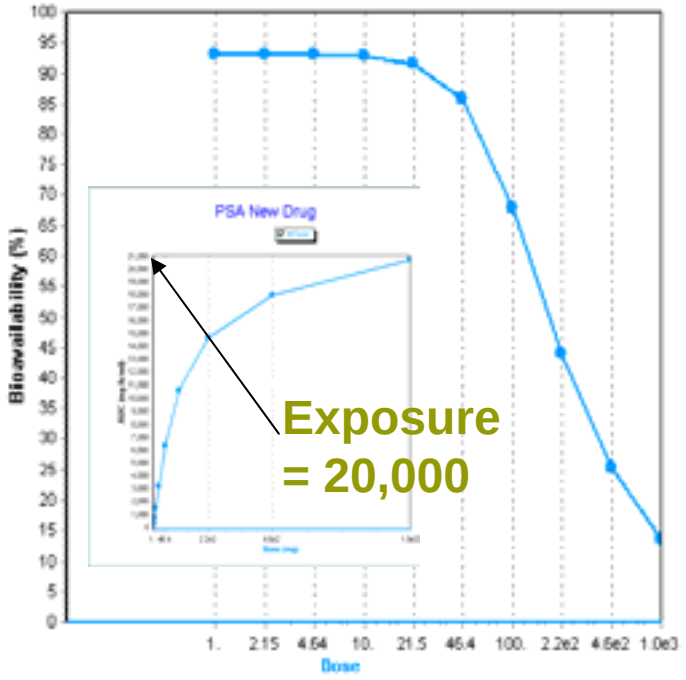
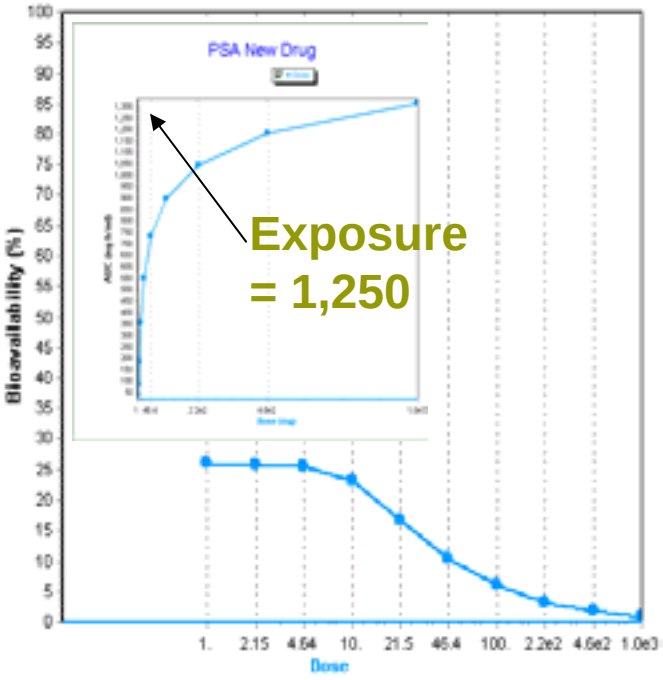
# Effect of permeability

- No fix for permeability: affects exposure/bioavailability and linearity at high dose

**High Perm**




**Same but low Perm**

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# So insufficient permeability may mean:

- Insufficient exposure;
- High cost of goods (due to low fraction absorbed);
- No formulation fix available;
- Controlled release not an option

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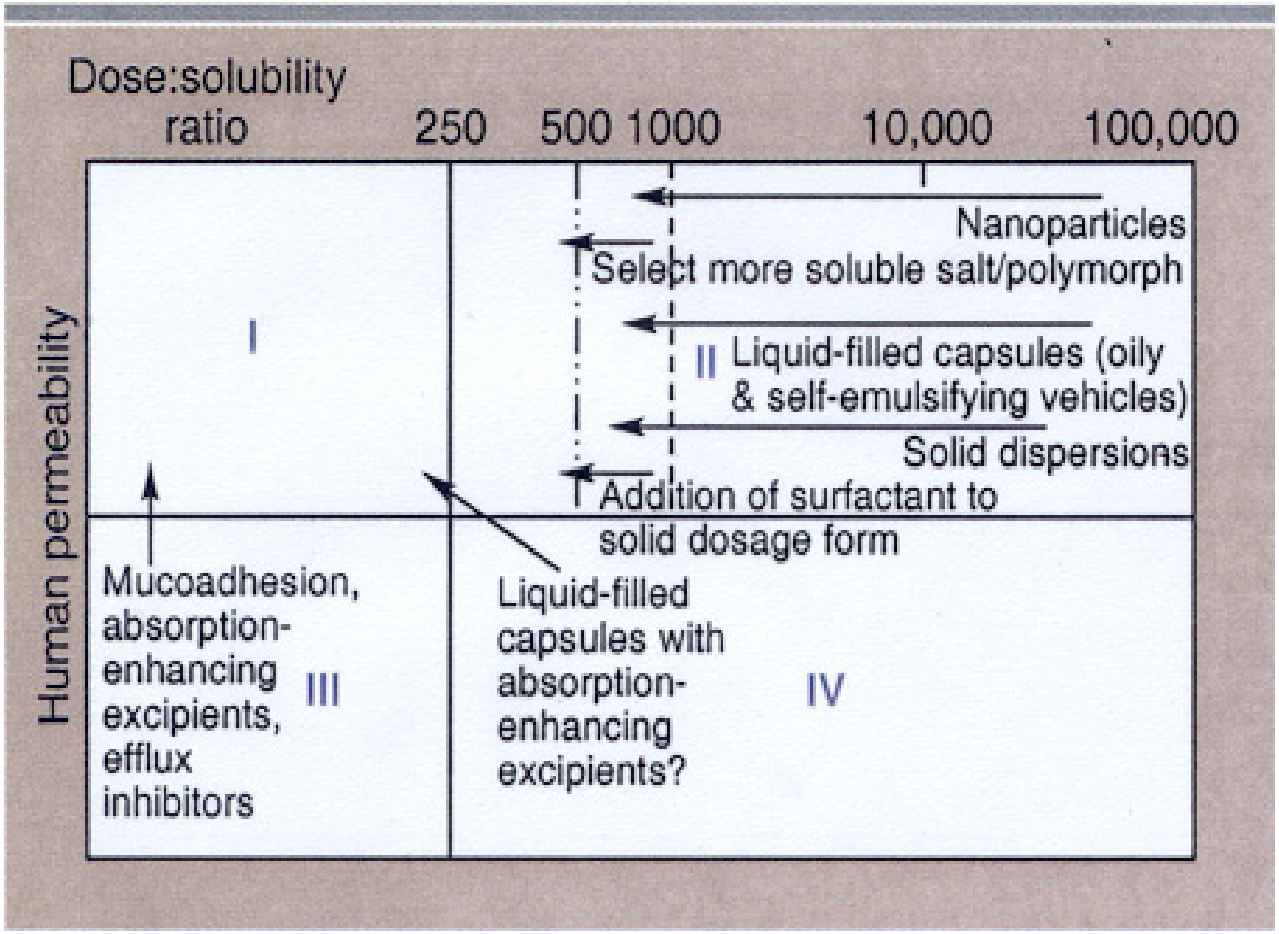
## By understanding biopharm can understand what formulation approach is appropriate for FTiM, preclinical and commercial

Dressman *et al*. (2001) Pharm Tech. July: 68.

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# Improving Solubility

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# Improving Solubility - Salts

- High biopharmaceutical Risk:
  - Salt Selection applied to compounds with high biopharmaceutical risk from a dissolution rate limited exposure perspective;
- Salt selection methodology:
  - 2 pKa rule:
    - pKa of acid must be two units or greater below that of the pKa for the base
    - pKa of base must be two units or greater above that of the pKa for the acid
- Intrinsic solubility ($S_0$):
  - has a bearing on what salts can form in an aqueous system;
  - The lower the intrinsic solubility, the lower the pHmax, the stronger the acid required to form stable salts;
- Aim of salts:
  - To predict or show improved exposure from salt form dosed at a relevant clinical dose in in vitro and/or in vivo models

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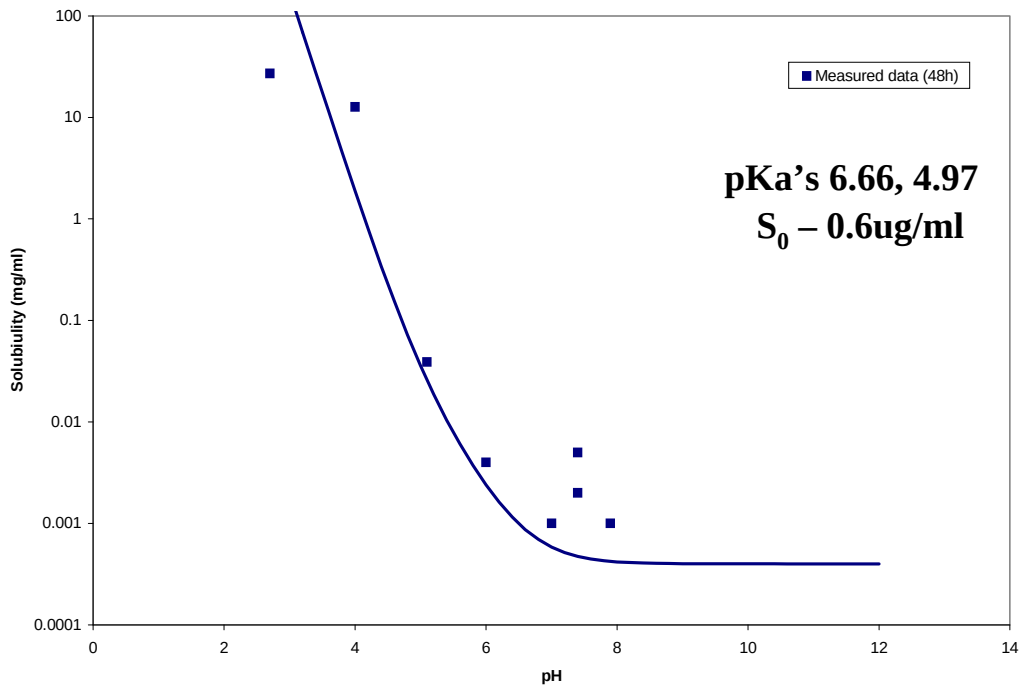
# Predicted and Measured pH Solubility Profile of a Weakly Basic Drug




➢**Intrinsic Solubility:**

- **Defined as the solubility of the unionised or neutral form;**
- **Can be useful to measure accurately in order to give good predictions of pH solubility profile;**
- **Is not independent of crystalline form;**
- **For a weak base with a ionisation constants *k*1 and *k*2 solubility (S) at a given pH is given by the following equation:**

$$S/S_O = 10^{\log k1 + \log k2 - 2\,pH} + 10^{\log k1 - pH} + 1$$

# Salt Selection - Haloperidol Example

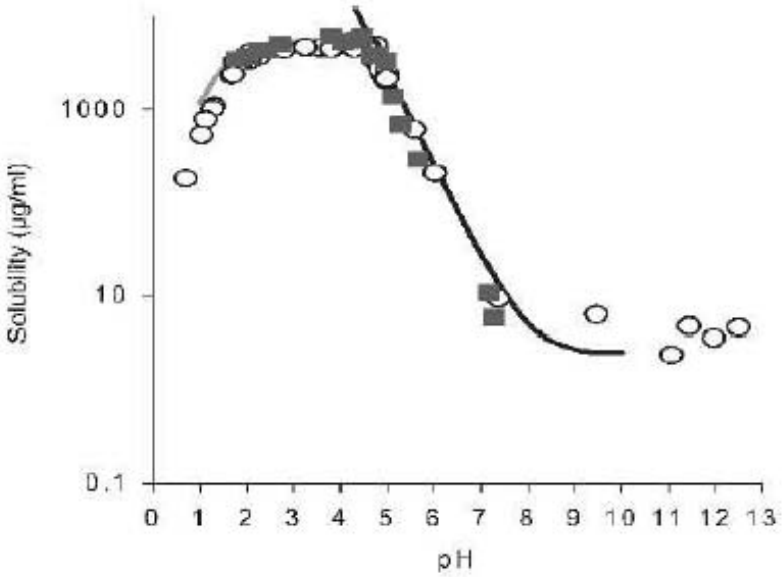
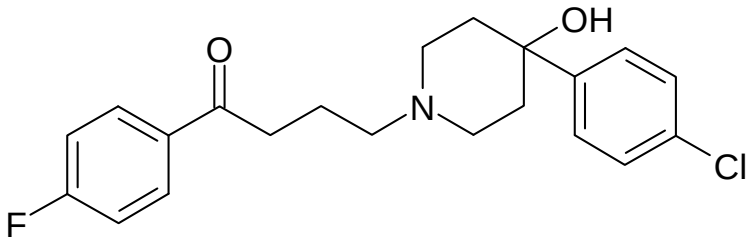



**Fig. 2.** pH-solubility profile for haloperidol free base (■) and its HCl salt (○).




**pKa = 8.0**

**$S_o$ = 2.5µg/ml**

$$S/S_0 = 10^{\log k\,1-pH} + 1$$

$$pH_{\max} = pK_a + \log\frac{S_0}{\sqrt{K_{sp}}}$$

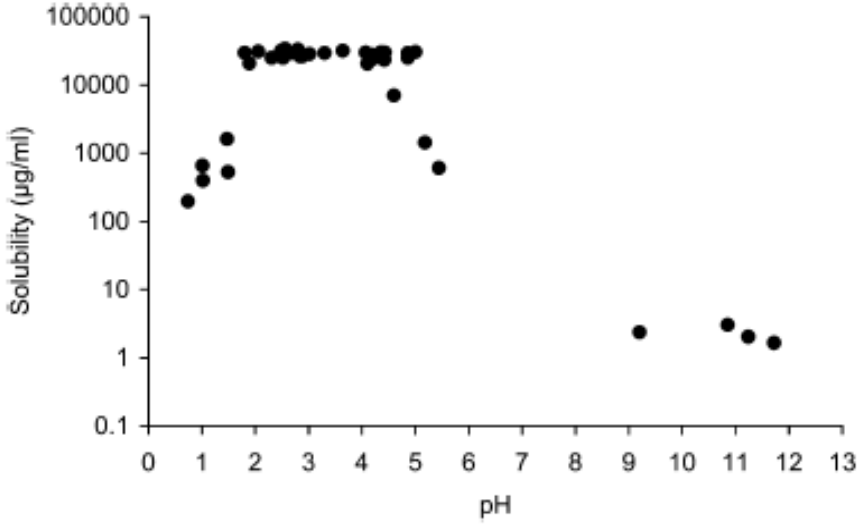



**Fig. 3.** pH-solubility profile for haloperidol mesylate (●).

L Shoufen et al, Pharm Res, Vol 22, No. 4, April 2005, 628-635

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# Formulation Development

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# Overview

- Increasing numbers of poorly soluble compounds in industry
- Growing need for enabling technologies
- Need to move rapidly to get into clinic at earliest opportunity
  - Know if drug has potential to be a product
- Challenge is to integrate development of these potentially complex technologies, without delaying the overall drug development program

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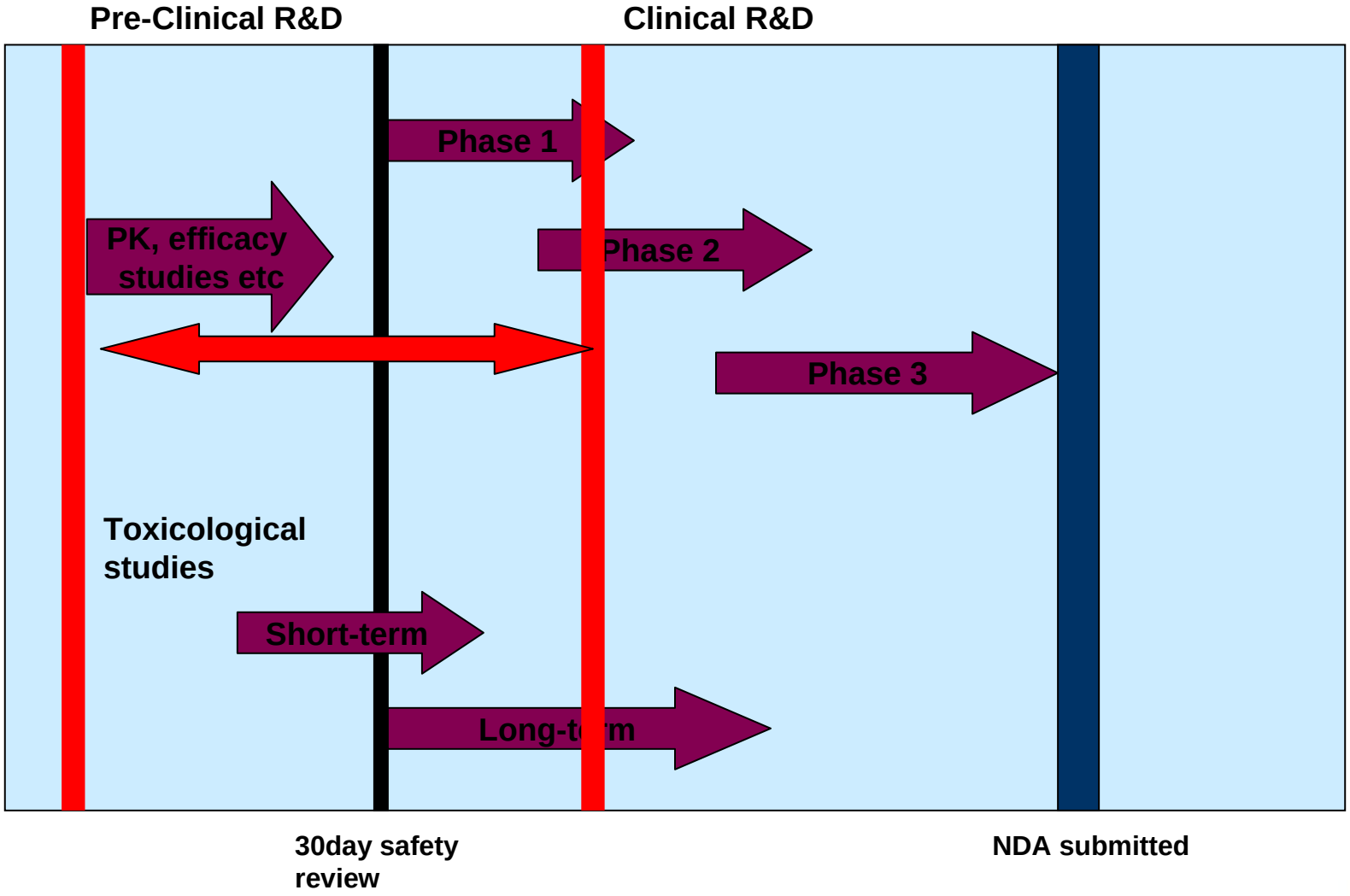
# Early Formulation - which studies and when?




Adapted from FDA CDER Handbook – New Drug Development and Review

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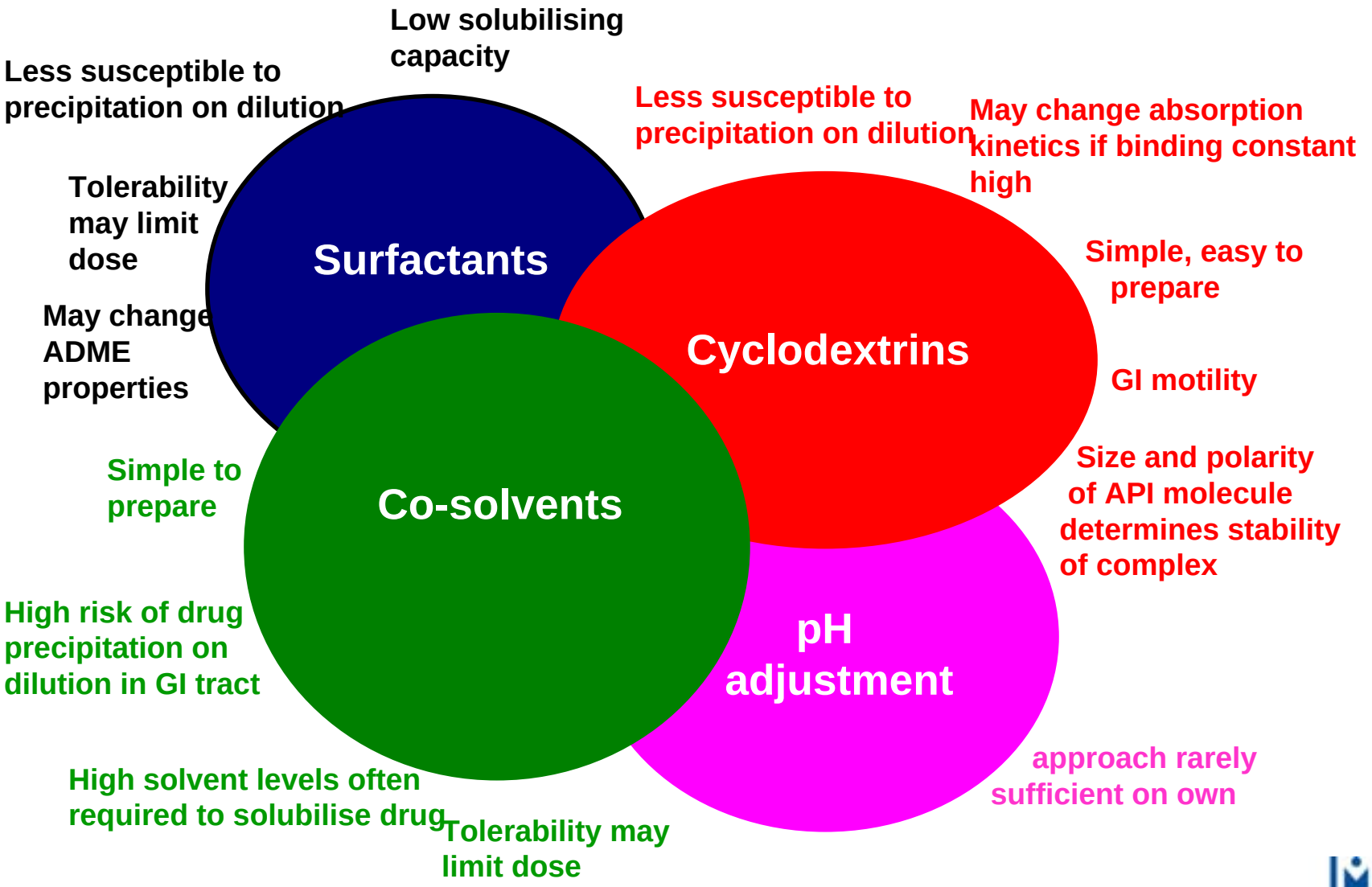
# Solution formulation options



# Drug Delivery technologies

- Solid dispersions
- Lipid-based drug delivery systems (LB-DDS) – Lipidics
- Crystalline nanosuspensions/nanoparticles
- Amorphous nanosuspensions

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# Lipid-based drug delivery systems (LB-DDS)

- Liquid or semi-solid lipidic formulations
- Dosed as a liquid, pre-dispersed in aqueous media or as a capsule/tablet
- Lipid Formulation Classification System proposed by Colin Pouton

| Formulation type | **Materials** | **Characteristics** |
|---|---|---|
| Type I | Oils without surfactants (e.g. tri-, di-and monoglycerides) | Non-dispersing, requires digestion |
| Type II | Oils and water-insoluble surfactants | SEDDS formed without water-soluble components |
| Type III a/b | Oils, surfactants, cosolvents (both water-insoluble and water-soluble excipients) | SEDDS/SMEDDS formed with water-soluble components |
| Type IV | Water-soluble surfactants and cosolvents (no oils) | Formulation disperses typically to form a micellar solution |

- SEDDS = Self emulsifying drug delivery systems, SMEDDS = Self microemulsifying drug delivery systems. Both disperse under gentle agitation in gut
- Adapted from Pouton C.W. and Porter, C. J. H., (2007) Adv Drug Del Rev, 60(6) 625-637

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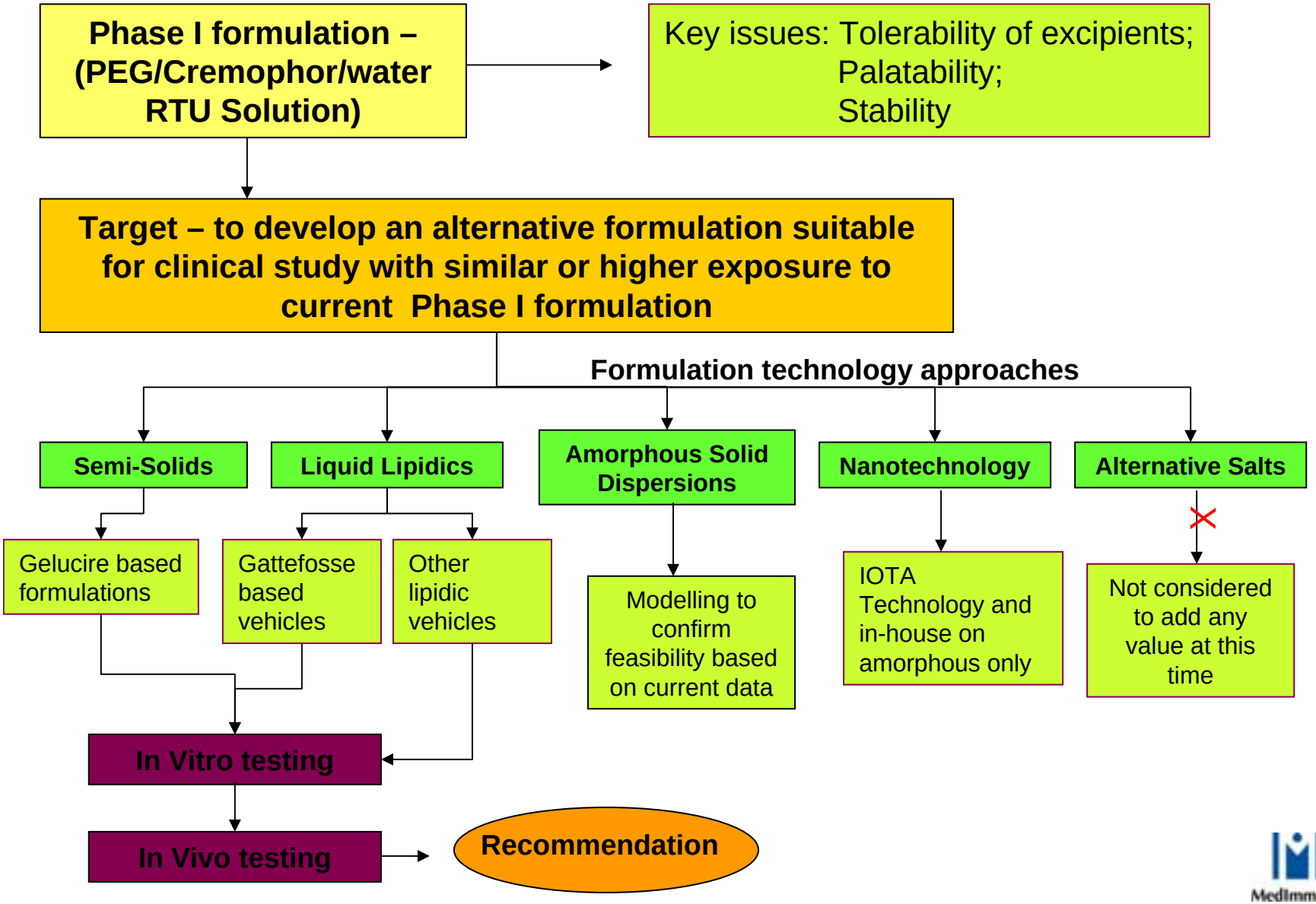
# Formulation Feasibility Case Study



# Summary

- Multiple formulation options exist for early formulation development of poorly solubles
  - Clinically and preclinically
- Decision of which technology to apply based on many factors
  - Theoretical assessments combined with screening
  - Provide recommendation on way forward and associated risks/opportunities
- No one technology suitable for all API’s

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# Summary

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# Summary

"*Novel observations in Research constitute Discoveries, novel observations in late Development constitute Disasters, Pharmaceutical Development includes those elements of research that may limit Development Disasters*"

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# Back ups



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# Biopharmaceutics Classification System

- Defines drugs based on solubility (dose in <250mL pH 1 to 7.5) and permeability (fa >90%).

- Class 1: high solubility and high permeability.
- Class 2: low solubility and high permeability.
- Class 3: high solubility and low permeability.
- Class 4: low solubility and low permeability.

**A regulatory guidance that allows us to avoid some clinical studies**

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# Dissolution and Solubility

**Modified Noyes-Whitney Equation:**

$$\frac{dX_d}{dt} = A \cdot \frac{D}{h} \cdot \left[ C_s - \frac{X_d}{V} \right]$$

| Factor | Physicochemical parameter | Physiological parameter |
|---|---|---|
| Surface area (**A**) | Particle size<br>Wettability | Gastric surfactants<br>SI bile salts |
| Diffusivity of drug (**D**) | Molecular size, | Viscosity of luminal contents, 'bile' micelle size |
| Boundary layer thickness (**h**) | | Motility pattern and flow rate |
| Solubility (**Cs**) | Hydrophilicity<br>Crystal structure | pH, buffer capacity, bile, food components |
| Amount of already dissolved drug (**Xd**) | | Permeability |
| Volume of solvent availble (**V**) | | Secretions,<br>Co-administered fluids |

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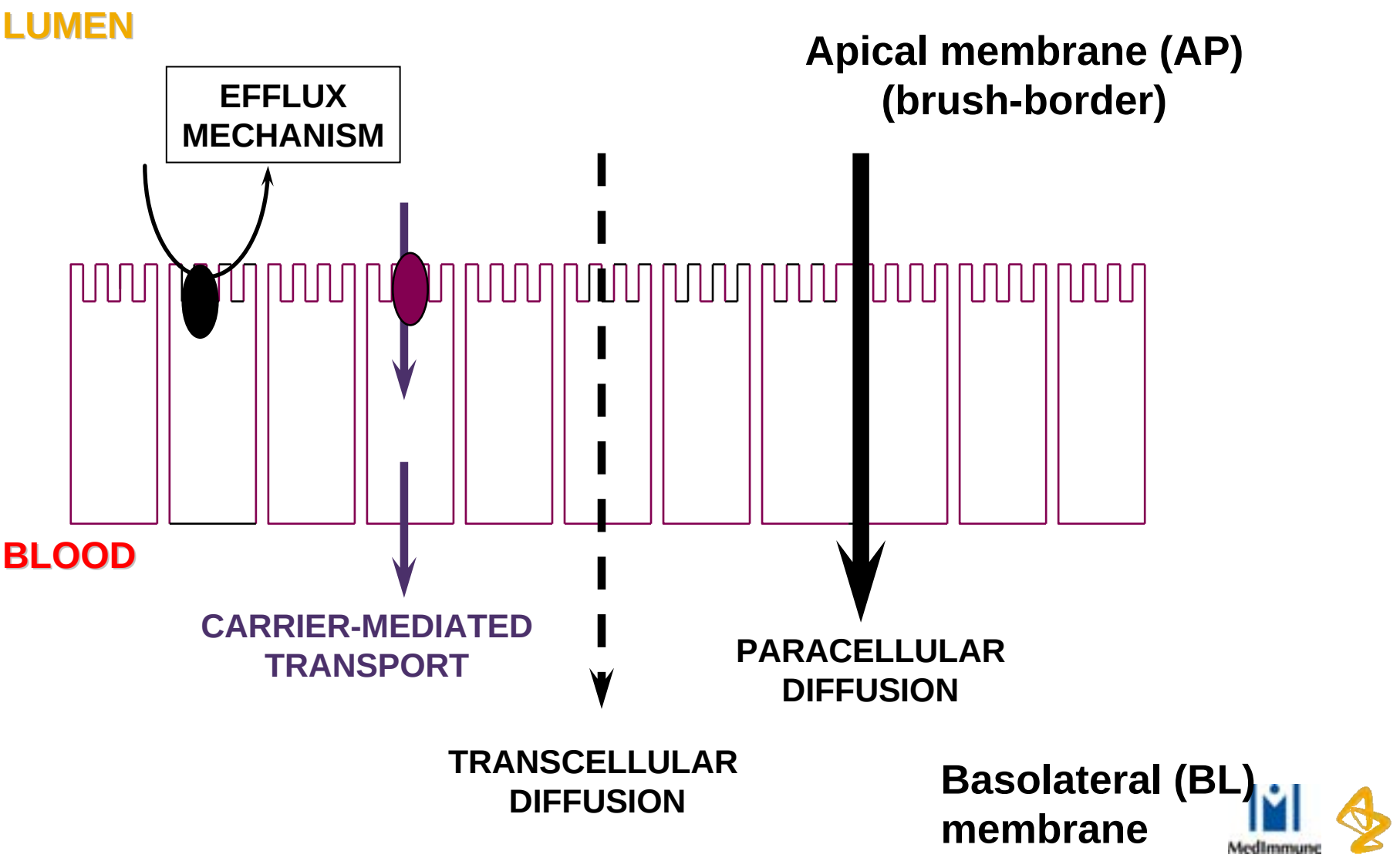
# Permeability:
# Transport Pathways across intestinal epithelial cells



# Lipid-based drug delivery systems (LB-DDS)

**Solid dosage form manufacturing methods include**

- **Liquid or semi-solid filled capsules**
- **Conversion to solid particles for filling into capsules, sachets, compression to tablets via**
  - melt granulation, melt pelletisation or spray congealing of semi-solids
  - Adsorption onto inert matrices (liquid or semi-solid lipidics)
- **Complex in vivo behaviour**
- **Bioavailability may be enhanced via ***
  - Maintaining drug in solution/solubilising drug along GI tract
  - Alteration of composition of intestinal fluids
    - Activation of Lipid digestion
  - Inhibition of efflux/CYP enzymes
  - Protection from chemical/enzymatic degradation in GI tract
  - Alteration of gut permeability
  - Promotion of lymphatic uptake (compounds with logP>5, oil solubility >50mg.ml)

* O'Driscoll, C.M. and Griffin, B.T (2008) Adv. Drug. Del. Rev. 60(6) 617-624

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# Lipid-based drug delivery systems (LB-DDS)

- API criteria
  - Log P>2, (log P >4 for oily vehicles)*
  - Log P >5 may be absorbed through lymphatic pathway
  - Increased drug bioavailability in fed state

- Key issues
  - Predicting in vivo performance from in vitro data
  - Regulatory and Safety status of lipidic excipients
    - High surfactant levels in type IIIa/b and IV lipidics
  - Characterisation of semi-solid lipidics
  - Batch to batch variability in excipients

* Pouton C.W (2000) Eur J. Pharm. Sci., 11(2) S93-S98

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# Solid dispersions

- Dispersion of API in polymer matrix (Shanbhag *et al* *)
  - molecularly dispersed drug
  - multiparticulate dispersed drug
    - crystalline or amorphous drug as domains
- Commonly used polymers types include PVP, PEG & HPMC
- Bioavailability enhanced by
  - increasing dissolution rate
  - increasing solubility in GI tract (supersaturated)
  - prevention of subsequent drug precipitation
- Manufacturing methods include:
  - evaporation-based methods ie drug/polymer dissolved in organic solvent which is subsequently removed by spray drying, vacuum/heat driven methods
  - hot melt methods ie mixing of molten drug/polymer or drug dissolves in molten polymer eg melt extrusion, hot-melt encapsulation
- Solid dosage form or pre-disperse in aqueous media for early studies

*** Shanbhag, A. et al, (2008) Int. J. Pharm. 351, 209-218**

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# Solid dispersions

- General API properties
  - Solvent solubility (spray drying)
  - High temperature stability (melt extrusion)

- Key issues
  - Physical and chemical instability of drug/formulation
  - Residual solvents
  - Hygroscopicity (excipients may be hygroscopic and water uptake may potentiate recrystallisation where drug is amorphous)
  - Analytically more challenging to characterise

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# Crystalline Nanosuspensions

- Crystalline drug nanoparticles stabilised with surfactants/polymers *
- Prepared by number of techniques eg wet milling, high pressure homogenisation, microfluidisation
- Bioavailability enhanced by increasing drug dissolution rate due to high surface area
- Potential for high drug:excipient ratio
  - less risk of excipient tolerability limiting dose
- Viscosity may limit concentration achievable and hence dose

*** Rabinow, B.E., (2004) Nat Rev Drug Disc, 3 785-796**

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# Crystalline Nanosuspensions

- API properties */**
  - Dissolution-rate limited bioavailability
  - Free form  and most stable form preferred
  - Low solubility reduces Ostwald ripening
  - More likely to succeed with low aqueous solubility and high melting point API's than other technologies eg lipidics
- Key issues
  - Physical instability
    - Agglomeration – overcome by electrostatic repulsion or steric stabilisation
  - Potentially long processing times (milling)

*** Rabinow, B.E., (2004) Nat Rev Drug Disc, 3 785-796, ** Kesisoglou, F et al (2007), 59, 631-644**

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