INTERNATIONAL COLLEGE OF PHARMACEUTICAL INNOVATION

国际创新药学院

Solubility Enhancement Strategies (I, II, III)

Course	**BSc (Pharm) or BSc (ATT)**
Year	**2024-2025 I**
Module	**Medicines: Pharmaceutics 1 (MP1)**
Lecturer	**Dr. Shi Du**

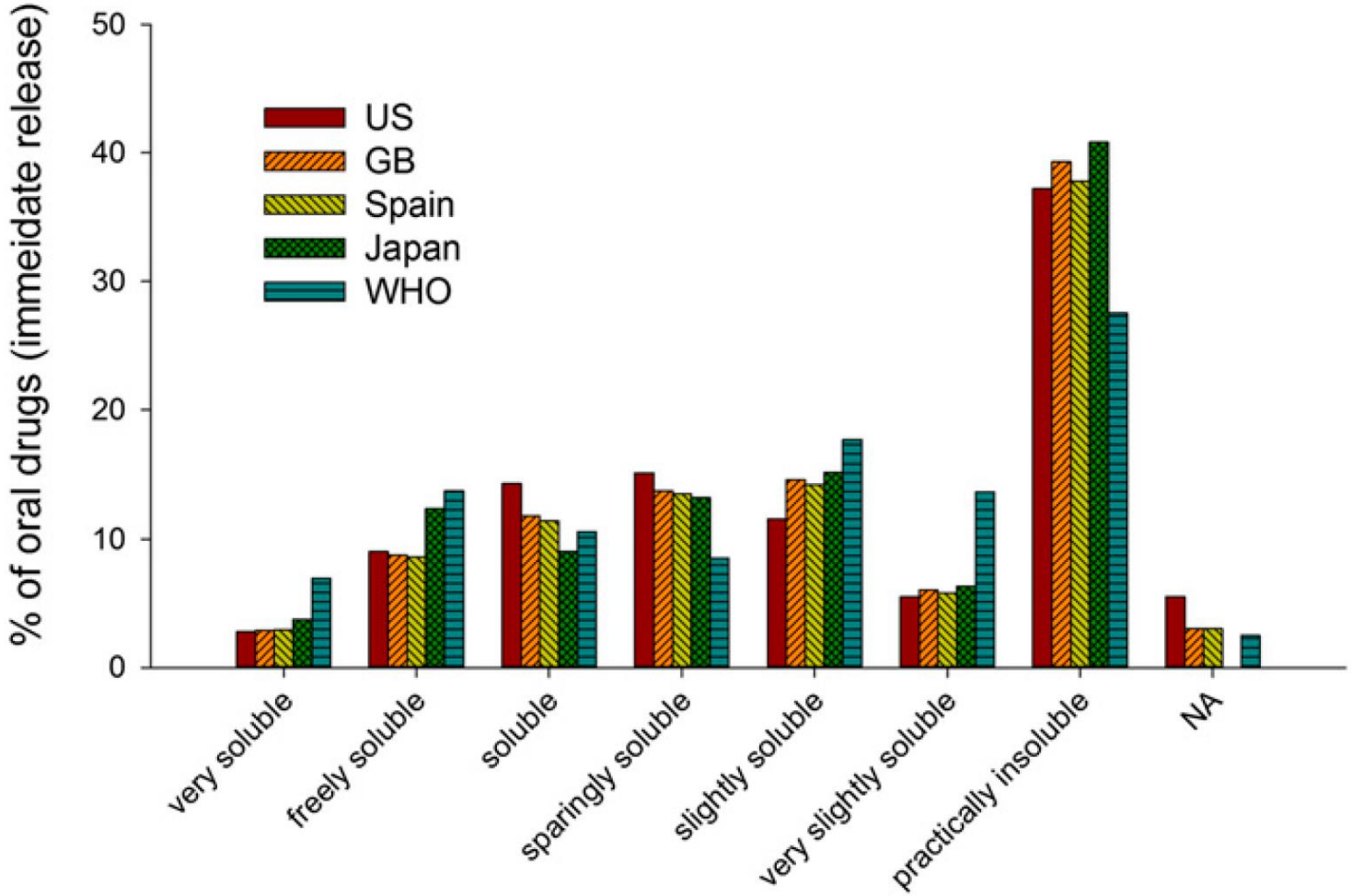
LEARNING OUTCOMES

1. Highlight the pharmaceutical problem posed by poor solubility
2. Describe the strategies used to improve drug solubility

WHAT IS LOW DRUG SOLUBILITY?

- Many receptor mediated interactions are (in part) by hydrophobic interactions (drug:receptor)
- High lipophilicity is a common problem in pharmaceutical drug development
    - 40% of marketed drugs have low aqueous solubility
    - Up to 75% of compounds in currently under development
- Risk: low and variable absorption

SOLUBILITY OF THE TOP 200 MARKETED ORAL DRUG PRODUCTS



EXAMPLES OF DOSE, SOLUBILITY AND VOLUME REQUIRED FOR A RANGE OF POORLY WATER SOLUBLE DRUGS

Drug	Dose	Solubility	Volume required for complete solubilisation	Absorption
Piroxicam	20mg	7 mcg/mL	2857	Low variable
Digoxin	0.5mg	24 mcg/mL	21	Good
Griseofulvin	500mg	15 mcg/mL	33,333	Low, variable
Chlorthiazide	500mg	780mcg/mL	636	Intermediate

BRICK DUST AND GREASE BALLS

BRICK DUST

- Hydrophobic and exhibit strong intermolecular forces in the solid state
- Poorly soluble in aqueous and non-aqueous solvents

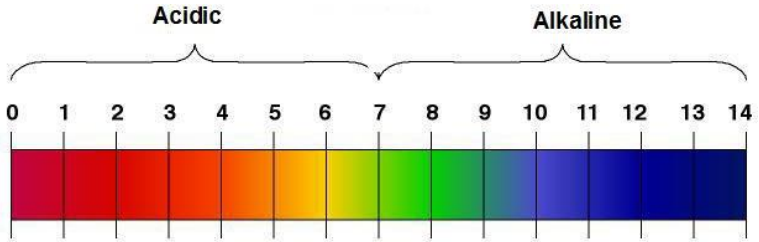
GREASE BALLS

- Hydrophobic solutes where solubility is not limited by solid state properties
- Soluble in non-aqueous solvents
- Hydrophobic and lipophilic

STRATEGIES TO ENHANCE SOLUBILITY

1. MANIPULATION OF pH
2. SALT FORMATION
3. CRYSTAL ENGINEERING
4. PARTICLE ENGINEERING
5. CO-SOLVENCY
6. SOLID DISPERSIONS
7. SURFACTANT SOLUBILISATION
8. PRODRUG
9. DRUG DERIVATION
10. LIPID BASED FORMULATIONS
11. LIPID-BASED DRUG DELIVERY SYSTEMS
12. INCLUSION COMPLEXES
13. EMERGING STRATEGIES

MANIPULATION OF PH



- Adjusting solution pH provides an effective means of increasing the proportion of a weakly acidic and weakly basic drug that is present in the more polar ionised form
    - Effectiveness of pH manipulation is a function of pKa and Log D
    - Useful when preparing solution dosage forms (e.g. for parenteral delivery)

75% of drugs are weak bases
20% of drugs are weakly acidic
5% non-ionic and amphoteric

PHARMACEUTICAL SALTS

- In many ways salts of weak acids and bases are the solid state equivalent of pH adjustment. Salts are formed by an ionic interaction between weakly acidic or basic drugs and an oppositely charged basic or acidic counterion.

- When placed in water the salt form dissociates and the oppositely charged counterion which they where derived from shift the pH of the solution to provide an analogous endpoint to that obtained by pH adjustment. The salt form also alters the crystal lattice

- A drug may exist in several salt forms which have different physicochemical properties

Regulatory agencies do not consider different salt forms as equivalent

SALT FORMATION

$$CH_3COONa \rightarrow CH_3COO^- + Na^+$$

$$CH_3COO^- + H_2O \leftrightarrow CH_3COOH + OH^-$$

$$NH_4Cl \rightarrow NH_4^+ + Cl^-$$

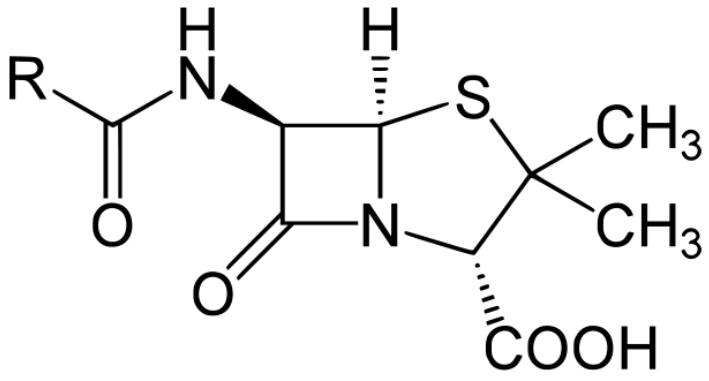
$$NH_4^+ + H_2O \leftrightarrow NH_3 + H_3O^+$$

COMMON COUNTER IONS IN ORAL DELIVERY

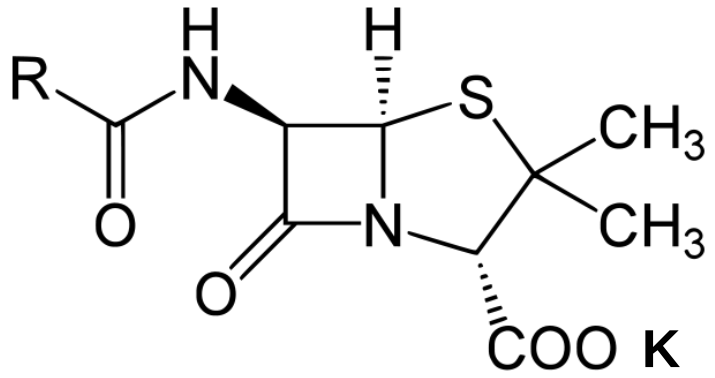
BASIC COUNTERIONS	ORAL %
Sodium	65
Potassium	13
Calcium	12
Magnesium	3
Tromethamine	3
Tartrate	3
Succinate	2

ACIDIC COUNTERIONS	ORAL %
Chloride	57
Sulphate	8
Maleate	7
Mesylate	4
Bromide	4
Phosphate	3
Tartrate	3

SALT FORMATION AND SOLUBILITY



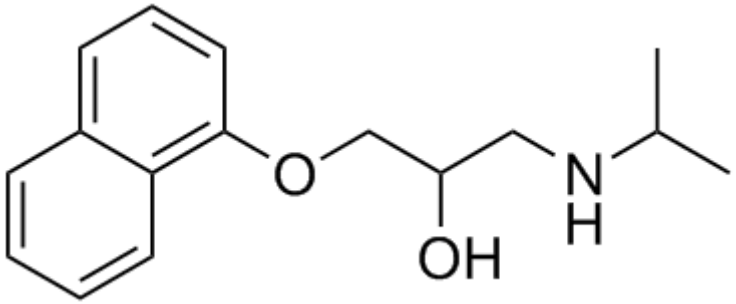
- Penicillin
- Mw: 334 Da
- Water solubility: 210mg/1000mL



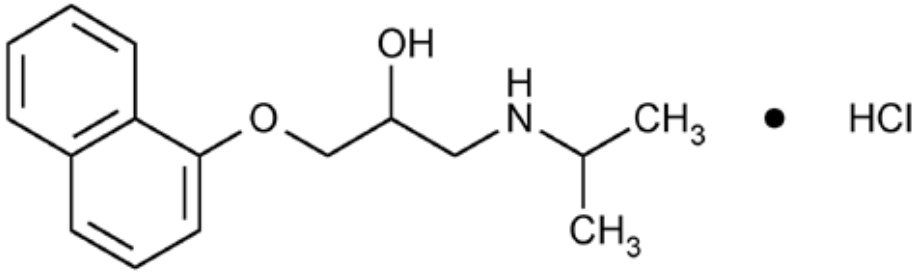
- Penicillin Potassium
- Mw: 372 Da
- Water solubility >100mg/1mL

Acids donate protons to hold a formal anionic charge (conjugate base form) making them soluble in the salt form (e.g. Na salt)

SALT FORMATION AND SOLUBILITY



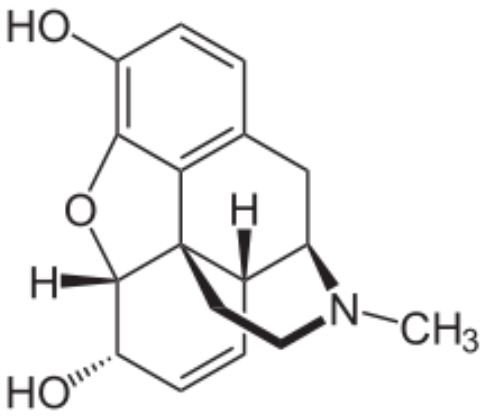
- Propranolol
- Mw: 259.34 Da
- Water solubility: 1g/956mL



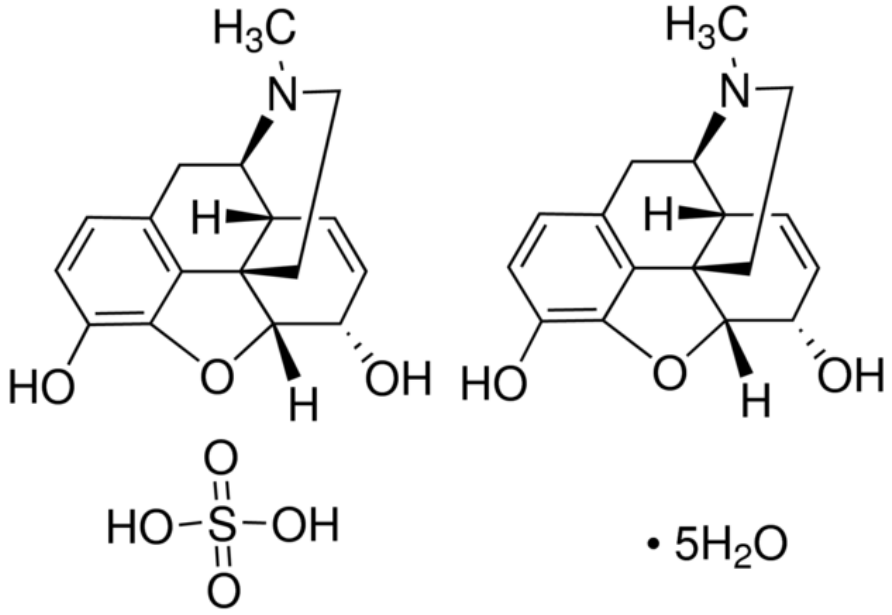
- Propranolol HCl
- Mw: 295.8 Da
- Water solubility 1g/20mL

Bases accept protons to hold a formal cationic charge (conjugate acid form) that makes them soluble in the salt form (e.g. hydrochloride salt)

SALT FORMATION AND SOLUBILITY



- Morphine base
- Mw: 285.34 Da
- Water solubility: 149mg/L



- Morphine sulphate
- Mw: 668.83 Da
- Water solubility 10g/L

SALT FORMATION CAN INCREASE OR DECREASE SOLUBILITY TO TAILOR RELEASE

Drug	Solubility (mg/mL)
Tetracycline	1.7
Tetracycline HCl	10.9
Tetracycline phosphate	15.9
Erythromycin	2.1
Erythromycin Estolate（酯化物）	0.16
Erythromycin stearate（硬脂酸盐）	0.33
Erythromycin lactobionate（乳糖双酸盐）	20

THE LIMITATIONS OF SALT FORMS

CASE: A sodium salt of an acidic drug (pKa 5.5) dissolves in a dissolution bath at the pH of the stomach (~pH 2) and subsequently forms a fine precipitates (comes out of solution as solid particles). Comment on this phenomena……

COMMON ION EFFECT

- Hydrochloride salts and sodium salts of weak acids and weak bases are common drug salts because they are physiologically abundant (safe)

- These ions are abundant in blood and the GI tract and these ions (Cl, Na) can suppress the solubility of the drug that they are intended to enhance through the common ion effect

The common ion effect is the displacement of an ionic equilibrium by addition of more than one of the ions involved

- Equilibrium will shift so that common ion in solution is reduced, leading to precipitation

$$\left(BH^+X^-\right)_{solid} \overset{K_{sp}}{\rightleftharpoons} \left[BH^+\right] + \left[X^-\right]$$

CASE DRUG AND SALT FORMS

- The two most common oxidation states of iron are the ferrous [Fe(II)] and ferric [Fe(III)] forms

Fe^{2+}

F_{ABS}: 10-15%
Relatively good solubility

Solid form
- Ferrous sulphate (Ferrograd® Tablets)
- Ferrous fumarate (Galfer® Capsules)
- Ferrous Gluconate (Floradix® Liquid)

Side effects
- Constipation
- Heart burn
- Abdominal pain
- Nausea

Prevalence of side effects
Ferrous sulphate: 31.6%
Ferrous fumarate: 44.8%

Fe^{3+}

F_{ABS}: 2.5-5%
Relatively poor solubility

Solid form
- Fe(III) Polymaltose Complex (Ferrum®)

Side effects
- Constipation
- Heart burn
- Abdominal pain
- Nausea

Prevalence of side effects
Ferric iron: 7%

ADDITIONAL FUNCTIONS OF SALT FORMATION

- Sustained release (depot injection, procaine penicillin)
- Taste masking (e.g. Erythromycin ethyl succinate)
- Improved chemical stability (Erythromycin propionate)
- Process optimisation (flowability, compaction)

PHYSICAL PROPERTIES OF PHARMACEUTICAL SALTS

- Salt properties vary depending on the drug, salt properties and solvent used to isolate the salt

- Salts exist in many chemical forms
  - Crystalline form
  - Crystalline solvates/hydrates
  - Liquid crystals
  - Irregular amorphous states

- Crystals typically have greater physical stability compared with drug base

- Hygroscopicity can be an issue for salt forms

- Drug bases with low melting point are often soft and plastic which creates problems in formulation (disintegration, friability, uniformity) and process (flowability, compressibility, dissolution) development

SALT FORMATION CAN INCREASE OR DECREASE SOLUBILITY TO TAILOR RELEASE

ADVANTAGES	DISADVANTAGES
•Altered solubility and dissolution	•Only ionisable drugs
•Controlled release	•Decreased % active
•Improved thermal, hydrolytic & photostability	•Increased potential for formation of solvates and polymorphs
•Improved processability	•Salt corrosion
•Improved permeability	•Additional processing step in production
•Improved organoleptic properties	•Possible for release of hydrohalide gas resulting in reaction with excipients or processing chemicals
•Reduced pain on injection	

CRYSTAL ENGINEERING

- Crystal engineering: Deliberate design and control of molecular packing within a crystal structure with the intention of generating solid that shows a particular and desirable characteristic

- Any manipulation that results in altered crystal packing
  - Traditional approaches: salt, solvate, polymorph screening
  - Recent approaches: cocrystals
  - Particle engineering

  - HELPS TO OVERCOME SOLUBILITY LIMITATIONS RESULTING FROM STRENGTH OF THE CRYSTAL LATTICE

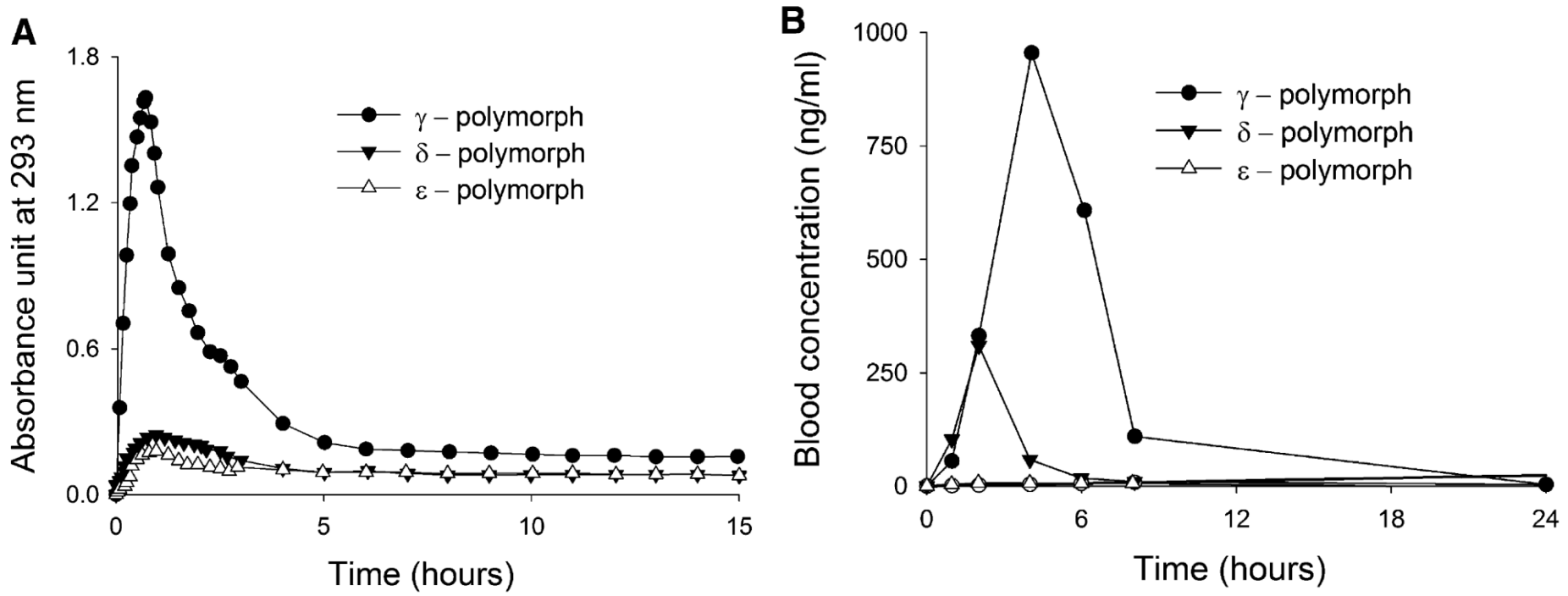
BONDING IN A CRYSTAL

- VAN DER WAALS FORCES (0.5-2 kJ/mol)
- π- πSTACKING (0.5-2 kJ/mol)
- ELECTROSTATIC INTERACTION (0.5-2 kJ/mol)
- HYDROGEN BONDING (5-30 kJ/mol)
- IONIC INTERACTIONS (150 kJ/mol)

- Higher the lattice energy the greater the stability (and lower solubility)

- PREPARATION OF A HIGH ENERGY POLYMORPH CRYSTAL OFTEN HAS MODEST IMPROVEMENT OF SOLUBILITY (DUE TO RECRYSTALISATION) BUT GREATLY IMPROVED ABSORPTION, BUT CAN SUFFER FROM INSTABILITY

INFLEUNCE OF POLYMORPH SELECTION ON DISSOLUTION, SOLUBILITY AND ABSORPTION OF RIFAXIMIN



COCRYSTALS

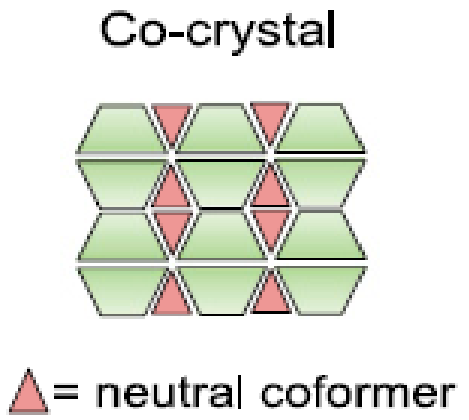
- **COCRYSTALS**: Mixed crystals consisting of two or more molecular species (that alone are solid at ambient conditions) held together by non-covalent and non-ionic forces

- Constitute a complex between drug and cocrystal former. Similar to salt formation, only proton exchange does not occur.

- Stabilisation of high energy crystal form that prevents unstable polymorphs from reverting to their stable form, while retaining improved solubility/absorption

- Dramatic increase in dissolution over simple crystals

- Some coformers can purposefully lower solubility



EXAMPLE COCRYSTAL COFORMERS

DRUG	COFORMER
INDOMETHACIN	SACCHARIN
EXEMESTANE	MALEIC ACID

COSOLVENTS

- **COSOLVENTS**: water miscible organic solvents that are widely used to increase solubility of poorly water soluble substances.

- Suited to drugs that lack ionisable functional groups
- Typical log P between 1-3
- Blending alters the dielectric constant such that the solvent polarity matches the drug polarity (like dissolves like), and reduces interfacial tension
- Safety and pharmacological action can be a concern (e.g. haemolysis)
- Occasionally a non-aqueous co-solvent blends are used
- Solubility in mixed solvents is difficult to predict
- A drug will often have higher solubility in a solvent mixture than neither neat solvent

COMMON COSOLVENTS IN PARENTERAL DELIVERY

COSOLVENT	DRUG	FORMULATION	ROUTE
PROPYLENE GLYCOL (40%) ETHANOL (10%)	DIAZEPAM	VALIUM	IV bolus (1mL/min)
ETHANOL (49%)	PACLITAXEL	TAXOL	IV infusion (dilute to <10% before infusion)

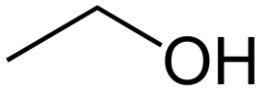
- 10-15 % of FDA approved parenteral products
- Increased risk of mechanical and chemical
  - Can irritate the injection site (phlebitis)
  - Systemic effect are more serious (e.g. pulmonary embolism)

COSOLVENTS IN ORAL DELIVERY

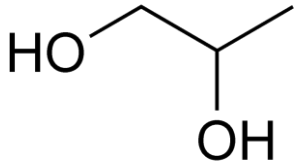
COSOLVENT	DRUG	FORMULATION	ROUTE
PROPYLENE GLYCOL	Emtricitabine	Emtriva	Liquid dosage form
ETHANOL	Morphine	Oramorph	Liquid dosage form
Low Mw PEGs	Bexarotene	Targretin	Liquid filled capsules
Glycerol	Ethosuxide	Zarontin	Liquid dosage form

- Higher volumes permissive via the oral route
- Intestinal mucosal perturbation can be noted with selected solvents
- Pharmacological Side effects can also be noted orally

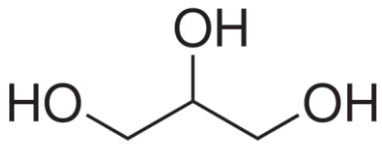
COMMON COSOLVENTS



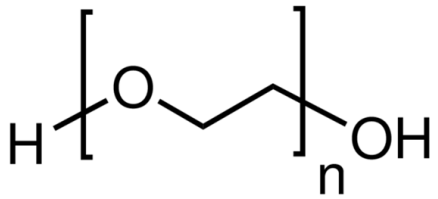
- Ethanol
- Mw: 46 Da
- LogP -0.31
- ε 25
- Monohydric



- Propylene glycol
- Mw: 76 Da
- LogP -1.1
- ε 32.1
- Polyhydric



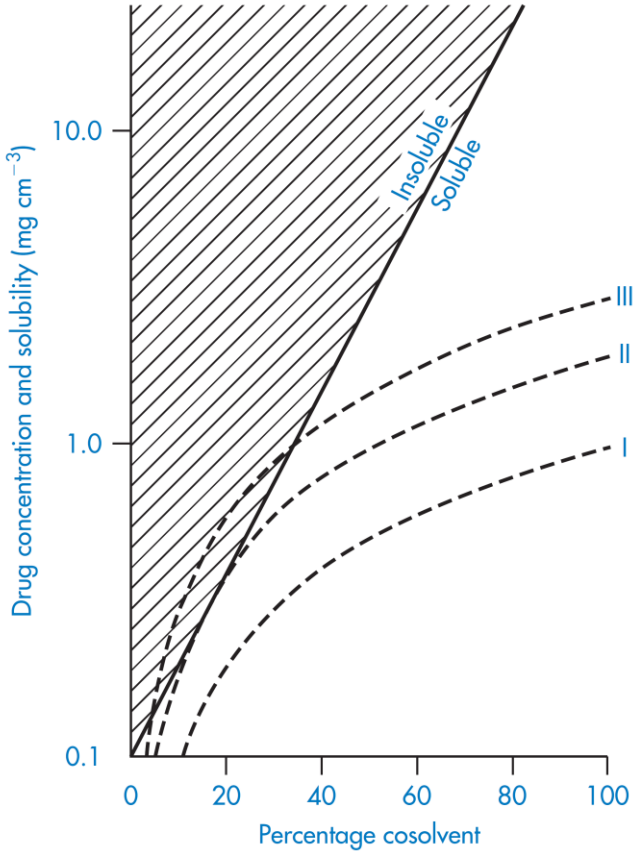
- Glycerol
- Mw: 92 Da
- LogP -1.9
- ε 42.5
- Polyhydric



- PEG400
- Mw: 400 Da
- LogP -0.38
- ε 12.4
- Monohydric

PROBLEMS PERTAINING TO DILUTION OF COSOLVENT BASED FORMULATION

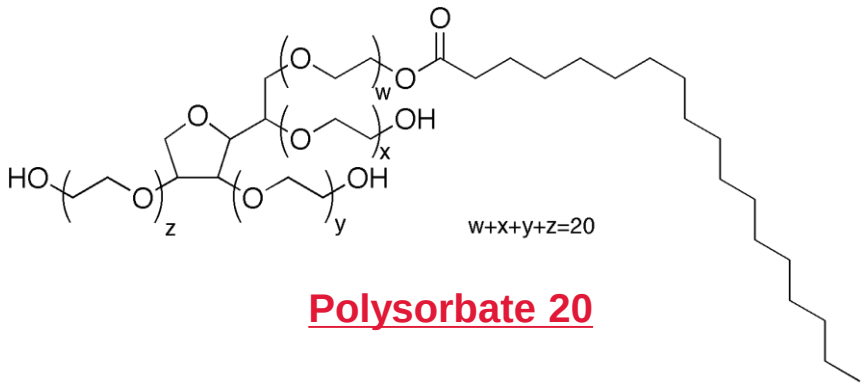
- Significant risk of drug precipitation depending on the rate of administration
  - Problematic for injectables
  - SC/IM Mechanical irritation
  - IV possibility of Embolism



SURFACTANT SOLUBILISATION

SURFACTANTS: Are amphipathic substances that possess hydrophilic and hydrophobic moieties at distinct ends of the molecule. Surfactants align themselves at interfaces (boundaries between phases of matter (e.g. water and air) to remove the hydrophobic region (lowering surface tension)

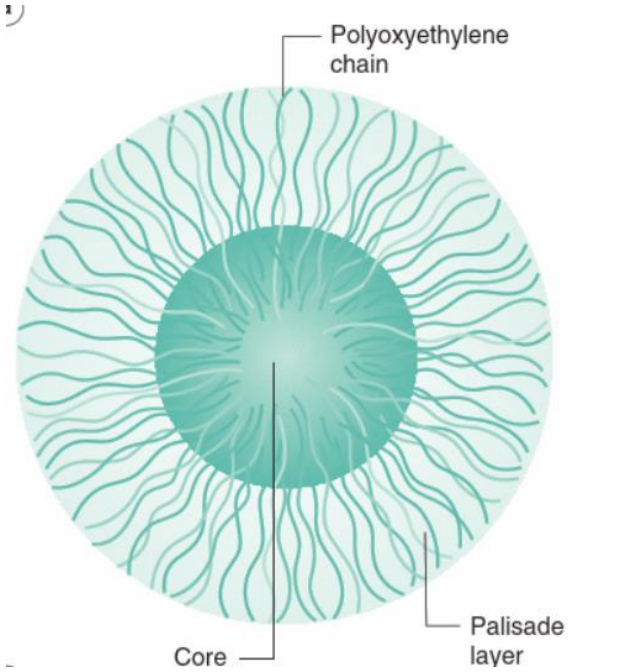
Hydrophilic: water loving
Hydrophobic water hating
Amphipathic water loving and hating



Polysorbate 20

MICELLE

- **MICELLES**: At a specific concentration soluble surfactants will associate into spherical aggregates called micelles. Micelles provide a nandroplet oil core that permit solubilisation of drugs



Micellar solubilisation is the process whereby water-insoluble substances are brought into aqueous solution by incorporation into micelles

MICELLAR SOLUBILISATION IN PARENTERAL FORMULATIONS

DRUG	SURFACTANT	FORMULATION
Paclitaxel	Cremophor® EL	Taxol
Cyclosporin A	Cremophor EL	Sandimmune
Amiodarone HCl	Polysorbate 80	Cordarone
Calcitriol	Polysorbate 20	Calcijex®

SAFETY OF SURFACTANTS IN SOLUBILISATION

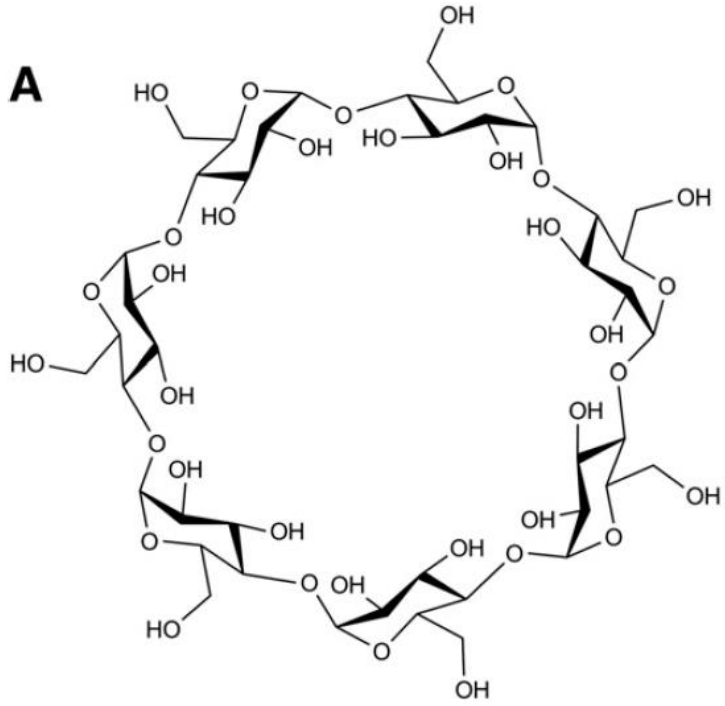
- Surfactants used in solubilisation are often capable of interfering in cell membrane structure and so restrictions are in place to ensure patient safety

  - Can cause pain at the injection site or lead to more hypersensitive reactions
  - Non-ionic and amphoteric solubilisers are more commonly used in parenteral and oral formulations
  - Anionic and cationic solubilisers are more commonly used in products for external use (e.g. creams)
  - Dilution can lead to precipitation

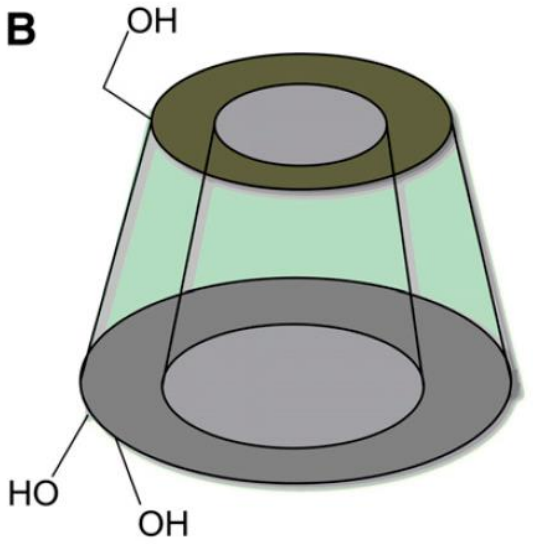
  - **CASE**: Taxol®

INCLUSION COMPLEXES

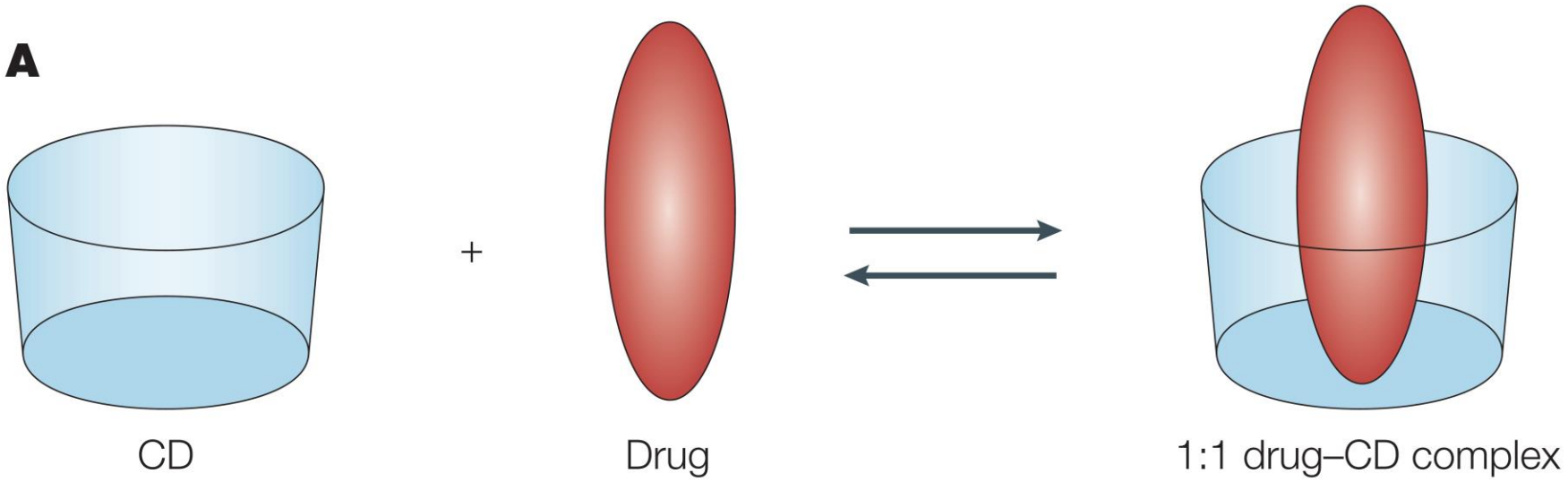
CYCLODEXTRINS: Are macrocyclic oligosaccharides consisting of a hydrophilic exterior and a hydrophobic interior cavity, within which non-ionic inclusion complexes are form that increase apparent drug solubility



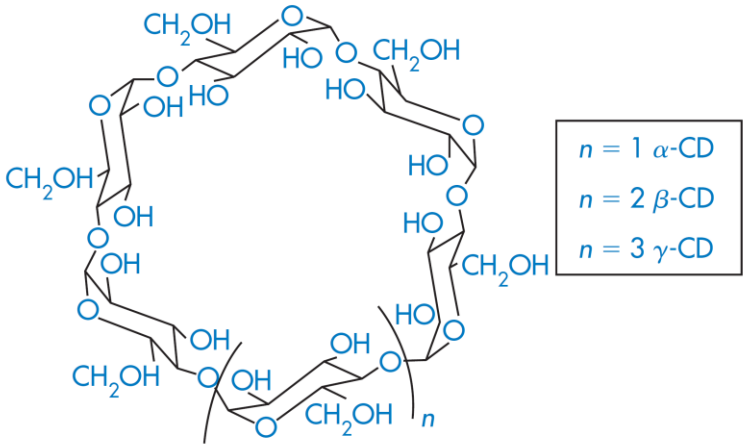
- Shape resemble a “bottomless flower-pot”
- Exterior-hydrophilic
- Interior-hydrophobic (cavity to fit drug)
- Used in oral and parenteral delivery
- Polarity of the cavity is likened to a water ethanol blend
- Generally 1:1 ratios
- Increase dissolution and bioavailability
- Solubility limited by solubility of CD
- Other examples: calixarines



CYCLODEXTRIN INCLUSION COMPLEX

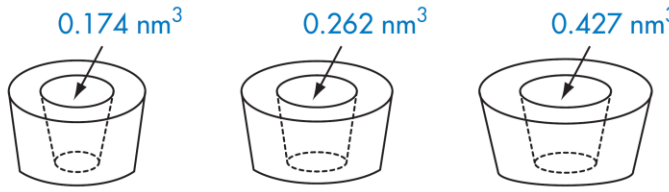


COMMON CYCLODEXTRINS

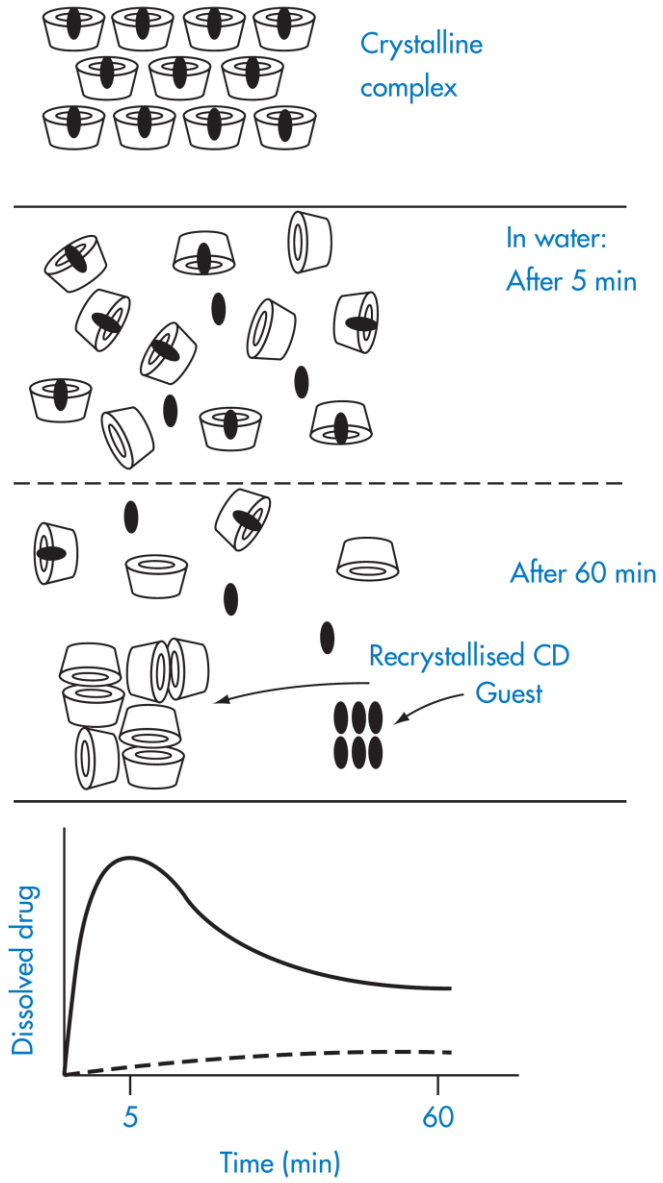


Cyclodextrin structure

Cavity volume:



	α-CD	β-CD	γ-CD
In one mole:	104 cm^3	157 cm^3	256 cm^3
In one gram:	0.10 cm^3	0.14 cm^3	0.20 cm^3

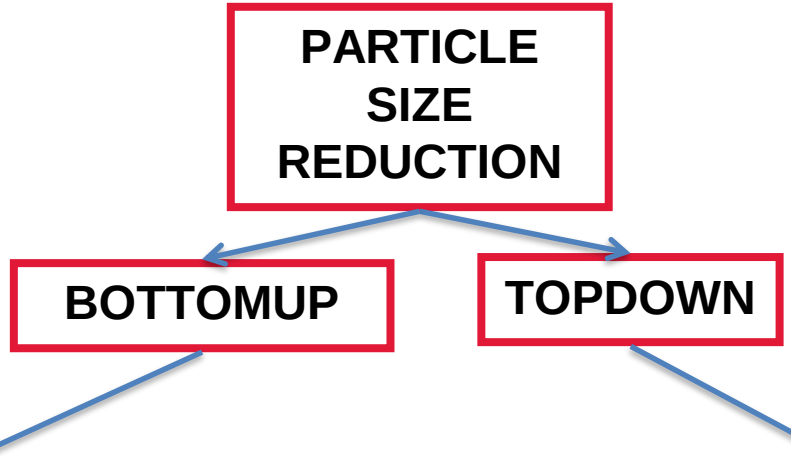


EXAMPLE FORMULATIONS IN ORAL & PARENTERAL DELIVERY

DRUG	FORMULATION	CD	ROUTE
ITRACONAZOLE	SPORANOX	HP-B-CD	ORAL, IV
OMEPRAZOLE	OMEBETA	B-CD	ORAL
ABILIFY	ARIPIPRAZOLE	SBE-CD	IM

PARTICLE ENGINEERING

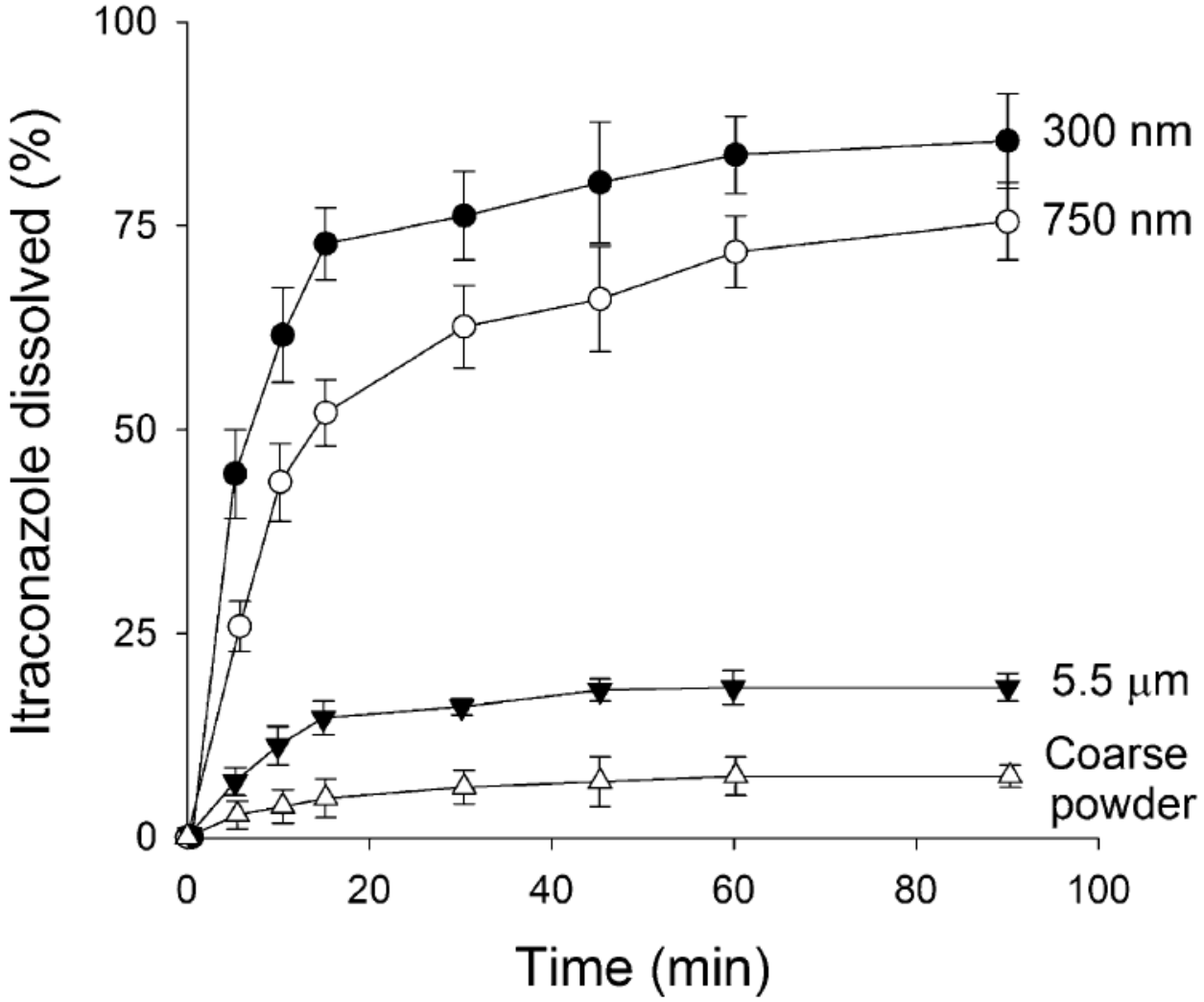
- **Particle size reduction**: Increases the surface area for solvation which increases the dissolution rate which in turn improves absorption



- Controlled crystalisation yielding nanoparticles
- Problems: Aggregation stabilisation

- Traditional: dry impact (high shear)
- Examples: Micronisation (2-5µm) via hammer, ball or air jet mills
- Newer technologies and stabilisers allows nanoparticles to be developed 200-500nm
- Examples: Nanocrystal® technol

IN VITRO DISSOLUTION OF ITRACONAZOLE FROM DIFFERENT PARTICLE SIZES



PARTICLE SIZE REDUCTION CAN INCREASE SOLUBILITY

- Sub-micron (<1 µm) particles are not physically stable, and effort to reduce energy in the system results in increased solubility

- Ostwald Freundlich equation $$\log \frac{C_s}{C_\infty} = \frac{2\sigma V_m}{2.303RT\rho r}$$

Methods

- **Pearl milling**: continuous stirring and wet milling of an aqueous drug slurry with durable milling “pearls” to create nanosuspensions (<400nm).
- Surfactant prevents destabilisation
- Nanocryatals® (Elan®, Ireland) are the most common pearl milling technology

MARKETED NANOSIZED DRUGS

DRUG	FORMULATION	TECHNOLOGY	ROUTE
Rapamycin	Rapamune	Nanocrystal®	Oral, tablet
Aprepitant	Emend	Nanocrystal®	Oral, capsule
Fenofibrate	Triglide	Dissocubes	Oral, Tablet

SOLID DISPERSIONS

- Solid dispersions increase drug dissolution and solubility via several mechanisms including:
    - REDUCED PARTICLE SIZE
    - IMPROVED WETTING
    - ENHANCED SOLUBILISATION
    - REDUCED LATTICE ENERGY

- Stability can be problematic and while many formulations are in development, there are relatively few marketed products

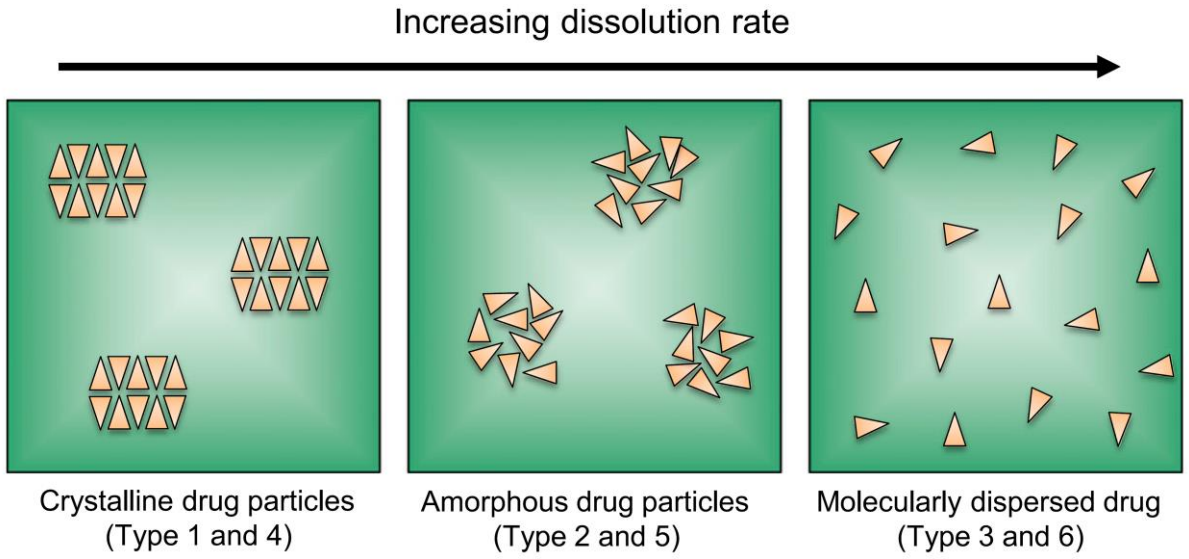
- Drugs are dispersed within a carrier matrix (e.g. HPMC, PVA) that can attenuate drug recrystallization (via reduced mobility or bonding with drug)

EXAMPLE MARKETED SOLID DISPERSIONS

DRUG	FORMULATION	DISPERSION CARRIER
ITRACONAZOLE	SPORANOX, CAPSULES	HPMC
TACROLIMUS	PROGRAF	HPMC
NABILONE	CESAMET	PVP

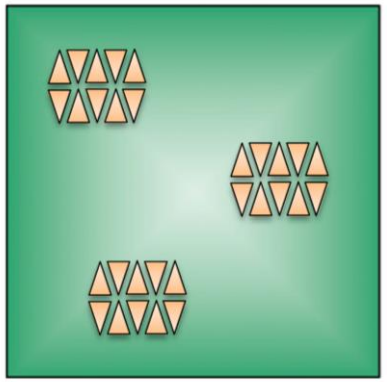
CLASSIFICATION OF SOLID DISPERSIONS

DISPERSION TYPE	DRUG FORM	CARRIER FORM
SOLID SUSPENSION (EUTECTIC MIX)	CRYSTALLINE	CRYSTALLINE
SOLID SUSPENSION	AMORPHOUS	CRYSTALLINE
SOLID SOLUTION	MOLECULAR DISPERSION	CRYSTALLINE
GLASS SUSPENSION	CRYSTALLINE	AMORPHOUS
GLASS AMORPHOUS SUSPENSION	AMORPHOUS	AMORPHOUS
GLASS SOLUTION	MOLECULAR DISPERSION	AMORPHOUS

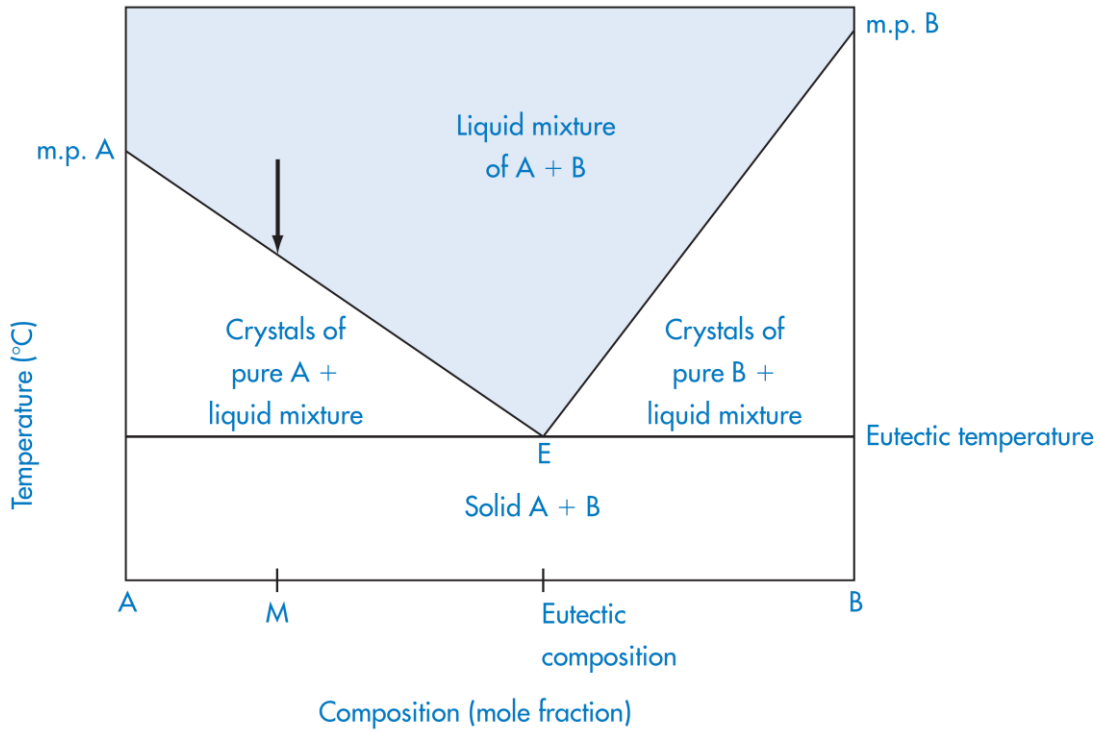


EUTECTIC MIXTURE

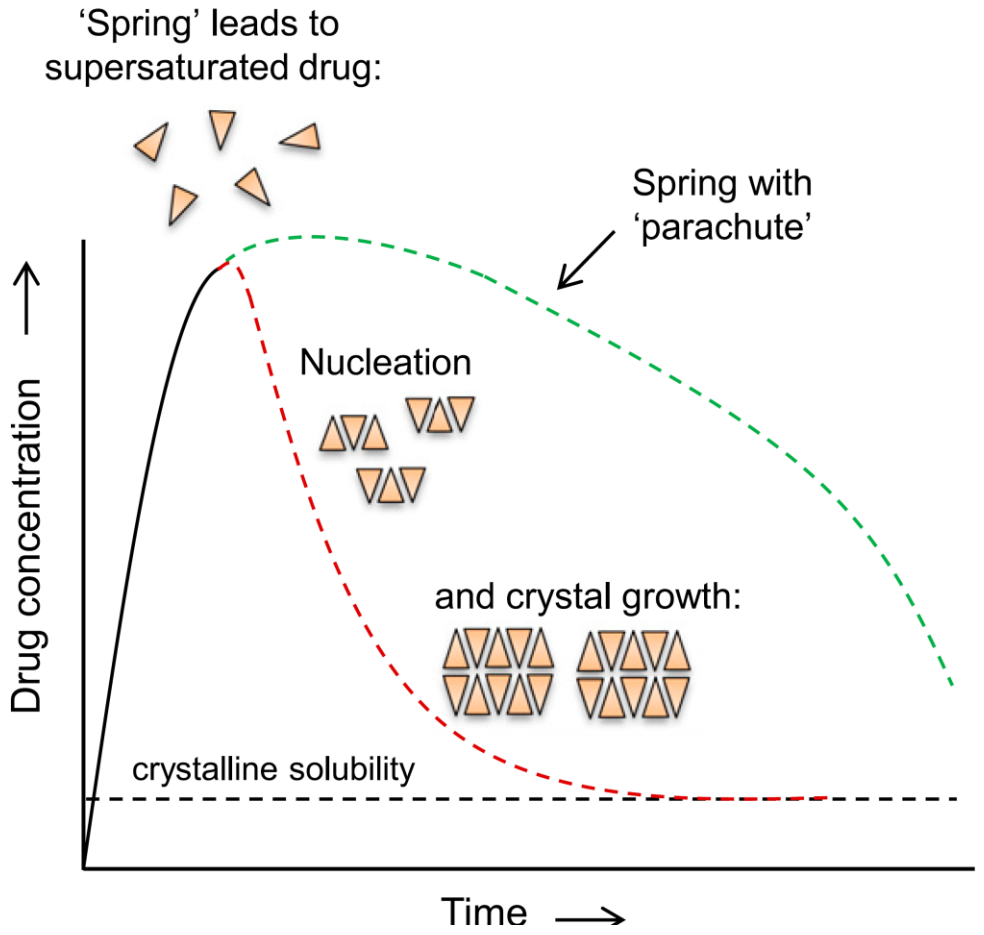
- Eutectic mixtures are crystalline drug suspended in a crystalline carrier. Substances are miscible in the liquid state, but little miscibility in solid state, however the unique mixture (eutectic composition) that yields the lowest melting point (eutectic point).



Crystalline drug particles



SOLUBILITY DYNAMICS FROM SOLID DISPERSIONS



SCHEMATIC ILLUSTRATING IMPROVED DISSOLUTION AND TEMPORARY INCREASE IN SOLUBILITY (SUPER SATURATION) OF CRYSTALLINE MATERIAL PROCESSED INTO A HIGH ENERGY AMORPHOUS DRUG FORM

LIPID BASED FORMULATIONS

- The human body possesses highly specialised lipid processing pathways that routinely permit solubilisation and absorption of water insoluble substances (lipids, vitamins).
- Lipid based formulations harness these endogenous transport pathways by delivering insoluble drugs in lipids
- In early cases drugs were co-administered with food (e.g. griseofulvin)
- LBF are not simply solutions or suspensions, rather lipid dispersion (micellar, microemulsions or coarse emulsions)

SANDIMMUNE VERSUS SANDIMMUNE NEORAL

SANDIMMUNE

- CsA
- Olive oil
- Labrafil M2125 CS
- Ethanol
- Soft gelatin capsules

CAPSULE RUPTURES TO GRADUALLY FORM A POLYDISPERSE COURSE EMULSION

SANDIMMUNE NEORAL

- CsA
- Corn oil glycerides
- Cremophor RH40
- Ethanol, propylene glycol
- Tocopherol
- Soft gelatin capsules

RUPTURES TO SPONTANEOUSLY FORM A MICROEMULSION

LIPID FORMULATION CLASSIFICATION SYSTEM

Increasing hydrophilicity and dispersibility

Composition (%)	Type I	Type II	Type IIIA	Type IIIB	Type IV
Triglycerides or mixture of glycerides	100	40-80	40-80	<20	-
Water insoluble surfactant	-	20-60	-	-	0-20
Water soluble surfactant	-	-	20-60	20-50	30-80
Cosolvent	-	-	0-40	20-50	0-50

Increasing role of lipid digestion

DRUG DERIVATISATION

- Solubility of a drug may be altered by covalently attaching a functional group with the desired solubility properties.
  - **INCREASE WATER SOLUBILITY**
  - **DECREASE WATER SOLUBILITY**
- Functional groups: hydroxyl, carboxyl, primary & secondary amines
- Derivatised drug molecules are **prodrugs** because the drug remains active until the additional functional group is removed *in vivo*

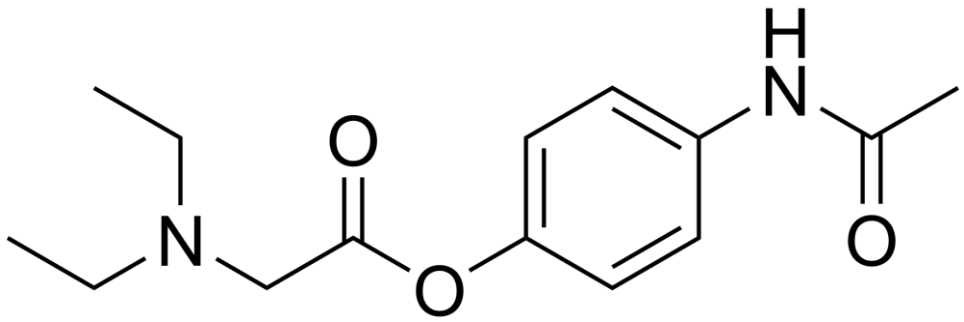
PRODRUGS

- **PRODRUG**: A prodrug is a drug form that remains inactive during its delivery across biologic membranes or until it reaches the site of action. In other words, a prodrug is an inactive precursor of a drug. Prodrug reconversion (i.e. its conversion into its active form) occurs in the body inside a specific organ, tissue, or cell. In most cases normal metabolic processes such as cleavage of an ester bond by esterases are utilised to achieve prodrug reconversion.
- Prodrugs are designed for many reason including:
  1. **MANIPULATION OF SOLUBILITY/PERMEABILITY (LADME)**
  2. **IMPROVED STABILITY**
  3. **TASTE MASKING**
  4. **MODIFIED RELEASE**
  5. **SITE SPECIFICITY**
  6. **IMPROVE PROCESSABILITY**
  7. **REDUCE TOXICITY**

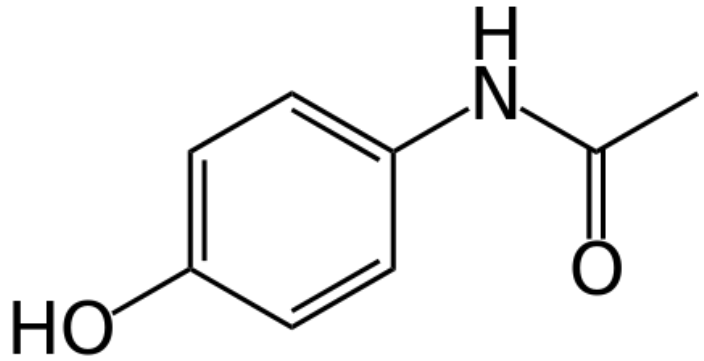
PRODRUGS

- Pro-moieties that increase solubility: phosphate, sulphate, succinate
- The drug must contain a functional group suitable for pro-moiety addition (e.g. alcohol, carboxylic acid, thiol, amine)
- Ester linkage is the most common (hydrolysis or esterase activity)
- Esterases

INCREASING SOLUBILITY THROUGH PRODRUG FORMATION
PARACETAMOL TO PROPACETAMOL



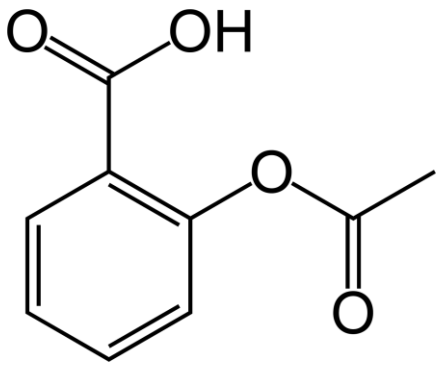
- PROPACETAMOL HCl
- LogP:

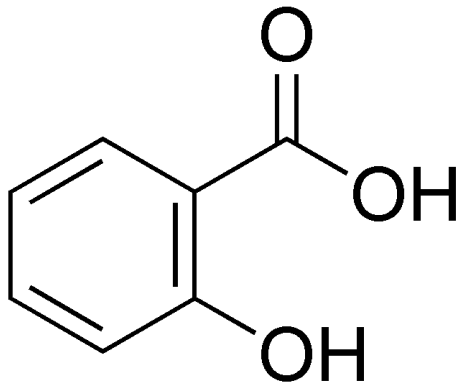


- PARACETAMOL
- LogP:

A CASE FOR INCREASING SOLUBILITY FOR IV ADMINISTRATION

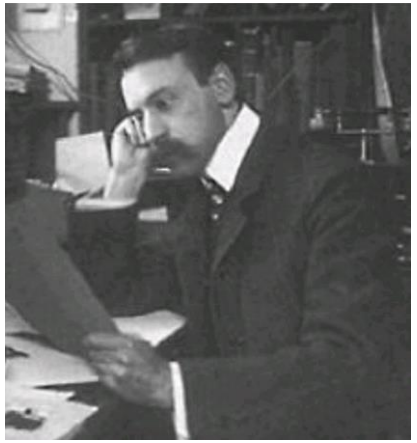
SALICYLIC ACID TO ASPIRIN
ALMOST A PRODRUG





- ASPIRIN
- LogP: 1.19

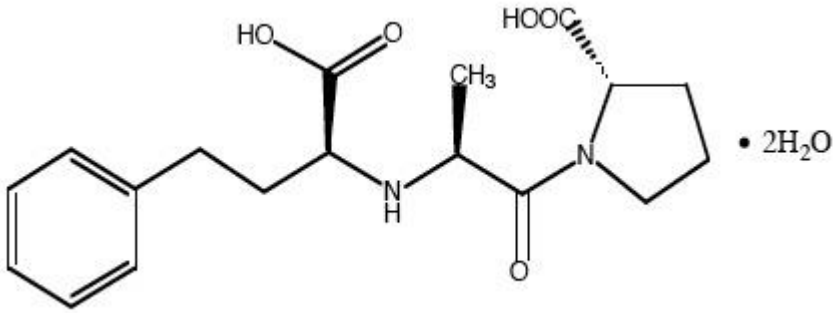
- SALICYLIC ACID
- LogP: 2.26



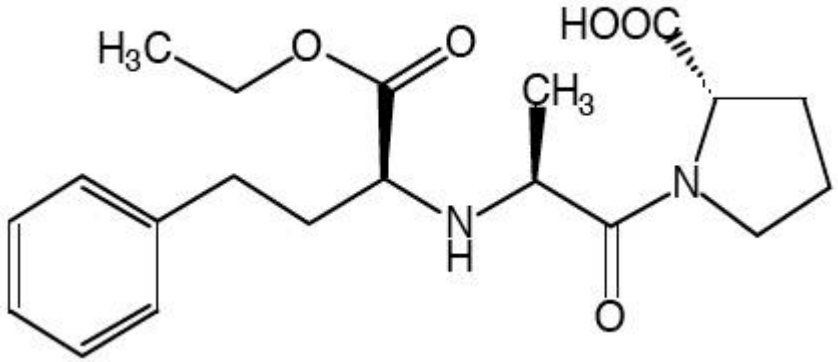
Arthur Eichengrün at Bayer

A COMBINED CASE OF SAFETY AND SOLUBILITY

MODULATING IONISATION THROUGH PRODRUG FORMATION
ENALAPRILAT TO ENALAPRIL

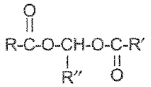
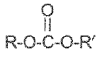
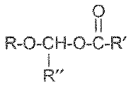
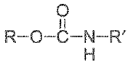
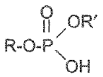
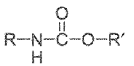
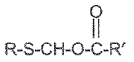


- ENALAPRILAT



- ENALAPRIL

FUNCTIONAL GROUPS INVOLVED IN PRODRUG FORMATION

Functional group	*Prodrug form*	*Linkage*
		Ester
		α-Acyloxyalkyl esters
		Carbonate esters
		Amides
R-OH		Esters
R-OH		α-Acyloxyalkyl ethers
R-OH		Carbamate
R-OH		Phosphate esters
$R\text{-}NH_2$		Carbamate
R-SH		Thioesters
R-SH		α-Acyloxyalkyl thioethers
R-SH	R–S–S–R′	Disulphides

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EXAMPLE EMERGING STRATEGIES

- **CARRIER ADSORPTION**: Microporous adsorbents (e.g. fumed silica) have a large surface area for adsorption and subsequent desorption upon exposure to solvent.
  - Carriers are believed to stabilise drug in the amorphous form
  - Large surface area for adsorption

- **SOLID LIPID NANOPARTICLES**: consist of a lipidic core that is solid at both room temperature and physiologic temperature and a surfactant-stabilised outer surface.
  - Colloidal system
  - Molecularly dispersed

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