super

How medicines work PHR2021

Week 1 26/2/2018

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I) Optimizing dosage regimen design

Introduction

- Interrelationship between physicochem props of the drug, dosage form, route of admin.
  → impact on the rate & extent of systemic drug absorption

Any changes to any of these parameters will alter the rate & extent of absorption
→ Advantage to exert a particular effect on a patient

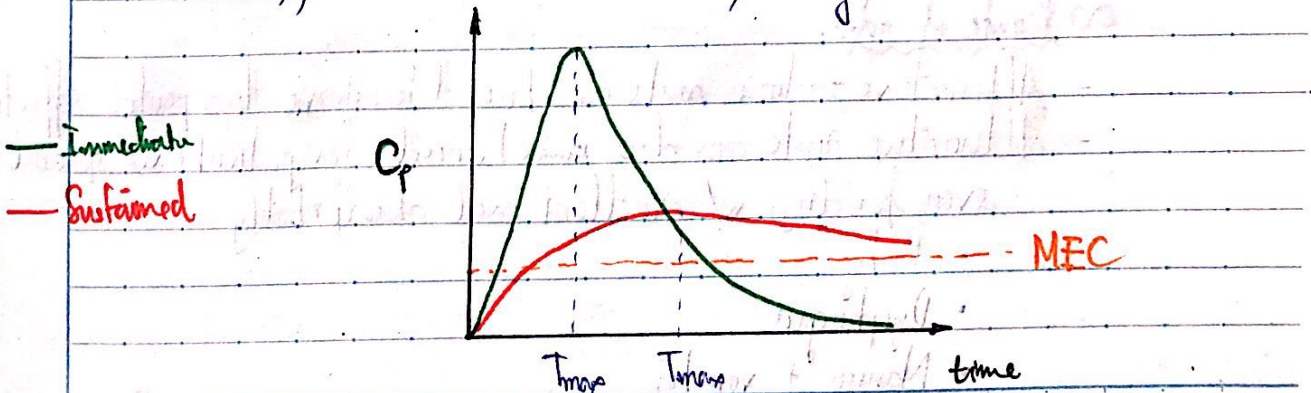
Parameters

~ Dosage form

- The concept of sustained & controlled-release

- The drug will lead to ~~a~~ therapeutic levels in plasma, if they exhibit appropriate solubility & absorption property (eg. good membrane permeability, limited interaction w/ efflux transporter)

- 2 types of tablets & capsules:
  - Immediate release (= conventional): rapid, short T_{max}
  - Sustained, controlled-release: slow, long T_{max}



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∾ Physicochemical props

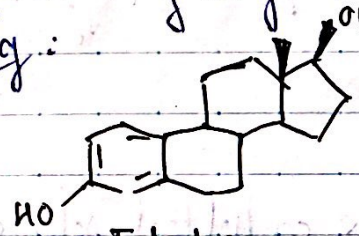
- Many drug candidates cannot become drugs due to inappropriate physicochem prop (low lipophilicity, high MW, ...)

- Lipinski's rule of 5s:
  - Log P ≤ 5
  - MW < 500
  - H bond donor < 5
  - H bond acceptor < 10

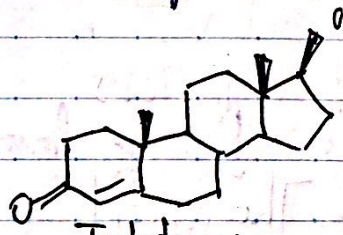
} Not applicable if the drug is transported via a influx transporter

- Some other drug may exhibit low Cp due to high 1st pass effect

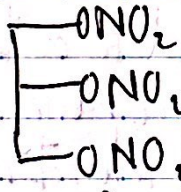
Eg.:



Estradiol



Testosterone



Trinitro Glyceryl

→ Need alternative route of administration other than oral.

∾ Route of adm.

- Alternative admin route can be used to achieve therapeutic effects.
- Alternative route can also be used for patients w/ special needs, even for drugs w/ excellent oral absorbability:
  - Baby
  - Dysphagia
  - Nausea + vomiting
  - Gastric surgery.

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- Each formulation has some possible admin. route:

Solution	Oral Intravenous (IV)** Subcutaneous Intramuscular (IM) Ocular
Mixture	Oral
Suspension	Oral Intramuscular
Ointment	Transdermal Buccal Nasal
Cream	Transdermal Rectal
Paste	Transdermal Buccal
Paint	Transdermal Vaginal
	** Presence of particles can be fatal

As each route also presents w/ single or multiple layers of epithelial cells, it is still important for drugs to have appropriate absorption property.

- Moderately lipophilic → crossing membrane
- Low MW → promote passive diffusion
- Low polar surface area (PSA) → solubility

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- Another benefit of having other routes than oral is the local effects
  Eg: Eyedrop, cream

However, still important to know the amount of drug absorbed into the systemic circulation to be aware of systemic side effect, despite the change of admin route.
Eg: β-blocker eyedrop can be absorbed into the body & block other β receptors in the heart & lung

Calculation of the correct dose when changing from IV to other route

- In hospital, patient is given drug under IV dose form (infusion or multidose)
  However when release, tabs & caps are for more convenient

- Factor when calculating dose:
  - Steady state Conc. (C_{ss})
  - Clearance (CL), interrelated w/ elimination rate const (k) & V_D
  - Bio availability (F) via the alternative route
  - Dose & drug interval (τ)

$$D_{ss} = \frac{F \cdot Dose}{CL \cdot \tau}$$

When calculate, it is best to set the τ near $t_{1/2}$ of the drug

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I) General lab intro for extemporaneous formulation

Materials:

- APF & Le
  - Formulary & dosing guidelines
  - Ancilary & warning labels
  - Cornelly & trigger point
  - Useful to decipher latin abbrev.
  - Estimate BSA & body weights by age
  - Professional standards
- Martindale, the extra Pharmacopoeia
- AMH

Extemporaneous dispensing

* Module will be filled later, pls leave some space

- A properly dispensed med must:
  - be safe
  - have a known composition
  - represent an accurate interpretation of the prescriber's intention
  - be effective & stable
  - be in a form that is convenient & safe & easily transported
  - be elegant
  - have a proper & accurate documentation & records

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Expiry date for drugs in the dispensary area

- A drug should have exp date stated on the container (known or estimated)

In general, unless stated specifically, an exp date of 28 days from the day of opening should apply to all extemporaneous formulations.
Exp date longer than 28 days must come w/ reliable records, but under no circumstances should an exp date >6 months be assigned for compounded me

- Factor to considered before assigning an exp date:
  - Nature of the drug & dosage form
  - Potential for microbial growth
  - Final container
  - Storage condition
  - Duration of treatment

- Products that are freshly made → dispense w/in 24h
  Products that are recently made → dispensed w/in 7 days, & an exp date of 28 days from opening should apply

- 2 labels for exp date:
  - 7a: freshly made, discard after x days from day of preparation
  - 7b: recently made, discard after x days from opening

- For 7a, do not just write "Shelf-life: 28 days"
  Must write the day of discard onto the label based on the day of preparation.

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Ancillary labels

- Must be attached to the primary container, wherever possible:
  - Warn against undesirable effects, interactions.
  - Optimize medicine efficacy.

Label 1

- "This medicine may cause drowsiness and may ↑ effect of alcohol. If affected, do not drive or operate machinery"
- For meds whose primary & secondary effect is sedation
- Alcohol may elevate the drowsy effects (CSN depression)

Label 1a

- "This preparation is to aid sleep. Drowsiness may continue the following days. Do not drive or operate machinery if affected."
- For meds whose primary effect is to aid sleep.

Label 2

- "Do not take alcohol while treated w/ this med"
- For meds that can interfere w/ alcohol metabolism
- Also for when alcohol consumption is contraindicated

Label 3a

- "Take on an empty stomach at least half an hour before meal & at bedtime"
- For meds that are admin. 4 times/day & where ingestion w/ food can cause significant reduction in bioavailability.
- Skipping a meal will not ↓ effectiveness of treatment

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Label 3b

- "Take on an empty stomach at least half an hour before food or 2 hrs after fo
- For meds that are admin. <4 times/day & ingestion w/ food causes a significant ↓ in bioavailability

Label 4a

- "Do not take dairy products, antacids or mineral supp. w/in 2 hrs of each dose of this med"
- For drugs that can chelates w/ metallic ion. → insoluble, ↓ bioavailability
  Eg.: tetracyclines, oral biophosphates, fluoroquinolone antibiotic, ...

Label 4b

- "Ask your doctor or pharmacist before taking any meds for heartburn, reflux or indigestion"
- For meds whose absorption is reduced by ↑pH

Label 5

- "Ask your doctor / pharmacist before using any other meds including OTC or health products"
- For meds that can cause an number of interactions → therapeutic failure
  Mechanism: enzyme inhibit/induce, ...
- Also recommended for meds w/ narrow therapeutic indices

Label 6

- "Refrigerate. Do not freeze"
- Store from 2 - 8 °C to minimize decomposition
  Should be stored in the main compartment of the fridge, not the door

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Label 7a

- "Discard contents after __/__/____"
- For meds w/ limited shelf life due to microbes & contamination
  For freshly prepared products

Label 7b

- "Discard after XX days from opening .. Opening date __/__/____"
- For recently made meds
  Usually 28 days if not specified

Label 8

- "Avoid excessive skin exposure to sunlight/sunlamps"
- For meds that can induce significant photosensitivity reactions
  Eg: cytotoxic meds, immunosuppressants
- Advise the use of broad-spec sunscreen (sun protection factor of atleast 30+)

Label 9

- "Don't stop taking this med abruptly unless otherwise advised by doctor"
- Abrupt cessation can cause serious consequences:
  - Anti-convulsants: ↑ frequency of seizures
  - Antiplatelets: ↑ myocardial infarction, ↑ platelet aggregation
  - Benzodiazepines: anxiety, insomnia, irritability, hallucination
  - β-blockers: rebound hypertension, ventricular arrhythmia
  - Immunosupp: ↗ transplant rejection
  - Long term oral corticosteroid: adrenal suppression, acute adrenal insufficie

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Label 10a

- "Do not take > 1 aspirin tablet/capsule each day while treating"
- For meds treating diabetes (including insulins)
  High-dose aspirin can stimulate insulin secretion → hypoglycemia

  Also for NSAIDs → ↑ GI adverse effects
  Also for antiplatelet

Label 10b

- "Do not take aspirin or anti-inflammatory meds while treating unless advised by doc"
- For oral anticoagulants, antiplatelets.

Label 11

- "Do not take potassium while being treated unless advise"
- For potassium-sparing meds, ACE inhibitors, AT II antagonists → hyperkalemia

Label 12

- "This med may affect mental alertness and/or coordination. If affected, do not drive or operate machinery"
- For meds that cause CNS disturbances & impair psychomotor performance

Label 13

- "Do not remove from original packaging until dose required"
- For meds that can cause risk if taken by children or prone to decapacitation
  Not applicable for bottle containers or other confusing containing methods.

Label 14

- "Rinse mouth w/ water after each use"
- For inhaled meds that ↑ risk of oral dryness, irritation, fungal infections

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Label 15a ☐ Label 15b ☰

- "Do not use both"
- For substituted meds
  Ensure the name the active ingredient to ↓ the incident of doubledosing

Label 16

- "Thismed may cause dizziness, especially when stand up quickly"
- For meds that cause orthostatic hypotension
  Advise to rise slowly, hydrate, avoid excessive heat

Label 18 ☐

- "Avoid eating grapefruit or drinking grapefruit juice"
- For meds that are extensively metabolized by CYP3A4

Label 19a

- "Contain paracetamol. Consult gen doc/pharm before taking other paracetamol me
- For all paracetamol products

Label 19b

- "Consult your doc/pharmacist before taking other pain or inflammatory products"
- For oral & rectal NSAIDs containing products → GI bleeding, renal fail

Label 20

- "Take once weekly on the same day"
- For meds in inflammatory conditions, infections...
  Eg: anti-inflammatory, immunosuppressants, antimalarials

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Label 21

- "Special handling & disposal required - ask your pharmacist"
- For meds that can cause harm from unintended exposure
  Eg: Modified formulation can cause unwanted contact thru skin & inhalat
  Also for transdermal patches, where residue may be harmful.

Label 22

- "Use w/ appropriate device"
- Powder containing capsules for inhalation, not oral admin.

Label 23

- "This product has been compounded by the pharmacist"
- For extemporaneous products, manufactured in a facility that is not licensed by the TGA

Label 24

- "For 3 day use only. Can cause addiction"
- For non-prescribing codeine-containing analgesics or dihydrocodeine

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Additional instructions → appropriate use & storage

Label A
- "Swallow whole. Do not crush or chew"
- For enteric-coated & modified-release meds
  - Some coated can be broken into sections, but the sections must be swallo
  - Some capsules contain pelletised product, but the pellets must be swallowed.

Label B
- "Take w/ or soon after food"
- For meds that can cause GI ulceration, or hypoglycaemial agents
  Also for meds w/ high-fat absorption

Label C
- "Take at least half an hour before food"
- Same as 3b

Label D
- "Until all taken/used"
- For meds whose completion of use can improve therapeutic outcome
- May not be appropriate when the total number of dose is greater than needed

Label E
- "Continue for 14 days after symtoms cease"
- For topical antifungal agents to prevent recurrence

Label F
- "Take immediately before food"
- Some meds need to be taken before food to minimize side effects

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Label G
- "Take in the morning. Drink plenty of water"
- Drugs can cause severe hemorrhagic cystitis
  → Void frequently to avoid

Label H
- "Store frozen"
- Meds need to be stored <0°C

Label I
- "Certain foods & juices should be avoided"
- Monoamine oxidase inhibitors may interact w/ some foods & juices
  Other meds may interact w/ juice other than grapefruit juice

Label J
- "Shake well before use"
- For suspension

Label K
- "For external use only"
- For meds admin. topically to the skin & not in body cavity
  Eg. cream, lotion, ointment

Label L
- "Caution. Not to be taken"
- Med admin. within body cavity (look like tablet)
  Eg. suppository, pessary

Label M
- "Do not swallow"
- Meds admin sublingually

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Label N
- "Contains peanut oil"
- Check the product info & patient medical history

Label O
- Intentionally left blank

Label P
- Additional instruction

Appendix L — Pregnancy risk
- Statements should be assign to drug w teratogenic effects:
  - Warning – causes birth defects
  - Caution – (substance) should not be used by pregnant women
  - Do not use if pregnant
  - Do not use if pregnant or likely to become pregnant
  - Do not became pregnant during use or within (time) of stopping treatm
  - Warning – may cause birth defects
  - (Name) remains in the body for many months after stopping treatment
    Do not become pregnant or father a child before consulting your do

Pharmacy Calculation Practice

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Body cavity delivery system

∞ Definitions

- Suppository : • Solid bodies for rectal administration
  • Meds for local & systemic effect
  • Melt at body temp.
  • If not specified, 1.0g suppositories are used.
  • Made by pouring melted mass into the mold.

- Pessary : • Insertion to vagina
  • Mainly for local effect but can be systemic sometimes
  • 3 types: molded, compressed, .. capsule

- Bougy : • Small suppository weigh between 0.5 – 1 g but longer & narrower than rectal suppository
  • Insertion to the urethra, nasal passage, ears.

- Enema : • Aqueous / oily solution or suspension for rectal adm.
  • Volume used 100 - 200mL, should be warmed before use

∞ The use of suppositories

- Suppositories may be better than other routes of adm.
  • Exert direct action on the rectum
  • Systemic effect w/o having 1st pass effect
  • To promote evacuation of the bowel

- The drug is absorbed via the mucosal layer in to the inferior hemorrhoidal veins → bypass the liver

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∞ Types of suppository bases

Fatty bases:

- Theobroma Oil B.P (Cocoa butter)
  - Melt 30 - 35°C
  - Shrinking while solidifying → poor molding profile
  - Stinky
- Hard-fat
  - Theobroma B.P. alternatives

Water-soluble bases:

- Glyco-gelatin bases
  - Translucent, resilient
- Macrogels (PEG - Polyethylene Glycols)
  - Warmed w/ water before use

∞ Formular 1: specifying the drug by %

- Remember: if not specified, the weigh of the supp. is 1g.
  The volume of the drug in the supp. may be insignificant
  → Use %m (by weight)

Eg: "15 supp. of Benzocaine 5% in fatty base" means the weight of the drug = 5% the weight of the supp.

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∞ Formulae 2: specifying the drug as a unit dose

- When the val. of the drug has to be made, since the density of the drug usually different from that of the base
  → Displacement value

> The displacement value (DV) of a drug is the weight of the drug that occupies the same vol. as 1.0g of either type of fatty base OR 1.2g of either type of water-soluble base.

- Before making the supp., the molds have to be calibrated since not all molds have the same size → Usually use Hand fat
  Common suppository mold hold 1g of base. The weight of base which a mold will contain naturally varies w/ the nature of the base
  → Necessary to calibrate the mold for accurate dosing.

- Formular:

$$\text{Weight of Y supp.} = \left(\text{Mold calibration} - \frac{\text{Drug dose}}{DV}\right) \times \text{Base density} \times Y$$

where Y = n° of supp
Mold calibration (g.)
Drug dose (g.)
DV (g/mL)
Base density (g/mL)

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Clinical calculation

∞ Body mass index (BMI)

- The body weight, adjusted for height, which is associated w/ longest high quality life expectancy. = "healthy weight range"

Most commonly used: BMI

$$BMI = \frac{\text{weight (kg)}}{\text{height (m)}^2}$$

BMI can be misleading sometimes eg: body builders w/ high BMI

BMI classification:

- < 18.5 : underweight low
- 18.5 - 24.9 : healthy average
- 25 - 29.9 : overweight increased
- 30 - 34.9 : obesity (class 1) moderate
- 35 - 39.9 : obesity (class 2) severe
- > 40 : morbid obesity (class 3) very severe

∞ Creatinine & Creatinine CL

- Creatinine is eliminated predominantly via glomerular filtration (only)
  → Assay to determine GFR, which is an indicator for renal function
  - Low levels: protein starvation, liver disease, pregnancy
  - High levels: kidney failure, muscle degeneration, drug interaction

$$\text{Creatinine CL} = \frac{(140 - \text{Age}) \times \text{Ideal bodyweight}}{815 \times \text{Serum creatinine}}$$

where CL (mL/min)
Age (year)
Ideal body weight (kg)
Serum creatinine (mmol/L)

*Note: multiply by 0.85 for ♀

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- Creatinine CL & height.

$$GCL = \frac{0.042 \times \text{height}}{\text{Serum creatinine}}$$

where GCL (mL/min)
Height (cm)
Serum creatinine (mmol/L)

Body surface area (BSA)

- Usually the dose is dependent on characteristics of individual.
  → Use BSA to calculate the dose (not the weight)

$$BSA = \sqrt{\frac{\text{height} \times \text{weight}}{3600}}$$

where Height (cm)
Weight (kg)
BSA (m^2)

$$BSA = (\text{weight})^{0.425} \times (\text{height})^{0.725} \times 71.84.1$$

where BSA (cm^2)
weight (kg)
height (cm)

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Moles, equivalents & osmolarity

∿ Moles & Millimoles

- 1 mol of a substance is defined as the MW of that substance, expressed in gram

$$n = \frac{m}{M}$$

where n = mol
m = mass (g)
M = MW

$$1 \text{ mol} = 1000 \text{ mmol}$$

∿ Equivalents & Millieequivalents

- Another unit that is occasionally used to quantify electrolytes is "Equivalent". When a compound dissociates, the same number of "equivalents" of positive & negative ions are produced & vice versa.

The number of equivalents of an ion is determined by multiplying the mole number by the absolute value of the valence

$$Eq = n \times q$$

where Eq = equivalent (Eq)
n = mole (mol)
q = charge / valence (absolute; dimensionless)

$$1 Eq = 1000 \text{ m}Eq$$

∿ Osmolarity

- When a solution of a drug contact w/ a body fluid, there is a potential for the cells to be damaged
  → The drug solution must be isotonic

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To achieve isotonicity, there needs to be the same osmotic pressure of the administrated solutions & that of the body fluid (iso-osmotic)
The osmotic pressure is generated by the present of electrolytes, proteins & other small constituent

- The drug of low osmotic pressure → RBC swell & burst (hemolysis)
- The drug of high osmotic pressure → RBC shrink (crenation)

For an isoosmotic solution to be called isotonic, solutes in the solution mustn't pass through the cell membrane or alter integrity
Therefore, solution which are isosmotic w/ the body fluid to be considered as isotonic only if:

- Membrane in contact w/ the solution are impermeable to solutes
- The solute does not alter permeability of membrane to any substance present
- No chemical reaction leads to a change in total concentration of dissolved ions or molecules

Osmotic pressure

- Osmotic pressure depends on the number of particles dissolved in a unit volume of solvent

An ideal non-electrolytes dissolved in water, each molecule produce 1 particle in solution

> One osmole (Osm) is defined as the weight (g) of a solute osmolarity to 1 gram-MW (1 mol) of an ideally behaving non-electrolyte.

For an ideal non-electrolyte

- 1 mol = 1 Osm
- 1 mmol = 1 mOsm
- 1 Eq = 1 Osm

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∞ Osmolarity & Osmolality

- Osmotic pressure is determined by the concentration of osmoles in solution rather than the absolute number.

Osmotic pressure is an example of colligative property since it depends on the number of particles in solution.

- 2 terms are used for osmole concentration:
  - 1 osmolar solution = 1 Osm / L of solution
  - 1 osmolal solution = 1 Osm / kg of water

Adjusting tonicity of a solution

∞ Freezing point depression ($FD_{1\%}$)

- Freezing point depression is a colligative property that is based on the n° of particle in a solution.

Blood serum & lachrymal secretion freeze at -0.52°C.
Normal saline isosmotic w/ these fluid since it also freezes at -0.52°C
→ Other solution that freeze at -0.52°C is isosmotic w/ these body fluid

$$C_{iso} = \frac{0.52}{FD_{1\%}} \ \%$$

where: C_{iso} = Isosmotic conc. of the substance in water
$FD_{1\%}$ = $FD_{1\%}$ of that substance

$$\%\ adjusting = \frac{0.52 - [(\%A \times FD_{1\%}A) + (\%B \times FD_{1\%}B)]}{FD_{1\%}\ adjust}$$

where %A, %B is the conc of known solutes (do not devide by 100)

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∿ Sodium Chloride Equivalent (SCE)

- The SCE of a substance is the mass (g) of NaCl that has the effect on the $FD_{1\%}$ equivalent to that produce by 1g of substance

$$SCE = \frac{0.9}{0.52} \cdot FD_{1\%}$$

where: $FD_{1\%}$: the freezing point depression of a 1% solution of that substance

$$\%\ adjusting = \frac{0.9 - [(\%A \times SCE_A) + (\%B \times SCE_B)]}{SCE_{adj}}$$

∿ Calculation based on C_{ISO}

$$\frac{\%\ adj}{C_{ISO\ adj}} = 1 - \left(\frac{\%A}{C_{ISO}A} + \frac{\%B}{C_{ISO}B}\right)$$

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Week 3 12/3/2018

Good manufacturing practice

Compounding: General aspects

- The aim of compounding:
  - To make meds that are difficult to find or is discontinued
  - To create personalized meds

- Medicine compounding facilities:
  - Standard pharmacy: simple compounding only
  - Compounding - specialized pharmacy: small-scale simple & complex compounding
  - Compounding companies: large scale compounding

Large pharmaceutical companies eg. GSK, Pfizer manufacture drugs in large premises that are very regulated & need to comply to the Good Manufacturing practice (GMP)

Good manufacturing practice

- Good manufacturing practice (GMP): a set of principles & procedures that pharmaceutical industries need to follow to ensure quality products.

TGA hosts this document for Aus, but all countries have their own GMP

- The role of the TGA for health professional
  - TGA is a part of the Department of health, regulates therapeutic goods in Aus, including how they're manufacture & advertised
  - Only certain therapeutic goods are regulated by the TGA, which are used for
    - + For preventing, diagnosing, curing or alleviating a disease / injury / defect
    - + For modifying, inhibiting or influence a physio process
    - + For testing the susceptibility of ppl to a disease
    - + Influencing, controlling or preventing conception
    - + For testing for pregnancy

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- Therapeutic goods include :
  + Prescription meds, including vaccine
  + Biologicals
  + Blood & tissue products
  + OTC meds
  + CAMs
  + Medical devices

} Manufacturing & Advertising

- How? TGA has systems in place to:
  + Ensure manufacturing standard
  + Authorize supply
  + Monitor products once they are on market
  + Identify illegal action

+ TGA-regulated meds have an AUST R number on the label, while CAMs & low-risk meds have an AUST L number
+ Therapeutic goods must be entered on the Australian Register of Therapeutic Goods (ARTG) before they can be lawfully supplied in Aus., unless exempt.
+ While the pharmacists assess the risk/benefit of meds to individuals, the TGA assess the risk/benefit for the population

∞ Why do we want to learn abt GMP? Do the activities involved in compounding require you to comply with GMP?

- Compounding products doesn't require pharmacists to comply w/ GMP, however they still need to ensure the product quality. → Better to be aware of GMP

To have a basic knowledge → Titles of the GMP document chapters & the associated principle in each chapter.

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∞ Chapters & principles

Chapter 1: Quality management

- Principle: Do not place patient at risk due to inadequate safety, quality or efficacy
  - Quality assurance: Matters which can influence the quality of a product must be ensured objectively to meet the quality required.
  - Quality control: Testing of a product to make sure the results comply w/ the specifications
- GMP: med. products are consistently produced & controlled to the quality standards appropriate to their intended use

Chapter 2: Personnel

- Principle: The correct manufacture of medicinal products relies upon people
- Training: should be provided for all the personnel whose duties are involved in the production area or may affect the quality of a product.
  Newly recruited trainees should receive training appropriate to the assigned duties

Chapter 3: Premises

- General:
  - Premises should be carefully maintained, ensuring that repair & maintenance operations do not present any hazard to the quality of products. They should be clean & where applicable, disinfected according to detailed written procedures.
  - Lighting, t°, humidity & ventilation should be appropriate & such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture & storage, or the accurate functioning of equipment.

Chapter 4: Documentation

- Principle: Good documentation constitutes an essential part of the quality assurance system. Clearly written documentation prevents errors from spoken communication & permits tracing of batch history

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- General:
  - Specifications describe in detail the requirements for the product & materials
  - Manufacture Formulae, Processing & Packaging Instruction state all the starting materials & proces
  - Procedures give directions for performing certain operations
  - Records provide a history of each batch of product
  - Docs. should not be hand-written
  - Any alterations made to the entry on a doc should be signed & dated.
  - The records should be made or completed at the time each action is taken
  - Docs. should be retained for at least a year after exp date

- Documents required.
  - Manufacture Formula
  - Processing Instructions

Chapter 5: Production

- Packaging operation:
  - Stipulation 5.44: When setting up a program for the packaging operation, minimize risk of contamination, mix-ups or substitutions. Different products should not be made in close proximity unless there is physical distinction.
  - Stipulation 5.45: Ensure packaging areas are clean, & free from any other products materials or documents previously used if they are not required for the current operation

Compounding of drugs in a pharmacy.

~ TGA document "Compounded medicines & GMP"

- This document was released to ensure that professionals make the products according to standard to prevent quality or safety problems.

This document is only applicable to licensable manufactures (companies that manufacture

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compounded products as a wholesale), not the pharmacies that do simple compounding. However, it can be used as a guidance for pharmacists.

- Compounding: The preparation, mixing, assembling, altering, packaging & labelling of a medicines, medicine-delivery devices or device in accordance w/ a doc's script, or initiative based on the doc/patient/pharmacist/compounder relationship in the course of professional practice.

Dispensing: The manipulation of a commercially available product, in accordance w/ the manufacturer's instruction, in order to produce a medicine in a "ready to administer" form.

∞ Professional Practice standards: Standard 5 - Compounding

- Principle: The pharmacist prepares & dispenses compounded preparations to ensure timely access to a safe, efficacious & quality product.
- It contains some background & scope for compounding & explains that pharmaceutical products need to be manufactured in licensed premises (that comply w/ GMP) but compounded products don't need to comply w/ this law.

However, professional standards are still needed to ensure product quality/safety.

∞ Pharmacy Board of Aus: "Guidelines on compounding medicine"

- The PBA also provides guidance on compounding.

The definition of compounding in the PBA shows the distinction between simple & complex compounding.

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PBA compounding guidelines

Simple & complex compounding

- Simple: prep & supply of a single "unit of dose" of a therapeutic product intended for supply for a specific patient in response to an identified need.

Complex: prep & supply of a single "unit of dose" of a therapeutic product intended for supply for a specific patient & that requires or involves special competencies, equipment, processes or facilities.

- For a pharmacy, only simple compounding is allowed for new grads, until further training is undertaken.

Sterile product.

- Sterile products can only be made by trained professionals.
Hospital pharmacists produce many sterile products that are to be administered IV

- When the professionals don't follow rules & guides & law
→ Compounding can go wrong

Medication recalls: consequence of non-compliance

- Every pharmacist will be exposed to recalls in career, whether receiving a notification for recalling a product manufactured by a pharmaceutical company or if compounded a faulty product, bringing back from the customers.
  - If the product quality is off while still in the production site → Destroy
  - If the product quality is off after leaving the production site → Recall

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- Recalls are permanent removal of an affected therapeutic good from supply or use in the market.
Recalls have different levels of seriousness

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Week 4: 19/3/2018

I) Liquid formulations & excipients

Examples

∞ **Solutions**

- Homogenous 1-phase system consisting of 2 or more ingredients (solute + solvent)
In most formulation, H_2O is the most common solvent & present in greater amount
These solutions can be commercially available or prepared by a pharmacist.

- Advantages:
  - Easier to swallow
  - ↗ absorption
  - Uniformity
  - Gastric irritation ↓
  - Tailored dosage by changing volume

- Disadvantage:
  - Stability problem
  - Growth of microorganism
  - Disguising taste
  - Inconvenient
  - Accidental breakage of container.

∞ **Excipients**

- Additional excipients, eg. flavoring agent & preservation, are needed to:
  - Mask color, flavor, smell
  - ↓ microorganism
  - pH, stability
  - Viscosity

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- Challenges:
  - Drug stability, solubility
  - Incompatibility
  - Chemical degradation
  - Microbial contamination

- Ideal properties of excipients used in pharmaceutical products
  - Functionality (promote solubility, adjust pH for drug stability)
  - No acute or chronic toxicity
  - No inherent biological activity or unknown effect on the biological activity of the drug
  - Inherent stability & no unknown effect on the stability of the drug
  - Reliable & reproducible
  - Taste, color & smell should be appropriate

- Common excipients used in solution formulation
  - Solvent/vehicles
  - Buffer
  - Flavor & smell & color
  - Preservatives
  - Antioxidants & chelating agents
  - Isotonicity adjusting agents

Vehicles used in solution formulations

- Water:
  - Physiologically compatible
  - Strongly ionized materials are freely soluble
  - Weak acid/base can be soluble at proper pH
  - Don't make close to solubility limit → prevent precipitation

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- Co-solvents (water miscible solvents):
  - ↑ solubility of drug
  - ↑ stability of drug
  - ↑ solubility of weak electrolyte & non polar
  - Eg: alcohol, sorbitol, glycerol, propylene glycol

- Non-aqueous vehicles:
  - For drug w/ low water solubility
  - Consider toxicity, irritancy, injectability, stability, compatibility
  - Eg: soy/almond/olive/sesame oil

Buffers

- Resist change of pH, containing weak acid & its salt (base combo used but weak bases are usually volatile)
  Eg: CO_3^{2-}, citrate, gluconates, lactates, phosphates, borates

- Buffer can be used to improve the solubility of weakly acidic/basic drugs or:
  - Prevent pain/irritation & tissue damage
  - ↑ membrane absorption
  - ↑ antimicrobial activity of preservatives which is influenced by the extent of ionization

Preservatives

- Microbial growth is a major cause of degradation. Source ← ripple material processes

Risk of contamination is higher when product has a large amount of water & nutrient source

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- If the product mainly contains solvent w/ antimicrobial activity → no need for additional preservative
Injection for single use daily will not contain any preservatives

- Preservatives must be:
  - Safe & effective
  - Stable & Soluble at product pH (incorporate)
  - Compatible w/ active & other excipients

Sweetening & flavoring agents

- Sucrose is most widely used, colorless & soluble at pH 4-8.

- Sugar-free oral solutions may contain sorbitol or mannitol & artificial sweeteners such as saccharin or aspartame which are suitable for diabetic use

- Common: syrup, glycerol, mannitol, sorbitol, saccharin, orange syrup, lemon syrup, strawberry & vanilla flavoring

Coloring agents

- Usually to match color to flavor & for product identification
Coloring agents should be:
  - Non-toxic
  - Harmless
  - Inactive
  - Defined chemically
  - H_2O soluble
  - High coloring power
  - Light resistant/t^c/microbes
  - Compatibility

- The use of coloring agents is controlled w/ a list of permitted dyes due to allergies & carcinogenicity concerns.

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Antioxidants

- Prevent chemical degradation due to oxidation
  Eg: $Na_2S_2O_5$, $NaHSO_3$, Na_2SO_3, ascorbic acid

- Chelating agents are used to complex metals that catalyze oxidation
  Eg: EDTA

In parenteral formulation, O_2 is removed & N_2 (usually) is inserted to prevent oxidation

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II) Colligative properties

Introduction

- Colligative properties of solution depend almost entirely on the number of particles presenting in the solution, & much less on the actual chem props. of the particles

Colligative properties are:

- Freezing point depression
- Elevation of boiling point
- Lowering of vapour pressure
- Osmotic pressure

Info about colligative props. ⟶ molar concentration ⟶ calculate osmotic pressure

Freezing point depression

- The freezing point, or t° of a solution is always lower than that of the pure solvent. This is caused by the interference of the solute particles w/ the ice crystal formation by pure solvent at normal freezing t°.

- The lowering of the freezing point is directly proportional to the molal concentration of the solute or the number of particles present in the solution.

$$\Delta T_f = K_f \, m$$

Where ΔT_f = freezing point depression ($^\circ C$)
K_f = cryoscopic constant of solvent ($^\circ C.kg.mol^{-1}$)
m = molality of solution ($mol.kg^{-1}$)

Electrolytes will dissociate & produce more than 1 particle in solution. Van't Hoff factor (i) takes into account dissociation of electrolytes.

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$$\Delta T_f = i K_f m$$

where $i = 1 + \alpha(v-1)$ (for dissociation)
where i = Van't Hoff factor
α = degree of dissociation ($\alpha = 1$ for strong electo)
v = number of particles per solute molecule

where $i = 1 - \alpha\left(1 - \frac{1}{v}\right)$ (for association)

- The ΔT_f can be used to determine the osmotic pressure of a solution
  Solutions w/ same ΔT_f may have same osmotic pressure value

Osmotic pressure, Osmosis, Isoosmosis, Isotonic

- Osmosis: the mvt of water across the semi-permeable membrane
  Osmotic pressure: the force to drive the water movement
  Iso osmotic: Solutions w/ same osmotic pressure, but not isotonic
  Iso tonic: Isoosmosis + impermeable membrane

- Solutions having the higher osmolarity need to be infused into a large vein w/ greater blood flow to dilute the solution quickly to avoid development of thrombophlebitis

Examples of different solutions:

- Hypotonic saline solution (NaCl 0.45%) may be used to restore fluid into the intracellular compartment for patients w/ hyper-natremia
- Hypotonic saline solution may be given to lysate hypertonic sickle RBC & ↓[Hb]
- Hypertonic parenteral nutrition solutions are infused to replenish nutrients, fluid & electrolytes via deep vein infusion
- Hypertonic laxative solution, administered orally or rectally to induce osmotic diarrhea & relieve constipation.

Week 5: 26/3/2018

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Pharmaceutical suspensions

Intro

- Pharmaceutical suspension: liquid dosage form containing fine drug particles suspended uniformly in a liquid medium & can be adm. orally, parenterally or topically.
  - Orally: analgesics eg paracetamol
    antibiotics eg amoxicillin
    antacids eg Mylanta
  - Parenterally: intramuscular eg. Haarvix
    subcutaneously eg. Isophane (insulin)
  - Topically: eye drops eg. Prednephrine
    nasal spray eg. mometasone
    aerosol spray eg. Qvar
    skin eg Calamine lotion

What are suspensions?

- Suspension: solid in liquid dispersions where the solid phase containing undissolved solute drug particles, dispersed in a liquid phase.
  - Solid phase dispersed drug particles → dispersed phase / internal phase
  - Liquid phase containing solvent → dispersion medium / external phase

~ Classification based on the particle size of the dispersed phase

- If the undissolved drug particles are < 1μm in size & dispersed → colloidal disp
  - If these particles are solvated by the liquid phase & readily dispersible
    → Lyophilic colloidal dispersion
  - If these particles do not like the solvent they are in & not solvated
    → Lyophobic colloidal dispersion

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- Coarse dispersions (or suspensions) contains larger particles (1-10 μm for oral ; 30-50 μm for topical)

∞ Advantages

- Formulation for poorly soluble drugs
- Formulation of controlled release
- Masking taste as the drug is not in the solution
- Extemporaneous compounding for unavailable commercial products

∞ Desirable properties of suspension

- Safe
- Efficacious
- Stable
- Solid phase not settle rapidly
- Easily re-dispersible
- Homogenous after shaking
- Constantly uniform dosage
- Good flow, easy to measure
- Will not cake upon storage
- Appropriate particle size
- Ease of administration
- Elegant

∞ Limitations

- Unstable due to aggregation of particles → not re-dispersible after shaking
  → Excipients are required to slow down the precipitation

∞ Suspension stability

Suspension stability is affected by the particle size of the dispersed phase.
Smaller particles → ↑ surface area → ↑ particle-particle interaction
→ aggregation → sedimentation → caking → not re-dispersible
→ can't dispense a uniform dose → treatment failure

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Dispersion method

- Dispersion method involves using of a mortar & pestle (mix & grind). During this process, small particles can come together due to inter-particle forces & mechanical forces
- Excipients eg. wetting agents or surfactants are included during mixing & grinding to prevent particle-particle contact & agglomeration to ↓ rate of sedimentation & caking.

- Wetting agents may be used to wet the surface of particles to prevent aggregation. Addition of a suspending agent eg. mucilage tragacanth (10-20%) or compound tragacanth powder (2-3%) will slow down sedimentation rate & will offer uniform dosage when shaking the bottles.

Factors affecting the stability of suspensions & formulation considerations

~ Particle size

- Drug particles have the capacity for mvt. (kinetic property)
  → Particle interaction, aggregation, sedimentation & caking

- Very small particles (< 0.5 μm) are subjected to Brownian motion, ↑ potential for particle-particle contact & aggregation.
  The velocity of particle mvt is inversely proportional to the viscosity of the dispersion medium & the size of the particle
  → 1 strategy is to ↑ viscosity of the medium
  However, larger particles are subjected to gravity (> 0.5 μm)

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∞ Velocity of sedimentation

- Stoke's law:

$$v = \frac{2r^2(\rho - \rho^{med})g}{9\eta}$$

where: v = velocity of sedimentation
r = radius of particle
ρ = density of particle
ρ^{med} = density of medium
η = viscosity of medium
g = gravitational acceleration

Stoke's law describes most for particles that are subjected to gravity & suspension containing drug particles of size $> 0.5\,\mu m$, since smaller drug particle may not be affected by gravity
→ Normal for suspending agent for small particles

Thus, for drug particles from 5-10 μm, should be formulated w/ excipients eg. suspending agents, wetting agents, thickeners to ↓ sedimentation & caking

∞ Particle interaction & attractive force

- Aggregation occurs due to VdW force acting at short inter-particle distance. These forces ↑ as distance ↓ & particle surface area ↑:

$$VdW \propto \frac{SA}{d}$$

- Formulation can be stabilized by ↓ attractive force between particles

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~ Particle solvent interaction

- Lyophilic particles will be solvated in liquid medium. A solvent sheath is formed around each lyophilic particle & this solvent will prevent particle from coming in close contact w/ one another
The higher affinity between particle & the solvent → More stable sheath & product

- However, if the solvent sheath surrounding is broken, drug particles would come to each other to aggregate, → undesirable

- The particle - solven interaction is affected by change in solvent composition:
  - Addition of solvents
  - Addition of electrolytes or solutes

The addition of solvents/electrolytes w/ lyophilic particles results in a phenomenon called "competitive de-solvation"
→ Less of solven sheath around drug particle
→ Aggregation & sedimentation

~ Competitive de-solvation

- Added solutes/solvents/electrolytes into the dispersion may cause precipitation

~ Electrical repulsion effect

- Same surface charge → repel of particles.
Electrical repulsive potential is influenced by added excipients eg. buffer salts, isotonicity adjusting salts, coloring agents
→ Alter the tendency to aggregate.

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∞ Steric repulsion effect

- Particles repulsion to prevent coagregation & potential for caking can be induced by the addition of excipients eg. surfactants & polymers into the formulation
The surfactants/polymers will interact w/ the drug particles
→ Separation due to steric effect or osmotic effect

∞ Flocculation

- Flocculation can prevent sedimentation & caking
Flocculation involves particles being loosely associated as a 3D. weakly aggregates w/ high sedimentation vol., which do not settle but can be easily re-dispersed upon gentle shaking.
→ Best for long-term storage
- Flocculation can be induced by extra excipients eg. polymer/surfactant to form bridge between particles to produce loose clusters.

∞ Crystal growth in suspension

- Solid phases are subjected to particle size growth (crystal growth)
In any dispersion, there is an equilibrium between rates of dissolution & precipitation
Smaller particles tend to have higher solubility & dissolve then precipitate out on larger particles, while the larger particles will grow at their expense
→ Ostwald ripening phenomenon
This is highly undesirable: alteration in physical stability & bioavailability

- To prevent crystal growth: All-in or All-out formulation approach
  - All-in solution
  - All-out in suspension

- The Ostwald ripening is a thermodynamically-driven spontaneous process: larger particles are energetically favorable, than smaller particles, due to

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the number of surface molecules.
The system tries to lower its own energy
→ Detachment of molecules from the small particle to longer particle
→ Dissolve then precipitate.

- Lifshitz & Slyozov equation in case Ostwald ripening where diffusion of material is the slowest process

$$\langle R \rangle^3 - \langle R \rangle_0^3 = \frac{8 \gamma C_\infty v^2 D}{9 R_g T} \cdot t$$

where $\langle R \rangle$ = average radius of all particles
γ = particle surface tension or surface energy
C_∞ = solubility of the particle material
v = molar volume of the particle material
D = diffusion coefficient of the particle material
R_g = ideal gas constant
T = absolute t°
t = time

Week 6 : 9/4/2018

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Creams & ointments

Info

- Pharmaceutical creams, lotions & emulsions : dispersion of 2 immiscible liquid phases where 1 phase is dispersed as liquid globules in the other liquid pha
  - If the internal phase = oil droplets in external phase = water
    → Oil in water (o/w) system
  - If the internal phase = water in external phase = oil
    → Water in oil (w/o) system

- Drug may be dissolved in the oil phase or water phase depending on its solubility in oils or water

Emulgents (emulsifiers) are needed to stabilize the product since the 2 phases are immiscible to each other
→ Rapid separation without emulgents, due to internal phase droplet - droplet interaction, leading to aggregation (coalescence) & phase separation (cracking)

Emulsion

Desired properties of emulgents :
- Quickly adsorbed around internal phase droplets
- Form a stable, coherent film around internal phase droplets
- Provide mechanical barrier
- ↓ interfacial tension
- Impact on electrical potential → droplet repulsion
- ↑ viscosity
- Effective at relatively low conc.
- Safe, non-interacting, cheap.

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Classification of emulgents

~ Finely divided solids

- Stabilize by adsorbing at the interface & form physical barrier to prevent coalescence

Eg: Powdered silica, carbon particles, bentonite clay particles

Particles need sufficient adhesion for one another to form film

- The phase where the particle preferentially resides is the external phase
  → If the particles are preferably wetted by water will form o/w emulsion.

~ Hydrophilic colloid & macromolecules

- Form strong multi-molecular films to prevent coalescence of internal phase globules

The film must break before the drug can be released
  → Potential problem for bioavailability & absorption

- This method provides significant ↑ in viscosity & stability, however doesn't ↓ surface tension

Eg: Methylcellulose, Gum acacia, high MW polysaccharides (uncooked starch, pectin, alginate)

Hydrophilic colloids

Eg Macromolecules: Proteins, Gelatin, Egg yolk, Lecithin, Gum

~ Surfactants or Surface active agents (SAA)

- Have both hydrophilic & hydrophobic characteristics
  → Can reside at the liquid & water interphase

They form a flexible mono molecular film at the interface
  → Can reform rapidly if broken or disturbed
  → Complex, closely-packed, condense film around each droplet

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- Surfactants ↓ surface tension due to their adsorption at the oil-water interface

∞ Emulgent classification based on hydrophilic lipophilic balance (HLB) value

- Emulgents may be predominantly hydrophilic or lipophilic depending on the number & nature of polar & non-polar groups present.
  Ratio of polar to nonpolar is indicated by the HLB scale ranging from 0-20
  - Low HLB (4-8): predominantly lipophilic → w/o systems
  - High HLB (9-20): predominantly hydrophilic → o/w systems
  - HLB 7-9 promote either o/w or w/o depending on other factors eg. chemical nature, quantities of each phase

- We can predict the type of cream by looking at the HLB value of each emulgent
  HLB value is additive:
  Eg: 3 part of A (HLB = 10)
  2 part of B (HLB = 2)
  → HLB surfactant system = $\left(\frac{3}{5} \times 10\right) + \left(\frac{2}{5} \times 2\right) = 6.8$
  → Stabilize w/o system

Surfactants

∞ Characteristics of ALL surfactants

- One portion is polar (Hydrophilic)
- The other part is non-polar (Lipophilic)
- 2 solubility characteristics in 1 molecule
- Have relative size & characteristics of polar vs non-polar portions
  → Type & stability of the emulsion produced

Eg of SAA:
- Na lauryl sulfate
- Cetrimide
- Cetostearyl alcohol
- Polyoxyethylene sorbitan mono-oleate
- Dodecylamine

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Types of surfactants:

~ Anionic surfactants

- Fatty acid salts (soaps) ⇒ stabilise o/w emulsion
  More stable in high pH
  Cream bases containing anionic surfactants are incompatible w/ cationic drugs ⇒ shouldn't be mixed together

~ Cationic surfactants

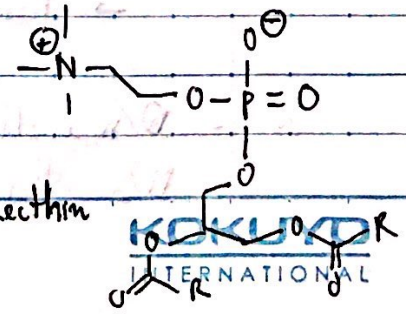
- Fatty amine salts or ammonium salt
  Used in antiseptic creams due to antimicrobial properties
  Are more irritating to the skin than anionic & non-ionic surfactants
  Incompatible w/ anionic drugs

~ Non-ionic surfactants

- Non-charged
  Eg: Cetomacrogol, Glyceryl mono-oleate (GMO)
  Widely compatible
  Generally less toxic / irritating & heat-sensitive, less sensitive to electrolyte & pH
  Used in food, drinks, pharmaceutical & skin-care products & some are suitable for parenteral products

~ Other

- Lecithin is an amphoteric surfactant w/ 2 ionizable groups & the nature of the charge depends on pH
  Commonly used in food & injectable emulsions.



Lecithin

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SAA stabilizing mechanism

- Having both lipo - hydrophilicity → Molecules reside at oil - water interphase
  to ↓ surface tention & provide mechanical barrier.
  → Prevent separation.

∾ Steric repulsion by non-ionic SAA

- Non-ionic SAA stabilize emulsion by steric repulsion effect
  The surfactant reacts as a barrier
  When 2 droplets approach, entropy ↓ → repulsion

∾ Electrical repulsion by ionic SAA

- Same charge repulsion effect.
  Charged SAA tends to promote o/w emulsion as water is a preffered medium for ion
- Charged SAA are not generally used in oral emulsion due to laxative effect (drawing out water from the intestine), unless for therapeutic use.

O/w & W/O systems

∾ How to identify

- If the product can be diluted w/ very few mL of water or can be incorporated w/ water miscible dye solution
  → O/W system. (water = external phase)
  Conductivity of o/w system can be measured if the surfactants are ionic

- Knowing the ionic nature of the .or cream base
  → Formulate active drug w/ compatible surfactant system

- O/w enables the incorporation of water soluble drug into the base
  W/o offers a barrier & ↑ permeation effect

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Emulsion stability

- Most pharmaceutical emulsions have dispersed droplets from 100nm - 100μm with large interfacial area.
  → Require energy → Thermodynamically highly unstable system
  - Mortar+pestle : micron particle size
  - Homogenizer : 500nm
  - Ultrasonicator : <200nm (IV emulsion)

Emulsion Instability

4 processes:
- Creaming
- Coalescence
- Cracking
- Phase inversion

~ Creaming

- Upward mvt of oil & downward mvt of water due to density & can occur during storage. This is a reversible effect since the droplet are still surrounded by emulgent film. Occur in o/w systems.
- Rate of creaming depends on :
  - Viscosity of external phase
  - Droplet size
  - Internal phase ratio (ϕ)

Similar to Stoke's law when describing mvt of internal phase globules, affected by :
- Density differences of the phase
- Size of the globules
- Viscosity of external phase

→ Prevention:
- ↓ droplet size (<2 micron)
- ↓ density differences
- ↑ viscosity of external phase

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~ Coalescence

- 2 droplets collide → 1 large droplet
  → Involve breaking the mechanical barrier & release of dispersed phase
  Irreversible, which is affected by:
  - Emulgents
  - t°
  - pH
  - Solubility
  - Addition of solutes
  - Internal phase ratio (ϕ) is high → coalescence

~ Cracking

- Complete separation of 2 phases

~ Phase inversion

- Change in emulsion type (eg. o/w → w/o)
  Addition of extra internal phase & ↑ ϕ will often invert the emulsion if the emulgent system is unable to handle such large amount of extra internal phase
  Change in nature of the interfacial film can be done by addition of salt, leading to phase inversion.
  Eg: CaCl$_2$ added to Na stearate → o/w → w/o system

Factors affecting physical stability of emulsion, cream & lotion

~ Summary

- Most important:
  - Electrical repulsion
  - Steric factors
  - Interfacial film
  - Viscosity
  - ϕ
  - Droplet size

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- Addition of solvents
- Addition of salts/electrolytes
- pH change

- Other factors:
  - Microbial contamination → formulated w/ preservative
    Preservative can be resided at 2 phases → ↓ effectiveness when microbial growth occurs in the water phase → Preservative must be in water.
    Preservative must be un-ionized → affected by pH
    Preservative must be un-bound → choice of emulgent
  - Oxidation → formulated w/ antioxidant
  - t° : non-ionic SAA are more affected than ionic SAA
    → O/w eventually invert phase into w/o at high t°
    This is due to less interaction between surfactants & water molecule
    → change in HLB of surfactant
    → phase inversion
    → Stored below phase inverting t° (usually < 30°C)

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