

« وإلا تفقد وتزحماني أكون من الخاصين »

A. pH - Partition Theory

- The extent to which a weakly acidic or basic drug ionizes in solution in the gastrointestinal fluid may be calculated using **Henderson - Hasselbalch equation**.

****Weak acids (e.g. aspirin):**

عند C_{acetic}

(pH) عند الدواء في



* الدواء يسفرق 20 دقيقة في Stomach

إذا ما دخلت

Acid Form

$$K_a = \frac{a_{H^+} \cdot a_{A^-}}{a_{HA}} \approx \frac{[H^+] \cdot [A^-]}{[HA]}$$

* إذا دخلت خفيف

للساعة

* إذا (كل ثقل ساعة - ساعة) أي (أي)

ناخذ من الفم oral

يسهل ال Stomach

Dissociation Constant equation - Weak Acids

Acid → medica

taking the negative log of both sides

Weak Acid [HA] لا يمتص

H^+

+

[A⁻]

ما يمتص الجسم

يعين يكون الدواء أغلب في unionized (Acid form)

Common form in Stomach

Conjugate base

A. pH - Partition Theory

(pKa) في ال Stomach صغيرة

(pKa) في ال intestine كبيرة

surface area صغيرة

$$-\log K_a = -\log [H^+] - \log \frac{[A^-]}{[HA]}$$

* ال pH في

Rearranging gives the following equation:

(pH) (7.4) (الدم)

Acidic Drug ionization قليل لا

$$pK_a - pH = \log \frac{[U]}{[I]} = \log \frac{[HA]}{[A^-]}$$

(pKa) بين 5 و 4

* 99% يكون بال unionized form

* الجسم يمتص دائماً ال unionized form فقط

Henderson - Hasselbalch Equation - Weak Acids

يكون

* يروح الدواء ال intestine ← $pK_a = 4.5 / pH = 6$

يعين يكون 99% من الدواء بال ionized form

pH في ال Stomach أقل منه بدرجتين

* الوقت يلي يقوده الدواء في الأمعاء

كيف نتحقق الامتصاص في ال intestine 1% يمتص لاسبب ال surface area كبيرة جداً و equilibrium

الوقت يلي استفرغه الدواء $\leftarrow$ Intestine في ال (الدواء ضعيف) $\rightarrow$ ionized form unionized form

A. pH - Partition Theory

Weak Bases:

عشاش ن يصير في قوارن يتحول جزء من 99% لا Unionized form وامتصه الجسم
 $pK_a - pH = \log \frac{[I]}{[U]} = \log \frac{[HB^+]}{[B]}$
 الجسم لمتن كل

Henderson - Hasselbalch Equation - Weak Bases

Limitations of the pH-partition hypothesis:

-Despite their high degree of ionization, weak acids are highly absorbed from the small intestine and this may be due to:

- 1- The large surface area that is available for absorption in the small intestine.
- 2- A longer small intestine residence time.

Weak Acid

$$pH = pK_a + \log \frac{\text{Base}}{\text{Acid}} \quad \frac{\text{ionized}}{\text{unionized}}$$

Weak Base

$$pH = pK_a + \log \frac{\text{Acid}}{\text{Base}}$$

A. pH - Partition Theory

- 3- A microclimate pH, that exists on the surface of intestinal mucosa and is lower than that of the luminal pH of the small intestine.

* إذا الأدوية للبشر ليس تأثر على الدواء ما أخذ الدواء orally هاهي الأفعاء شرحها

6
 PH عالية
 5 / 4.5
 Lumine of intestine mucosa
 unstaidd water layer
 PH تكون أقل بشوي
 يعني تحسن من امتصاص الدواء

* أغلب الأدوية بال Acidic form يعني لما تكون بال intestine بال lumine تكون 99% بال ionized وإذا انقل لد Water layer (PH) تختلف

تزيد نسبة ال unionized $\rightarrow$

Phospholipid bilayer membrane

الدواء والذائب في الدهون
يعني بدنه يذترق
ال membrane

B. Lipid solubility of drugs

السبب في
أو في يكون
Change
(ionisation)

Some drugs are poorly absorbed after oral administration even though they are non-ionized in small intestine. Low lipid solubility of them may be the reason.

The best parameter to correlate between water and lipid solubility is the partition coefficient.

lipid water
P إذا كان 1
P إذا كان 1
كيفية تغير عن ال Polarity

$$\text{Partition coefficient (p)} = \frac{[L] \text{ conc}}{[W] \text{ conc}}$$

extraction
أو Externantary لتقدير
lipid water
P

where, [L] conc is the concentration of the drug in lipid phase.

[W] conc is the concentration of the drug in aqueous phase.

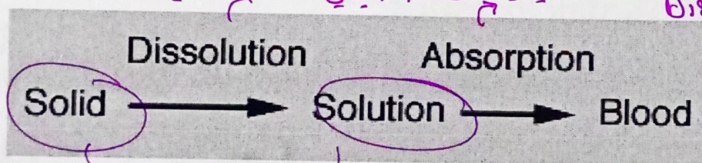
The higher p value, the more absorption is observed.

مثال: قبل (100) التركيز بعد إضافة Water ليس (70)

Concentration Water ونفيس ال Octan

C. Drug Dissolution :-

Many drugs are given in solid dosage forms and therefore must dissolve before absorption can take place.



If dissolution is the slow, it will be the rate determining step (step controlling the overall rate of absorption) then fact affecting dissolution will control the overall process.

* سرعة ال Dissolution تحدد سرعة ال Absorption
إذا كانت ال Dissolution بطيئة ال Absorption بطيء
إذا كانت ال Dissolution سريع ال Absorption سريع

C. Drug Dissolution

- Drug dissolution is considered to be diffusion controlled process through a stagnant layer surrounding each solid particle.

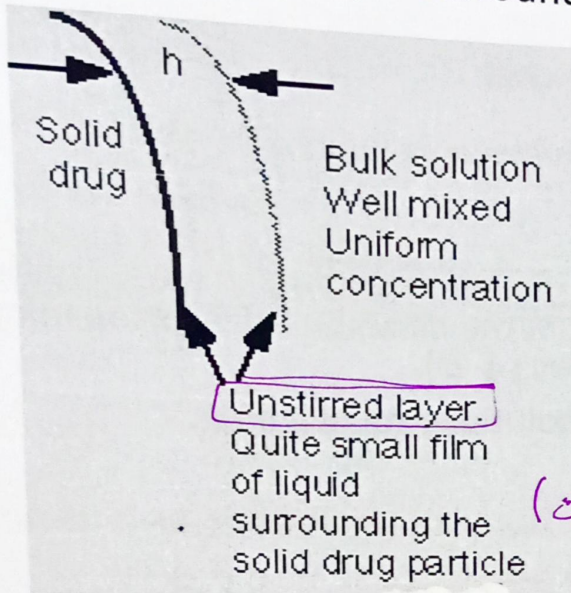


Diagram Representing Diffusion Through the Stagnant Layer

Factors → Dissolution تأثير على الذوبان

الدواء بالبدنية يصير له ^① disintegration (تفكك) الى قطع صغيرة وفيه على سطح

ال Target ← unstirred layer اسمها layer
ولذلك قطع الدواء الصغيرة تخترقها في layer

C. Drug Dissolution

- The dissolution of drugs can be described by the **Noyes-Whitney equation**:

سرعة اختراق الدواء Diffusion coefficient الجزء من surface area تركيز الدواء فيه distances من bulk الى layer

$$\text{Rate of Solution} = \frac{D \cdot A \cdot (C_s - C_b)}{h}$$

thicknes of layer

- Where D is the diffusion coefficient, A the surface area, C_s the solubility of the drug, C_b the concentration of drug in the bulk solution, and h the thickness of the stagnant layer.

تركيز الدواء → تركيز الدواء
 - If C_b is much smaller than C_s then we have so-called "Sink Conditions" and the equation reduces to

كلما ال Absorption أعلى كان CS أعلى

$$\text{Rate of Solution} = \frac{D \cdot A \cdot C_s}{h}$$

C. Drug Dissolution

تسمى ال factor التي تؤثر على معدل ذوبان الدواء

Factors affecting drug dissolution in the GIT:

1 Physiological factors affecting the dissolution rate of drugs:

- The environment of the GIT can affect the parameters of the Noye-Whitney equation and hence the dissolution rate of a drug.

A- Diffusion coefficient, D:

① Solubility

- Presence of food in the GIT → increase the viscosity of the gastrointestinal fluids → reducing the rate of diffusion of the drug molecules away from the diffusion layer surrounding each undissolved drug particles ($\downarrow D$)

→ decrease in dissolution rate of a drug.

① solubility

② viscosity

Diffusion Coefficient

تسمى الأشياء التي تؤثر على

لأنهم الدواء يذوب ويخترق الغشاء
كلما كان الدواء عالي viscosity → يقل معدل ذوبان الدواء
كلما كان الدواء عالي solubility → يزيد معدل ذوبان الدواء

C. Drug Dissolution

B- Drug surface area, A:

Surfactants in gastric juice and bile salts → increase the wettability of the drug → increase the drug solubility via micellization.

Micronized → أسرع ذوبان (مجمعة أظفر)

C. The thickness of diffusion layer, h:

② يتحكم فيها حركة GI

An increase in gastric and/or intestinal motility → decrease the thickness of diffusion layer around each drug particle → increase the dissolution rate of a drug.

تقلل من السمك layer

حركة GI زادت

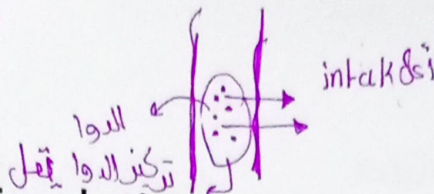
D. The concentration, C, of drug in solution in the bulk of gastrointestinal fluids:

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كيف تزيد العملية ؟
ناخذ حبة الدواء

Water يزيد

C. Drug Dissolution



يؤثر Absorption

Increasing the rate of removal of dissolved drug by (absorption) through gastrointestinal-blood barrier and increasing the intake of fluid in the will decrease in C → rapid dissolution of the drug.

dissolution أعلى

مرعة ال

تركيز الدواء

↑ Absorption

II Physicochemical factors affecting the dissolution rate of drugs:

A- Surface area, A:

- The smaller the particle size → the greater the effective surface of drug particle → the higher the dissolution rate.

* كلما كان حجم ال Particle صغير ← Solution لأفضل

* كلما انطحن الدواء ل Particle كثر Fine

منع يجمع Clumping مع يوفى ليهك احط Surfactant

* كيف اخفف ال Concentration ل Drug ؟ اخذه مع Water
عشان تعمل للدوا dilution وازيد Absorption

C. Drug Dissolution

* اقل ال Surface tension

- Methods of particle size reduction include: mortar and pestle, mechanical grinders, mills, solid dispersions in readily soluble materials (PEG's).

- However very small particles can clump together. Therefore

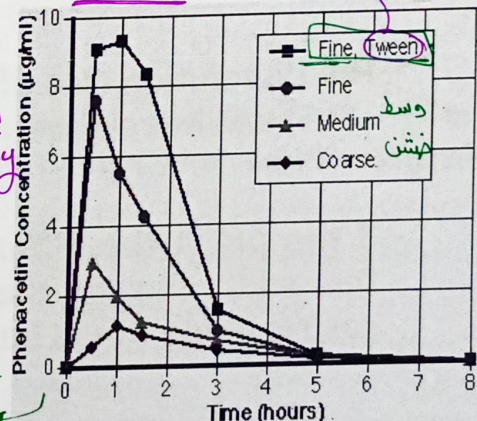
a wetting agent such as Tween 80 can have a beneficial effect on the overall absorption.

wetting agent
Emulsion agent

Surface Tension يقل

يعني مع Surfactant

↑ motability



* اخذناه حبة الكور

← انه لما يقل Surface tension يزيد Emulsion للماديت وتخلط بشكل أفضل

* معجن يبين امتصاص للدوا باختلاف حجم ال Particle لنفس الدواء

C. Drug Dissolution

B-Diffusion coefficient, D : يُعرف D

The value of D depends on the size of the molecule and the viscosity of the dissolution medium.

يعني وجوده في الوسط

* درجة ذوبان الدواء ← Solubility

C- Solubility in the diffusion layer, C_s :

- The dissolution rate of a drug is directly proportional to its intrinsic solubility in the diffusion layer surrounding each dissolving drug particle.

الذوبان في الطبقة الانتشارية
Solubility of Drug

C. Drug Dissolution

D- Salts:

* درجة ذوبان Salts يزيد مع Solubility

- Salts of weak acids and weak bases generally have much higher aqueous solubility than the free acid or base.
- The dissolution rate of a weakly acidic drug in gastric fluid (pH - 3.5) will be relatively low.
- If the pH in the diffusion layer increased, the solubility, C_s , of the acidic drug in this layer, and hence its dissolution rate in gastric fluids would be increased.

C. Drug Dissolution

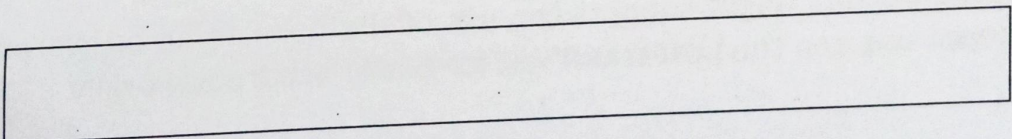
- The pH of the diffusion layer would be increased if the chemical nature of the weakly acidic drug was changed from that of the free acid to a basic salt (the sodium or potassium form of the free acid).
- The pH of the diffusion layer would be higher (5-6) than the low pH (1-3.5) of the gastric fluids because of the neutralizing action of the strong (Na^+ , K^+) ions present in the diffusion layer.
- The drug particles will dissolve at a faster rate and diffuse out of the diffusion layer into the bulk of the gastric fluid, where a lower pH.

C. Drug Dissolution

- Thus the free acid form of the drug in solution, will precipitate out leaving a saturated solution of free acid in gastric fluid.

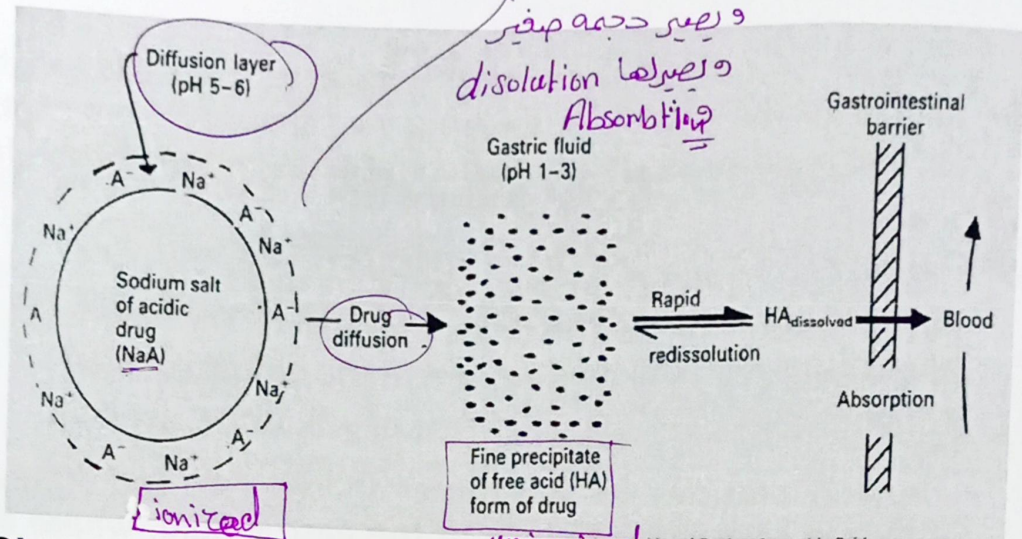
This precipitated free acid will be in the form of:

- very fine,
- non-ionized,
- wetted particles which have a very large surface area in contact with gastric fluids, facilitating rapid redissolution when additional gastric fluid is available.



* الدواء و محام بار Salt لما يواجه ال pH المنخفضة

Drug Dissolution



Dissolution process of a salt form of a weakly acidic drug in gastric fluid.

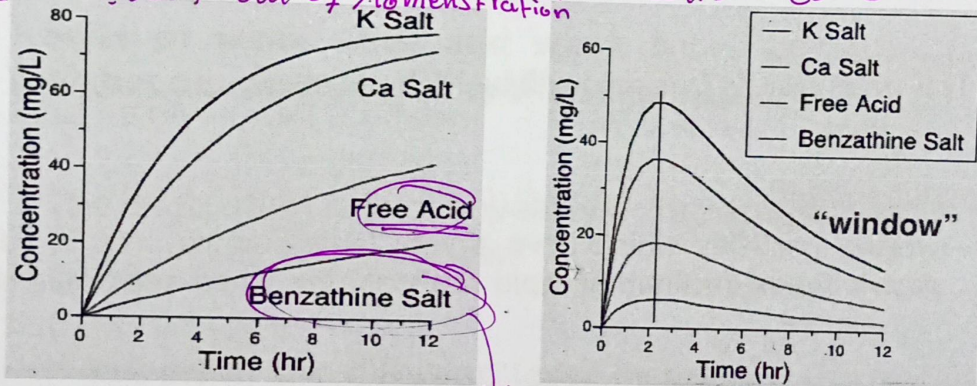
فولت استخدام ال Salt

- 1) Small Partical size (fine) حمار الدوا
- 2) و حمار الدوا بال unionized form
- 3) يعتبر من Weting agent ما احتاج اضيف اية مواد تامة في الحاصل على نفس rate redissolution

Drug Dissolution

- One example is the dissolution and bioavailability profiles of Penicillin V various salts.

* اختلاف نوع ال Salt حسب route of Administration (الطريقة لدوا ياتي بي)



لتقليل ال Solubility

These results might support the use of the benzathine or procaine salts for depot use and the potassium salt for better absorption orally.

عن ياتر على -

① Stability

② Solubility

Crystal بار
Solubility او حادة ال
* عن تلاخي Drug
عالي و يكون unstable

Drug Dissolution

stable * ونفس الدوا لكن به Crystal ثانية

E- Crystal form: Solubility قليلة

1- Polymorphism:

- Some drugs exist in a number of crystal forms or polymorphs. These different forms may have different solubility properties and thus different dissolution characteristics.

* لازم ندرس Characteristics للمركب ونشوف كم Polymorphs الي عشان نحدد لهم
- Chloramphenicol palmitate is one example which exists in three crystalline forms A, B and C.

A → is the stable polymorph

B → is the metastable polymorph (more soluble)

C → is the unstable polymorph

- The plasma profiles of chloramphenicol from oral suspensions containing different proportions of

* يعني اذا عندنا Polymorph
له 6 أشهر
يصير Stable و هيك
يفقد ال Dissolution
طبيعت

← unstable *
← stable *

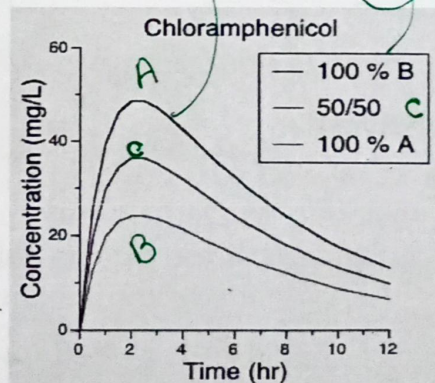
Drug Dissolution

Polymorphic forms A and B were investigated.

-The extent of absorption of Chloramphenicol increases as the Proportion of the polymorphic form B is increased in each suspension. This is attributed to the more rapid Dissolution of the metastable Polymorphic form B.

* لهيك نحصيهم على شكل Suspension
Stable
و مع الوقت يتحول لـ
و تقل bioavailability

- Shelf-life could be a problem as the more soluble (less stable) form may transform into the less soluble form (more stable).



Drug Dissolution

Dissolution شرح

2- Amorphous solid:

solubility عالية

- The amorphous form dissolves more rapidly than the corresponding crystalline form.

Crystalline form لا في الوقت يتحول

- The more soluble and rapidly dissolving amorphous form of novobiocin antibiotic was readily absorbed following oral administration of an aqueous suspension to humans. However, the less soluble and slower-dissolving crystalline form of novobiocin was not absorbed (therapeutically ineffective).

Crystalline لا في الوقت يتحول

Antibiotic

و يصبح inactive

- The amorphous form of novobiocin slowly converts to the more stable crystalline form, with loss of therapeutic effectiveness.

amorphous form ← Absorption ← Dissolution ← منح

Crystalline إذا كان بال

Dissolution (بشرط) mis soluble

الذائبة قليلة

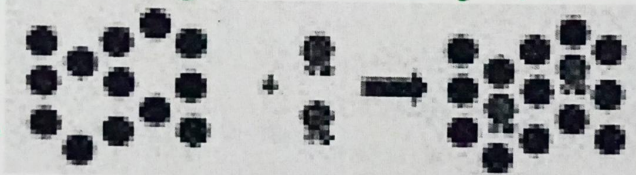
Drug Dissolution

Water ممتزج بال

3- Solvates:



solvent موجود بين crystal



Solubility لا
Hydrate أقل
Anhydrate فن

Solvates: If the drug is able to associate with solvent molecules to produce crystalline forms known as solvates.

Water ← Solubility أكبر ← Form Anhydrous ← كلما كان

Hydrates: drug associates with water molecules.

- The greater the solvation of the crystal, the lower are the solubility and dissolution rate in a solvent identical to the solvation molecules.

Drug Dissolution

- 1995-2
- The faster-dissolving anhydrous form of ampicillin was absorbed to a greater extent from both hard gelatin capsules and an aqueous suspension than was the slower-dissolving trihydrate form.

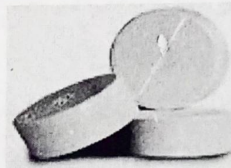
ampicillin دواءه اقل إذا كان بار Anhydrous
 ampicillin دواءه اقل إذا كان بار (aqueous) hydrous

D- Drug stability and hydrolysis in GIT

- Drugs that are susceptible to acidic or enzymatic hydrolysis in the C suffer from reduced bioavailability.
- How to protect drugs (erythromycin) from degradation in gastric fluid ??

enteric coating نقي

- 1- Preparing enteric coated tablets containing the free base of erythromycin
 The enteric coating resists gastric fluid but disrupts or dissolves at the acid pH range of the small intestine.



acid
 * إذا عني دواء OH^- أو N^+ اشترك مع
 و يصير عني ester ← و عني esterases
 يحسب ان acid الموجودة وتحول الى
 erythromycin

- 2- The administration of chemical derivatives of the parent drug. The prodrugs (erythromycin stearate) exhibit limited solubility in gastric fluid but liberate the drug in the small intestine to be absorbed.

E- Complexation ^{منع} ^{لكن عندنا أشياء} * أغلبه فش منع

- Complexation of a drug may occur within the dosage form and/or in gastrointestinal fluids, and can be beneficial or detrimental to absorption

1- Intestinal mucosa (mucin) + Streptomycin = poorly absorbed complex

2- Calcium + Tetracycline = poorly absorbed complex (Food-drug interaction)
* ^{فستقان الطبيب} يمنع امتصاص الـ Tetracycline

3- Carboxyl methylcellulose (CMC) + Amphetamine = poorly absorbed complex (tablet additive – drug interaction)
absorbance

4- Lipid soluble drug + water soluble complexing agent = well-absorbed w soluble complex (cyclodextrin)
water

F- Adsorption ^{امتزاز}

- Certain insoluble substances may adsorb co-administered drugs lead to poor absorption.

• Charcoal (antidote in drug intoxication). ^{حبوب الفحم عشان تسمم الأدوية} ^{يمنع امتصاص بعض الأدوية}

• Kaolin (antidiarrhoeal mixtures) ⇒ ^{تخلص من} ^{maintenances}

• Talc (in tablets as glidant) ^{exotoxic} ^{من البكتيريا (coliera)}

يمنع امتصاص الأدوية

* عشان الدواء يضل هاتين في tablet machine

* أدوية التخلص من بكتيريا الكوليرا

هي تخلصنا من البكتيريا هاتين
و يضل مواد تفرزها
البكتيريا (الكوليرا) تخلص

فلزقة على الأظفار و تفعل

Kaolin و الـ diarrhoea يخلصنا من هاتين المواد

