



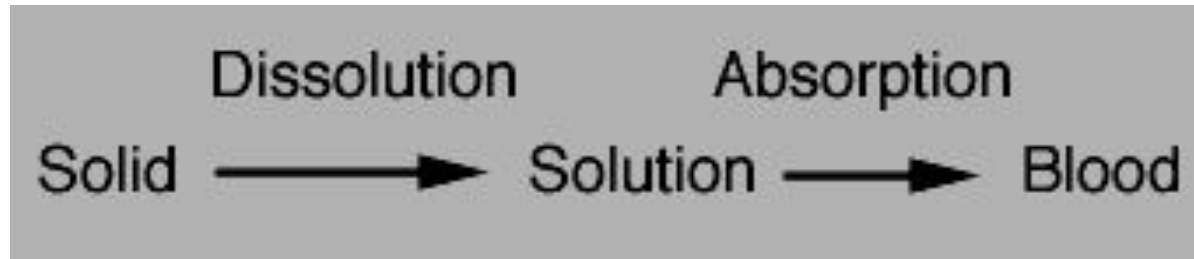
Bio Pharma

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Drug absorption

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 (the step controlling the overall rate of absorption) then factors affecting dissolution will control the overall process.

الدواء ال solid لو ما صار إلو disintegration بعدها تحول ل solution عن طريق ال dissolution أنا ما بستفيد منو إشي سواء كان lipophilic أو أي إشي ثاني المهم يصير إلو dissolution عشان هيك انا بعتبر ال dissolution هو ال rate limiting step في عملية ال absorption لانو بدونو ما بحدث absorption .

هسا في عندي أشي اسمو ال rate of dissolution هو المعدل اللي بحتاجه الدواء حتى يتحول من small particles ل solution بوقت معين .

C. Drug Dissolution

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

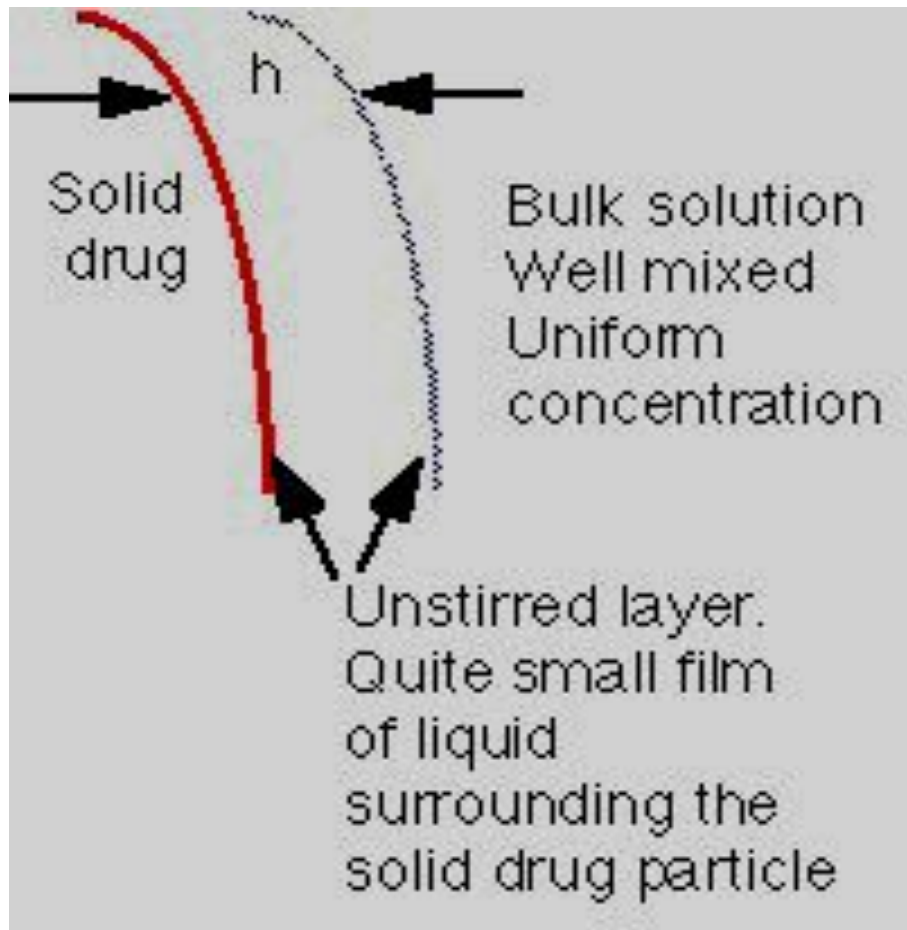


Diagram Representing Diffusion Through the Stagnant Layer

هسا الدواء اول ما يتصنع بكون عليه stagnant layer هاي الطبقة بتتحكم بال dissolution فبتتحكم كم من الدواء طلع من هاي الطبقة وصار إلو dissolution. القانون اللي بالسلايد اللي بعد هاد السلايد بشبه ال Fick's first law لكن هاد اسمو noyes whitney equation ويعتمد على ال diffusion coefficient وال h معناها ال thickness لل stagnant layer وال C_b هو ال concentration حولين ال drug يعني outside وال C_s هي ال solubility لل drug particles.

C. Drug Dissolution

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

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

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

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

هسا لو اجي على Cs-Cb كل ما قلت ال Cb كل ما كان ال rate of solution
أعلى فمتى يكون مهمل وقليل جدا ؟
أول أشي وقت ما يكون في تركيز للدواء في المحيط أو يكون ال الذائبية عالية
مقارنة بال Cb فتهمل وهاي بنسميها ال sink condition .

C. Drug Dissolution

Factors affecting drug dissolution in the GIT:

I Physiological factors affecting the dissolution rate of drugs:

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

A- Diffusion coefficient, D :

- 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.

الاشياء اللي بتأثر على ال dissolution ك physiological factors:

ال diffusion coefficient بتأثر عن طريق ال lipophilic أو ال viscosity الأكل اذا كان موجود بزيد ال viscosity وبالتالي بقلل ال diffusion coefficient أو ال particle size كل ما كانت كبيرة كل ما قللت ال diffusion coefficient.

ال surface area زي ما حكينا قبل انو ال bile salt بترتبط بال drug فبتزيد ال surface area وبتزيد ال solubility وال wettability.

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.

C. The thickness of diffusion layer, h:

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.

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

ال thickness ال gastric and intestinal motility بتضغط ال particle
فبتقلل ال thickness.

ال Cb كل ما قل يعني ال absorption عالي أو كمية الماء عالية فيتكون ذائبة بالماء
فالفرق بكون أعلى وال dissolution أعلى .

ك physicochemical أول أشي ال surface area بتزيد كل ما قلت ال
particle size وبالتالي ال dissolution أعلى .

C. Drug Dissolution

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

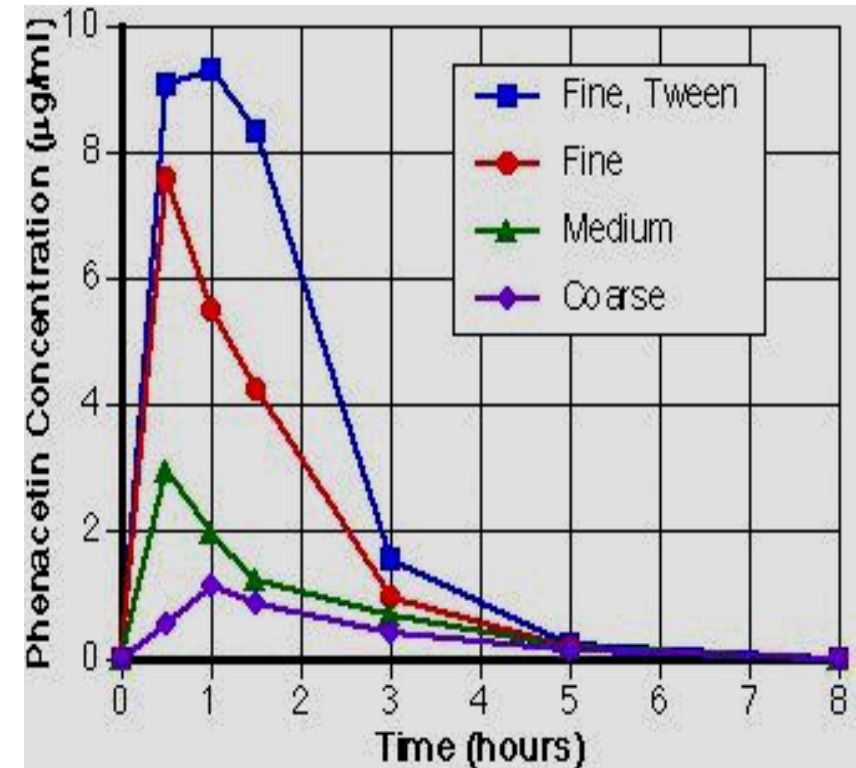
II Physicochemical factors affecting the dissolution rate of drugs:

A- Surface area, A:

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

C. Drug Dissolution

- *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.



بهاد الشكل بين علاقة ال particle size مع ال dissolution كل ما كان الحجم كبير
كل ما كان ال dissolution أقل والأحسن يكون fine particles هسا إحنا حكيينا قبل
إنو ال particle size لحد معين بتكون منيحة لكن لما تصغر كتيير بصير في زي ال
aggregation فعشان نتجنب هاد الاشئ بتصيف tween agent فبصير عادي لو صغر
حجم الجزيئات

C. Drug Dissolution

B-Diffusion coefficient, D :

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

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.

ال diffusion coefficient يعتمد هون على ال particle size كل ما قل كل ما
كان أحسن وبعتمد على ال viscosity كل ما قلت كل ما كان أحسن .
ال Cs يزيد لما تزيد ال solubility فلما تزيد رح يزيد معها ال dissolution.

C. Drug Dissolution

D- Salts:

- 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 1 – 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.

ال salt هسا الأدوية ممكن تكون weak acid or weak base أو salt فالذوبان يكون ثابت باختلاف ال PH فعشان هيك أنا بروح بعملو على شكل salt فمثلا في molecules بتكون إشارتها negative بروح بضيف إلها sodium وبالتالي بتصير salt وبحصل dissolution rate أعلى .

ال weak acid بصير إلها absorption أكثر في ال stomach وبتتحول unionized فبتقل ال solubility وبقل ال ionization وبقل ال dissolution فأننا بروح بغير ال PH وبحول ال unionized ل ionized لكن ما بخلي كلو ionized لأنو عشان يصير لجزء absorption.

فأنا بروح برفع ال pH لخمسة أو ستة فبتتحد ال A- مع ال k او ال Na فبزيد ال diffusion layer المحيطة بالدواء .

أنا بدي أرف كيف أختار الملح المناسب لأنو مو كل الأملاح مناسبة وبتعمل dissolution rate أعلى مثال عليه ال pinicillin v لو فاعلتو مع ال benzathine salt رح يكون ال dissolution إلو قليل وأقل من ما هو free عشان هيك لما يتحد مع هاد الملح مستحيل ينعطى oral لكن إذا فاعلتو مع K او Na بتزيد ال solubility .

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 bulk 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 bulk pH.

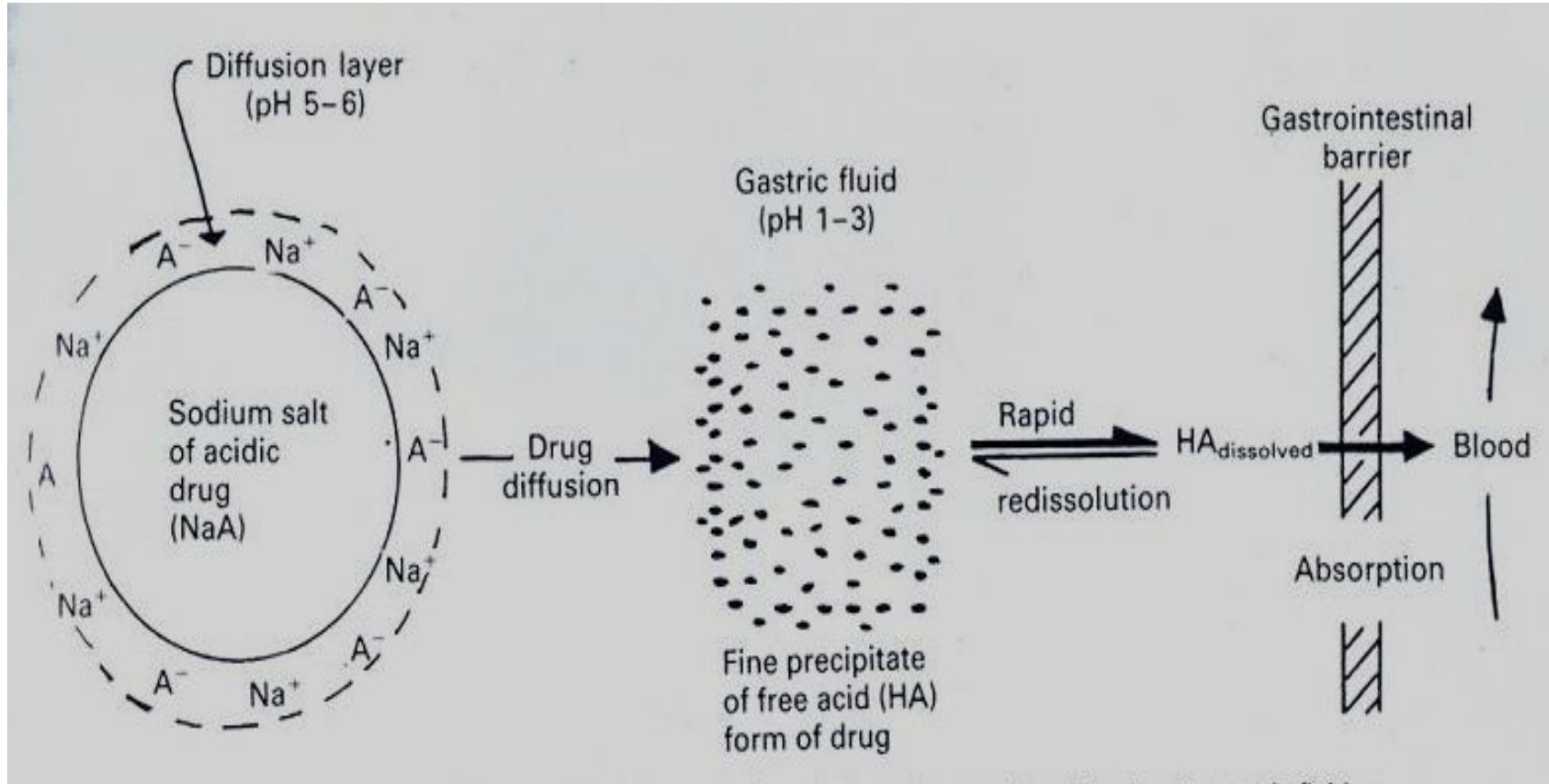
C. Drug Dissolution

- 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.

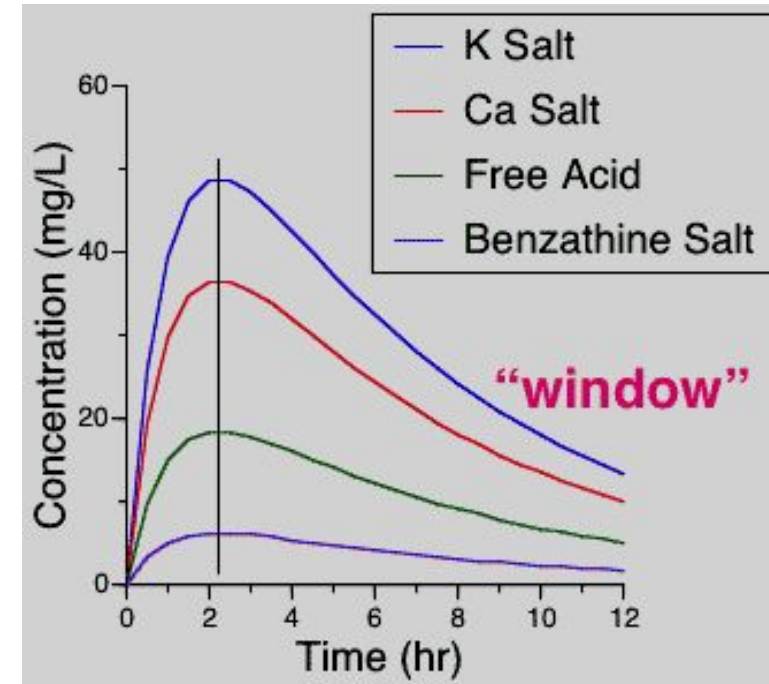
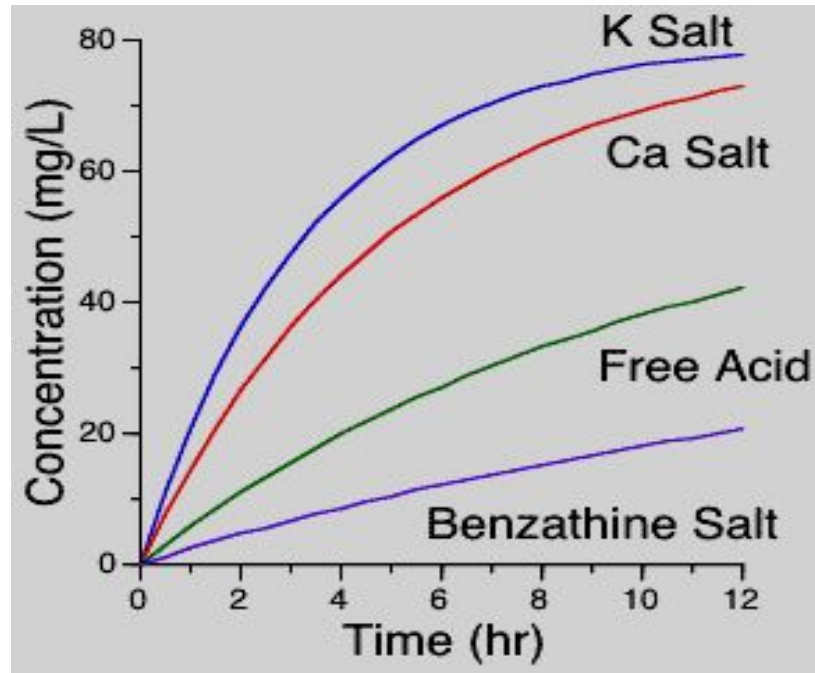
Drug Dissolution



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

Drug Dissolution

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



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

ال crystal form : ال polymorphism معناها متعدد الأشكال يعني دواء أو مادة ال crystal form يكون متعدد إلو او ترتيب ال crystal مختلف كل واحد عند الثاني .

بدنا نعرف إنو كل ما كان الدواء crystal كل ما كان more stable وبالتالي ال dissolution rate قليل لكن polymorph كل ما كان unstable وبالتالي ال dissolution rate عالي وبالتالي يحصل على أعلى absorption.

Drug Dissolution

E- Crystal form:

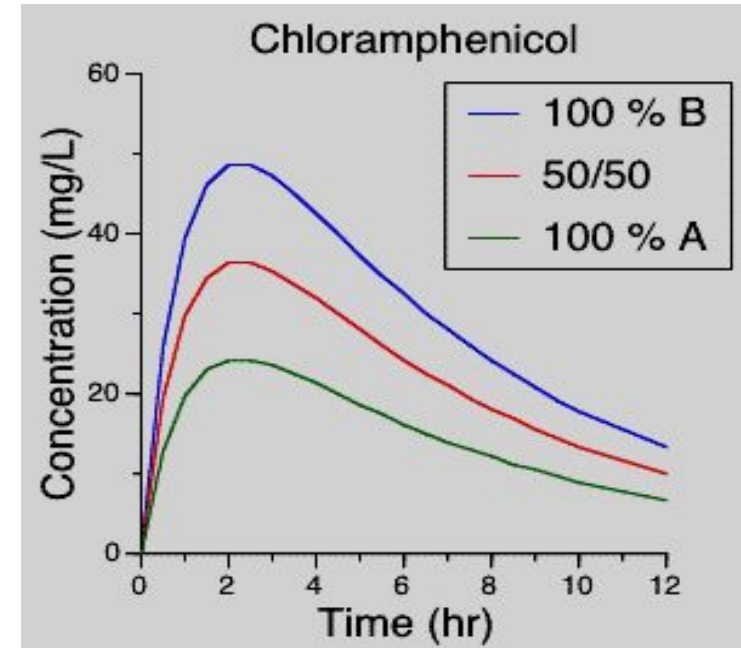
1- Polymorphism:

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

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.



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

بالشكل اللي بالسلايد اللي قبل هاد بيين تأثير ال amorphous وال crystal على ال concentration in plasma وبالتالي ال more stable اللي هي A كانت أقل concentration .

هسا بدنا نعرف كمان انو ال amorphous ما بكون سكل ال crystal ثابت عشان هيك بكون unstable.

ال salvates بكون في crystal وما بتكون محيطة فيه water يعني solvent ما بكون water أما ال hydrates بكون الأشي اللي محيط بال crystal هو water أما ال anhydrous ما بكون في water وهاد ال dissolution rate عالي إلو وبكون stable أكثر .

في كمان مصطلح إسمو ال monohydrate بكون بسجزي ماء واحد مرتبط وفي
ال trihydrate الي بكون ثلاثة مرتبطين

Drug Dissolution

2- Amorphous solid:

- The amorphous form dissolves more rapidly than the corresponding crystalline form.
- 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).
- The amorphous form of novobiocin slowly converts to the more stable crystalline form, with loss of therapeutic effectiveness.

Drug Dissolution

3- Solvates:



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

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

- 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.

III Formulation Factors Affecting Oral Absorption

- The role of the drug formulation in the delivery of drug to the site of action should not be ignored.
- Since a drug must be in solution to be absorbed efficiently from the G-I tract, you may expect the bioavailability of a drug to decrease in the order solution > suspension > capsule > tablet > coated tablet.

A. *Solution dosage forms:*

- In most cases absorption from an oral solution is rapid and complete, compared with administration in any other oral dosage form.

ال formulation معناها كيف بنصنع الدواء بالبداية بدنا نعرف مين اللي ال form الأسهل إمتصاص أول إشي ال solution لانو اصلا ما بحتاج أعملو dissolution بعدها ال emulsion لأنو بكون tow phase of liquid التالت هو ال suspension لأنو في particles من ال solid بعدها ال capsule بعدها ال tablets بعدها ال coated tablets بعدها ال sustained tablets واللي هي بتطلع الدواء بكميات ثابتة على فترة معينة . هسا أحياناً ال solution بكون lipophilic عشان هيك ما بكون soluble فأنا بضيف Co solvent وبخلطها مع الماء وبتصير solubility للدواء أعلاو بعملو على شكل emulsion

III Formulation Factors Affecting Oral Absorption

- Some drugs which are poorly soluble in water may be:
 - 1- dissolved in mixed water/alcohol or glycerol solvents (cosolvency),
 - 2- given in the form of a salt (in case of acidic drugs)
 - 3- An oily emulsion or soft gelatin capsules have been used for some compounds with lower aqueous solubility to produce improved bioavailability.

السuspension يعتمد ال absorption لإلو على حجم ال particle فكل ما كانت صغيرة كل ما كان solubility عالية لإنو ال diffusion coefficient أعلى .
ال capsule هي gelatin وموضوع فيها الدواء لكن أحيان يكون الدواء مضغوط فبصير زي clumps فأنا بضيف إلو dispersion agent فبزيد ال dissolution.

ال tablets بتكون ال most hard وما في tablets بكون فيها بس ال active drug لحالو في إشي اسمو excipients مثل ال surfactant أو ال antioxidant وهم بكونو pharmacodynamics inert يعني مواد خاملة ما إلها تأثير وكل ما زاد مش معناها أحسن هي لحد معين لكن اذا زاد هاد الحد بتقلل ال absorption.

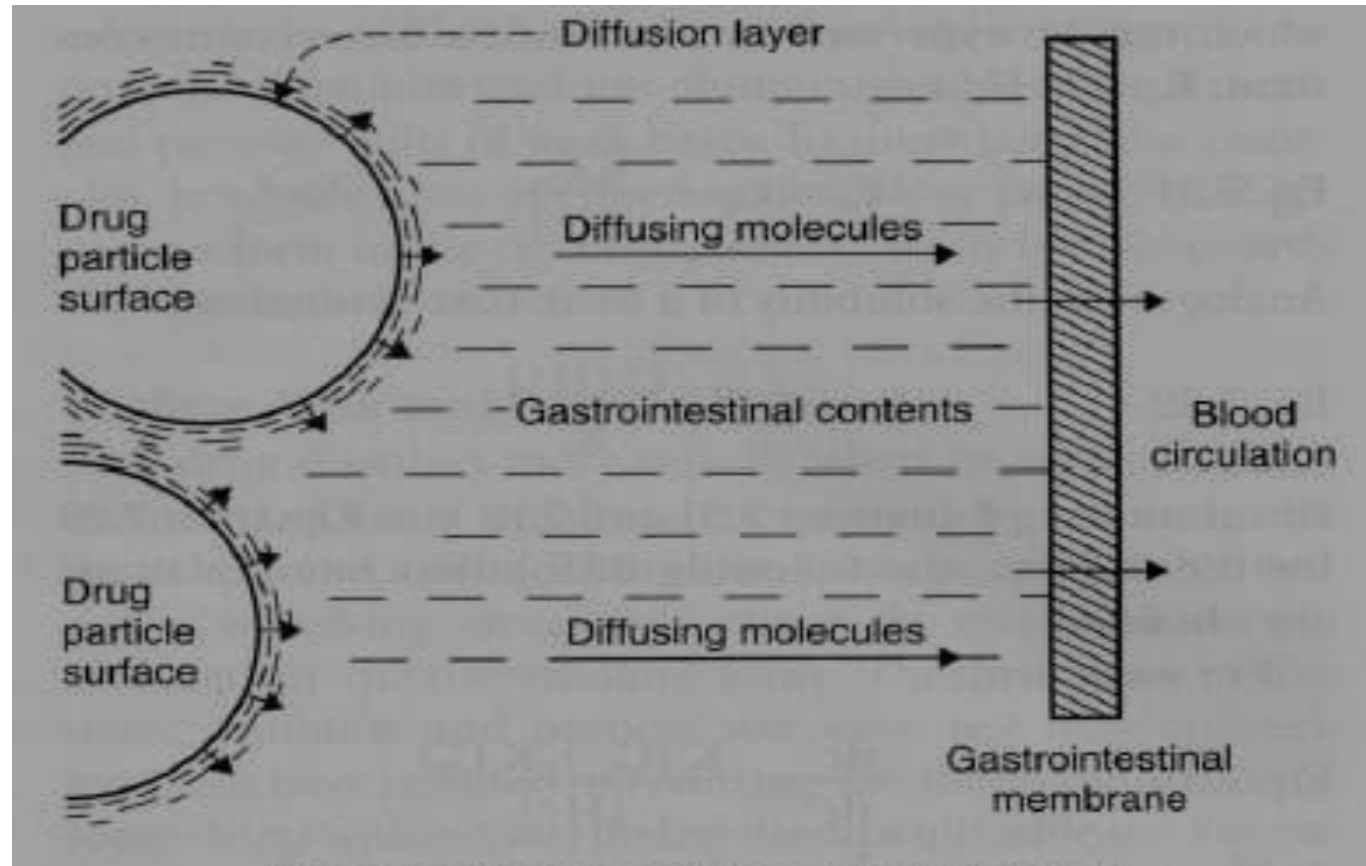
وقت التخزين كل ما زاد رح يغير على ال stability للدواء عشان هيك بنضع تاريخ انتهاء ولكن حتى لو انتهى بضل 80% من المادة الفعالة لكن بقل ال absorption .

III Formulation Factors Affecting Oral Absorption

B. Suspension dosage forms:

- A well formulated suspension is second to a solution in terms of superior bioavailability.
- A suspension of a finely divided powder will maximize the potential for rapid dissolution.
- A good correlation can be seen for particle size and absorption rate.
- The addition of a surface active agent will improve the absorption of very fine particle size suspensions.

III Formulation Factors Affecting Oral Absorption



Absorption of drugs from aqueous suspensions

III Formulation Factors Affecting Oral Absorption

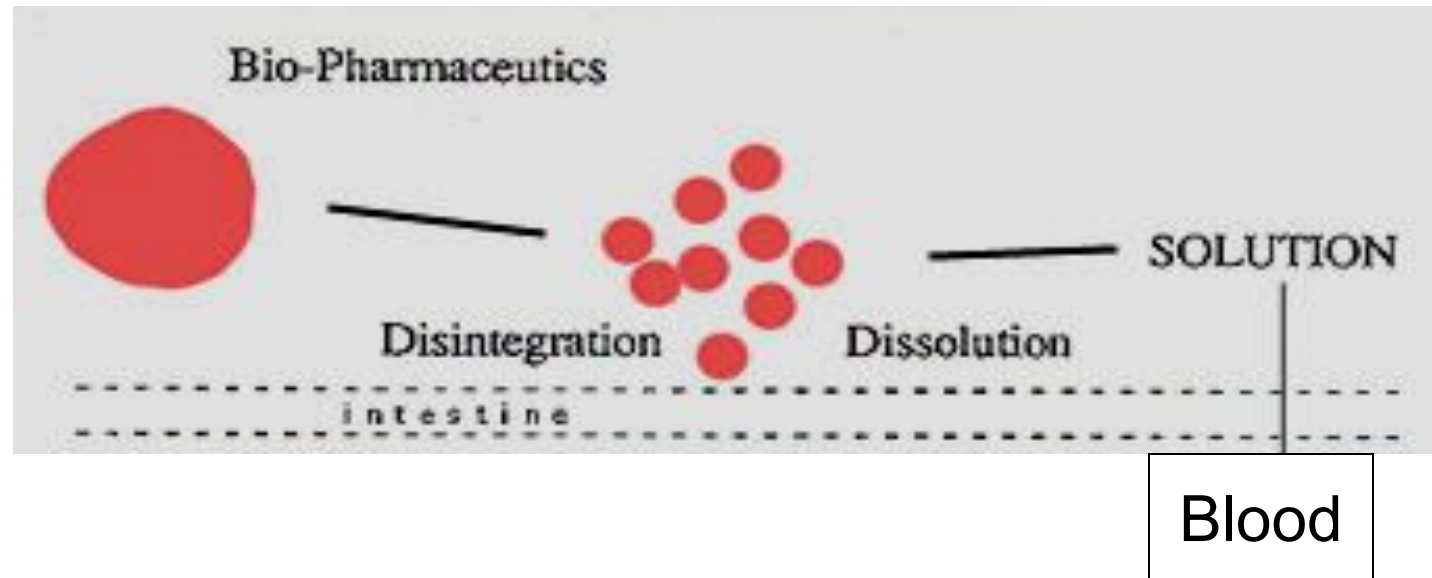


C. Capsule dosage forms:

- The hard gelatin shell should disrupt rapidly and allow the contents to be mixed with the G-I tract contents.
- If a drug is hydrophobic a dispersing agent should be added to the capsule formulation. These diluents will work to disperse the powder, minimize aggregation and maximize the surface area of the powder.
- Tightly packed capsules may have reduced dissolution and bioavailability.

III Formulation Factors Affecting Oral Absorption

D. Tablet dosage forms:



III Formulation Factors Affecting Oral Absorption

- The tablet is the most commonly used oral dosage form.
- It is also quite complex in nature.

1-Ingredients

Drug : may be poorly soluble, hydrophobic

Lubricant : usually quite hydrophobic

Granulating agent : tends to stick the ingredients together

Filler: may interact with the drug, etc., should be water soluble

Wetting agent: helps the penetration of water into the tablet

Disintegration agent: helps to break the tablet apart

