ROLE OF DOSAGE FORM IN GASTRO-INTESTINAL ABSORPTION

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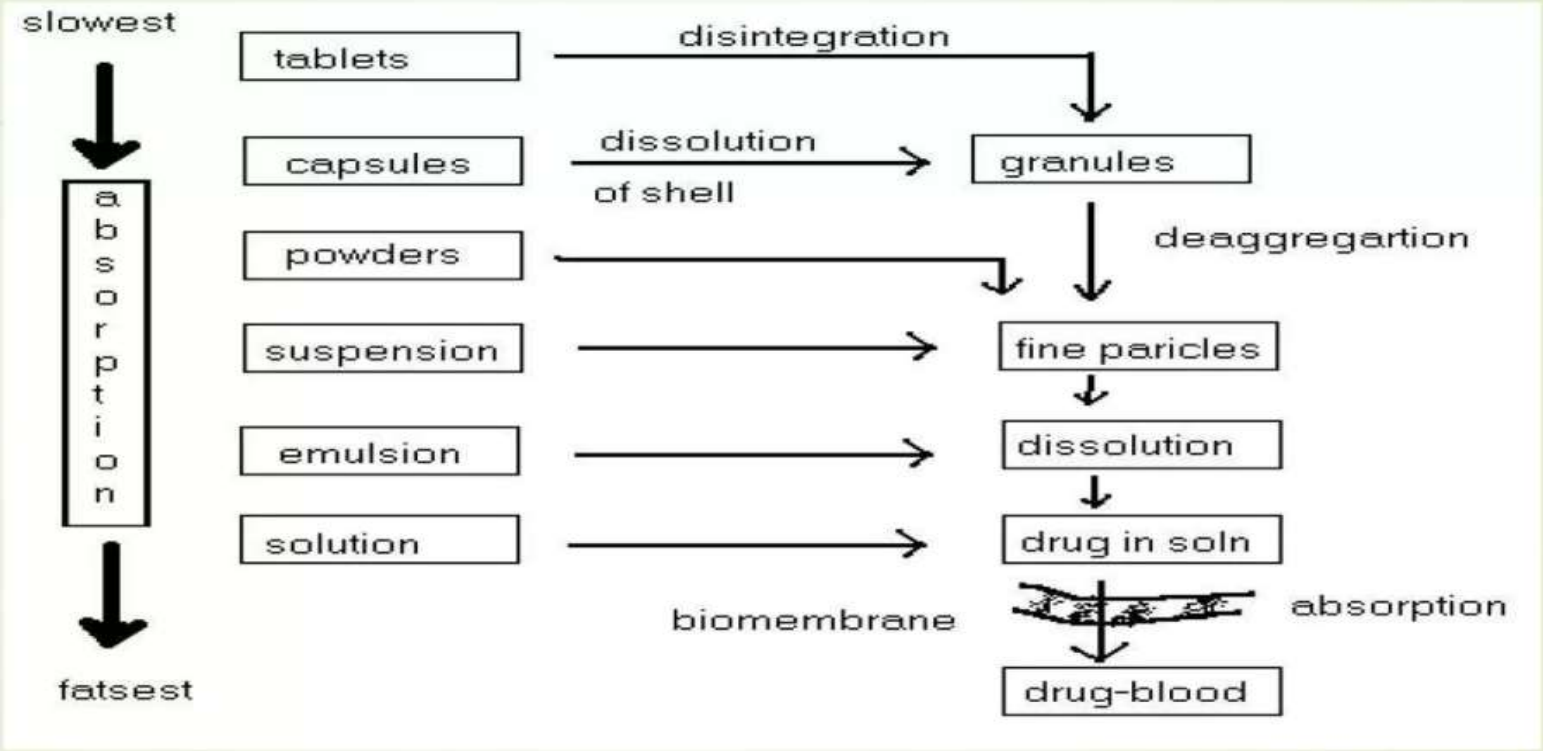
INTRODUCTION

- A drug injected intravascularly directly enters the systemic circulation and exerts its pharmacological effects. But **Majority** of drugs administered **extravascularly** (orally).
- If intended to act systemically, such drugs can exert their pharmacological actions only when they come into blood circulation from their site of application. So, absorption is an important step.
- **ABSORPTION :-** Movement of active drug (or prodrug) from the site of administration to the systemic circulation.

- Drug formulations are designed to provide an attractive, stable, and convenient method to use products.
- Conventional dosage forms may be broadly characterized as;
  - **SOLUTIONS**
  - **SUSPENSION**
  - **CAPSULES**
  - **TABLETS**
- The bioavailability of a drug to decrease in the following order:

  solution > suspension > capsule > tablet> coated tablet
- One drug can routinely produce a **2 to 5-fold difference in the rate or extent** of gastro-intestinal absorption depending on the dosage form of the formulation.
- In some cases, even greater difference observed. A difference of more than 60-fold- has been found in the absorption rate of spironolactone from the worst formulation to the best formulation.

NATURE AND TYPE OF DOSAGE



In the following figure, the stages in drug abs. from the various dosage form, has been illustrated

SOLUTIONS

- Solutions such as syrups and elixirs show fast and often complete absorption of drug because they do not have dissolution problem.
- However, dilution of the drug solution with gastric fluid may result in precipitation that may re-disperse rapidly due to extremely fine nature of precipitate.
- The factors that affect drug absorption from solution include viscosity, reversible complexation , chemical stability and micellar solubilization.
- The vehicle used in syrups , elixirs and emulsions may be aqueous or non-aqueous(e.g., PEG, PG, alcohol) or non-water miscible(e.g., vegetable oils).
- The rate of drug absorption from non-aqueous or non-water miscible vehicle based solution is less than the rate of drug absorption from water based solution.

- The selection of vehicle for solution dosage form depends on the physiochemical properties of the drug.
- Ex. Paracetamol drop is prepared with PEG 400 as it is sparingly soluble in water.
- Certain materials such as sorbitol or hydrophilic polymers are added to a solution dosage form, to improve pourability and palatability by increasing the viscosity of the preparation.
- Due to good systemic availability, solutions are frequently used as bioavailability standards against which other dosage forms are compared.

- Rapid and complete absorption may be observed in some instances, particularly if the oil is administered in emulsified form.
- Administration of indoxole dissolved in the oil phase of Lipomul-Oral(o/w).
- Resulted in a three fold improvement in the extent of absorption compared to that observed after administration of an aqueous suspension and a nine fold improvement compared to a hard gelatin capsule.

SUSPENSIONS

- Drug in a suspension is in solid form, but is finely divided and has a **large surface area**. Drug particles can diffuse readily between the stomach and small intestine so that absorption is relatively insensitive to stomach emptying rate.
- Adjusting the dose to a patient's needs is easier with solutions and suspensions than with solid dosage forms.
- Several studies have demonstrated the superior bioavailability characteristics of suspensions compared to those of solid dosage forms.
  - Ex. the blood levels of trimethoprim and sulfamethoxazole were compared in 24 healthy subjects following oral administration of 3 forms, The absorption rate of each drug was significantly greater with the suspension than with the tablet or capsule.
  - Penicillin blood conc. following oral administration of various dosage forms show higher level with suspension of Phenoxymethyl penicillin

- Finally divided solid particles in suspension are stabilized with suspending agents.
- Suspending agents retard the rate sedimentation of dispersed particles.
- Absorption of drug in suspension form is not greatly affected by stomach emptying rate.
- But suspending agent may increase the viscosity of drug vehicle and thereby may diminish rate of drug dissolution.
- Other critical factors that affect drug absorption include particle size, crystal forms and formation of non-absorbable complexes
- Suspending agent may form non-absorbable complexes with drug eg., divalent metals form in suspension of multivitamins and essentials elements form complex with sodium carboxymethylcellulose that poorly get absorb in body.
- As dissolution is taking place at the surface of solute smaller particle having larger surface area may dissolve rapidly.

- Bioavailability studies with drugs suspended in oi1-in-waier emulsions have yielded some promising results.
- One study compared the absorption of micronized griseofulvin after its administration to healthy subjects in a corn oil-in-water emulsion, an aqueous suspension, and two different commercial tablets.

  The extent of absorption of the drug after administration of the emulsion was about twice that observed after administration of the aqueous suspension or tablets.
- MOA ; based on the ability of fatty acids, liberated during the digestion of corn oil, to inhibit gastrointestinal motility (which would increase the residence time of the drug in the small intestine) and to stimulate gallbladder evacuation

CAPSULES

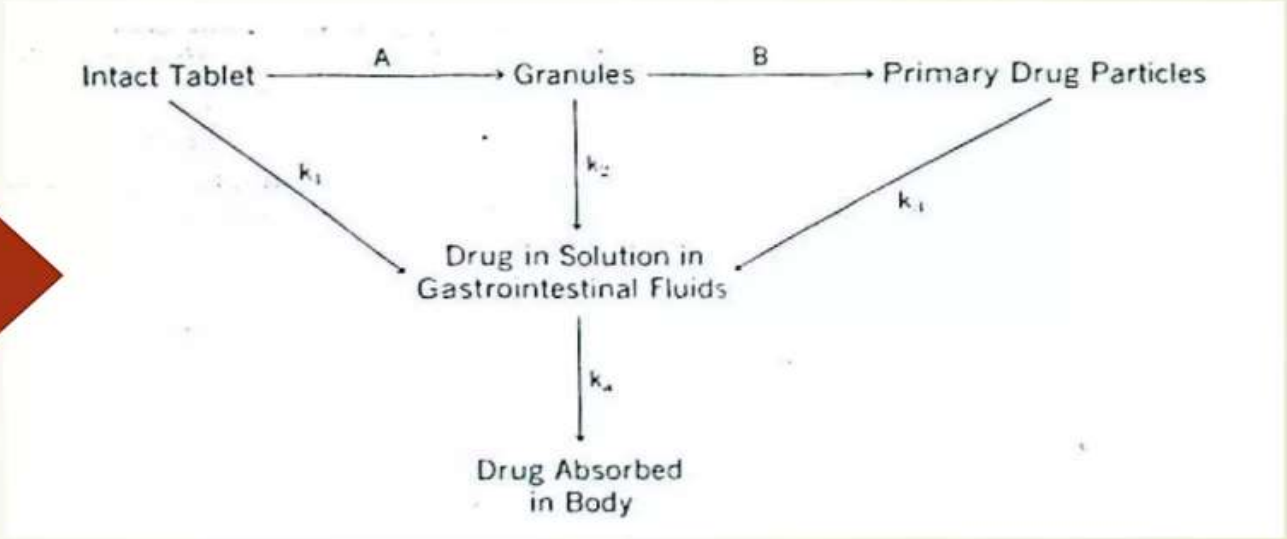
- In capsule on disruption of the shell, the encapsulated powder mass should **disperse rapidly** to expose a large surface area to the gastrointestinal fluids.
- Diluents added to capsules dosage form may affect the dissolution of filled drug in capsule shell.
- Hydrophilic diluents are added in the capsule of a poorly water soluble drugas they enhance the dispersion rate of the aqueous fluid to the contents of the shell.
- This results in better dissolution of the drug in the biological fluid.
- Sometimes wetting agents are also added to improve dispersion rate

- Further, drug absorption from capsule may also be affected by particle size and chemical and physical incompatibility of the drug with a filler and other ingredients.
- Certain drugs are formulated in soft gelatin capsule as a solution from which drug disperses and dissolves more rapidly as compared to hard gelatin capsule.
- Moreover, soft gelatin capsule leaves less residual drug in gut and hence causes minimal irritation.
- This approach is more useful for the drugs that causes local irritation

- The use of dicalcium phosphate as a diluent in tetracycline capsules has been found to significantly impair absorption because a poorly soluble calcium-tetracycline complex is formed in the powder mass or during dissolution.
- Factors that influence drug absorption from capsule dosage forms includ- particle size and crystal form of the drug, and selection of diluents and fillers.
- A soft elastic capsule containing 0.4 mg of digoxin is about equivalent to a tablet containing 0.5 mg of the drug i.e; mean absorption *was* 75% of the dose from the tablet and 97% from the capsule.

TABLETS

Disintegration and dissol. processes that precede drug absorption ofter administration of a tablet dosage form.
k, is a first-order rate constant



- Many factors related to the formulation or production of tablets may affect drug dissolution and absorption.
- Most formulations require the incorporation of hydrophobic lubricants, such as magnesiurn stearate, to produce an acceptable tablet. In general, the larger the quantity of lubricant in a formulation the slower is the dissolution rate.
- Compression force may also be an important factor in drug bioavailability from compressed tablets.
- The in vitro disintegration time of tablets has been shown to be directly proportional to compression force and tablet hardness.
- High compression forces may also increase the strength of the internal structure of the granules and retard dissolution of drug from the granules and disintegration of the granules.

- A novel approach to enhance the availability of poorly water-soluble drugs from tablets has been used in a marketed griseofulvin product.
- A molecular dispersion of the drug in
  - polyethylene glycol 6000,
  - a water-soluble waxy polymer that congeals at about 60C,

  is prepared and suitably modified for incorporated into a tablet dosage form.
- The absorption of griseofulvin from this product appears to be complete and about twice that observed from commercial tablets containing micronized drug.

COATED TABLET

- The coating must dissolve or disrupt before tablet disintegration and drug dissolution can occur.
- The disintegration of certain coated tablets appears to be the rate-limiting process in drug absorption.
- Film-coated tablets are compressed tablets that are coated with a thin layer or film of a material that is usually water soluble or dispersible.
- A number of polymeric substances with film forming properties may be used including hydroxypropyl methylcellulose and carboxymethylcellulose.
- The film coat should disrupt quickly in the fluids of the gastrointestinal tract, independent of pH.
- Sugar coating may affect the bioavailability of a drug. Alternatives include the film-coated tablet and the press coated tablet.

ENTERIC COATED TABLETS

- Enteric coated is special film coated tablet which are used to bypass gastric fluid so that the drug gets dissolve in intestine.
- They show a delayed absorption and therefore a delayed onset of action.
- They also show high inter and intra subject variability due to difference in gastric emptying rate.
- The modern approach to enteric-coating makes use of polymer like cellulose acetate phthalate that are "insoluble' at pH I to 3 but 'soluble" at pH5 to 7.

- The thickness of the coating may also affect bioavailability.
- Studies with **quinine tablets** coated with **cellulose acetate phthalate** show a decrease in both rate and extent absorption with increasing thickness of the coating.