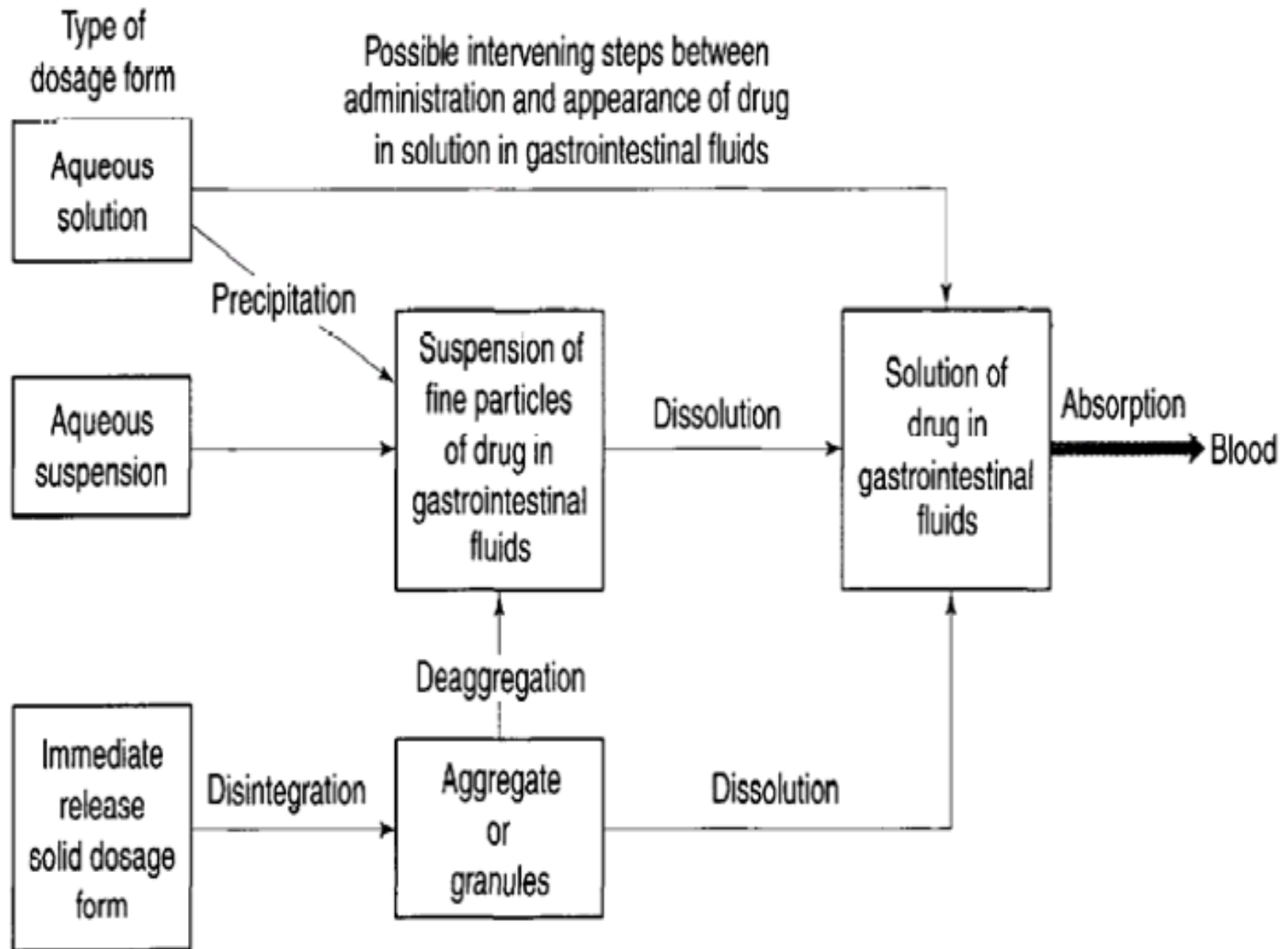


Formulation factors affecting Bioavailability

Introduction

- Type of DF and its method of preparation or manufacture influence bioavailability
- Whether particular drug is administered in form of solution, suspension or solid DF influence its rate and/or extent of absorption from GI tract
- Type of DF influence number of possible intervening steps b/n administration and appearance of dissolved drug in GI fluids
 - * Greater number of intervening steps means greater number of potential obstacles to absorption and greater likelihood of DF to reduce bioavailability



Bioavailability of drug from:

- **Solution > Suspension > Capsule > Uncoated tablet > Coated tablet**
→ Ranking is not universal, it provides useful guideline!
- Solutions and suspensions are most suited for drugs intended to be rapidly absorbed.

Aqueous solution

- With rare exceptions, drugs are absorbed more rapidly from solution than any other oral DF
- Eliminates *in vivo* dissolution step and presents drug in most readily available form for absorption
 - Poorly water-soluble drug whose aqueous solubility is increased by *cosolvency, complex formation or solubilization*

Factors influencing drug bioavailability from aqueous solutions:

- **Chemical stability** of drug in aqueous solution and GI fluids
- **Complexation** of drug and excipient included aqueous solution
- **Solubilization** of drug in micelles to increase solubility
- **Viscosity** of solution if viscosity-enhancing agent is included
(Pourability)

Aqueous suspension

- Suspension is useful for insoluble or poorly soluble drug
- The rate limiting step in suspension dosage form is **dissolution**.
- * Well formulated, finely subdivided suspension is regarded as efficient oral delivery system
 - present *huge total SA to GI fluid*
 - Facilitates dissolution and absorption
- * Dissolution of particles begin immediately on dilution in GI fluids

- Several studies have demonstrated superior bioavailability of suspensions over solid DFs
- **Trimethoprim and sulfamethoxazole suspension**
 - Rate of absorption was significantly higher vs. HGC and Tablet
 - Extent of absorption was not significantly affected

- Factors influencing bioavailability of suspension DFs:
 - Particle size and effective SA of dispersed drug
 - Crystal form of drug
 - Complexation, i.e. formation of non-absorbable complex b/n drug and excipient such as suspending agent
 - Inclusion of surfactant as wetting agents.
 - Viscosity of suspension.

Liquid-filled capsule

- Liquids can be filled into soft or hard gelatin capsules
- * Following release of contents
 - Water-miscible vehicle readily disperse and/or dissolve in GI fluid
 - Liberate drug as solution or fine suspension
 - Conducive to rapid absorption
 - Water-immiscible vehicle disperse in GI fluids
 - Dispersion is facilitated by emulsifier in vehicle or bile

- Factors influencing bioavailability of liquid-filled capsules:
 - Solubility of drug in vehicle (and GI fluids)
 - Particle size of drug (if suspended in vehicle)
 - Nature of vehicle, i.e. hydrophilic or lipophilic)
 - Inclusion of surfactant as wetting/emulsifying agent in lipophilic vehicle or as vehicle itself
 - Inclusion of suspending agent (viscosity-enhancing agent) in vehicle
 - Complexation, i.e. formation, of non-absorbable complex b/n drug and any excipient

Powder-filled capsule

- Bioavailability of well formulated powder-filled HGC is better than or at least equal to compressed tablet
- Unlike the tablet dosage form, drug particles in a capsule are not subjected to high compression forces, which tend to compact the powder or granules and reduce the effective surface area.
- Hence upon disruption of the shell, the encapsulated powder mass should disperse rapidly to expose a large surface area to the GI fluid

- Overall rate of dissolution of drug from HGC is complex function of rates of different processes
 - Dissolution rate of gelatin shell
 - Rate of penetration of GI fluids into encapsulated mass
 - Rate at which mass de aggregates (i.e. disperses) in GI fluids
 - Rate of dissolution of dispersed drug particles

- Excipients have significant effect on rate of dissolution (especially for poorly soluble and hydrophobic drugs)
 - → Diluents, Lubricants and Surfactants
- Hydrophilic diluent (e.g. sorbitol, lactose) often serves to increase rate of penetration of aqueous GI fluids into contents of capsule
 - → aid dispersion and subsequent dissolution of drug
- *Capsule-filling process affect packing density and liquid permeability of capsule contents*
- High packing density result in decrease liquid permeability and dissolution rate
 - → particularly if drug is hydrophobic, or if hydrophilic drug is mixed with hydrophobic lubricant such as magnesium stearate

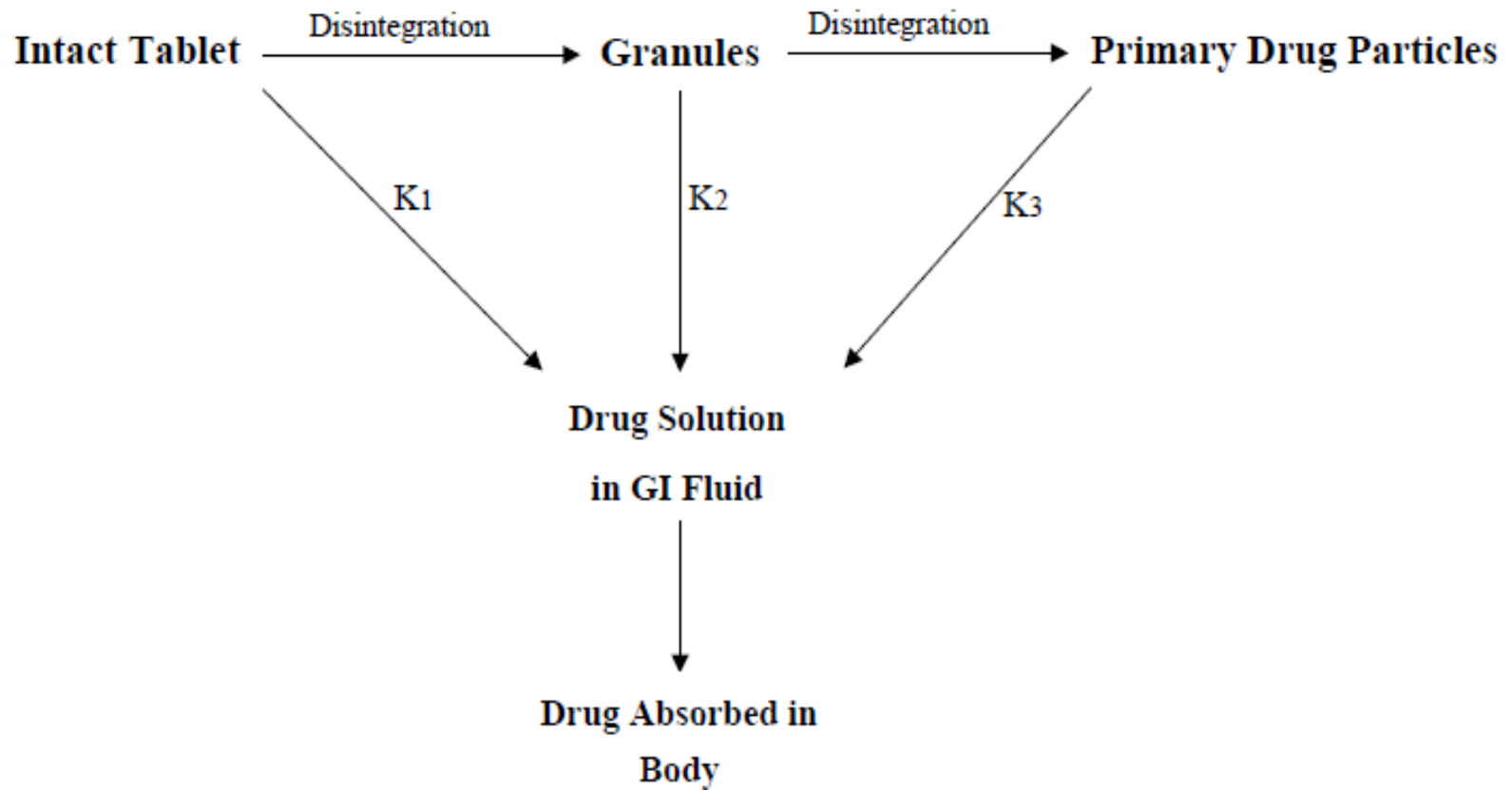
- Factors influencing bioavailability from HGC:
 - SA and particle size of drug (particularly effective SA exhibited by drug in GI fluids)
 - Use of salt form of drug in preference to parent weak acid or base
 - Crystal form of drug
 - Chemical stability of drug (in dosage form and in GI fluids)
 - Nature and quantity of diluent, lubricant, wetting agent, ...
 - Drug-excipient interactions (e.g. adsorption, complexation)
 - Type and conditions of filling process
 - Packing density of capsule contents
 - Composition and properties of capsule shell
 - Interactions b/n capsule shell and contents

Tablets

- Compressed tablets are most widely used DF
- Generally produced by
 - Wet granulation
 - Direct compression
- Wet granulation consist
 - Mixing drug with powdered additives
 - Wetting mixture with aqueous binder solution (gelatin or starch)
 - Screening wet mass → granules (flowability and compressibility)
 - Compression into tablet

Direct compression

- Mixing drug with additives
- Compression of mix
 - Drug must have desirable crystallinity and cohesiveness
 - Formulate with suitable diluents – direct compression diluents (*dicalcium phosphate dihydrate, tricalcium phosphate, calcium phosphate, calcium sulfate, anhydrous lactose, spray dried lactose, pregelatinized starch, microcrystalline cellulose*)
- Most bioavailability problems of compressed tablets are related to
 - Large reduction in effective SA in tableting
 - Difficulty in regenerating well-dispersed primary drug particles



$$K_1 \ll K_2 \ll K_3$$

- Factors influencing dissolution rate and bioavailability of drug from uncoated conventional tablet:
 - -Physicochemical properties of drug particles in GI fluids
 - E.g., wettability, effective SA, crystal form, chemical stability
 - Type and quantity of excipients (diluent, binder, disintegrant, lubricant, any wetting agent, ...)
 - Drug-excipient interactions (e.g. complexation)
 - Method of granulation (wet vs. dry) and size of granules
 - Compaction pressure, speed of compression in tableting
- Conditions of storage and age of tablet
- Bioavailability also depend on drug being in dissolved state
 - *Suitable dissolution characteristics of tablets is very important!*

Coated tablets

- Tablet coating may be used simply to mask unpleasant taste or odor or to protect ingredient from decomposition during storage
- **Film coating is currently most commonly used**
- Several older preparations, such as vitamins and ibuprofen, still have **sugar coats**
- Presence of coating presents *physical barrier b/n core and GI fluid*
→ *Physicochemical nature and thickness of coating*

Sugar coating:

- Tablet core is usually sealed with thin film of poorly water soluble polymer such as *shellac* or *cellulose acetate phthalate*
 - Protect core from aqueous fluids used in subsequent steps
 - Water-impermeable sealing potentially retard drug release
- **Annealing agents (*PEGs* or *calcium carbonate*) may be added**
 - Dissolve readily in gastric fluid to reduce barrier effect

Film coating:

- Coating of tablet core by *thin film of water-soluble polymer*, such as **HPMC**, have no significant effect on rate of disintegration and dissolution
- If *hydrophobic water-insoluble film-coating materials*, such as **ethylcellulose or certain acrylic resins**, are used,
 - Film coat acts as barrier to delay and/or reduce rate of drug release
→ Affect bioavailability
 - Used in *controlled release drug delivery*

Enteric-coated tablets

- Designed to resist low pH of gastric fluids but to disrupt in higher pH of SI
 - Protect drugs unstable in gastric fluid
 - Protect stomach against drugs causing nausea or irritation
 - Aspirin
- * HPMCP, polyvinyl acetate phthalate and copolymers of methacrylic acid and their esters
- * Drug release depends on *gastric residence time*

Limitation:

- Significant delay in release of drug results from longer gastric residence time
→ Delay onset of therapeutic response
- Gastric emptying of intact tablets is *all-or-nothing process*
 - Tablet is either in stomach or in duodenum (not released or released)
 - Gastric residence time vary from ~ 5 min to several hours
 - Considerable intra- and inter-subject variation in onset of action exhibited by drugs administered as enteric-coated tablets

INFLUENCE OF EXCIPIENTS

- Drugs are almost never administered alone but in form of DFs

Drug(s) + Excipients

- *Disintegrating agents, Diluents, Lubricants, Suspending agents, Emulsifying agents, Flavoring agents, Coloring agents, Chemical stabilizers, etc*
- Historically considered as inert
- * Have ability to influence rate and/or extent of absorption
 - poorly soluble, non-absorbable complex b/n
 - tetracyclines and dicalcium phosphate
 - amphetamine and sodium CMC
 - phenobarbitone and PEG 4000

Diluents

- diluents can affect BA of drugs by
 - Forming Complexation
 - *calcium-phenytoin complex*
 - Decrease GI absorption
 - Affecting porosity

Surfactants

- Used in DFs as emulsifying agents, solubilizing agents, suspension stabilizers or wetting agents
- Capable of either increasing / decreasing transfer of drugs across biological membranes
- * Surfactant monomers potentially disrupt integrity and function of biological membrane
 - Enhance drug penetration across GI barrier
 - May result in toxic side-effects

- * In poorly soluble drugs (*dissolution-rate limited*), *solubilization in* surfactant micelles could result in more rapid rates of dissolution and absorption
- * Release of poorly soluble drugs from tablets and HGCs may be increased by inclusion of surfactants
 - Wet solid more effectively
 - Increase effective SA of drug
 - Increase dissolution and absorption rates

Lubricants

- Required to reduce friction b/n powder and metal surfaces during manufacture
- Often hydrophobic in nature
- **Magnesium stearate**
 - commonly included during tablet compression and capsule filling operations
 - Retards liquid penetration into capsule/tablet ingredients
→ Decrease dissolution rate
- Overcome by addition of wetting agent (i.e. water-soluble surfactant) and use of hydrophilic diluent

Disintegrants

- Required to break up capsules, tablets and granules into primary powder particles
→ Increase SA
- Tablet that fails to disintegrate or disintegrates slowly may result in incomplete absorption or delay onset of action

Viscosity-enhancing agents

- Employed in liquid DFs for oral use to control palatability, pourability and rate of sedimentation of dispersed particles
- Often hydrophilic polymer
- Number of mechanisms by which viscosity-enhancing agent may produce change in GI absorption of drug
 - Complex formation b/n drug and hydrophilic polymer
 - → Reduce drug in solution available for absorption
 - Increase viscosity of GI contents
 - Decrease dissolution rate and/or rate of movement of drug molecules to absorbing membrane

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