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
    \( \text{(dicalcium phosphate dihydrate, tricalcium phosphate, calcium phosphate, calcium sulfate, anhydrous lactose, spray dried lactose, pregelatinized starch, microcrystalline cellulose)} \)

- Most bioavailability problems of compressed tablets are related to
  - Large reduction in effective SA in tabletting
  - Difficulty in regenerating well-dispersed primary drug particles
Intact Tablet → Disintegration → Granules → Disintegration → Primary Drug Particles

\[ K_1 \quad K_2 \quad K_3 \]

Drug Solution in GI Fluid

Drug Absorbed in Body

\[ K_1 \ll K_2 \ll K_3 \]
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 tabletting
- 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
  \[\rightarrow\text{Increase SA}\]

- 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