PHAR2823 Notes

Tablets

Advantages of oral tablets as dosage form	Limitations
Greater stability than liquids	More difficult to alter dose (scoring)
Unit dose – premeasured, accurate dose	Difficulty swallowing tablets (size, shape)
Convenient	Bioavailability – stomach acid (easily degrades proteins), first pass metabolism, polarity
Systemic and local (e.g. antacid in GI tract) effects	
Easy, fast, cheap to manufacture in large quantities	Heat generated by tableting machinery may melt some ingredients (compounds with low MP)

Requirements	Specifications
Uniformity of mass (weight variation)	<80mg tablet: ±10% deviation >80 but <250mg: ±7.5% ≥250mg: ±5%
Content uniformity	Content of active substances
Disintegration	Should be <15min in water for uncoated tablets
Dissolution	Tested for in drugs with *poor* water solubility
Friability (<1%)	Limit of <1% weight difference following rotation/mechanical stimulation >1% means tablet is not robust enough and will chip or undergo breakage
Hardness	Force/pressure required to crush tablet must meet certain requirements

Tablet manufacturing processes

Process	Description
Direct compression	Drug + excipient → mixing → tableting
Dry granulation	D+E → mixer → slugger (slugs/large tablets) → milling (mill slugs down into smaller fragments) → fragments/granules → sieve → excipients → tableting
Wet granulation	D+E → mixer → add binder (liquid excipient, binds powder into granules) → granulator → dryer (removes liquid) → granulator → excipients → tableting

Direct compression

- Compressed tablets – solid *unit* dosage forms, compressed formulation of drug + excipient
    - Lower punch = tablet weight; upper punch = tablet hardness
- Most common and simplest process, easy to validate, no heat/liquid/binder required
    - Used when both compressibility and flow are good
- Low cost (time, machinery) and less spatial requirements (no granulator needed)
- High cost of excipients – must be of "compressible grade" (good compressibility)
    - Maximum content of poorly compressible drug in a powder = 16-20%
    - E.g. 50mg of poorly compressible drug in 250mg tablet
- Segregation of drug from excipients reduces uniformity

Granulation

- Process of particle size enlargement – improves flowability and compressibility
- Versatile and flexible process
- Improves content uniformity
    - Binder (wet granulation) or mechanical force (dry) enable particles to remain mixed
    - In direct compression, segregation of contents reduces uniformity
- Dissolution rate can be modulated
    - Hydrophobic drug + hydrophilic excipients – excipients draw water in to ↑ drug dissolution
    - Hydrophilic drug + hydrophobic excipients – controlled release, ↓ dissolution rate
- Binder solutions – mainly aqueous, but can be alcohol-based (PVP)
    - Moisture-sensitive drugs – use organic solvents or melts as binder
- Dry granulation – no heat/liquid, shorter process but tablets have poorer appearance than WG
- Lubricants (DG) and binders (WG) may retard drug release, solvent (WG) may affect drug stability

Excipients

- Biologically inactive – no therapeutic activity, non-toxic
- Physio-chemically inert – unreactive with API or other excipients
    - Drug incompatibility – lactose and 1^{o} amine groups; tetracyclines may complex Ca^{2+}
- Meet regulatory requirements set by TGA, economically viable, commercially available
- Improves flow, granulation, compressibility, hardness, friability, stability, ease of administration
    - Achieves desired release characteristics
- One excipient can have many functions – e.g. starch >5% diluent, <5% disintegrant

Excipient	Purpose and examples
Diluent	- Bulking agent, e.g. lactose, starch, microcrystalline cellulose - Mannitol – in buccal and chewable tablets, endothermic upon dissolving to give cooling sensation in mouth - Sorbitol – hygroscopic when relative humidity >65% - Calcium sulfate – for acidic, neutral and basic drugs - Calcium carbonate (basic) – may react with acidic drugs
Binders, adhesives	- Used for granulation – e.g. glucose, PVP, gums, gelatin, syrup
Disintegrants	- Break tablet into smaller fragments by: o Drawing water through pores/channels of drug by capillary action o Swelling and expansion of drug o Presence of water and disintegrant causes stress recovery - E.g. 10% microcrystalline cellulose, >5% starch, clay, surfactants
Anti-adherents	- Reduce picking that results from melting - E.g. talc, corn starch, metal stearates, sodium lauryl sulfate
Glidants	- Increases flowability – minimises forces that oppose flow - E.g. starch, talc, magnesium stearate
Colourants/dye	- Identification, aesthetics, marketing
Flavours/sweeteners	- If water-sensitive or volatile on heating, add in after granulation and drying

<u>Lubricants</u>

- Reduce friction/shear at die cavity wall and tablet surface interface for ejection
- Excessive use causes:
    - Waterproofing of tablet – reduces disintegration and dissolution
    - Bonding between particles
    - Over-blending – prolonged mixing causes re-separation of components
- Insufficient lubrication – scratches on tablet, noise, machinery wear
- E.g. stearic acid, talc, boric acid, NaCl, acetate, lauryl sulfate, carbowax (PEG)
    - Metal (magnesium) stearates – widely used, greasy, slightly alkaline, metallic aftertaste
    - Stearic acid – less efficient, may react with base
        - MP $70^{o}C$ – high speed manufacture may generate local heat, causing melting in some parts of tablet → stickiness → "picking" (damaged tablet surface)

Flowability

- Powder needs sufficient flowability to allow flow from hopper into die cavity
- Measured as rate (mass per second) of powder flowing into beaker
- Driving force for flow = gravitational force
    - ↑ Diameter = ↑ mass = ↑ gravitational pull
- Forces opposing flow:
    - Electrostatic attraction between particles
    - Friction due to uneven particle surface at microscopic level
    - Humidity – moisture between particles may join the particles together via capillary forces
    - Van der Waals forces
- Very small particles/fines – relatively large specific surface area (SA:V)
    - Higher resistance to flow due to higher SA (adherence) and lower gravitational force
- Large (>1200µm) particles – form bridge in hopper's orifice, preventing entry into die cavity