PHAR 535: Pharmaceutics

Tablets and Capsules: Design and Formulation

Larry L. Augsburger, Ph.D.
Compressed Tablets

A. Compaction
B. Tablets as a Dosage Form
C. Minimum Running Characteristics
D. Overview of Manufacturing Methods
   1. Direct Compression
   2. Granulation
E. Tablet Composition
   1. Formulation
   2. Excipients: functionality and mechanism
F. Factors Affecting Drug Release
G. “Fast-Melt” Tablets
Tableting is a **COMPACTION Process** and Involves Two Steps:

- **Compression**
  - Reduction in bulk volume by eliminating voids and bringing particles into closer contact.

- **Consolidation**
  - Increased mechanical strength due to interparticulate interactions
Rearrangement

Plastic Deformation (and/or viscous flow)

Brittle Fracture

Elastic limit exceeded

Stages of Compression

Single-Ended Compression
The Role of the Compressive Force...

- Is primarily to bring the adjacent particulate surfaces together so that forces active at surfaces may form lasting linkages.
  - Interparticle forces are weak and only significant if the particles are touching one another or very close
    - van der Waals
    - H-bonding
  - The mechanical strength (e.g. hardness) is a function of the nature of the attractive forces and the area over which they act.
Compactibility is...

- The ease with which mechanically strong tablets can be made.
  - Tablet mechanical strength may be measured by..
    - Hardness (Breaking strength)
    - Friability (Resistance to abrasion and chipping)
The % weight loss due to chipping, abrasion and erosion is reported as % Friability.
Measuring Hardness
(Breaking Force)
Compaction Profiles of Some Direct Compression Fillers
(0.75% magnesium stearate)

- Avicel PH 101 (microcrystalline cellulose)
- Fast Flo Lactose
- Emcompress (dicalc. phosph. dihydrate, unmilled)
- Dipac (coprocessed sucrose)
- Starch 1500 (pregelatinized starch)

Diagram showing compaction profiles with compression force (kg) on the x-axis and hardness (kg) on the y-axis. Each filler has a distinct line indicating its compaction profile.
RDWF = Residual Die Wall Force
EF = Ejection Force

EF = RDWF \times \mu_w
\mu_w = \text{coeff. friction at die wall}
Die wall lubricants reduce friction by interposing a film of low shear strength between the tablet mass and the confining die wall...

- Magnesium stearate
- Stearic Acid
The structure formed must be strong enough to withstand the stresses of decompression, as well as those induced by ejection.
Elastic recovery in combination with poor bonding
Possible cause of capping/lamination
Double-Ended Compression Rotary (Multistation) Press
Examples of Tooling
View of Punch Train
High Speed Production Rotary Tablet Press

55 stations
495,000 tabs/hour
Compressed Tablets as a Dosage Form

- Ease of Administration and Patient Acceptance
  - Swallowing
    - Size
    - Coating
  - Chewable Formulations
  - Elegence
- Convenience/Compactness
- Accurate Dosage
- Stability
Compressed Tablets as a Dosage Form (continued)

- Control of Release Possible
  - Delayed Release
  - Extended Release

- ER CORE
- IR DOSE

- Barrier Coating
- IR DOSE

- ER CORE
- IR DOSE

- Barrier Coated Beads
- IR DOSE
What can go wrong?

- Problems in attaining acceptable content uniformity (accuracy and precision of unit dose content) for low dose drugs.
- Large dose drugs usually lack the properties to be formed into tablets.
- Compromised bioavailability (poor drug solubility; malformulation)
Design and Formulation of Compressed Tablets (IR)

- Minimum running characteristics
  - Compactibility
  - Fluidity
  - Lubricity

*Excipients and the method of manufacture are selected to provide these characteristics.*
Manufacturing Methods

- Granulation
  A complex process of first forming granules from the mix and then tableting the granules.
  - Wet
  - Dry

- Direct Compression
  Simply mix and compress.
Choice of Method Depends on Several Factors

- Size of Dose
- Compactibility and/or Fluidity of Drug
- Stability Characteristics of the Drug
A Consideration of the Dose of Drug is the Starting Point...

- **LOW DOSE (<25MG)**
  
  *(Most of the tablet will be excipients)*
  ➔ Content Uniformity

- **High DOSE (>250mg)**
  
  *(Most of the tablet will be drug)*
  ➔ Compactability
  ➔ Fluidity

*Is drug solubility also an important consideration? Why? Is it equally important in each case?*
Lower Dose Drugs Generally Can Be Directly Compressed

- Can compensate for any lack of compactibility and/or lack of flowability by the use of special direct compression fillers (*aka*: filler-binders)
- Can provide lubricity by addition of die wall lubricant
- Can help fluidity by adding a glidant
- Can assure rapid disintegration by adding disintegrant
**General Formula for a Direct Compression Tablet**

<table>
<thead>
<tr>
<th>Component</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>1 Part</td>
</tr>
<tr>
<td>Filler-Binder</td>
<td>2 - 3+ Parts</td>
</tr>
<tr>
<td>Disintegrant</td>
<td></td>
</tr>
<tr>
<td>Starch</td>
<td>10 - 20%</td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>Super Disint.</td>
<td>2 - 5%</td>
</tr>
<tr>
<td>Glidant</td>
<td></td>
</tr>
<tr>
<td>Colloidal Silica</td>
<td>0.5 - 1%</td>
</tr>
<tr>
<td>Lubricant</td>
<td></td>
</tr>
<tr>
<td>Mag. Stearate</td>
<td>0.5 - 1%</td>
</tr>
</tbody>
</table>
Advantages of Direct Compression over Granulation

- More economical (less time, space, materials, personnel, fewer steps)
- Avoids heat and moisture of wet granulation
- Disintegrate more directly into primary particles
Disadvantages of Direct Compression

- Problem of content uniformity for low dose drugs
- Not practical for large dose poorly compactible/poorly flowing drugs
- Requires tight control over physical properties of filler-binder
Generally, direct compression Filler-Binders are common fillers that have been physically modified.
Examples of Direct Compression Filler-Binders

- Microcrystalline Cellulose (MCC) (isolated from cellulose fibers by acid hydrolysis) [Avicel]
  ➔ Most compactible material available for pharmaceutical use
  ➔ When made from mostly MCC, tablets self-disintegrate and require little lubricant.
- Spray processed lactose [Fast Flo Lactose]
  ➔ minigranulation of lactose crystals glued together by small amount amorphous lactose
Examples of Direct Compression Filler-Binders

- Dicalcium phosphate dihydrate, unmilled [Ditab, Emcompress]
  - minigranules made up of agglomerated crystallites
- Spray processesd sucrose [Dipac]
  - Used in chewable tablets
  - minigranulation of sugar crystals "glued" together with amorphous dextrins
Granulate

- Granulation is a size enlargement process: *Improves Flowability*
- Addition of a BINDER that "glues" the particles together into granules helps to hold the overall tablet together: *Improves Compactibility*

*i.e. large-dose, poorly compactible and/or poorly flowing drugs*
The Traditional Granulation Method is *Wet Granulation*

- Involves wetting the powders with binder solution ("glue") and then a drying step.
  - Wet Massing Techniques
    - Low Shear Granulation
    - High Shear Granulation
  - Fluid Bed Granulation

- Not practical for drugs sensitive to water or heat.
  - Alternative: *Dry Granulation*
    - Slugging or Roller Compaction
Fillers (General) That May Be Used in Granulation

- lactose
- dicalcium phosphate
- sucrose
- microcrystalline cellulose (adjunctive)

Standard or conventional forms - not modified for DC
Typical Wet Granulation Formula for a drug with 300 mg dose...

Per Tablet

- Drug: 300 mg
- Filler: 182.5 mg (e.g. lactose powder)
- Disintegrant: 15 mg (3% croscarmellose)
- Lubricant: 2.5 mg (0.5% magnesium stearate)

*In this example, total tablet weight = 500 mg*

> Option to reduce or omit filler and make smaller tablets
<table>
<thead>
<tr>
<th>Fillers</th>
<th>Purified Water</th>
<th>0.1M HCl</th>
<th>0.01M HCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anhydrous Lactose</td>
<td>21.9</td>
<td>6.27</td>
<td>0.90</td>
</tr>
<tr>
<td>Lactose Monohydrate</td>
<td>12.4</td>
<td>5.37</td>
<td>0.69</td>
</tr>
<tr>
<td>Dicalcium Phosphate, Dihydrate</td>
<td>0.1M HCl – 6.27</td>
<td>0.01M HCl - 0.90</td>
<td></td>
</tr>
<tr>
<td>Anhydrous Dicalcium Phosphate</td>
<td>0.1M HCl – 5.37</td>
<td>0.01M HCl - 0.69</td>
<td></td>
</tr>
<tr>
<td>Calcium sulfate dihydrate</td>
<td>1.15</td>
<td>1.15</td>
<td>0.75</td>
</tr>
</tbody>
</table>

LUBRICANTS
The Three Lubricant Roles

- **True Lubricant Role**
  - Reducing friction between sliding surfaces, traditionally at the tablet-die wall interface during tablet formation and ejection. Also applies to capsule plugs.

- **Antiadhesion Role**
  - Preventing sticking to surfaces, e.g., the faces of tablet punches, capsule tamping pins.

- **Glidant Role**
  - Improving flow by modifying the interaction between particles
## Lubricants

*In a general sense*

<table>
<thead>
<tr>
<th>Lubricant</th>
<th>Typical Level</th>
<th>True Lubricant Activity</th>
<th>Anti-adherent Activity</th>
<th>Glidant Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metallic Stearates e.g. mag. st., calcium st.</td>
<td>0.5 - 1%</td>
<td>Excellent</td>
<td>Good</td>
<td>Poor*</td>
</tr>
<tr>
<td>Stearic Acid</td>
<td>1-5%</td>
<td>Good</td>
<td>Good</td>
<td>Nil</td>
</tr>
<tr>
<td>Colloidal Silicas</td>
<td>&lt;1%</td>
<td>Nil</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>Talc</td>
<td>1-5%</td>
<td>Poor</td>
<td>Excellent</td>
<td>Good</td>
</tr>
</tbody>
</table>
**Concept of a "Lubricant System"**

- Frequently two substances are used in a formulation to maximize overall lubricant effect in all three areas:
  - For example, combining magnesium stearate with a colloidal silica
Some Lubricant Issues

- The most effective true lubricants are hydrophobic and if too much is used, they can interfere with disintegration and dissolution
  - Magnesium stearate
  - Calcium stearate
- Lubricant generally interfere with bonding and can soften tablets
- Alkaline metal stearates are incompatible with some drugs, e.g. aspirin and ascorbic acid.
Some Lubricant Issues (continued)

- Laminar lubricants (magnesium stearate, calcium stearate) are "mixing sensitive."
  - Under the rigors of mixing they delaminate to increase their Nw
  - The effect can be equivalent to adding too much lubricant!
Laminar Structure of Magnesium Stearate
Some Lubricant Issues (continued)

- Lubricants are always added last after all other components have been thoroughly mixed.
  ➔ Mixing time of 2-5 minutes
- Water soluble lubricants are not nearly as effective as the hydrophobic lubricants.
  ➔ Used when a tablet must be completely water soluble (e.g., effervescent tablets)
  ➔ Examples: DL Leucine, sodium benzoate, polyethylene glycol 8000
Glidants

- Usually added to enhance the flowability of direct compression mixtures.
- There is an optimum concentration at which flow is best:
  - Usually <1% and often 0.25 - 0.5% for the colloidal silicas
  - The optimum concentration is related to the amount needed to just coat the bulk powder particles
- Higher concentrations may be needed to correct serious adhesion (sticking) to punch faces.
Effect of Concentration of Glidant on Flow Rate

Effect of Glidant on the Flowability of Microcrystalline Cellulose

Source: S.T. David and L.L. Augsburger
DISINTEGRANTS
DISINTEGRANTS

Substances routinely included in tablet formulations and in many hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids to expose primary drug particles.
Disintegrant Mechanisms

- All disintegrants are hygroscopic and draw liquid into the matrix ("liquid uptake" or "wicking action").
  - May generate a hydrostatic pressure.
- As they sorb liquid, they may:
  - Swell extensively (Sodium Starch Glycolate, NF)
  - Recover shape with little swelling (Crospovidone, NF; Starch, NF)
  - Swell radially and straighten out [fibrous material] (Croscarmellose Sodium, NF)
Together, these phenomena create a disintegrating force within the matrix.

The rapid buildup of a disintegrating force promotes rapid disintegration.

The liquid uptake may also contribute by initiating binder and/or matrix dissolution to weaken the tablet.
Types and Use Levels of Disintegrants

- Starch: 5-15%
- Croscarmellose sodium*
  - DC: 1-3%
  - Wet Granulation: 2-4%
- Crospovidone*
  - 2-4%
- Sodium Starch Glycolate*
  - 4-6%

___________________

* "Super-Disintegrants"

Note: For powder filled hard gelatin capsules, 4-8% is usually used. Crospovidone and Starch not recommended for capsules.
Classification of Super Disintegrants

- Modified Cellulose [Croscarmellose Sodium, NF]
  (Sodium carboxymethyl cellulose which has been crosslinked to render it insoluble)
  - AcDiSol (FMC Corp.)

- Crosslinked Polyvinylpyrrolidone [Crospovidone, NF]
  (High MW and cross linking render it insoluble)
  - Polyplasdone XL (ISP Corp.)

- Modified Starch [Sodium Starch Glycolate, NF]
  (Sodium carboxymethyl starch; crosslinking reduces solubility)
  - Primojel (Generichem Corp.)
  - Explotab (Edward Mendell Co.)
Sodium Starch Glycolate

Upon Exposure to 100% RH Air
When formulations are granulated (wet or dry), disintegrants are best added...

- 1/2 before granulation (intragraanular)
- 1/2 after granulation (extragraanular)
An interesting relationship...

An optimum porosity for best disintegration
Theoretical Representation of the Relationship Between Disintegrant Swelling and Bed Porosity

\[ D_0 = \text{Mean Pore Diameter} \]
Fast-Disintegrating Tablets for the Mouth

*Disintegrate in mouth in ~10 secs or less.*

- Can enhance compliance in patient populations that have difficulty in swallowing conventional tablets.
  - Those elderly persons or children who have difficulty chewing or swallowing tablets and capsules
- Bed-ridden patients
- Active working people who may not have access to water for swallowing solid dfs
Formulating Fast-Disintegrating Tablets for the Mouth

- Rapidly soluble components
  - Amorphous sucrose
  - Mannitol (imparts cooling sensation due to uptake of heat of solution) [Also used in chewable tabs]
  - Amorphous or partially amorphous lactose
- Superdisintegrants (some formulations, up to 10%)
- Moderate compression force to achieve high tablet porosity and adequate hardness/friability.
- Freeze-drying to produce a porous matrix
Capsules

A. Hard Shell Capsules
   1. Types, properties and manufacture of shells
   2. Overview of filling equipment with emphasis on formulation requirements.
   3. Factors Affecting Drug Release
      Formulation and Excipients
B. Soft Shell Capsules
   1. Composition/excipients
   2. Manufacture
   3. Factors Affecting Drug Release
The capsule can be viewed as a container dosage form...

- Odorless
- Tasteless
- Easily swallowed
- Elegant
# Hard Gelatin vs Soft Gelatin "Softgels" Capsules

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Soft gelatin Capsules</th>
<th>Hard Gelatin Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shell</td>
<td>Plasticized (glycerin, propylene glycol, sorbitol)</td>
<td>Not plasticized</td>
</tr>
<tr>
<td>Content</td>
<td>Usually liquids or suspensions (dry solids possible)</td>
<td>Usually dry solids (liquids/semi-solid matrices possible)</td>
</tr>
<tr>
<td>Manufacture</td>
<td>Formed/filled in one operation</td>
<td>Shells made in one operation and filled in a separate process</td>
</tr>
</tbody>
</table>
# Hard Gelatin vs Soft Gelatin "Softgels" Capsules

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Soft gelatin Capsules</th>
<th>Hard Gelatin Capsules</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Closure</strong></td>
<td>Hermetically sealed (inherent)</td>
<td>Traditional friction-fit; mechanical interlock, banding and liquid sealing possible</td>
</tr>
<tr>
<td><strong>Sizes and Shapes</strong></td>
<td>Many</td>
<td>Limited</td>
</tr>
<tr>
<td><strong>Formulation Technology</strong></td>
<td>Liquids</td>
<td>Solids</td>
</tr>
<tr>
<td><strong>Fill Accuracy</strong></td>
<td>1-3%</td>
<td>2-5% (with modern automatic machines)</td>
</tr>
</tbody>
</table>
Some hard shell capsules are made from materials other than gelatin...

- Starch hydrolysate: "Capill"
- Hydroxypropyl methyl cellulose ("Vegicaps" and others)

Such alternatives to gelatin will be of interest to those who, for religious, cultural or other reasons wish to avoid capsules made from animal derived components.
HARD GELATIN CAPSULES
Advantages of Hard Gelatin Capsules

- Rapid drug release possible.
- Flexibility of formulation
  - Easily compounded (Rx practice).
  - No need to form a compact that must stand up to handling.
  - Unique mixed fills possible.
  - Role in drug development.
  - Role in clinical tests.
- Sealed HGCs are good barriers to atmospheric oxygen.
Disadvantages of Hard Gelatin Capsules

- Very bulky materials are a problem.
- Filling equipment slower than tableting.
- Generally more costly than tablets, but must judge on a case-by-case basis.
- Concern over maintaining proper shell moisture content.
  - Shell should have moisture content of 13-15%
    - If too dry – become brittle/easily fractured
    - If too moist – become too soft and can get sticky
  - Unprotected capsules are best stored at 45-65%RH.
  - Caution using strongly hygroscopic drugs.

- Cross-linking [can affect soft gelatin capsules, hard gelatin capsules, gelatin coated tablets]
## Sizes and Approximate Capacities

<table>
<thead>
<tr>
<th>Size</th>
<th>000</th>
<th>00 el</th>
<th>00</th>
<th>0 el</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volume (mL)</strong></td>
<td>1.37</td>
<td>1.02</td>
<td>0.91</td>
<td>0.78</td>
<td>0.68</td>
<td>0.50</td>
<td>0.37</td>
<td>0.30</td>
<td>0.21</td>
<td>0.10</td>
</tr>
<tr>
<td><strong>Capacity (mg) at packing density = 0.8 g/mL</strong></td>
<td>1096</td>
<td>816</td>
<td>728</td>
<td>624</td>
<td>544</td>
<td>400</td>
<td>296</td>
<td>240</td>
<td>168</td>
<td>104</td>
</tr>
</tbody>
</table>

*“DB” Capsule*
Composition of Hard Gelatin Shells

- Gelatin
  - Bone Gelatin (Type B)
  - Skin Gelatin (Type A)
- Water
- Dyes and Other Colorants
- Opaquing Agent (TiO2)
- Preservative
Most important properties of gelatin

- **Bloom strength**
  - A measure of relevance to cohesive strength of gelatin film
  - Typically 150-280 "bloom-grams"
    - The weight in g required to depress a plunger 12.7 mm diameter 4 mm into a 6.67% gel held for 17 hours at 10 degrees (O.T. Bloom, 1925)

- **Viscosity**
  - Single most important factor controlling shell thickness
  - Capillary viscometer; 6.67% soln.
  - Typical range 25-45 millipoise.
The Dipping Process of Making Hard Gelatin Capsules

Manufacturers in N. Amer.

- Shionogi Qualicaps
- Capsugel div. Pfizer
- Pharmaphil (Canada)
Sealing and Positive Closure

- Reasons/Need
  - Tamper resistance/tamper evidence
  - Prevents inadvertent separation on handling/shipping
  - Makes liquid/semi-solid filling of hard gelatin capsules possible
  - Sealed capsules are excellent barriers to $O_2$
Mechanically Interlocking Caps and Bodies

- Interlocking rings or bumps molded into the cap and body side-walls
  - Posilok (Shionogi)
  - Snap-Fit and Coni-snap (Capsugel)
  - Lox-it (Pharmaphil)
Mechanical Interlock - Snap-Fit (Capsugel)

Traditional

Prefit

Locked
Sealing and Welding Methods

- Banding
  - Original banded hard gelatin capsule - Parke Davis' "Kapseal"
  - Modern banding process - Shionogi's Qualiseal
- Liquid sealing
  - Capsugel's Licaps
# Study of Oxygen Permeation

<table>
<thead>
<tr>
<th>CAPSULE TYPE</th>
<th>cm³ O₂ /24 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traditional Friction Fit (Non-interlocking)</td>
<td>0.280</td>
</tr>
<tr>
<td>Posilok (interlocking)</td>
<td>0.0650</td>
</tr>
<tr>
<td>Posilok + Band</td>
<td>0.0011</td>
</tr>
</tbody>
</table>

Source: Shah and Augsburger (1989)
# Output Capacities of Some Capsule Filling Machines

<table>
<thead>
<tr>
<th>Method</th>
<th>Machine Type</th>
<th>Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semi-automatic</td>
<td>No. 8 Machine</td>
<td>120,000 - 140,000/Shift</td>
</tr>
<tr>
<td>Fully Automatic</td>
<td>Zanasi Z-5000/R3</td>
<td>150,000/hr</td>
</tr>
<tr>
<td></td>
<td>MG2 G100</td>
<td>100,000/hr</td>
</tr>
<tr>
<td></td>
<td>Bosch GKF 3000</td>
<td>180,000/hr</td>
</tr>
<tr>
<td></td>
<td>Osaka R-180</td>
<td>165,000/hr</td>
</tr>
</tbody>
</table>
TODAY, HARD GELATIN CAPSULES ARE MOST OFTEN FILLED BY AUTOMATIC MACHINES WHICH RESEMBLE TABLET PRESSES TO THE EXTENT THAT -

- THEY FORM POWDER PLUGS BY COMPRESSION, AND
- EJECT THEM INTO EMPTY CAPSULE BODIES
Dosator Principle
MG2 Futura Dosator Machine

36,000 caps/hr
Dosing Disc Principle
Bosch
GKF 1500
Dosing Disc
Machine
90,000/hr
Factors Affecting Drug Dissolution From Hard Gelatin Capsules

- Overall Dissolution Rate is a Function of:
  - Dissolution Rate of the Shell
  - Rate of Penetration of Dissolution Medium
  - Rate of Deaggregation of Powder Mass
  - Nature of Primary Drug Particles

*Except for the shell, sounds like tablets!*
Shell Dissolution and Rupture

Normally, shell ruptures and dissolves within about 4 minutes.

- Rupture occurs first at the shoulders where shell wall is thinnest.
- Ends fall away and as liquid penetrates and deaggregation occurs, formulation tend to spill out of the two ends.

Cross-linking can reduce shell solubility in water.

- Aldehydes, or prolonged exposure to elevated temperatures and/or high humidity.
- In moderate cases, not physiologically significant since GI fluids contain proteolytic enzymes.
- Two-tiered dissolution test recommended to USP by Industry-FDA Working Group
Active Ingredient

- Highly water soluble drugs exhibit few formulation problems in terms of drug release from either tablets or capsules.
- Micronization of poorly soluble drugs can improve dissolution from tablets and capsules.
  - Affect on flow and mixing
    - Adsorption to surfaces of filler particles (a form of ordered mixing) may help
  - Effective surface area may be reduced by agglomeration of micronized particles.
    - Addition of a wetting agents (surfactants) may help.
Filler (Diluent)

- Fillers include lactose, starch, dicalcium phosphate.
  - Forms modified for direct compression tableting are useful for flow/compactibility - especially important for plug forming machines.
- Consideration the solubility of drug in selecting a filler.
  - Water soluble fillers are preferred for poorly soluble drugs
  - In certain instances, a large percent of soluble filler in the formulation has slowed the dissolution of a soluble drug.

- Possible incompatibilities
  - Classic example: Tetracycline formulated with calcium phosphate.
Interesting Case History

(Tyrer et al.)
Lubricants

- Glidants (colloidal silicas such as Cab-O-Sil)
  - Optimum concentration generally <1%, typically 0.25-50%.

- True Lubricants and Antiadherents (e.g. metallic stearates, stearic acid)
  - Best lubricants are hydrophobic
    - Increasing concentrations usually retard dissolution.
    - Blending time an issue with laminar lubricants.
      - Avoid overmixing
  - Effect is exacerbated at higher degrees of compaction.
Combined Effect of Magnesium Stearate and Compaction

Fig. 19.5 Effect of intake machine on drug release (Samyn, J. C. and Jung, W. Y. (1970) J. pharm. Sci., 59, 169–175)

(Samyn & Jung)
Disintegrants: sodium starch glycolate; croscarmellose sodium*

- Speed up drug dissolution by...
  - Promoting liquid penetration (wicking)
  - Promoting deaggregation
- Efficiency often improves with increased tamping force.
- May be effectively used at levels from 4-8%.

*Crospovidone not as effective in capsules at equivalent concentrations
Surfactants: sodium docusate; sodium lauryl sulfate

- Speed up dissolution by...
  - Increasing wetting of powder mass (can overcome the waterproofing effect of hydrophobic lubricants)

- Typical use levels
  - SLS, 1-2%
  - Sodium docusate, 0.1-0.5%
SOFT GELATIN CAPSULES
(aka “Softgels”)

- Similar to hard gelatin shell, except plasticizer is incorporated (sorbitol, propylene glycol, glycerin)
- Usually filled with liquids or suspensions (dry solids are possible, including compressed tablets (“Geltabs”).

Reminder
Advantages of Soft Gelatin Capsules

- High Accuracy/precision possible
- Hermetically sealed (inherently)
- Possible bioavailability advantages
- Reduced dustiness; lack of compression stage in manufacture
- Possible reduced gastric irritancy compared to tablets and hard shell capsules
- Specialty packages available
Examples of Soft Gelatin Capsules

Seam

Suppositories
Disadvantages of Soft Gelatin Capsules

- Generally, product is contracted out to a limited number of specialty houses, e.g. Scherer, Banner.
- Generally more costly to produce than tablets or hard shell capsules.
- More intimate contact between the shell and contents than with dry-filled hard shell capsules - stability a concern.
- Not adaptable to incorporation of more than one kind of fill into the same capsule (compare with hard shell capsules).
Formulation

- Pure liquids, mixtures of miscible liquids, or solids dissolved or suspended in a liquid vehicle.
- Vehicles
  - Water immiscible non-volatile liquids
    - vegetable oils
    - Mineral oil not recommended for drug formulations.
  - Water-miscible, non-volatile liquids
    - Low molecular weight PEG's
    - Nonionic surfactants such as polysorbate 80
Limitations of Liquid Contents

- Water cannot exceed 5% of contents
- pH must be between 2.5 and 7.5
- Low molecular weight water soluble and volatile compounds must be excluded
- Aldehydes, in general, must be excluded (Cause cross-linking)
- Contents must flow under gravity at < 35 degrees
Most Soft Gelatin Capsules are Made Using a Rotary Die Process

- Original Rotary Die Process (R.P. Scherer: 1933)
  - Only for pumpable fills
- Accogel Process (Stern Machine) - Lederle: 1948
  - A rotary die process for filling powders, granules into soft gelatin capsules
1. Gelatin ribbon
2. Rotary die
3. Filling Wedge
4. Filled capsule
5. Webbing
6. Pumping mechanism
Rotary Die process