Capsules

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Credit: Prof. Dr Nizar Al-Zoubi

Capsules

- Capsules are solid dosage form in which medication is contained in gelatin shell
- Hard and soft gelatin capsules differ from each other in:
  - the shell composition
  - manufacturing and filling methods.
- The medication to be filled may be solid, semisolid or liquid.
- There are two types of capsules:
  - **Hard capsule**: two pieces, a cap and a body.
  - **Soft capsule**: one piece

Hard-shell capsules

Cap

Body

Soft-shell capsules

Capsules

Hard Capsules	Soft Capsules
• Two pieces, a cap and a body.	• One piece
• For filling of solids, semisolids or liquids.	• For filling of solids, semisolids or liquids.
• Fixed shape and standard sizes	• Various shapes and sizes
• Manufactured empty and then filled with product	• Manufactured and filled with product in the same process
• No drug is added in the shell formulation	• Drug can be added in the shell formulation

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Capsules

- **Advantages of capsules**
  1. They are elegant
  2. They are easily swallowed
  3. They can be used for drugs with bad taste or color
  4. They can contain a variety of materials
  5. Can be produced economically on large scale
  6. They provide rapid release since powder (granules) is readily available for dissolution (little pressure and excipients)

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Capsules

- Limitation for capsule use:
  a) Can not be used for administration of extremely soluble materials such as KCl and NH_4Cl. Since the sudden release of them result in irritating concentrations
  b) Can not be used with materials that react with the shell (e.g. Formaldehyde)
  c) Can not be used with deliquescent or efflorescent materials
     - deliquescent materials may cause dryness of the capsule shell (KOH, salts)
     - efflorescent materials may cause softening of the capsule shell(borax)

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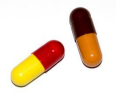
Hard capsules



- They are manufactured empty and then filled with product

Raw materials used in empty capsules

- Gelatin
- Colorant
  - Two types: water soluble dyes or insoluble pigments
- Process aids
  - Sodium lauryl sulfate (not more than 0.15 %) serves as a wetting agent and ensure uniform covering of the moulds with gelatin solutions
  - Preservatives were formerly added but not used now.

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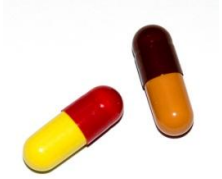
Gelatin



- Gelatin is the main constituent of capsule shell

Sources of gelatin

- It is a protein which does not occur naturally but prepared by hydrolysis of collagen
- It is obtained from collagen of animal bones and skin

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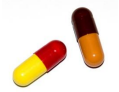
Gelatin



Reasons for using gelatin

A. Nontoxic and widely used in food
B. Readily soluble in body fluids
C. It is good film-forming material (thickness of hard capsule shell is about 100 μm)
D. Solutions at high concentrations (40 %) are mobile at 50 ^{o}C
E. Its aqueous solutions undergo a reversible change from a sol to a gel at temperatures above ambient

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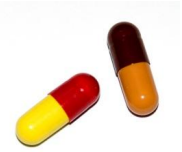
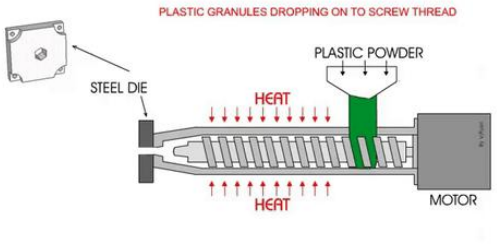
Gelatin



Gelatin types according to agent used in hydrolysis of collagen

- Type A gelatin:
  - Derived by acid treatment of the precursor
  - Take 7-10 days for preparation
  - Mainly for animal skins
- Type B Gelatin
  - Obtained by alkali treatment of the precursor
  - Takes 10 times as long as Type A
  - Mainly for bovine bones



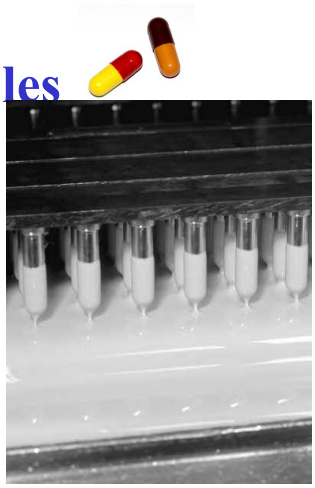
After **hydrolysis**, the gelatin is extracted by hot water, Solution is evaporated and the concentrated solution is extruded and dried.

Usually a mixture of both types is used for capsule production

Manufacture of Empty Capsules

1) A concentrated solution of gelatin (35 – 40 %) is prepared using demineralized hot water (60 –70 ^{o}C)
2) The solution is stirred until the gelatin has dissolved and vacuum is applied to remove entrapped air bubbles
3) Dye solutions or pigment suspensions are added to the solution
4) Viscosity is measured and adjusted by the addition of hot water (viscosity control the thickness of the capsule shell).

Manufacture of Empty Capsules



5) Pins of machine are dipped into the solution and are slowly withdrawn and then rotated during their transfer to the upper level of machine in order to form a film of uniform thickness
6) The films are dried by blowing large volumes of air over the pins (moulds)
7) The dried films are removed from the moulds, cut to the correct length , the two parts joined together and the complete capsule delivered from the machine.

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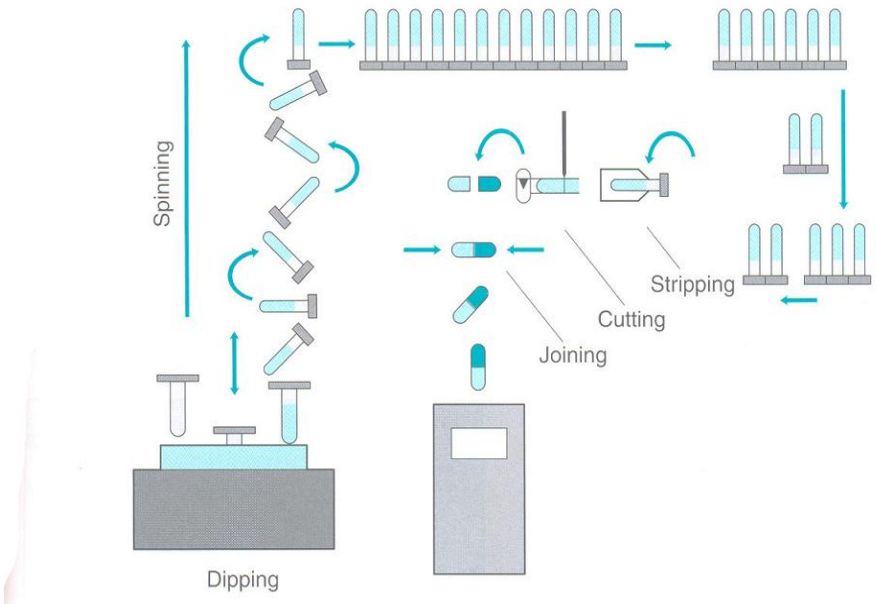

Fig. 34.1 The sequence of two-piece hard gelatin capsule shell manufacture.

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Gelatin

- Many materials used in the manufacture of pharmaceuticals are manufactured from raw materials of bovine origin, e.g. stearates and gelatin.

- The outbreak of BSE, which started in the UK, has led to strict rules being introduced by the EU to minimize the risk of transmitting animal spongiform encephalopathy agents (TSEs). prion
- BSE Bovine Spongiform Encephalopathy

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Capsules prepared from gelatin alternatives

Quali-V capsules *(Shiongoi Qualicaps Co.)*

- These capsules are based on HPMC with carrageenan (to act as gelling agent) and potassium chloride (to act as gelation promoter).
- This system has similar gelling properties to gelatin

Vcaps *(Warner Lambert Co.)*

- They use HPMC gelling system with gellan gum (as gelling aid) and either EDTA or sodium citrate as a gelation promoter.

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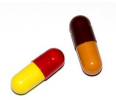
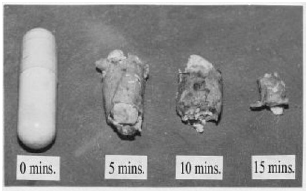
Empty capsule properties



- Empty gelatin capsules contain a significant amount of moisture which act as a plasticizer for the gelatin film.
- Standard moisture content for the hard gelatin capsules is between 13% and 16%.
- At low level humidity they will lose moisture and become brittle and at high humidity they will gain moisture and soften.
- Gelatin capsules are readily soluble in water at 37 °C, but their rate of dissolution decreases significantly with decreasing temperature.
- HPMC-based capsules contain less moisture (~4-7%), they don't become brittle by drying, and they readily dissolve at temperature as low as 10 °C.



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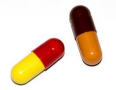
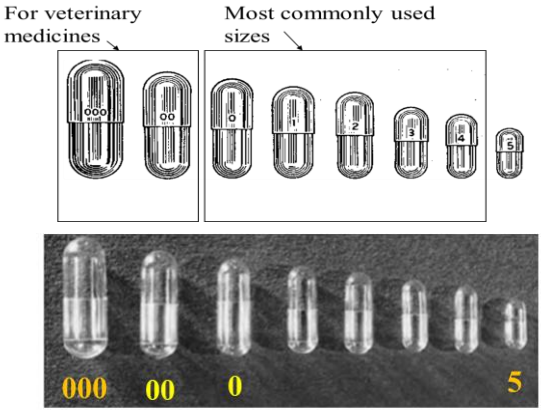
Capsule sizes



- Hard capsules are manufactured in a range of fixed sizes.
- The size (body volume) decrease with increasing the number



Capsule size	Body volume (ml)
0	0.69
1	0.50
2	0.37
3	0.28
4	0.20

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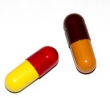
Capsule sizes



- For a powder the simplest way for estimating the fill weight is by multiplying the tapped bulk density X the body volume.
- For liquids the fill weight is calculated by multiplying the specific gravity of the liquid by the capsule body volume × 0.8

Density= mass/volume

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Capsule locking (sealing)

- The self-locking capsule were introduced during the 1960s, when automatic filling and packaging machines were introduced.
- Filled capsules were subjected to vibration during this process, causing some to come apart and spill their contents.

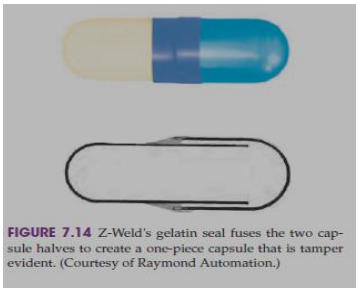

FIGURE 7.14 Z-Weld's gelatin seal fuses the two capsule halves to create a one-piece capsule that is tamper evident. (Courtesy of Raymond Automation.)

1. sealing them with a colored band of gelatin.
2. sealed through a heat-welding process that fuses the capsule cap to the body through the double wall thickness at their juncture
3. uses a liquid wetting agent then thermally bonds the two parts using low temperatures (40°C to 45°C)

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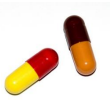
Capsules shell filling



- Hard gelatin capsules can be filled with a variety of materials of different physicochemical properties taking into consideration the following limitations:
  1. The material must not react with gelatin
  2. The material must not contain a high level of free moisture
  3. The volume of unit dose must not exceed the sizes of capsule available

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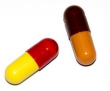
Capsules shell filling



Types of materials for filling in Hard gelatin capsules:

Dry solids

Powders
Pellets
Granules
Tablets

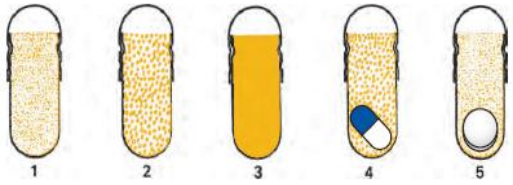


FIGURE 7.8 Examples of fill in hard gelatin capsules. 1, powder or granulate; 2, pellet mixture; 3, paste; 4, capsule; and 5, tablet. (Courtesy of Capsugel Division, Warner-Lambert.)

Semisolids

Thermosoftening mixtures
Thixotropic mixtures (by stress by becoming less viscous)
Pastes

Liquids

Nonaqueous liquids

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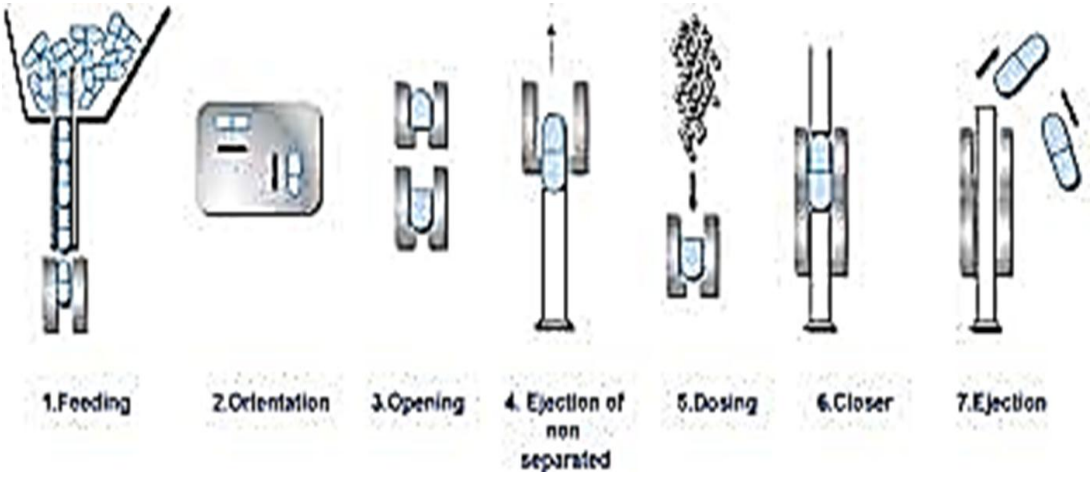

Ejection of unseparated capsules

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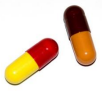
Capsule filing machines



- The same set of basic operations is carried out for simple and complicated machines.
- The filling comprises the following steps:
  1. Rectification (The empty capsules are oriented so that all point the same direction)
  2. separation
  3. filling
  4. closing
  5. ejection

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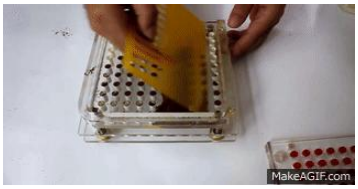
Capsule filing machines

Filling of powder: B*ench scale filling*

- This is done by simple equipments which consist of a set of plastic plates which have predrilled holes to take from 30 - 100 capsules of a specific size.
- Empty capsules are fed into the holes, the bodies are locked in their place by means of a screw and the caps in their plate are removed.
- Powder is placed on to the surface of the body plate and is spread with a spatula so that it is filled into the bodies.
- The cap plate is then repositioned over the body one and the capsules are rejoined using manual pressure.

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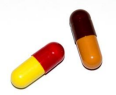
Capsule filing machines



Filling of powder

Industrial scale filling

- There are different shapes and sizes of industrial capsule filling machine varying from automatic to semiautomatic.
- The dosing system is divided into two groups:
  - Dependent: Dosing system uses the capsule body to measure the powder
  - Independent: the powder is measure independently of the capsule body volume

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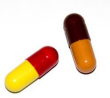
Capsule filing machines



Dependent systems

- Empty capsules are fed into a pair of ring holders, the caps being retained in one half and the bodies in the other (vacuum is used for separation).
- The body holder is placed on a variable speed revolving turntable.
- The powder hopper is put on top of the body plate, which revolves underneath it.
- In the hopper a revolving **auger forces** powder down to the capsules bodies

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powder hopper

revolving turntable

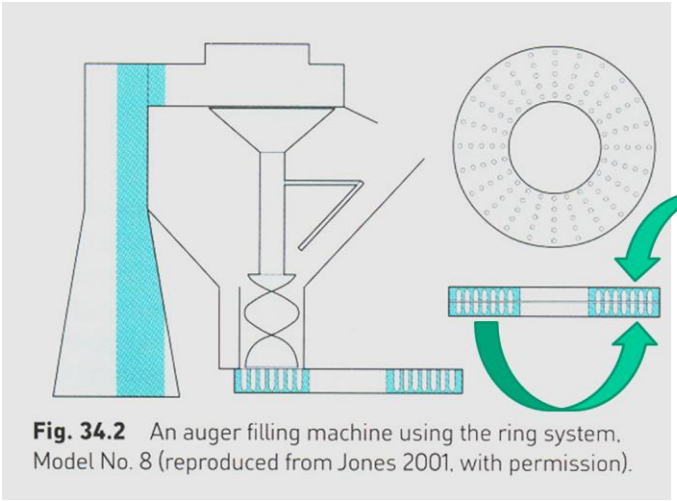
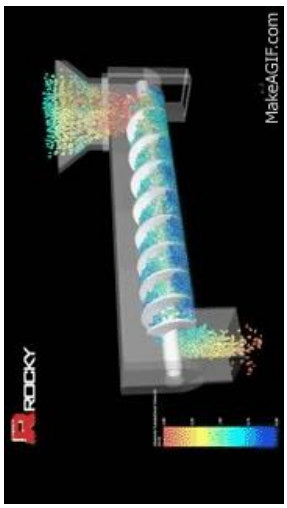


Fig. 34.2 An auger filling machine using the ring system, Model No. 8 (reproduced from Jones 2001, with permission).



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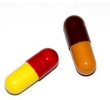
Capsule filing machines



Dependent systems

- The weight of powder filled into the body is dependent mainly upon the time the body is underneath the hopper during the revolution of the plate holder (speed of rotation must be controlled).
- This is a semiautomatic method, requiring an operator to transfer the capsule holders from one operation to the next
- Capacity 15 000 - 25 000 per hour and is dependent upon the skill of operator

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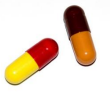
Capsule filing machines



Independent

- These are fully automatic machines which are using dosing mechanisms that form a plug of powder (soft compact formed at low compression forces)
- There are two types of plug forming machines, those that use a dosator system and those that use a tamping finger and dosing disk system

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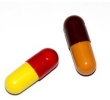
Capsule filing machines



Independent

Dosator system

- This system is probably the most widely used in the world and is the one that is described the most in the literature.
- Examples of machines that use this system are:
  - *Intermittent motion:* Zanasi (IMA), Pedini, Macophar and Bonapace. Their outputs range from 5000 to 60 000 per hour.
  - *Continuous motion:* MG2, Matic (IMA).Their outputs range from 30 000 to 150 000 per hour.

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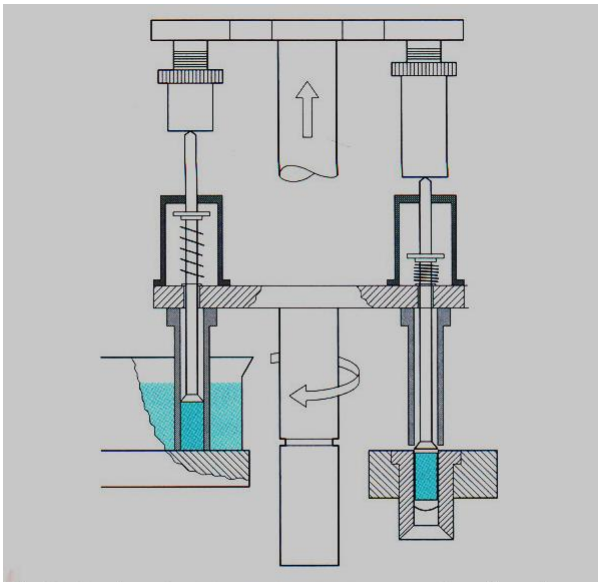

Fig. 34.3 A dosing tube or dosator-type machine, Zanasi RM63 (reproduced from Jones 2001, with permission).

Intermittent motion: Zanasi (IMA

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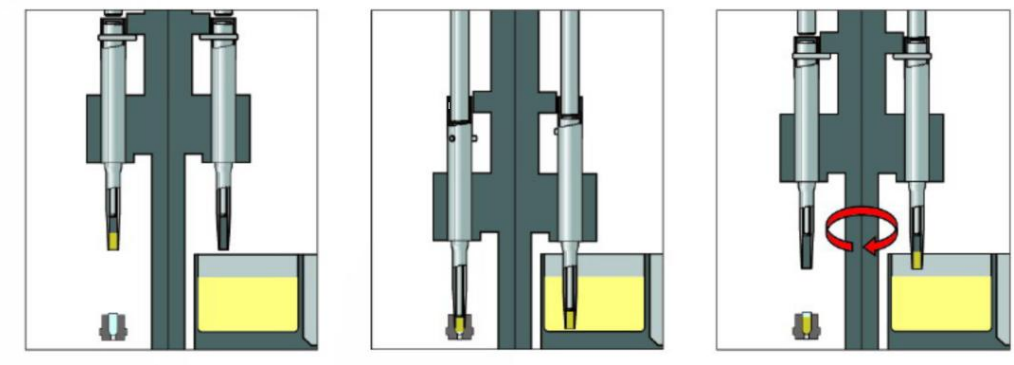

Intermittent motion:

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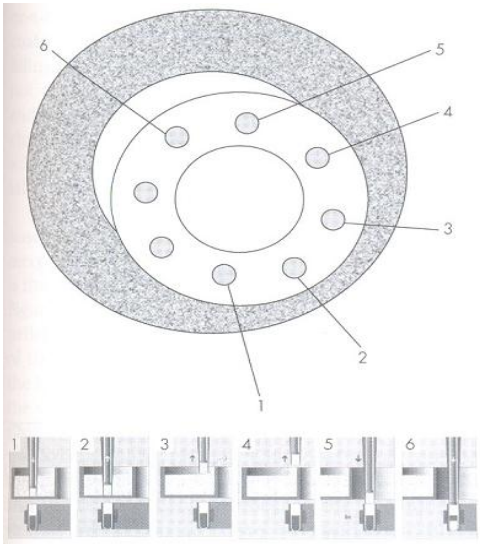
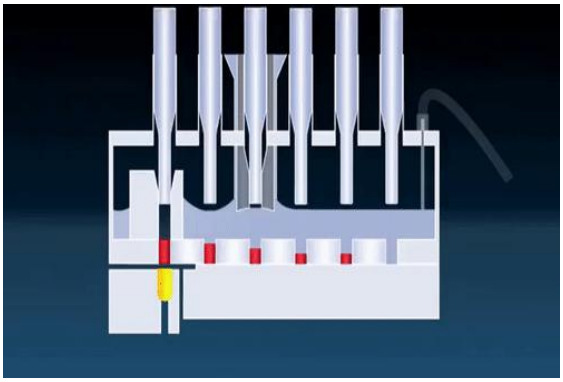


Figure 6.18 Continuous capsule filling with dosator nozzles. Position and relative size of the ring-shaped powder bowl and turret (top). (Schematic drawings to illustrate steps 1 to 6 reproduced from MG2 Customer Leaflet, with permission of MG2, Italy).

Continuous motion



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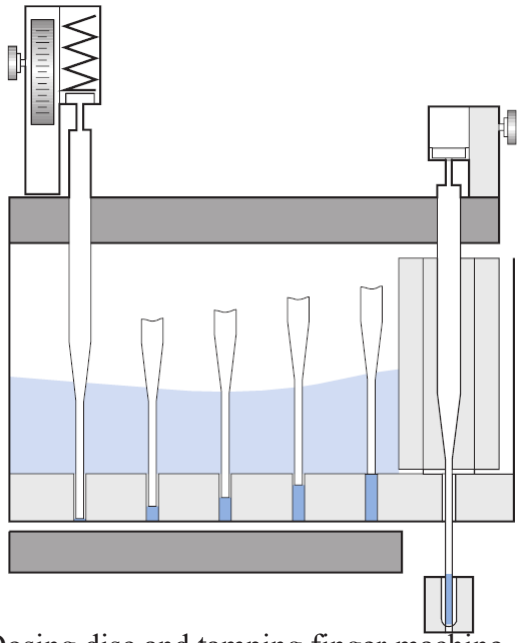
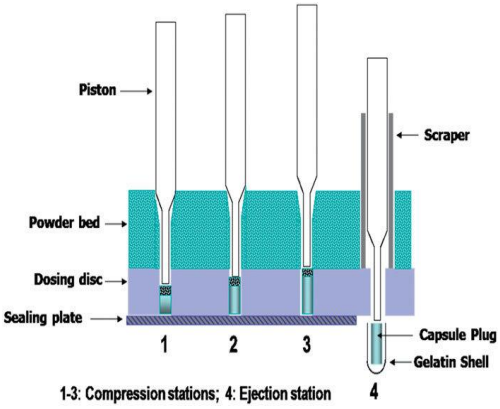


Dosing disc and tamping finger machine



1. The powder slug is compressed to 1/5 thickness of dosing disk.
2. The powder slug is compressed to 2/5 thickness of dosing disk
3. The powder slug is compressed to 3/5 thickness of dosing disk
4. The powder slug is compressed to same as thickness of dosing disk
5. The compressed slug of powder is inserted into the capsules

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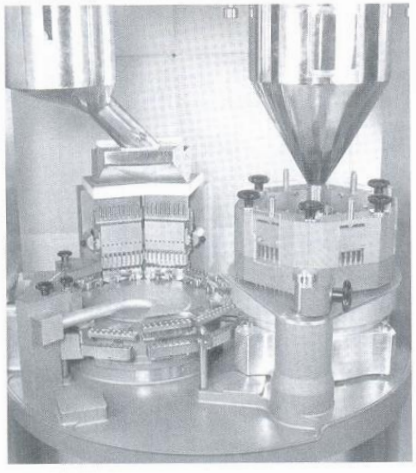

Figure 6.13 View into the GKF 2500S capsule-filling machine. Capsules are fed from a hopper into the rectification system (left) and opened. Powder plugs are formed in the tamping unit (right) and transferred into the lower segments, which follow a circular path for opening, filling and closing (front). (Reproduced from Bosch Customer Leaflet VT/VFW 04/02-1E, with permission of Robert Bosch GmbH, Germany.)

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Capsule filing machines

Pellet filling

- Preparations formed as coated pellets are filled on industrial scale using machines adapted from powder use.
- All have a dosing system based on a chamber with a volume that can be easily changed.
- Pellets are not compressed and may have to be held inside the measuring device mechanically (e.g. inverting the dosator or applying vacuum).

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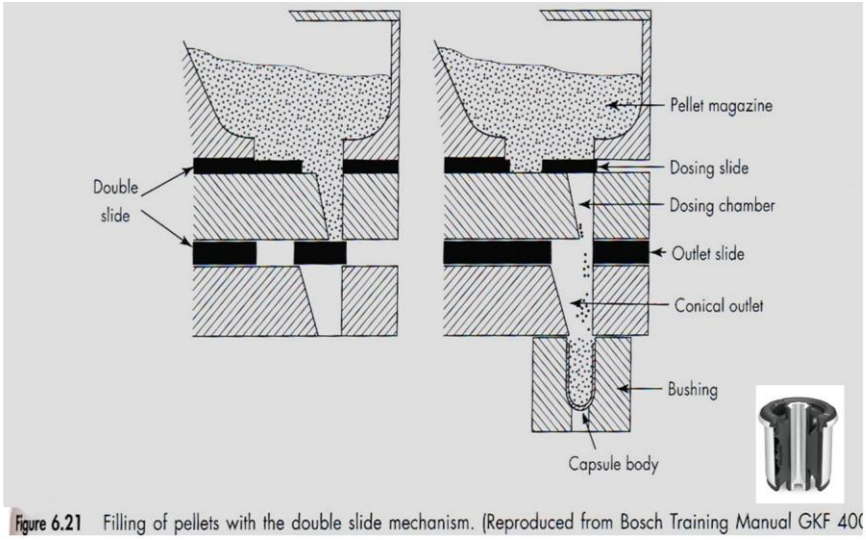

Figure 6.21 Filling of pellets with the double slide mechanism. (Reproduced from Bosch Training Manual GKF 40(

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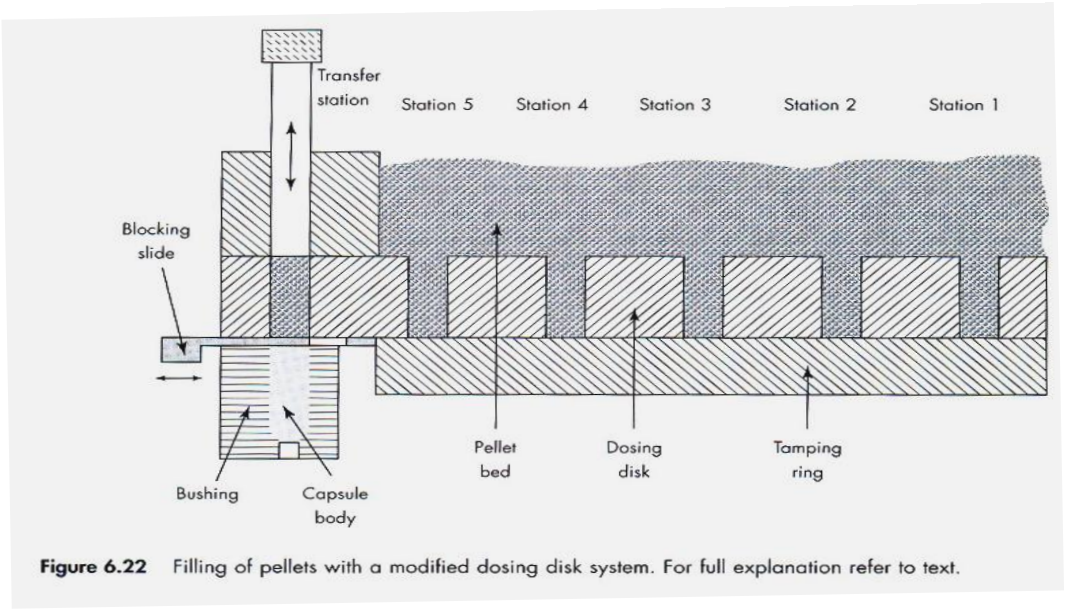

Figure 6.22 Filling of pellets with a modified dosing disk system. For full explanation refer to text.

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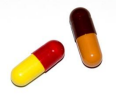
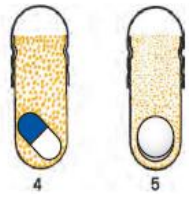
Capsule filing machines



Tablet filling

- Tablets are placed in hoppers and allowed to fall down tubes, at the bottom of which is a gate device that will allow a set number of tablets to pass.

- Tablets for capsule filling are normally film coated to prevent dust, and are sized so that they can fall freely into the capsule body.



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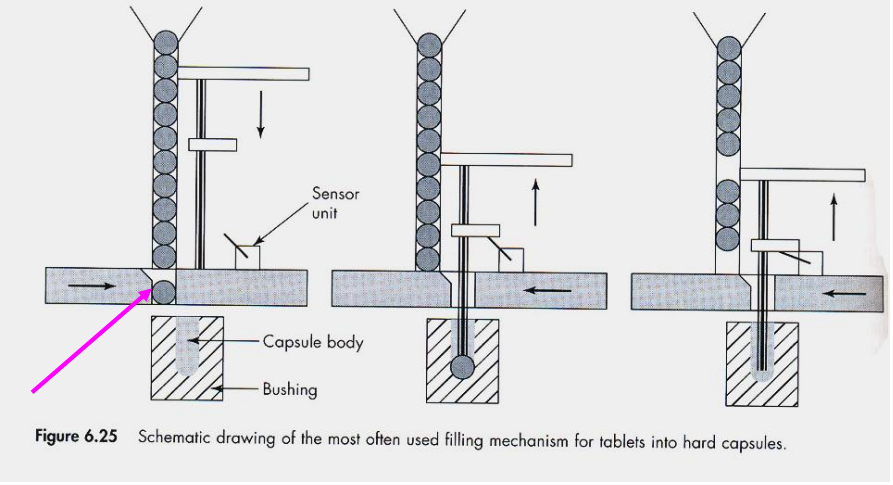

Figure 6.25 Schematic drawing of the most often used filling mechanism for tablets into hard capsules.

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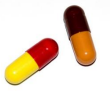
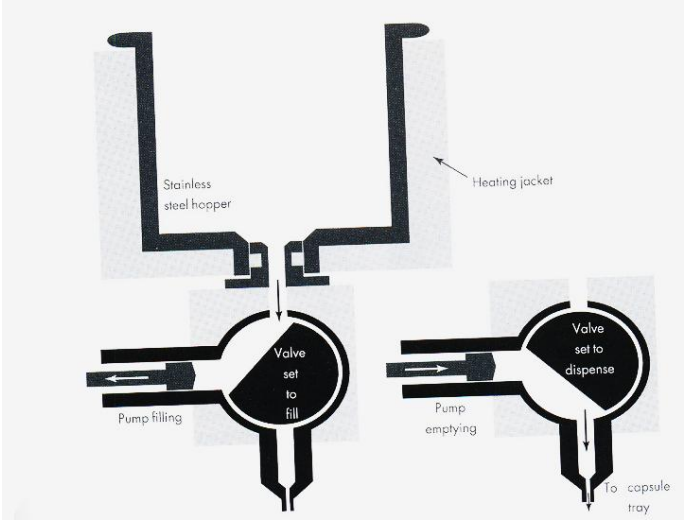
Capsule filing machines



Semisolid and liquid filling

- Liquids can easily be dosed into capsules using volumetric pumps.

Rotary dispensing pump



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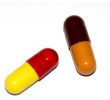
Capsule filing machines



Semisolid and liquid filling

- Non-aqueous liquids, which are mobile at ambient temperature require sealing.
- This is done by applying gelatin solution around the center of capsule after it has been filled, which forms a hermetic seal after drying.
- This prevents liquid leakage, contains odors inside the shell and significantly reduces oxygen permeation into the contents, protecting them from oxidation.

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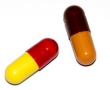
Capsule filing machines



Semisolid and liquid filling

- Semisolids mixtures are formulations that are solid at ambient temperature and can be liquefied for filling by either heating thermosoftening mixtures or by stirring thixotropic mixtures (Certain gels or fluids that are thick or viscous under static conditions will flow over time when shaken)
- These formulation are similar to those that are filled into soft gelatin capsules, but differ in one important respect: they can have melting points higher than 35°C, which is the maximum for soft gelatin capsules because this is the temperature used by the sealing rollers during their manufacture.

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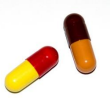
Formulation



- All formulations for filling into hard capsules have to meet the following requirements:
  - They must be capable of being filled uniformly
  - They must release their active content in form that is available for absorption by patient.
  - *E.g. Amlodipine besylate 10 mg capsule*
  - They must comply with the requirements of pharmacopoeias and regulatory authorities

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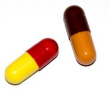
Formulation



Powder formulation

- These formulas are typically mixtures of active ingredient and different types of excipients.
- The selection of formula depends on:
  - The properties of active drug (flowability, compressibility, cohesiveness)
  - Its dose, solubility, particle size and shape
  - The size of capsules to be used
- The potent drugs are easier to formulate than drugs with high unit dose (why??).

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Types of excipients used in powder-filled capsules

Diluents: gives plug-forming properties

Antiadherents: reduced adhesion of powder to metal or gelatin shell

Glidants: Improve powder flow

Wetting agents: Improve water penetration to the powder mass

Super disintegrants: provides disruption of the powder mass

Stabilizers: improves products stability

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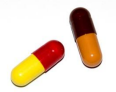
Formulation



Formulation for filling properties

- The main factors in powder formulation related to filling properties are:
  - Good flowability (using free-flowing diluent and glidant)
  - Low adhesion (using lubricants)
  - Cohesion (plug-forming diluent)

- The formulation is affected by the type of machine used (in case of dependent machines flowability is the most critical, while in independent (plug forming) the cohesion is the most important

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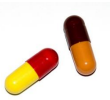
Formulation



Formulation for release of active ingredients

- The first step of release of active ingredient is disintegration of capsule shell (At 37 ^{o}C, the shell will split within 1 min.).
- The rate controlling step in product release is the formulation of the contents which ideally should be hydrophilic and dispersible.
- Particle size, diluent used and percentage of lubricant was found to affect the rate of absorption for several compounds.
- The use of wetting agents (e.g. Sodium lauryl sulfate) for poorly soluble drugs and superdisintegrants (for plugs){e.g. Sodium starch glycolate, croscarmellose sodium and crospovidone enhance the release of the active ingredient.

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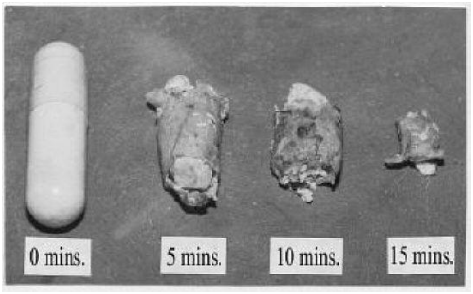

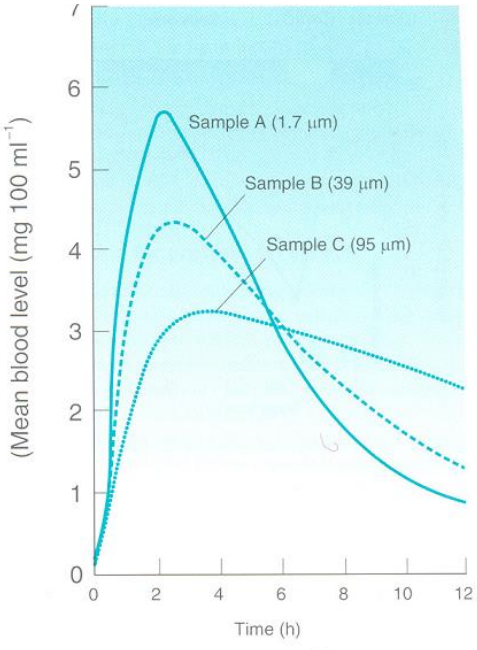

Fig. 34.5 Effect of particle size on bioavailability (after Fincher et al 1965, with permission).

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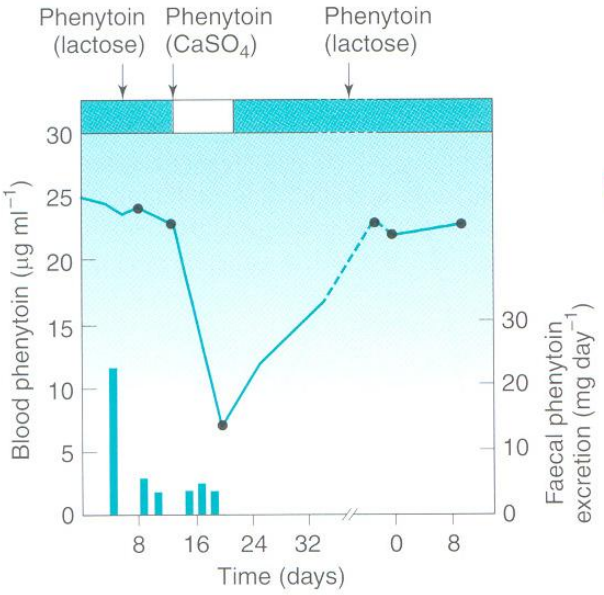
Phenytoin complexes with $CaSO_4$ making it less absorbable



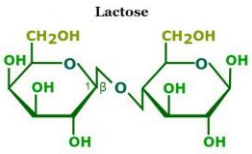


Fig. 34.6 Effect of diluent on bioavailability (after Tyrer et al 1970, with permission).

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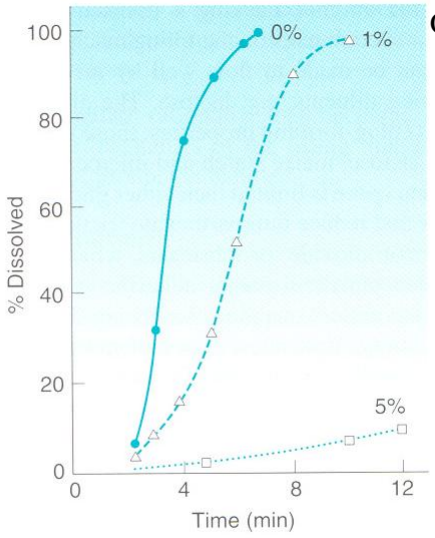

Optimum %

Fig. 34.7 Effect of lubricant on release of active ingredient (after Simmons et al 1972, with permission).

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Formulation

Formulation for position of release

- Capsules can be readily manipulated to release their contents at various positions along the GIT.

1. It has been suggested that for some compounds, the best way to improve their absorption is for the dosage form to be retained in the stomach so that it will dissolve slowly.

- **Floating capsules** have been made which contain various hydrophilic polymers such as methylcellulose, that swell on contact with water and form a mass that can float on the gastric liquids.

2. **Enteric products** can be made by either coating the filled capsule or by formulating the contents as pellets and coating them with enteric polymer.

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Formulation

Formulation for position of release

There is currently an interest in targeting compounds to the distal parts of intestines (e.g. for polypeptide drugs) and this can be achieved by:

- Formulating the drug as prolonged release and filling in a capsule that is enteric coated (e.g. Colpermin®).
- Coating with polymers that are only soluble at higher pHs, 6 –7, which is not reached until further along the small intestine

➢ Some capsules are used for products for inhalation

➢ Some capsules are intended for vaginal or rectal administration.

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Soft Gelatin Capsules (Softgels)

- Softgels consist of a drug formula inside a one – piece outer gelatin shell.
- Drug may be either in solution, suspension or emulsion. The fill matrix may be hydrophilic or lipophilic.
- They can be manufactured in many shapes.
- Can be coated with enteric resistant or delayed release material.

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Soft Gelatin Capsules (Softgels)

- Softgels can be formulated and manufactured to produce different drug delivery systems:
  - Orally administered softgels containing solution or suspensions, in an easy to swallow and convenient form, that release their content in the stomach.
  - Chewable softgels Where a highly flavored shell is chewed to release the drug liquid fill matrix. The drug may be present in both the shell and the fill matrix.
  - Suckable softgels which consist of gelatin shell containing the flavored medicament to be sucked and a liquid matrix or just air inside the capsule
  - Twist-off softgels which are designed with a tag to be twisted or snipped off, thereby allowing access to the fill material (can be used for unit dosing of topical, ophthalmic and otic preparations, and cosmetics).

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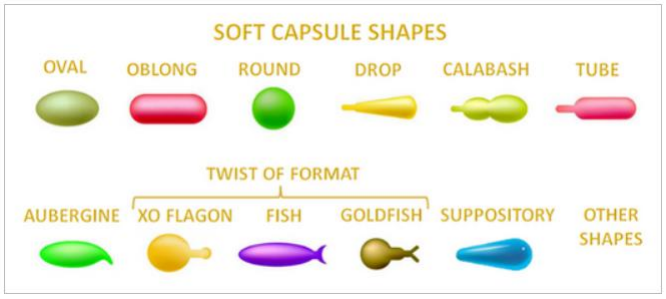

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Rationale for the selection of softgels as a dosage form

1. Improved drug absorption

- Absorption form drug-solution matrix in softgel is faster than from other solid dosage forms such as compressed tablets.
- This may be valuable for some drugs like those used for pain and migraine (e.g. ibuprofen).
- Formulation of poorly soluble drugs as solutions or micro emulsions in softgels can also increase bioavailability and decrease plasma level variability.

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Rationale for the selection of softgels as a dosage form

2. Patient compliance and consumer preference

- Softgels are preferred by consumers because of ease of swallowing, absence of taste, elegancy..etc.

3. Suitability for administration of oils, volatile materials and low melting-point drugs which are difficult to compress as tablets

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Rationale for the selection of softgels as a dosage form

4. Safety for potent and cytotoxic drugs

- ***In tablet and hard gel capsule,*** the mixing, granulation and compression or filling processes can generate a significant quantity of airborne powders. This can be of great concern for highly potent or cytotoxic compounds (operator and environmental concerns).

- By preparing a solution or suspension of drug in liquid such concerns can be significantly reduced.

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Rationale for the selection of softgels as a dosage form

5. Dose uniformity of low dose drugs

- E.g. digoxin (Lanoxicaps, GSK)
- Liquid dosing avoids the difficulty of poor powder flow and therefore poor content uniformity.
- Drug is distributed more uniformly in a solution than in a powder mixture.

6. Product stability

- Stability of drugs subjected to oxidation (preparation under nitrogen atmosphere) or hydrolysis (by formulating in lipophilic vehicle) can be increased by preparation in softgels.
- However, drug in **aqueous** solution may be less stable than in solid state.

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Manufacture of Softgels

- Softgels were used in the 19th century as a means of administering bitter-tasting or liquid medications.
- They were manufactured individually by preparing a small sack of gelatin by leather or iron molds, filling it with medication and then sealing it by heat.

- This manufacturing method was improved using a process that involved sealing two sheets of gelatin film between a film of matching flat brass(Cu+Zn) dies. Each die contained pocket into which gelatin sheet was pressed and into which the medication was filled.
- Manufacture on a production scale was possible after the invention of rotary die encapsulation machine (1933).

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Manufacture of Softgels

Rotary die encapsulation

- In this process the gelatin solution is spread onto two rotating drums to form a pair of continuous sheets (ribbons) of gelatin, which are fed between two matched rotary dies.
- Accurately metered volumes of the liquid fill matrix are injected from the heated wedge device (about 40 °C) into the space between the gelatin ribbons as they pass between the die rolls.
- The injection of liquid between the ribbons forces the gel to expand into the pockets of the dies, which govern the size and shape of the softgels.

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Manufacture of Softgels

Rotary die encapsulation

- The ribbon continues to flow past the heated wedge injection system and is then pressed between the die rolls.

- Here the two softgel capsule halves are sealed together by application of heat and pressure.
- The capsules are cut automatically from the gel ribbon by raised rims(frame) around each die on the rollers.
- After manufacture the capsules dried completely (tumble dryer then tray dryer), inspected and packaged into bulk containers.

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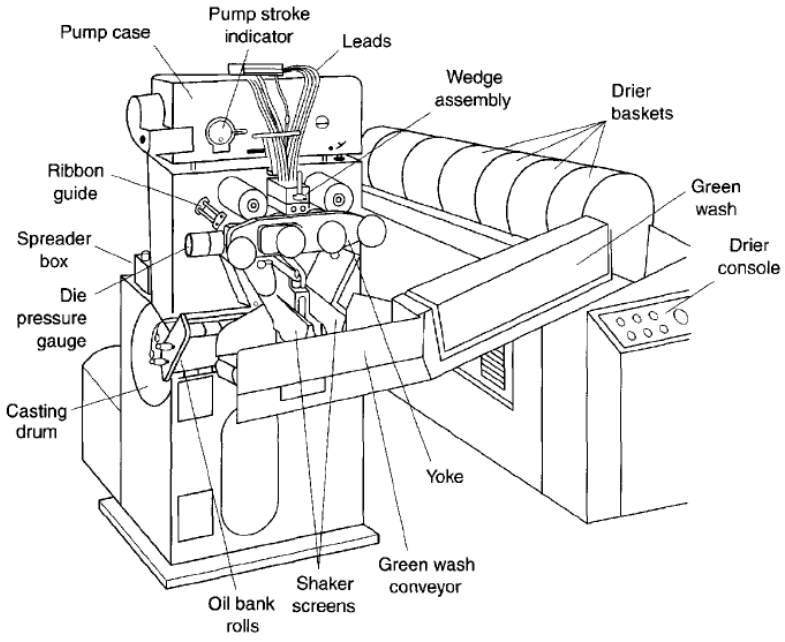

Fig. 30.6 Diagram of a soft gelatin encapsulation machine.

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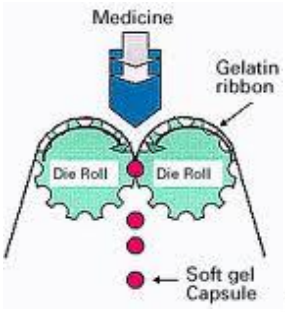
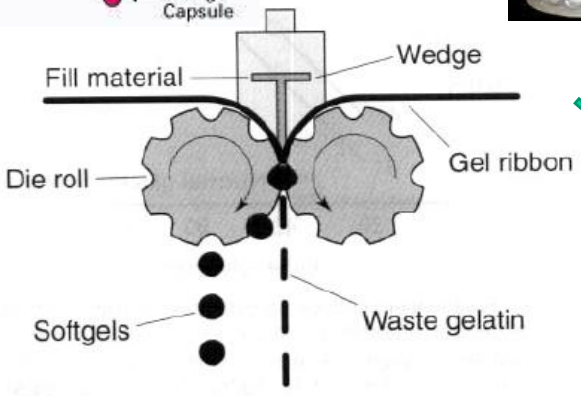


raised rims(frame) around each die



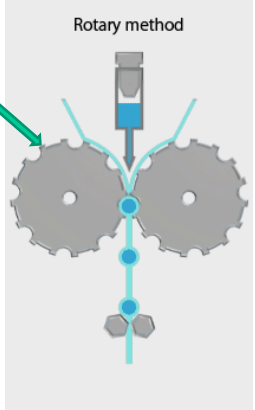


Fig. 30.8 Softgel formation mechanism.

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Formulation of softgels

Gelatin shell formulation

- Typically softgel shells are made up of gelatin, plasticizer, and other materials (colorants, opacifiers and sometimes flavor)
- Gelatin constitutes about 40 % of the solution
- The plasticizers (20 -30 % of the gelatin solution) are used to make the softgel shell elastic and pliable (flexible).
- The most commonly used plasticizer in softgels is glycerin, although sorbitol, propylene glycol and PEG 200 (low molecular weight) are also frequently used.

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Formulation of softgels

Gelatin shell formulation

- Plasticizers are chosen on the basis of their compatibility with the fill formulation, ease of processing and the desired properties of the final softgel.
- In dry softgels the water content is typically in the range of 5 - 8 % w/w, which represents the proportion of water that is bound to the gelatin.
- This level of water is important for good physical stability of the shell.
- Colors and opacifiers may be added also.
- Flavors and sugars are added in chewable and suckable soft gels

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Formulation of softgel fill material

- The liquid phase is selected from components with a wide range of different physicochemical properties.
- Ingredients that are solid at room temperature can also be encapsulated into softgels, similarly to liquids, provided they are at least semisolid below approximately 45°C
- Recently, rotary die encapsulation has been adapted for filling of tablets and pellets into capsules.

Formulation of softgel fill material

- The choice of components is made according to one or more of a number of criteria, including the following:
  - Capacity to dissolve the drug
  - Rate of dispersion in the GIT after rupture of the shell and release of matrix
  - Capacity to retain the drug in solution in the gastrointestinal fluids
  - Compatability with the softgel shell
  - Ability to optimize the rate, extent and consistency of drug absorbed.

Formulation of softgel fill material

Types of softgel matrices:

- Lipophilic liquids/oils: Triglyceride oils, such as soya are commonly used in softgels for drugs soluble in such oils (e.g. Vitamin D and oestradiol).

- Hydrophilic liquids: Polar liquids with a sufficiently high molecular weight (e.g. PEG 400).

- Self emulsifying oils: A combination of a pharmaceutical oil and a nonionic surfactant can provide an oil formulation which disperses rapidly in the gastrointestinal fluid and enables rapid drug absorption.

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Formulation of softgel fill material

Types of softgel matrices:

- Microemulsion and nanoemulsion systems:
  - A preconcentrate is formulated which form after release and dilution forms a microemulsion or nanoemulsion.

- Suspensions in different types of bases

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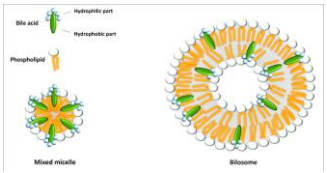
Formulation of softgel fill material



Types of softgel matrices:

- Lipolysis systems
  - The action of pancryatic lipase on triglycerides and partial glycerides to form 2-monoglycerides and fatty acids.
  - These interact with bile salts to form smaller and smaller vesicles resulting in the formation of mixed micelles that are approximately 3-10 nm in size.
  - If the drug has higher solubility in lipolysis product than in triglyceride oil then this is an advantage.
  - On the other hand, the absorption of a drug compound may be adversely affected by the presence of bile salts and in this case it is better to block or reduce the lipolysis.

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Product quality consideration for capsules

Empty hard capsules (QC)

- The test related to empty capsules manufacturing are:
  - Testing of components (e.g. purity, microbiological testing). This test is also performed for components of softgel shell.
  - In process control: viscosity of solution, color testing of gelatin solution.
  - Capsules testing: dimensions, mechanical strength, weight, appearance (defects, …) ….
- Most pharmacopoeias have test for filled capsule products, but most have nothing for empty capsules.
- The exceptions for this are the Chinese and Japanese pharmacopoeias
- The Japanese contain a purity test for empty capsules.

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Product quality consideration for capsules
In process testing for softgels

- During the encapsulation process the four most important tests are:
  - The gel ribbon thickness;
  - Softgel seal thickness at the time of encapsulation;
  - Fill matrix weight and capsule shell weight;
  - Softgel shell moisture level and softgel hardness at the end of the drying stage.

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Product quality consideration for capsules
Finished product testing

Finished capsule products are subjected to a number of tests in accordance with compendial requirements for unit dose capsule products.

These normally include:

Capsule appearance

- Shape, dimensions, defects (cracks, pinholes, color non-uniformity, foreign odors, …).

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Product quality consideration for capsules
Finished product testing

Active ingredient assay

- The actual average drug content divided by theoretical drug content.

Related substances assay

- The percentage content of impurities chemically related to drug substance (such as degradation products).

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Product quality consideration for capsules
Finished product testing

Uniformity of Mass

- The test is performed on capsule content.
- The weight of content is calculated from the weights of filled capsules and the empty capsule shell.
- The Ph Eur uses a sample of 20 capsules and applies a double limit test.
- For capsules containing less than 300 mg, not more than two out of the sample may be outside ± 10 % of the average and all must be within ± 20 %.
- 290-310 mg, 280-320 mg

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Product quality consideration for capsules
Finished product testing

Uniformity of Content

- Similarly to tablets, the test for uniformity of drug content is carried out by collecting a sample of capsules , normally 10, and determination of the amount of drug in each.

- The average drug content is calculated and the content of the individual capsules should fall within a specific limits in terms of percentage deviation from mean.

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Product quality consideration for capsules
Finished product testing

Disintegration

- The test is performed using the tablet disintegration apparatus.
- The end point is usually considered reached when there is no residue on the screen or only fragments of the shell are present.(6)
- Some pharmacopeias allow retesting. If 1 or 2 dosage units fail to disintegrate, the test is repeated on 12 additional dosage units. The requirements of the test are met if not less than 16 of the 18 dosage units tested have disintegrated.

Standard oral products

- The medium is water or 0.1 N HCl when justified and authorized
- The time limit for the standard test is:
  - 20 min for Japanese pharmacopoeia (JP)
  - 30 min for PhEur, USP and BP.

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Product quality consideration for capsules
Finished product testing

Disintegration

Enteric (Gastroresistant) products

- For capsules with a gastro-resistant shell the disintegration test is carried out without disc for 2 h in 0.1 N HCl and there should be no signs of disintegration or rupture permitting the escape of the contents.
- Then the acid is replaced by buffer solution pH 6.8 Add a disc to each tube. Operate the apparatus for 60 min. If the capsules fail to comply because of adherence to the discs, the results are invalid. Repeat the test on a further 6 capsules omitting the discs.
- For capsules prepared from granules or particles already covered with a gastro-resistant coating, a suitable test is carried out to demonstrate the appropriate release of the active substance(s), for example the test described in Dissolution test for solid dosage forms.
- USP does not have a disintegration test for enteric capsules.

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Product quality consideration for capsules
Finished product testing

Dissolution

- Normally performed in Basket or Paddle apparatuses
  - Standard products
    - Usually the samples are taken once at the end of test (normally after 30 – 60 min)
  - Sustained release products
    - Usually samples at different time intervals are taken covering the long period of release
  - Enteric products
    - Usually there is an acid stage followed by a buffer stage.

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Product quality consideration for capsules

Finished product testing

Dissolution

Interpretation (BP 2007) :

- Unless otherwise specified, the requirements are met if the quantities of active substance dissolved from the dosage units tested conform to Table 2.9.3.-1 for conventional dosage forms.
- Similar tables are found for enteric and sustained release dosage forms
- Continue testing through the 3 levels unless the results conform at either S1 or S2.
- The quantity ***Q***, is the specified amount of dissolved active substance, expressed as a percentage of the labelled content; the
- 5 per cent, 15 per cent, and 25 per cent values in the Table are percentages of the labelled content so that these values and ***Q*** are in the same terms.

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Table 2.9.3.-1

Level	Number tested	Acceptance criteria
S_1	6	Each unit is not less than $Q + 5$ per cent.
S_2	6	Average of 12 units ($S_1 + S_2$) is equal to or greater than Q, and no unit is less than $Q - 15$ per cent.
S_3	12	Average of 24 units ($S_1 + S_2 + S_3$) is equal to or greater than Q, not more than 2 units are less than $Q - 15$ per cent, and no is less than $Q - 25$ per cent.

Acceptance criteria for conventional dosage forms

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Product quality consideration for capsules
Finished product testing

- **Microbiological quality**
  - The microbiological quality of non-sterile pharmaceutical products is dependent upon their formulation and their method of use.
  - In PhEur (2002) capsules are listed in category 3B.
  - Limits per gram are:
    - Total viable count < 10^4 bacteria and < 10^2 fungi and <10^2 enterobacteria and other gram negative bacteria
    - Total absence of Salmonella, Escherichia coli and staphylococcus

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