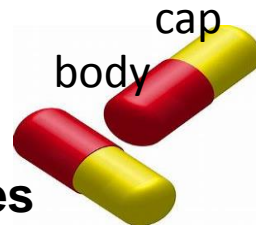


# **Hard gelatin capsules**

# INTRODUCTION

- The word capsule is derived from the Latin capsula, meaning a small box.
- In pharmacy the word is used to describe an edible package made from gelatin or other suitable material which is filled with medicines to produce a unit dosage, mainly for oral use.
- There are two **types of capsule**, 'hard' and 'soft'; better adjectives would be 'two-piece' instead of hard, and 'one-piece' instead of soft.

**Hard gelatin capsules**




- The hard capsule consists of two pieces in the form of cylinders closed at one end: the shorter piece, called the '**cap**', fits over the open end of the longer piece, called the '**body**'.

# RAW MATERIALS

- The raw materials used in the manufacture of both types of capsule are similar. Both contain **gelatin, water, colourants** and **optional materials** such as **process aids** and **preservatives**; in addition, soft capsules contain various **plasticizers**.
- The major pharmacopoeia; (European, Japanese and US) permit the use of gelatin or other suitable material, and in **recent years hard capsules have been manufactured also from hydroxypropyl methylcellulose in order to produce a shell with a low moisture content.**

# Gelatin

- Gelatin is the major component of the capsule , The reason for this is that gelatin possesses five basic **properties**:
  1. It is **non-toxic**, widely used in foodstuffs, and acceptable for use worldwide.
  2. It is **readily soluble** in biological fluids at body temperature.
  3. It is a **good film-forming material**, producing a strong flexible film.
    - The wall thickness of a hard gelatin capsule is about 100  $\mu\text{m}$
  4. Solutions of high concentration, 40% w/v, are **mobile** at 50°C. Other biological polymers, such as agar, are not.
  5. A solution in water or in a water-plasticizer blend **undergoes a reversible change from a sol to a gel** at temperatures only a few degrees above ambient.  **thixotropic material**

- This is in contrast to other films formed on dosage forms, where either **volatile solvents** or **large quantities of heat are required to cause this change of state**, e.g. tablet film coating.
- These films are formed by spraying and have a structure that could be described as formed of overlapping plates, whereas the gelatin films are homogenous in structure, which gives them their strength.

- Gelatin is a substance of natural origin that does not occur as such in nature.
- **It is prepared by the hydrolysis of collagen**, which is the main protein constituent **of connective tissues**.
- **Animal skins and bones** are the raw materials used for the manufacture.
- There are two main types of gelatin:
  1. type A, which is produced by acid hydrolysis,
  2. type B, which is produced by basic hydrolysis.

- The **acid process** takes about **7-10 days** and is used mainly for **animal skins**, because they require less pretreatment than do bones.
- The **basic process** takes about **10 times** as long and is used mainly for **bovine bones**.
- The **bones** must first be **decalcified** by washing in acid to give a soft sponge-like material, called **ossein**; **calcium phosphates** are produced as a byproduct. ▾

gelatin hydrolysis



- The ossein is then soaked in lime pits for several weeks.



Calcium oxide -containing inorganic mineral

- After hydrolysis the gelatin is **extracted** from the treated material using **hot water**.
- The **first extracts contain the gelatin with the highest physical properties**, and as the temperature is raised the quality falls.
- The resulting weak solution of gelatin is concentrated in a series of evaporators and then chilled to form a gel.
- This gel is then extruded to form strands, which are then dried in a fluidized-bed system.
- The dried material is graded and then blended to meet the various specifications required.

- The properties of gelatin that are most important to the capsule manufacturers are the Bloom strength and the viscosity:

### 1. The Bloom strength:

- is a measure of gel rigidity.
- It is determined by preparing a standard gel (6.66% w/v) and maturing it at 10°C.
- It is defined as the load in grams required to push a standard plunger 4 mm into the gel.
- The gelatin used in **hard capsule** manufacture is of a higher bloom strength (**200-250 g**) than that used for **soft capsules (150 g)** because a more rigid film is required for the manufacturing process.

# Colourants

- The colourants that can be used are of two types:
  - water-soluble dyes
  - insoluble pigments.
- To make a range of colours dyes and pigments are mixed together as solutions or suspensions.
- The dyes used:
  - are **mostly synthetic** in origin
  - can be subdivided in:
    1. the azo dyes - those that have an -N=N- linkage
    2. the non-azo dyes, which come from a variety of chemical classes.

- Most **dyes used currently** are of the non-azo class, and the three most widely used are erythrosine (E127), indigo carmine (E132) and quinoline yellow (E104).
- Two types of **pigment are used**: iron oxides (E172), black, red and yellow, and titanium dioxide (E171), which is white and used to make the capsule opaque.
- **In the last few years there has been a move away from soluble dyes to pigments, particularly the iron oxides, because they are not absorbed on ingestion.**

# Process aids


- The USNF describes the use of gelatin containing not more than **0.15% w/w of sodium lauryl sulphate** for use in hard gelatin capsule manufacture.
- This **functions as a wetting agent**, to ensure that the lubricated metal moulds are uniformly covered when dipped into the gelatin solution.

- **Preservatives** were formerly added to hard capsules as an in-process aid in order to prevent microbiological contamination during manufacture.
- **Manufacturers operating their plants to GMP guidelines no longer use them.**
- In the finished capsules the moisture levels, 13.0-16.0% w/v, are such that they will not support bacterial growth because the moisture is too strongly bonded to the gelatin molecule.

# MANUFACTURE

- The process in use today is the same as that described in the original patent of 1846
- Metal moulds at room temperature are dipped into a hot gelatin solution which gels to form a film.
- This is dried, cut to length, removed from the moulds and the two parts are joined together.
- The difference today is that the operation is now fully automated, carried out as a continuous process on large machines housed in air-conditioned buildings.
- There are only a comparatively **few specialist companies that manufacture empty capsule shells** for supply to the pharmaceutical and health-food industries, who fill them with their own products.
- Two companies, which have done most of the pioneering work in the field, have been making capsules for 100 years:
  - **Shionogi Qualicaps (formerly Eli Lilly & Co.) since 1897,**
  - **Warner Lambert's Capsugel (formerly Parke Davis) since 1902**

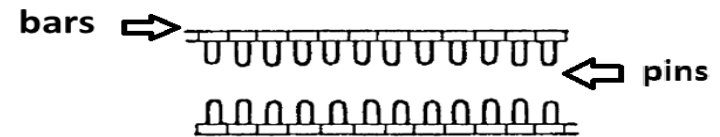
- The **first step in the process** is the **preparation of the raw materials**.
- A **concentrated solution of gelatin, 35-40%**, is prepared using demineralized **hot water, 60-70°C**, in jacketed pressure vessels.
- **This is stirred until the gelatin has dissolved and then a vacuum is applied to remove any entrapped air bubbles.**
- Aliquots of this solution are then dispensed into suitable containers and the required amounts of **dye solutions and pigment suspensions added.**

- The **viscosity** is measured and adjusted to a target value by the addition of hot water.
- 
- **This latter parameter is used to control the thickness of the capsule shells during production:**
  - the higher the viscosity the thicker the shell wall produced.
  - The prepared mixes are then transferred to a heated holding hopper on the manufacturing machine.

- The manufacturing machines are approximately 10m long, 2 m wide and 3m high.



- They consist of two parts, which are mirror images of each other: on one half the capsule cap is made and on the other the capsule body.
- The machines are also divided into two levels, an upper and a lower.
- **The moulds, commonly referred to as 'pins', are made of stainless steel and are mounted in sets on metal strips, called 'bars'.**

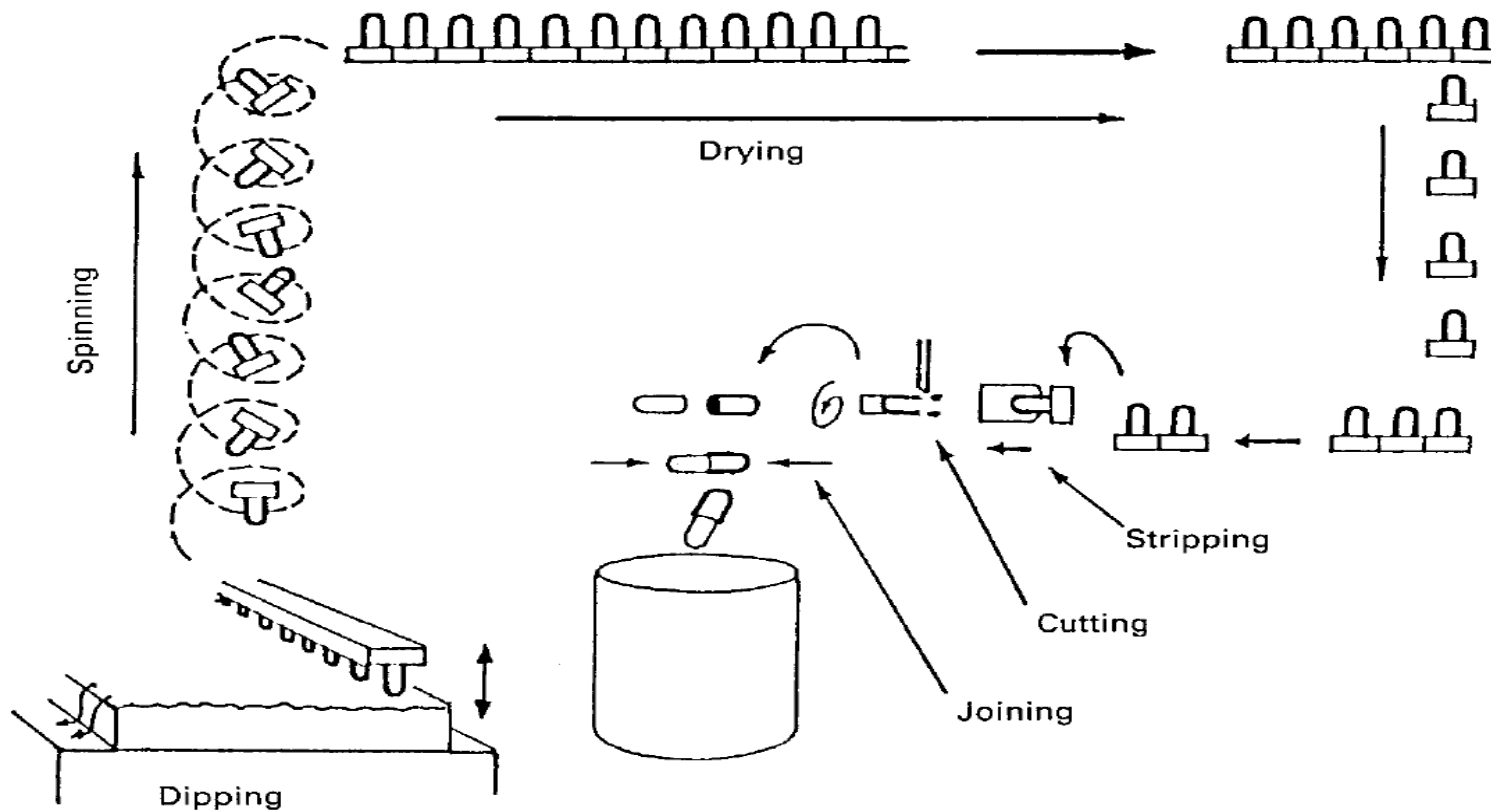


- There are approximately 40 000 mould pins per machine.
- The machines are housed in large rooms where the humidity and temperature are closely controlled.

# The sequence of events in the manufacturing process

- At the front end of the machine is a **hopper**, called a '**dip pan**' or '**pot**'. It holds a **fixed quantity of gelatin at a constant temperature, between 45° and 55°C**.
- The level of solution is maintained automatically by a feed from the holding hopper.
- **Capsules are formed by dipping sets of moulds, which are at room temperature, 22°C, into this solution. A film is formed on the surface of each mould by gelling.**
- The moulds are **slowly withdrawn** from the solution and then **rotated during their transfer to the upper level of the machine**, in order to form a film of uniform thickness.
- **Groups of 'pin bars'** are then passed through a series of drying kilns, in which large volumes of controlled humidity air are blown over them.
- When they reach the rear of the machine the bars are transferred back to the lower level and pass through further drying kilns until they reach the front of the machine.

- Here 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.
- The mould pins are then cleaned and lubricated for the start of the next cycle.
- **The output per machine is about 1 million capsules per day, depending upon the size: the smaller the capsule the higher the output.**



- The assembled capsules are not fully closed at this stage and are in a 'prelocked' position, which prevents them falling apart before they reach the filling machine.
- **The capsules now pass through a series of sorting and checking processes**, which can be either manual, mechanical or electronic, to remove as many defective ones as possible.
- **The quality levels are checked** through the process using standard statistical sampling plans,
- If required, **capsules can be printed** at this stage using an offset gravure roll printing process using an edible ink based on shellac.
- The information printed is typically either the product **name or strength**, a **company name or logo**, or an **identification code**.
- **The capsules are finally packed for shipment in moisture-proof liners, preferably heat-sealed aluminium foil bags, in cardboard cartons.**

# Empty capsule properties

- Empty capsules **contain a significant amount of water that acts as a plasticizer for the gelatin film** and is essential for their function.
- **During industrial filling and packaging operations** they are subjected to mechanical handling, and because the gelatin walls can flex these forces can be absorbed without any adverse effect.
- The **standard moisture content specification** for hard gelatin capsules is between **13.0% and 16.0% w/w**.
- This value can vary depending upon the conditions to which they are exposed: at low humidities they will lose moisture and become brittle, and at high humidities they will gain moisture and soften.

- The moisture content can be maintained within the correct specification by **storing them in sealed containers at an even temperature.**
- **Capsules are readily soluble in water at 37°C.**
- When the **temperature falls** below this their rate of **solubility decreases.**
- At below about 30°C they are insoluble and simply absorb water, swell and distort.

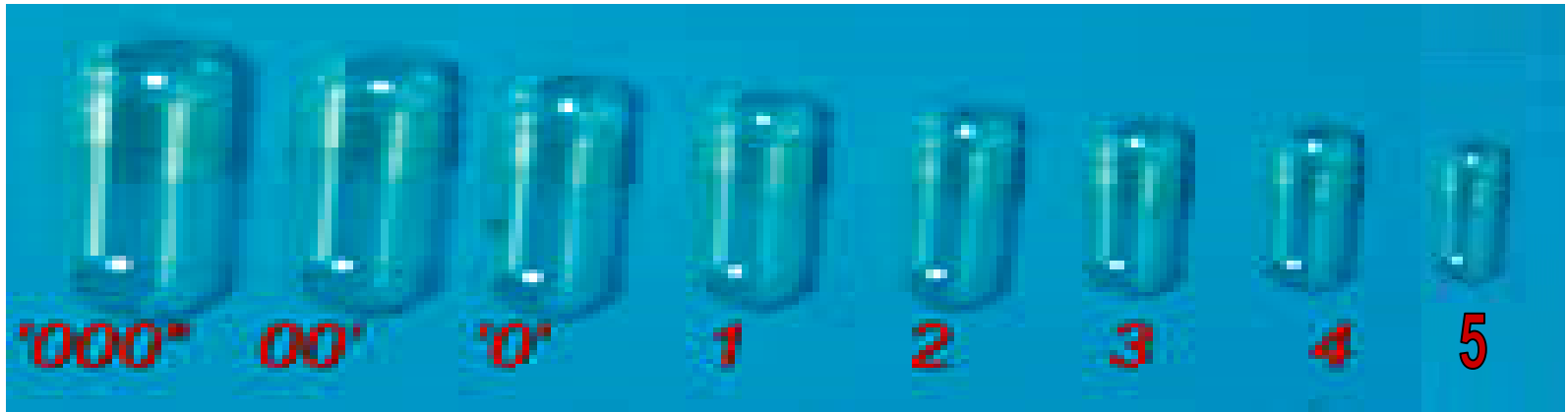
- This is an important factor to **take into account** during **disintegration and dissolution testing**.
- Because of this most Pharmacopoeiae have set a **limit of  $37^{\circ} \pm 1^{\circ}\text{C}$  for the media** for carrying out these tests.
- **Capsules made from HPMC have a different solubility profile, being soluble at temperatures as low as  $10^{\circ}\text{C}$**

# Capsule filling/*Capsule sizes*

- Hard gelatin capsules are **made in a range of fixed sizes**; the standard industrial sizes in use today for human medicines are from **0 to 4**.
- For a **powder** the simplest way in which to estimate the fill weight is to **multiply the body volume by its tapped bulk density**.
- For **liquids**, the fill weight is calculated by **multiplying the specific gravity of the liquid by the capsule body volume x 0.8**.

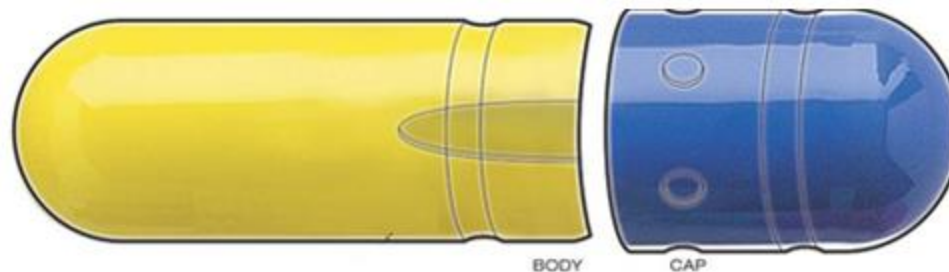
Capsule size	Body volume (mL)
0	0.67
1	0.48
2	0.37
3	0.28
4	0.20

- To accommodate special needs some intermediate sizes are produced, termed '**elongated sizes**', that typically have an extra 10% of fill volume over the standard sizes, e.g. for 500 mg doses of antibiotics elongated size 0 capsules are commonly used.



- The **shape of the capsule has remained virtually unchanged** since its invention over **150 years ago**, except for the **development of the self-locking capsule**.
- These 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.
- To overcome this, modern **capsule shells have a series of indentations on the inside of the cap and on the external surface of the body which**, when the capsule is closed after filling, form an interference fit sufficient **to hold them together during mechanical handling.**
- The manufacturer of the empty shells can be identified from the types of indent, which are specific to each one.



# *Capsule shell filling*

- Hard gelatin capsules can be filled with a large variety of materials of different physicochemical properties.
- Gelatin is a relatively inert material.
- **The substances to be avoided are:**
  1. those which are known to react with it, e.g. formaldehyde, which causes a crosslinking reaction that makes the capsule insoluble,
  2. those that interfere with the integrity of the shell, e.g. substances containing free water, which can be absorbed by the gelatin causing it to soften and distort.

**Table 29.2 Limitations in properties of materials for filling into capsules**

Must not react with gelatin

Must not contain a high level of 'free' moisture

The volume of the unit dose must not exceed the sizes of capsule available

**Table 29.3 Types of material for filling into hard gelatin capsules**

**Dry solids**

Powders

Pellets

Granules

Tablets

**Semisolids**

Thermosoftening mixtures

Thixotropic mixtures

Pastes

**Liquids**

Non-aqueous liquids



**POWDERS**



**GRANULES**



**BEADS**



**TABLETS**



**PASTES**



**LIQUIDS**

Edit by : M.sc Ruwaida Abdo

- Empty hard gelatin capsules are supplied in bulk containers.
- First, it is necessary for the filling machine to orientate them so that they are all pointing in the same direction, i.e. body first.
- To do this they are loaded into a hopper and from there pass down through tubes to a rectification section.
- Here the capsules are held in tight-fitting slots.

- Metal fingers strike them in the middle, and because the bodies have the smaller diameter, they rotate away from the direction of impact.
- Next the capsules are sucked through bushings that trap the caps, because of their greater diameter, separating them from the bodies.
- The bodies are then passed under the dosing mechanism and filled with material.
- The caps are then repositioned over the bodies and metal fingers push the bodies up into them to rejoin the two parts.

# Capsule-filling machines

- The **major difference** between the many methods available is **the way in which the dose of material is measured into the capsule body.**
- **Filling of powder formulations:**
  - *Bench-scale filling.*
  - *Industrial-scale filling.*
  - *Instrumented capsule-filling machines and simulators*
- **Pellet filling.**
- ***Tablet filling.***
- ***Semisolid and liquid filling***

# *Bench-scale filling*

- There is a requirement for **filling small quantities of capsules, from 50 to 10 000**, in community pharmacy, in hospital pharmacy, or in industry for special prescriptions or trials.
- There are several simple pieces of equipment available for doing this, e.g.
  1. the 'Feton' from Belgium
  2. the 'Labocaps' from Denmark.

- These **consist of sets of plastic plates** which have **predrilled holes to take from 30 to 100 capsules of a specific size.**
- Empty capsules are fed into the holes, either manually or with a simple loading device.
- The bodies are locked in their plate 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 uniformity of fill weight is very dependent upon good flow properties of the powder.
- The cap plate is then repositioned over the body one and the capsules are rejoined using manual pressure.



# *Industrial-scale filling*

- The machines for the industrial-scale filling of hard gelatin capsules come in:
  - **great variety of shapes and sizes,**
  - **varying from semi- to fully automatic**
  - **ranging in output from 5000 to 15 000 per hour.**
- **Automatic machines** can be either:
  1. **continuous in motion**, like a rotary tablet press,
  2. **intermittent**, where the machine stops to perform a function and then indexes round to the next position to repeat the operation on a further set of capsules.

# The dosing systems divided into two groups:

## *1. Dependent:*

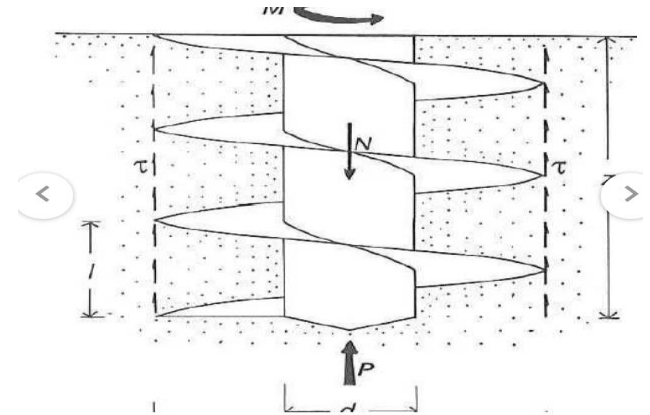
- dosing systems that **use the capsule body** directly to measure the powder.
- Uniformity of fill weight can only be achieved if the capsule is filled completely.

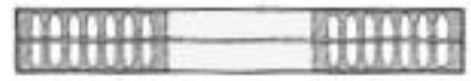
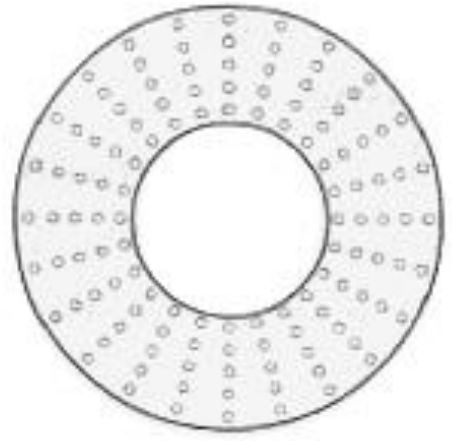
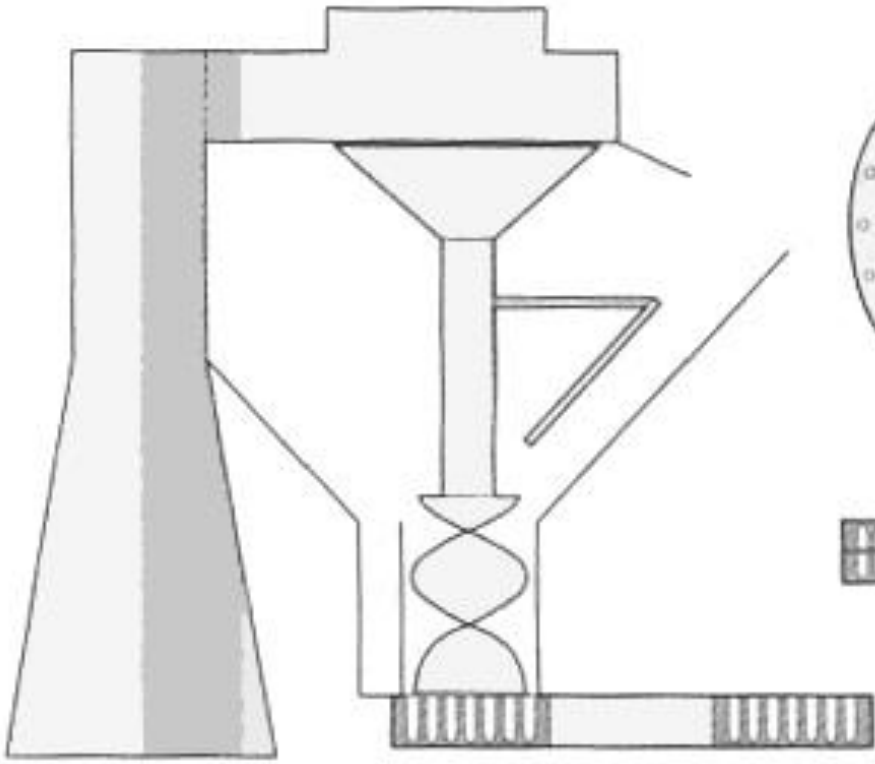
## *2. Independent:*

- dosing systems where the powder is measured independently of the body in a special measuring device.
- Weight uniformity is not dependent on filling the body completely.
- With this system the capsule can be part filled.

# Dependent dosing systems

- *The auger:*
- **Empty capsules are fed into a pair of ring holders, the caps being retained in one half and the bodies in the other.**
- **The body holder is placed on a variable-speed revolving turntable; the powder hopper is pulled over the top of this plate, which revolves underneath it.**
- **In the hopper a revolving auger forces powder down into the capsule bodies.**
- **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.**





- These **machines are semiautomatic** in operation, requiring an operator to transfer the capsule holders from one operation to the next.
- still **widely used** in many countries.
- The contact parts of these machines were originally made from cast iron, but are **now made from stainless steel to comply with GMP requirements**.
- all based on the original Colton Model No. 8 design.
- Their **output varies between 15 000 and 25 000 per hour** and is dependent upon the skill of the operator.

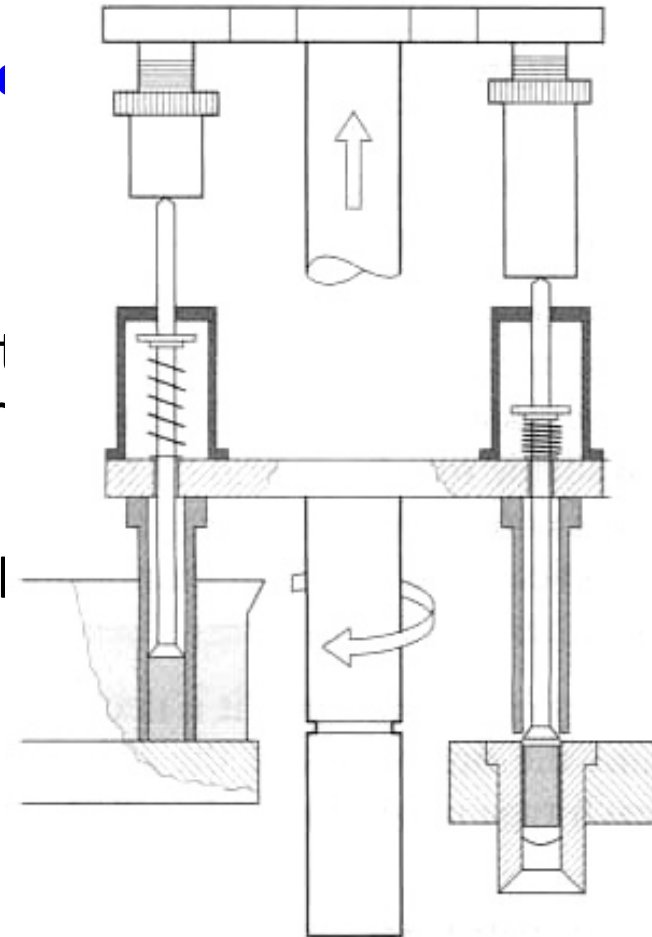
# *Independent dosing systems*

- Most industrial machines in use are **fully automatic** and use dosing mechanisms that form a **'plug' of powder**.
- ↓
- This is a **soft compact** formed at low compression forces - between 10 and 100 N - which are significantly less than those used in tableting.
  - The reason the plug is soft is because it is not the final dosage form, unlike the tablet, as the material will be contained inside a capsule shell.

- There are two types of plug-forming machine:
  1. those that use a 'dosator' system
  2. those that use a 'tamping finger and dosing disc' system.

# 1. Dosators

- This consists of a **dosing tube inside which** **spring-loaded piston**, thus forming chamber in the bottom of the cylinder
- The tube is lowered open end first into which enters the tube to fill the chamber
- This can be further consolidated by applying force with the piston.

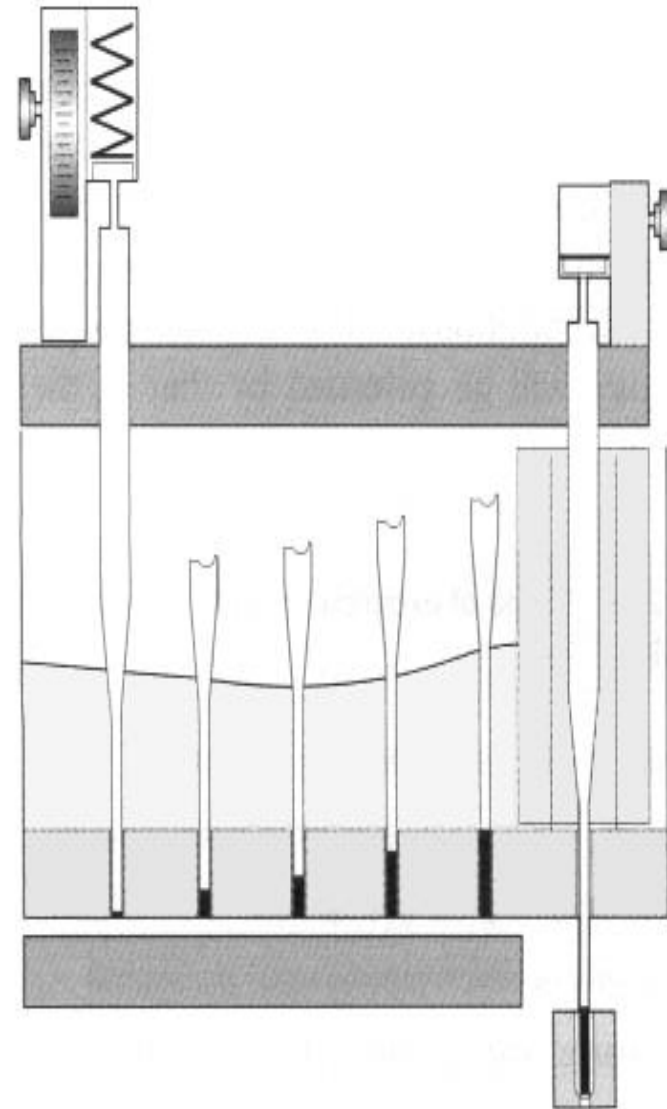


- **The assembly is then raised from the powder bed and positioned over the capsule body.**
- The piston is lowered, ejecting the powder plug into the capsule body.
- The weight of powder filled can be adjusted by altering the position of the piston inside the tube, i.e. increasing or decreasing the volume, and by changing the depth of the powder bed.

- This system is probably the most widely used.
- 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.

## 2. *Tamping finger and dosing disc*

- The dosing disc forms the bottom of revolving powder hopper.
- This disc has in it a series of sets of accurately drilled holes in which powder plugs are formed by several sets of tamping fingers – stainless steel rods that are lowered into them through the bed of powder.
- At each position the fingers push material into the holes, building up a plug before they index on to the next position.
- At the last position the finger pushes the plug through the disc into a capsule body.



- The machines that use **this system are all intermittent in motion.**
- Examples are
- the Hofliger and Karg, manufactured by Robert Bosch,
- The Shionogi Qualicaps F-80.

- The powder fill weight can be varied by
  1. the amount of insertion of the fingers into the disc,
  2. by changing the thickness of the dosing disc,
  3. by adjusting the amount of powder in the hopper.

# Pellet filling



- Preparations formulated to give modified-release patterns are often produced as granules or coated pellets.
- They are filled on an industrial scale using machines adapted from powder use.
- All have a dosing system based on a chamber with a volume that can easily be changed.
- **Pellets are not compressed in the process and may have to be held inside the measuring devices by mechanical means, e.g. either:**
  1. by inverting the dosator
  2. by applying a suction to the dosing tube.

- In calculating the weight of particles that can be filled into a capsule it is necessary to make an allowance for their size.
- Unlike powders, which have a much smaller size, they **cannot fill all the available space within the capsule** because of packing restrictions.
- The degree of this effect will be greater the smaller the capsule size and the larger the particle diameter.

# *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.**
- These **fall by gravity into the capsule bodies** as they pass underneath the hopper.
- **Most machines have a mechanical probe** that is inserted into the capsule to check that the correct number of tablets has been transferred.
- Tablets for capsule filling are:
  1. normally film coated to prevent dust,
  2. sized so that they can fall freely into the capsule body.

# *Semisolid and liquid filling*



- Liquids can easily be dosed into capsules using **volumetric pumps**.
- The problem after filling is to stop leakage from the closed capsule.
- This can be done in one of two ways, either
  - by formulation
  - by sealing of the capsule.

- **Semisolid mixtures are formulations** that are solid at ambient temperatures and can be liquefied for filling by either:
  1. heating thermosoftening mixtures:
    - after filling they cool and solidify
  2. by stirring thixotropic mixtures:
    - after filling they revert to their resting state in the capsule to form a solid plug.

- Both types of formulations are filled as liquids using volumetric pumps.
- **These formulations 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.

- **Non-aqueous liquids**, which are mobile at ambient temperatures, **require the capsules to be sealed after filling.**
- The industrially accepted method for this is to seal the cap and body together **by applying a gelatin solution around the centre of the capsule after it has been filled.**

When this has been dried it forms a **hermetic seal** that:

1. prevents liquid leakage,
2. contains odours inside the shell
3. significantly reduces oxygen permeation into the contents, protecting them from oxidation.

# FORMULATION

- All formulations for filling into capsules have to meet the same basic requirements:
  1. They must be capable of being filled uniformly to give a stable product.
  2. They must release their active contents in a form that is available for absorption by the patient.
  3. They must comply with the requirements of the Pharmacopoeias and regulatory authorities, e.g. dissolution tests.

# Powder formulation

- The majority of products for filling into capsules are formulated as powders.
- These are typically mixtures of the active ingredient together with a combination of different types of excipients.
- Excipients selected depend upon several factors:
  1. The properties of the active drug
  2. Its dose, solubility, particle size and shape
  3. The size of capsule to be used.

**Table 29.4 Types of excipient used in powder-filled capsules**

**Diluents**, which give plug-forming properties

**Lubricants**, which reduce powder to metal adhesion

**Glidants**, which improve powder flow

**Wetting agents**, which improve water penetration

**Disintegrants**, which produce disruption of the powder mass

**Stabilizers**, which improve product stability

- The **easier active compounds to formulate** are **low-dose potent** ones, which in the final formulation occupy only a small percentage of the total volume - <20% - and so the properties of the mixture will be governed by the excipients chosen,
- whereas those **compounds with a high unit dose**, e.g. 500 mg of an antibiotic, leave little free space within the capsule and **excipients must be chosen that exert their effect at low concentrations, <5%**, and the properties of the mixture will be governed by that of the active ingredient.

# Formulation for filling properties

- There are three main factors in powder formulation:
  1. Good flow, (using free-flowing diluent and glidant)
  2. No adhesion (using lubricant)
  3. Cohesion (plug-forming diluent).

- **The factor that contributes most to the uniform filling of capsules is good powder flow.**
  - This is because the powder bed, from which the dose is measured, needs to be **homogeneous** and **packed reproducibly** in order to achieve uniform fill weights.
  - Packing is assisted by mechanical devices on the filling machines.
1. Low-dose actives can be made to flow well by mixing them with **free-flowing diluents**, e.g. lactose.
- The diluent is chosen also for its **plug forming properties**: the most frequently used ones are **lactose, maize starch and microcrystalline cellulose.**

2. When space is limited then either **glidants**, which are materials that reduce interparticulate friction, such as **colloidal anhydrous silica**, or **lubricants**, which are materials that reduce powder to metal adhesion, e.g. **magnesium stearate**, are added, enabling the dosing devices to function efficiently.

Both of these types of material (**glidants** or **lubricants**) exert their effect by coating the surfaces of the other ingredients, and thus the mixing of these into the bulk powder has a significant effect on their functioning.

# Formulation for release of active ingredients

- The first stage in active ingredient release is **disintegration** of the capsule shell.
- When capsules are placed in a suitable liquid at body temperature, (37°C) the gelatin starts to dissolve and within 1 minute the shell will split, usually at the ends.
- With a properly formulated product the contents will start to empty out before all the gelatin has dissolved.
- **The official tests for disintegration and dissolution were originally designed for tablets.**
- Capsules have very different physical properties, and after the contents have emptied out the gelatin pieces remaining will adhere strongly to metal surfaces and may confuse the end-point of the test.

- The literature shows that the rate-controlling step in capsule disintegration and product release is the **formulation of the contents, which ideally should be hydrophilic and dispersible.**
- The factors that can be modified to make the active ingredients readily available depend upon their properties and those of any excipients being used.
- The **active ingredients** have a fixed set of physico-chemical properties which, except for **the particle size**, are out of the control of the formulator

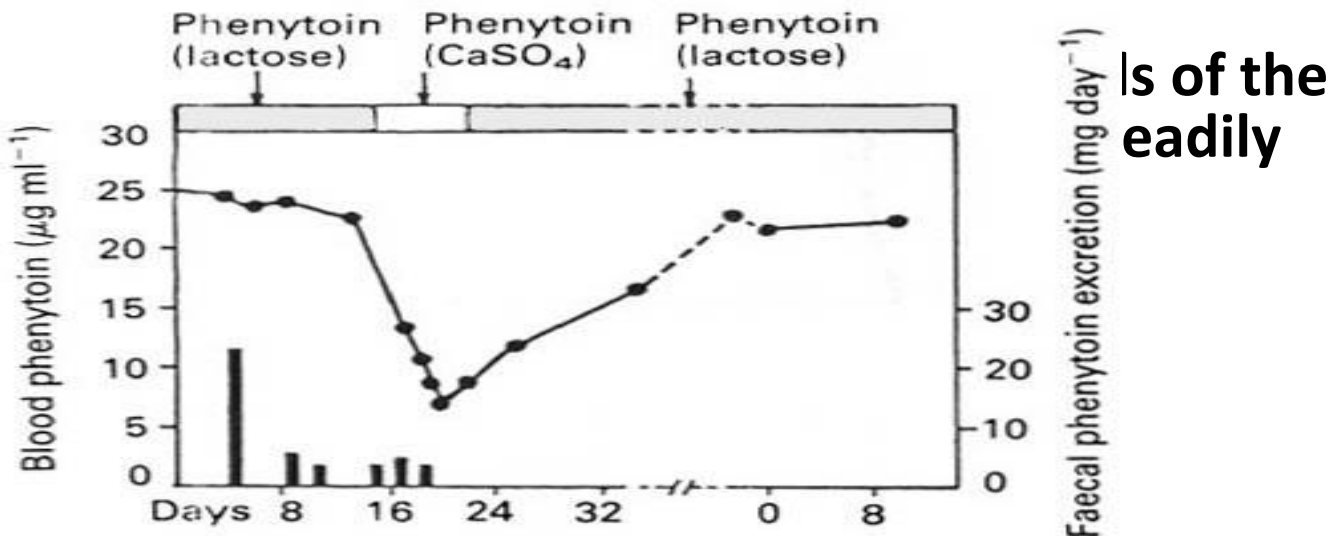
## particle size

- the particle size influences the rate of absorption for several compounds.
- the **dissolution rate is directly proportional to the surface area of the particles**: the smaller the particle the greater the relative surface area.
- However, this is not a panacea for formulation problems because small particles tend to **aggregate together and the effect is lost**.

- **Diluents** are the excipients that are usually present in the greatest concentration in a formulation.
- They were defined as inert materials added to a mixture to increase its bulk to a more manageable quantity.
- **Although they are relatively inert chemically, they do play a role in release.**
- The case that first demonstrated this happened in Australia in the late 1960s. A capsule was reformulated that contained diphenylhydantoin, which is used for the treatment of epilepsy and is

- The diluent used was changed from calcium sulfate to lactose.
- In the months following this change there was an upsurge in reports of side-effects similar to overdosing of product.
- It was demonstrated that the change had had a significant effect on the bioavailability of the active.

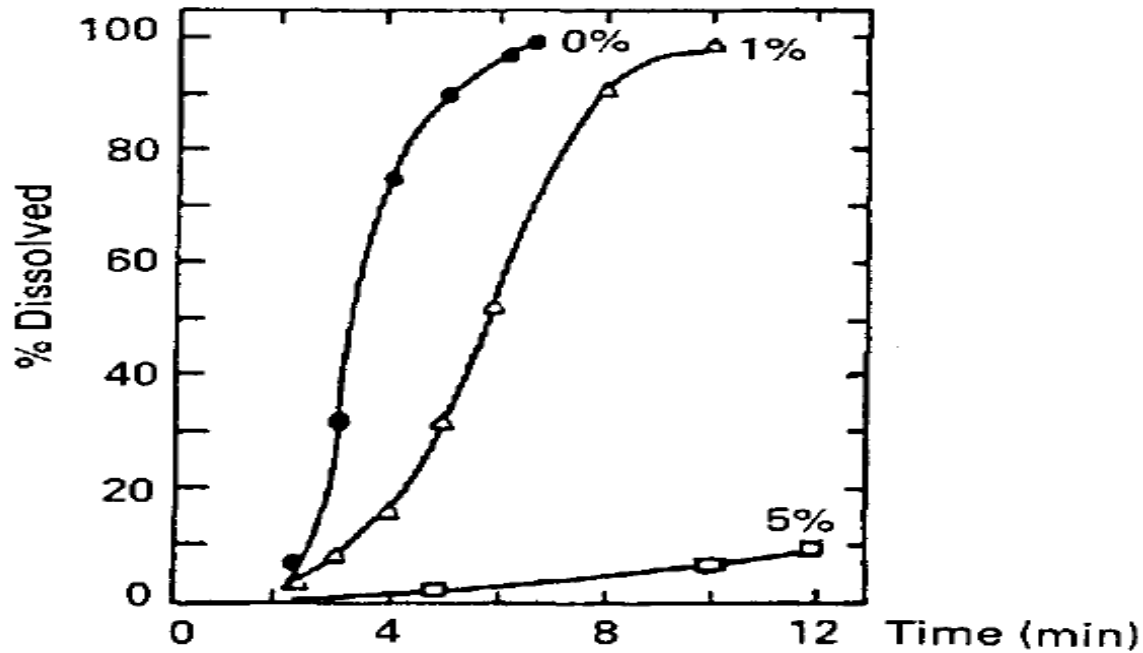
- The character of the drug, which is highly soluble



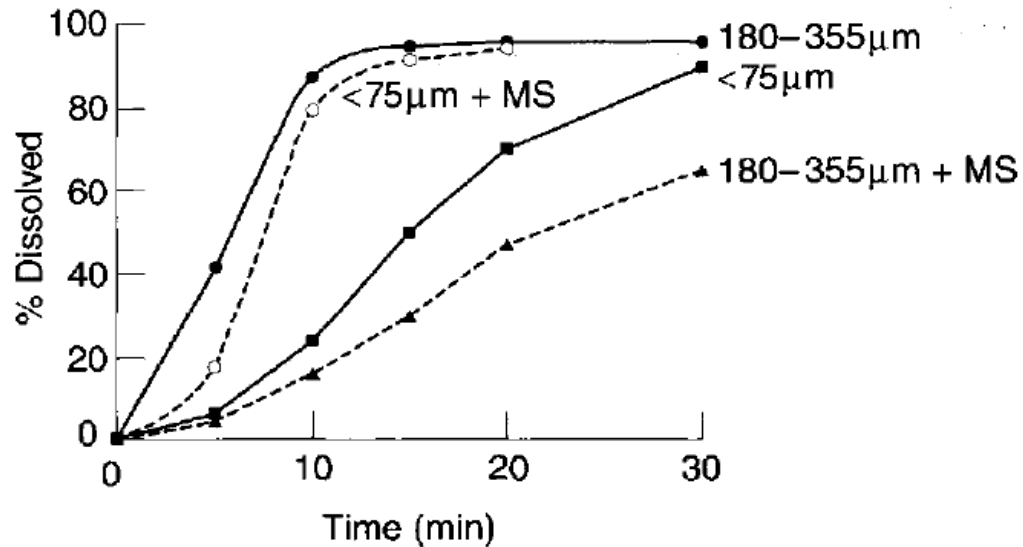
- The diluent used should be chosen in relationship to the solubility of the active.
- If a **soluble diluent** such as lactose is added to a poorly or insoluble compound it will make **the powder mass more hydrophilic**, enabling it to break up more readily on capsule shell disintegration.
- The converse is also true: **actives that are readily soluble** are best mixed **with insoluble diluents** such as starch or microcrystalline cellulose, because **they help the powder mass to break up without interfering with their solubility in the medium.**

# **lubricants and glidants**

- Some excipients, such as **lubricants and glidants**, are added to formulations to improve their filling properties, and these can sometimes have an effect on release.
- The important thing to avoid in formulations are materials that tend to **make the mass more hydrophobic**.
- The most commonly used lubricant for both encapsulation and tableting is **magnesium stearate**.



- the dissolution rate of chlordiazepoxide formulations with three levels of magnesium stearate, 0%, 1% and 5%:
- the dissolution rate was greatly reduced at the highest level of magnesium stearate, which they explained was due to the poor wetting of the powder mass.

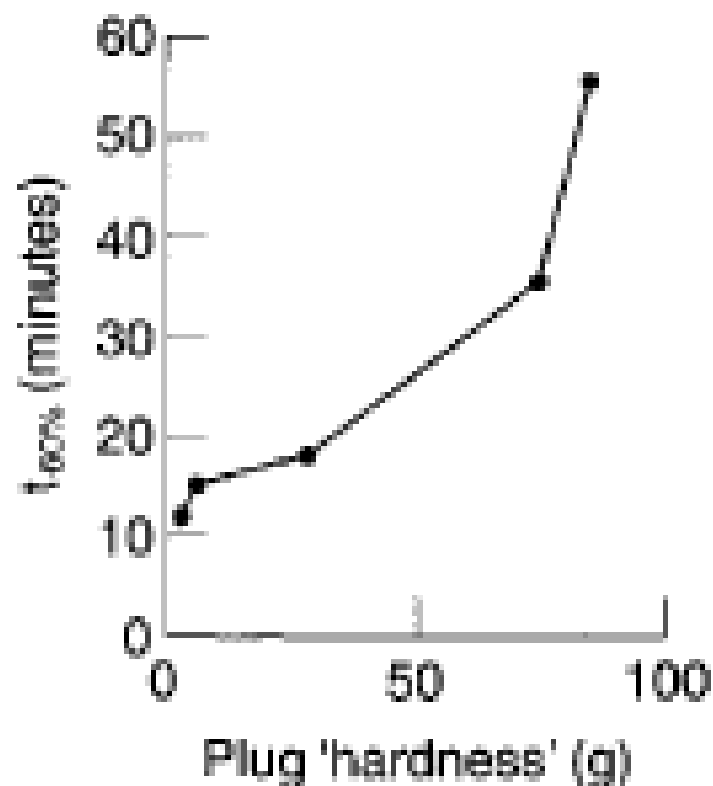
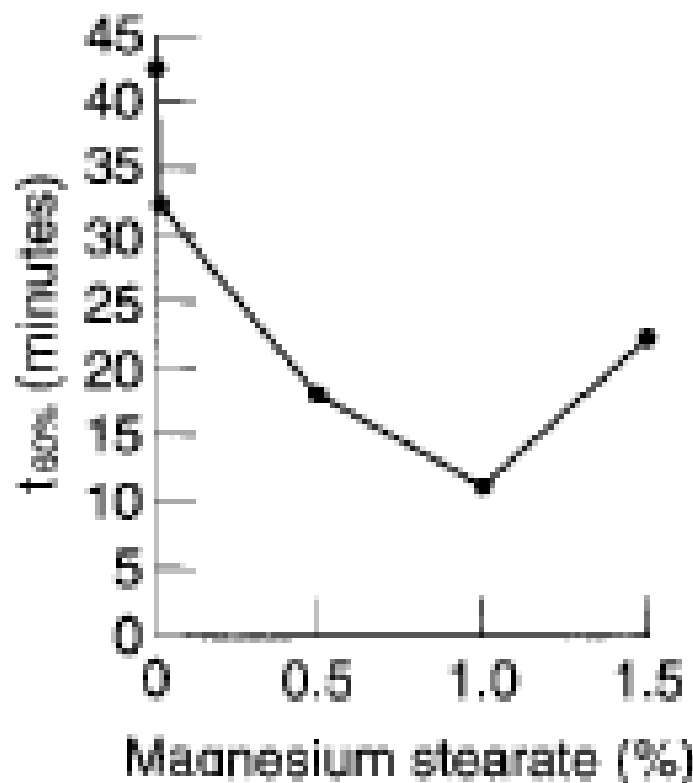


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- for the smaller particles (<75 μm) it increased the rate.
- This is because magnesium stearate reduces the cohesiveness of the small particles so that they spread more rapidly through the dissolution medium than the unlubricated material.

- hydrochlorothiazide, microcrystalline cellulose and various levels of magnesium stearate filled in capsules on an instrumented machine using the same compression force:
- as the concentration of magnesium stearate increased the dissolution rate improved to a maximum value at about 1.0% w/v, after which it fell.
- This was **correlated to the hardness of the powder plug**, which followed a similar pattern, **becoming softer - i.e. easier to break apart** - as the concentration of lubricant increased.
- **Above 1.0% the plug becomes too hydrophobic** for the increase in 'softness' to compensate for this.



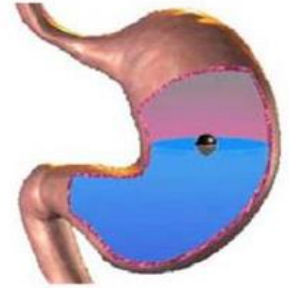
Effect of lubricant on in vitro release of hydrochlorothiazide (after Botzolakis et al 1982, with permission).

- **dissolution** testing for control purposes:
- For poorly soluble drugs the use of a soluble diluent together with **1% sodium lauryl sulphate**, a wetting agent, gave the best results.
- *'superdisintegrants'* have been introduced that either:
  1. swell many fold on absorbing water, e.g. sodium starch glycolate and croscarmellose,
  2. act as wicks, attracting water into the plug, e.g. crospovidone.
- These actions are sufficient to **help break up the capsule plug**.
- **The choice of disintegrant is dependent upon the solubility of the active and the diluent**, which governs whether either swelling or wicking is the main disruptive force required

- To summarize, the main factors in powder formulation release are:
  1. Active ingredient, optimum particle size
  2. Hydrophilic mass, relating solubility of active to excipients
  3. Dissolution aids:
    - wetting agent,
    - superdisintegrant

# Formulation for position of release

- Many products are formulated to release their contents in the stomach.
- However, this may not always be the best place for the absorption of the active ingredient, and capsule formulation can be readily manipulated to release their contents at various positions along the gastrointestinal tract.
- **In the stomach** the release of the active ingredient can be modified in a number of ways.
- 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, **releasing a continuous flow of solution into the intestines**

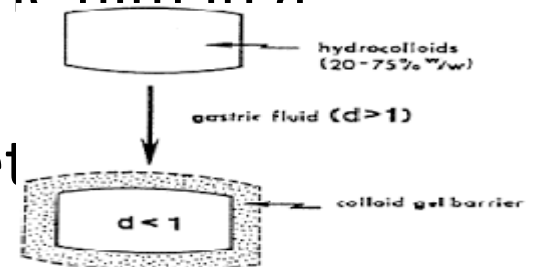


- **'Floating capsules'** have been made which contain various **hydrophilic polymers**, such as **methylcellulose**, that swell on contact with water and form a mass that can float on the gastric liquids.

- Some compounds are destroyed at acid pHs, and an enteric product can be made by either:

1. coating the filled capsule with an enteric film in a similar manner to a tablet,

2. or by formulating the contents as pellet them with an enteric polymer.



## **Prolonged release dosage forms:**

- **multiparticulates are better than monolith systems because they will be released in a stream from the stomach when the capsule shell disintegrates, and will not be retained for variable periods of time as would a monolithic product.**
- **They also avoid the risk of the dose being dumped at one point, which could cause problems of local gastric irritation.**

- Products can be formulated to give a **prolonged** release and filled into a capsule that is **enteric** coated,
- e.g. Colpermin (Pharmacia Upjohn), an enteric coated capsule filled with a prolonged-release formulation of peppermint oil.
- The capsule disintegrates and contents **slowly release** as a **smooth muscle relaxant** throughout the remainder of the tract.



- Products have also been prepared that have been coated with polymers that are **enteric and are soluble only at higher pHs, 6-7.**
- Currently many new chemical entities are **proteins or polypeptides**, and to make an oral dosage form it is necessary to deliver them **to the colon**, thereby avoiding the proteolytic enzymes in the stomach and small intestine.
- The release mechanisms for these capsules are **based on specific colonic conditions**, e.g. **coatings that are disrupted by colon-specific enzymes** or by pressure

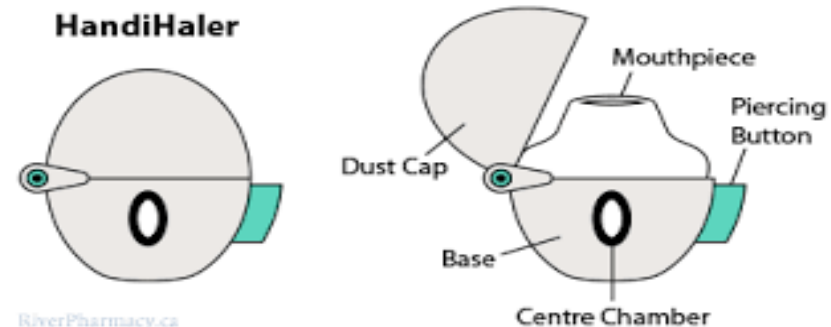
# Capsules for inhalation

The **active ingredient**, which is **micronized**, is filled into the capsule either 'as is' or dispersed on a carrier particle.

- The weight filled into a capsule is much lower than for other types of product, typically less than 25 mg.
- These formulations are filled on automatic machines that have **microdosing devices**, and the product is administered by using a **special inhaler**.



- A capsule is placed in the device and the powder is released either
  1. by the halves of the capsule being forced apart
  2. or by the capsule wall being punctured by sharp pins.
- The device is **breath actuated**.
- When the patient breathes in a turbulent airflow dislodges the carrier particles (if present) and the active powder is inhaled into the lungs.
- The system has the added advantage that the **patient can see how many capsules remaining**



**End of Lecture**