PRODUCT FORMS AND DEVELOPMENT

Compressed tables, wet granulation-dry granulation or slugging-direct compression-tablet presses, coating of tablets, capsules sustained action dosage forms-parental solutions-oral liquids-injections-ointments-Topical Application, Preservation, analytical methods and test for various drugs and pharmaceuticals, Labeling, PackingPacking Techniques, Quality Management, GMP.

Tablets

A **tablet** is a pharmaceutical dosage form. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose.

Excipients

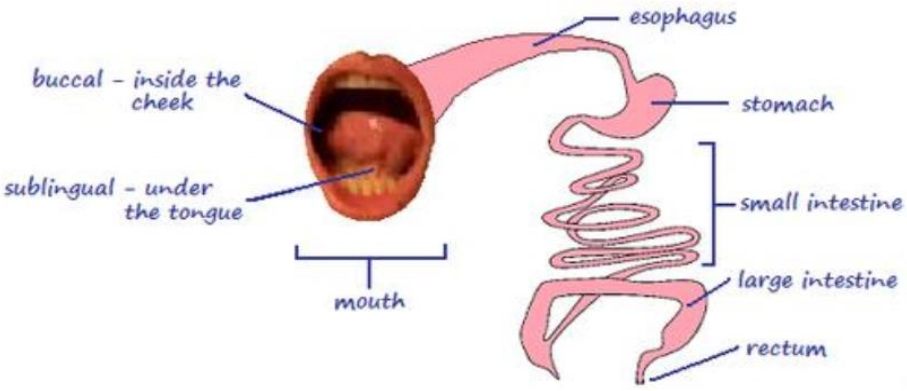
The **excipients** can include **diluents, binders or granulating agents, glidants (flow aids) and lubricants** to ensure efficient tabletting; disintegrants to promote tablet break-up in the digestive tract; **sweeteners or flavours** to enhance taste; and **pigments** to make the tablets visually attractive.

Coating the tablet

A **polymer coating** is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance.

Compressed tablets

The compressed tablet is the most popular dosage form in use today. About two-thirds of all prescriptions are dispensed as solid dosage forms, and half of these are compressed tablets. A tablet can be formulated to deliver an accurate dosage to a specific site; it is usually taken orally, but can be administered **sublingually, buccally, rectally or intravaginally.**

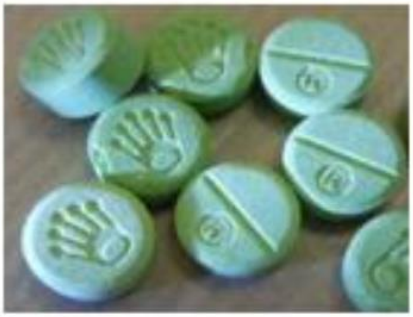


Forms of tablets

The tablet is just one of the many forms that an oral drug can take such as syrups, elixirs, suspensions, and emulsions. Medicinal tablets were originally made in the shape of a

disk of whatever color their components determined, but are now made in many shapes and colors to help distinguish different medicines.

Stamping of tablets



Tablets are often stamped with **symbols, letters,** and **numbers**, which enable them to be identified.

Size of tablets

Sizes of tablets to be swallowed range from a **few millimeters** to about a **centimeter.**

Shape of tablets

Some tablets are in the shape of capsules, and are called **"caplets".**

Other products are manufactured in the form of tablets which are designed to dissolve or disintegrate; e.g. cleaning and deodorizing products.

Medicinal tablets and capsules are often called **"pills",** though originally, "pill" referred specifically to a **soft mass rolled into a ball shape,** rather than a compressed powder.

Compressed tablets

A tablet prepared, usually as a large-scale production, by means of great pressure; most compressed tablets consist of the active ingredient and a diluent, binder, disintegrator, and lubricant.

Tablet formulation

In the tablet-pressing process, it is important that all ingredients be fairly dry, powdered or granular, somewhat uniform in particle size, and freely flowing. Mixed particle sized powders segregate during manufacturing operations due to different densities, which can result in tablets with

poor drug or **active pharmaceutical ingredient (API)** content uniformity but granulation should prevent this. Content uniformity ensures that the same API dose is delivered with each tablet.

Some **APIs** may be tableted as pure substances, but this is rarely the case; most formulations include excipients. Normally, a pharmacologically inactive ingredient (excipient) termed a *binder* is added to help hold the tablet together and give it strength.

Binders / binding agent

A wide variety of binders may be used, some common ones including **lactose, dibasic calcium phosphate, sucrose, corn (maize) starch, microcrystalline cellulose, povidone polyvinylpyrrolidone** and **modified cellulose** (for example hydroxypropyl methylcellulose and hydroxyethylcellulose).

Often, an ingredient is also needed to act as a **disintegrant** to aid tablet dispersion once swallowed, releasing the API for absorption. Some binders, such as **starch** and **cellulose**, are also excellent disintegrants.

Advantages and disadvantages

Tablets are **simple** and convenient to use. They provide an accurately measured dosage of the active ingredient in a convenient portable package, and can be designed to **protect unstable medications** or **disguise unpalatable ingredients. Colored coatings, embossed markings** and **printing** can be used to aid **tablet recognition.** Manufacturing processes and techniques can provide tablets special properties, for example, sustained release or fast dissolving formulations.

Some drugs may be unsuitable for administration by the oral route. For example, **protein drugs** such as **insulin** may be **denatured** by **stomach acids.** Such drugs **cannot be made** into **tablets.**

Some drugs may be **deactivated** by the **liver when they are carried there from the gastrointestinal tract** by the **hepatic portal vein** (the "first pass effect"), **making them unsuitable** for **oral use.**

Drugs which can be taken **sublingually** are absorbed through the **oral mucosae,** so that they **bypass the liver** and are **less susceptible to the first pass effect.** The **oral bioavailability** of some drugs may be **low** due to **poor absorption** from the **gastrointestinal tract.** Such drugs may need to be given in **very high doses** or **by injection**.

For drugs that need to have **rapid onset,** or that have severe side effects, the **oral route may**

not be suitable. For example **salbutamol,** used to treat problems in the **pulmonary system,** can have effects on the **heart** and **circulation** if taken **orally;** these effects are greatly reduced by **inhaling smaller doses direct to the required site of action.**

A proportion of the population have difficulties swallowing tablets either because they just don't like taking them or because their medical condition makes it difficult for them (dysphagia, vomiting). In such instances it may be better to consider **alternative dosage form** or **administration route.**

Granulation

Granulation is the act or **process of forming or crystallizing into grains.**

Granules typically have a size range between **0.2 to 4.0 mm** depending on their subsequent use.

Pharmaceutical industry

- In the pharmaceutical industry, granulation refers to the act or process in which **primary powder particles are made to adhere to form larger, multiparticle entities called granules.**
- It is the process of collecting particles together by **creating bonds** between them. Bonds are formed by **compression or by using a binding agent.** Granulation is extensively used in the manufacturing of **tablets and pellets** (or spheroids).
- The granulation process combines one or more powder particles and forms a granule that will allow tableting or spheronization process to be within required limits. This way predictable and repeatable process is possible and quality tablets or pellets can be produced using tabletting or spheronization equipment.

Purpose of granulation

- Granulation is carried out for various reasons, one of those is to **prevent the segregation of the constituents of powder mix.** Segregation is due to differences in the **size** or **density** of the **component** of the mix.

- Normally, the **smaller and/or denser particles** tend to **concentrate** at the **base** of the container with the **larger and/or less dense ones** on the **top.** An ideal granulation will contain all the constituents of the mix in the **correct proportion in each granule and segregation of granules will not occur.**

- Many powders, because of **their small size, irregular shape** or **surface characteristics**, are **cohesive** and **do not flow well.** Granules produced from such a cohesive system will be **larger** and **more isodiametric**, both factors contributing to **improved flow properties.**

- Some powders are **difficult to compact even if a readily compactable adhesive is included in the mix,** but granules of the same powders are often more easily compacted. This is associated with the **distribution of the adhesive** within the granule and is a function of the method employed to produce the granule.

For example, if one were to make tablets from **granulated sugar versus powdered sugar,** powdered sugar would be difficult to compress into a tablet and granulated sugar would be easy to compress. **Powdered sugar's small particles have poor flow and compression characteristics.** These small particles would have to be **compressed very slowly** for a **long period of time** to make a worthwhile tablet. Unless the powdered sugar is granulated, it could not efficiently be made into a tablet that has good tablet characteristics such as uniform content or consistent hardness.

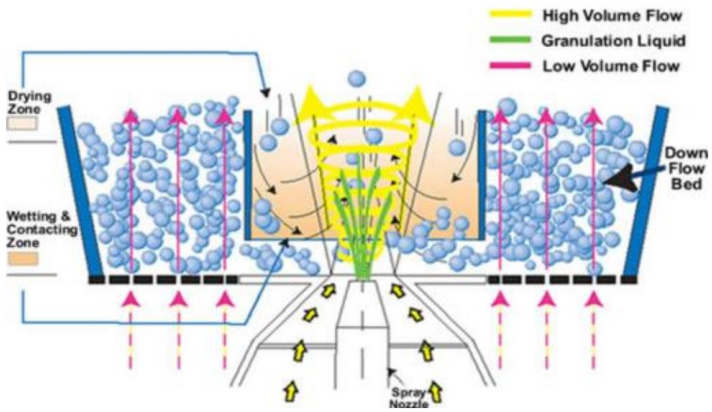
Granulation techniques

In pharmaceutical industry, two types of granulation technologies are employed, namely,

1. Wet granulation and
2. Dry granulation.

Wet granulation

In wet granulation, granules are formed by the addition of a **granulation liquid** onto a **powder bed** which is under the influence of an **impeller** (in a High shear granulator, screws (in a twin screw granulator) or air (in a fluidized bed granulator). The agitation resulting in the system along with the wetting of the components within the formulation results in the **aggregation of the primary powder particles to produce wet granules**.



The granulation liquid (fluid) contains a **solvent** which must be **volatile** so that it can be removed by **drying,** and be **non-toxic.** Typical liquids include **water, ethanol** and **isopropanol** either **alone** or in **combination.** The liquid solution can be either **aqueous based** or **solvent based.** Aqueous solutions have the advantage of being **safer** to deal with than solvents.

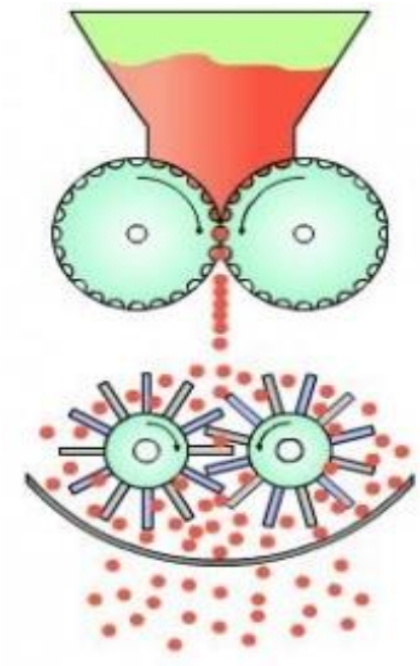
Water mixed into the powders can **form bonds** between powder particles that are strong enough to lock them together. However, once the **water dries,** the powders may **fall** apart. Therefore, water may not be strong enough to create and hold a bond. In such instances, a liquid solution that includes a **binder** (pharmaceutical glue) is required.

Povidone, which is a **polyvinyl pyrrolidone (PVP),** is one of the most commonly used pharmaceutical binders. **PVP is dissolved in water or solvent** and added to the process. When PVP and a solvent/water are mixed with powders, PVP forms a bond with the powders during the process, and the solvent/water evaporates (dries). Once the solvent/water has been dried and the powders have formed a more densely held mass, then the granulation is milled. This process results in the formation of granules.

The process can be very simple or very complex depending on the characteristics of the powders, the final objective of tablet making, and the equipment that is available. In the traditional wet granulation method the wet mass is forced through a sieve to produce wet granules, which is subsequently dried.

Dry granulation

The dry granulation process is used to form granules **without using a liquid solution** because the product to be granulated may be **sensitive to moisture and heat.**



Forming granules without moisture requires **compacting** and **densifying the powders.** In this process the primary powder particles are aggregated under **high pressure. Sweying granulator** or **high shear mixer-granulator** can be used for the dry granulation.

Dry granulation can be conducted under two processes; either a **large tablet (slug)** is produced in a **heavy duty tabletting press** or the **powder is squeezed** between **two counter-rotating rollers** to produce a **continuous sheet** or **ribbon of materials** (roller compactor, commonly referred to as a chilsonator).

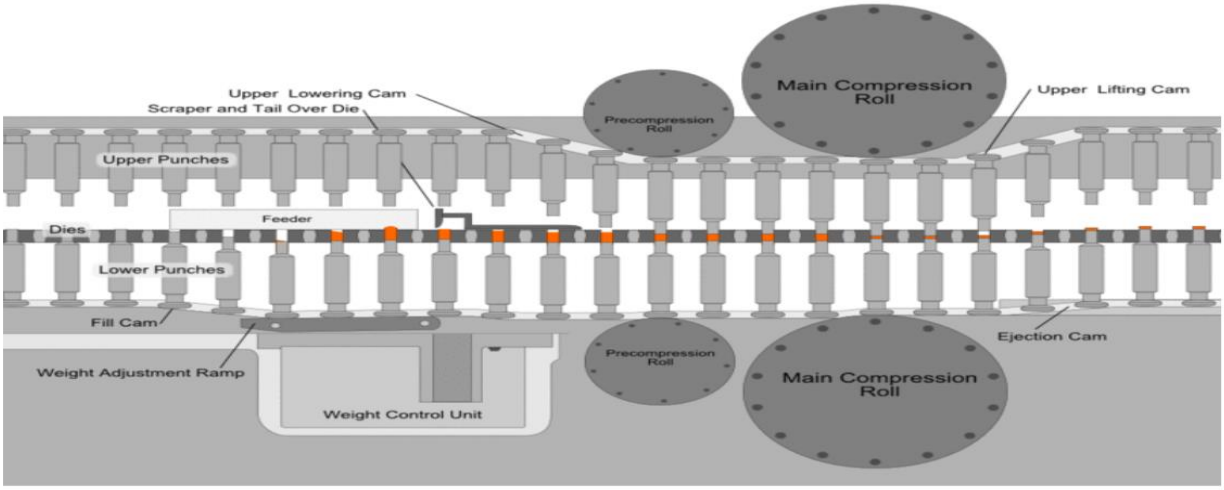
When a tablet press is used for dry granulation, the **powders may not possess** enough **natural flow to feed the product uniformly** into the die cavity, resulting in **varying degrees of densification.** The roller compactor (granulator-compactor) uses an **auger-feed system** that will consistently **deliver powder uniformly** between two pressure rollers. The powders are compacted into a ribbon or small pellets between these rollers and milled through a low-shear mill. When the product is compacted properly, then it can be passed through a mill and final blend before tablet compression.

Tablet Presses

A tablet press is a **mechanical device** that **compresses powder** into **tablets** of **uniform size** and **weight.** A press can be used to manufacture tablets of a wide variety of materials, including **pharmaceuticals, illicit drugs such as MDMA, cleaning products, and cosmetics**.

To form a tablet, the granulated material must be metered into a cavity formed by two punches and a die, and then the punches must be pressed together with great force to fuse the material together.

Working principle of tablet press



- A tablet is formed by the combined pressing action of **two punches** and a **die.** In the first step of a typical operation, the **bottom punch** is **lowered** in the **die creating** a **cavity** into which the **granulated feedstock** is **fed.**
- The exact depth of the lower punch can be precisely controlled to meter the amount of powder that fills the cavity. The **excess** is **scraped** from the **top** of the **die**, and the lower punch is drawn down and **temporarily covered** to **prevent spillage.**

- Then, the **upper punch** is **brought down into contact** with the **powder** as the **cover** is **removed.** The force of compression is delivered by **high pressure compression rolls** which fuse the **granulated material together** into a **hard tablet.**

- After compression, the **lower punch** is **raised** to **eject** the **tablet.**

Types of tablet presses

1. Single-punch press and
2. Rotary tablet press

- Most high speed tablet presses take the form of a rotating turret that holds any number of punches. As they rotate around the turret, the punches come into contact with cams which control the punch's vertical position.

- Punches and dies are usually custom made for each application, and can be made in a wide variety of sizes, shapes, and can be customized with manufacturer codes and scoring lines to make tablets easier to break.

- Depending on tablet size, shape, material, and press configuration, a typical modern press can produce from **250,000 to over 1,000,000 tablets an hour.**

Single-punch press

Rotary tablet press

Note

Die

A **die** is a specialized too used in manufacturing industries to cut or shape material using a press.

MDMA

3,4-methylenedioxy-*N*-methylamphetamine is an empathogenic drug of the phenethylamine and amphetamine classes of drugs.

The terms **empathogen** and **entactogen** are used to describe a **class of psychoactive drugs** that produce **distinctive emotional** and **social effects** similar to those of MDMA (ecstasy).

MDMA can induce,

Euphoria,
A sense of intimacy with others,
Diminished anxiety and
Mild psychedelia.

Many studies, particularly in the fields of psychology and cognitive therapy, have suggested MDMA has therapeutic benefits and facilitates therapy sessions in certain individuals, a practice for which it had been formally used in the past. Clinical trials are now testing the therapeutic potential of MDMA for post-traumatic stress disorder, anxiety associated with terminal cancer and addiction.

Euphoria

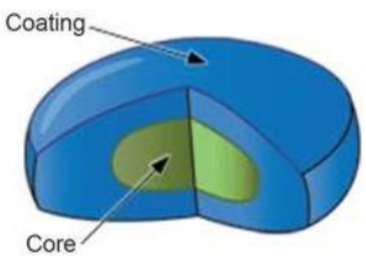
Euphoria is medically recognized as a mental and emotional condition in which a person experiences intense feelings of well-being, elation, happiness, excitement, and joy.

psychedelia

Psychedelic states are an array of experiences including changes of perception such ashallucinations, synesthesia, altered states of awareness or focused consciousness, variation in thought patterns, trance or hypnotic states, mysticalstates, and other mind alterations.

Coating of tablets

Many tablets today are coated after being pressed. Although sugar-coating was popular in the past, the process has many drawbacks.



Modern tablet coatings

Modern tablet coatings are **polymer and polysaccharide based,** with **plasticizers** (**dispersants** are additives that increase the plasticity or fluidity of a material). The dominant applications are for plastics, especially **polyvinyl chloride (PVC)** and pigments included.

Nature of tablet coatings

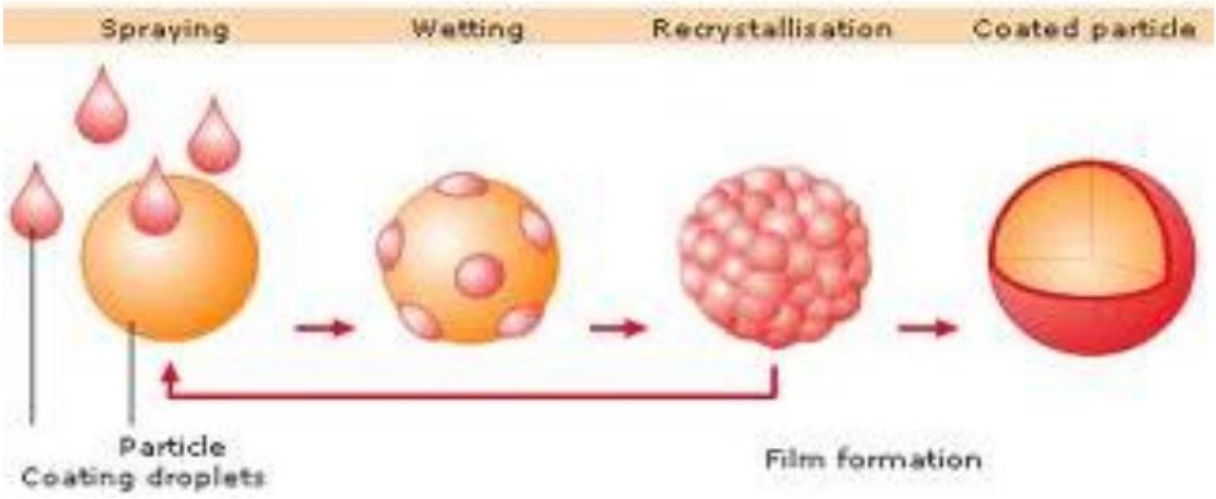
Tablet coatings must be **stable** and **strong** enough to survive the handling of the tablet, **must not** make tablets **stick together** during the coating process, and must **follow** the fine contours of **embossed characters** or **logos** on tablets.

Merits of tablet coatings

Coatings are necessary for tablets that have an **unpleasant taste**, and a **smoother finish** makes large tablets easier to swallow. Tablet coatings are also useful to **extend** the **shelf-life** of components that are **sensitive to moisture or oxidation. Special coatings** (for example with pearlescent effects) can enhance **brand recognition**.

Enteric coatings

- If the active ingredient of a tablet is **sensitive to acid**, or is **irritant** to the **stomach** lining, an **enteric coating** can be used, which is resistant to stomach acid, and dissolves in the less acidic area of the intestines.
- **Enteric coatings** are also used for medicines that can be negatively affected by taking a long time to reach the small intestine, where they are absorbed.
- Coatings are often chosen to control the rate of dissolution of the drug in the gastrointestinal tract. Some drugs will be absorbed better at different points in the digestive system.
- If the highest percentage of **absorption** of a **drug** takes place in the **stomach**, a coating that **dissolves quickly** and **easily in acid** will be selected.
- If the rate of absorption is best in the **large intestine or colon,** then a **coating** that is **acid resistant** and **dissolves slowly** would be used to ensure it reached that point before dispersing.



Tablet coating machines

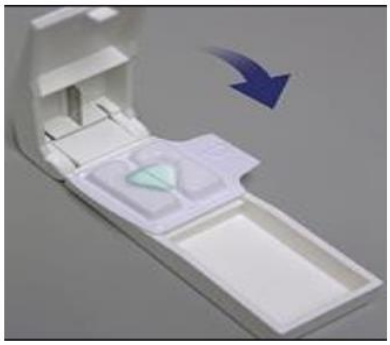
There are two types of coating machines used in the pharmaceutical industry:

1. Coating pans and
2. Automatic coaters.

Coating pans are used mostly for **sugar coating of pellets. Automatic coaters** are used for **all kinds of coatings;** they can be equipped with remote control panel, dehumidifier, dust collectors. The **explosion-proof design** is required for **alcohol containing coatings.**

Pill splitters

- It is sometimes necessary to split tablets into halves or quarters. Tablets are easier to break accurately if scored, but there are devices called pill-splitters which cut unscored and scored tablets.
- Tablets with special coatings (for example enteric coatings or controlled-release coatings) should not be broken before use, as this will expose the tablet core to the digestive juices, circumventing the intended delayed-release effect.



Scored and unscored tablets

A **scored tablet** is any tablet that has an indentation where it looks like the tablet **has** been **pre-cut**. An **unscored tablet** has **no pre-cut line**.

Capsules

In the manufacture of pharmaceuticals, **encapsulation** refers to a range of techniques used to enclose medicines in a relatively stable shell known as a **capsule**, allowing them to, for example, be taken orally or be used as suppositories.

Types of capsules

The two main types of capsules are:

- **Hard-shelled capsules,** which are typically made using gelatin and contain dry, powdered ingredients or miniature pellets made by, e.g. processes of extrusion or spheronisation. These are made in two halves: a lower-diameter "body" that is filled and then sealed using a higher-diameter "cape".

- **Soft-shelled capsules**, primarily used for oils and for active ingredients that are dissolved or suspended in oil.

Both of these classes of capsules are made from aqueous solutions of gelling agents like:

- **Animal protein** mainly **gelatin;**
- **Plant polysaccharides** or **their derivatives** like **carrageenans** and **modified forms** of **starch** and **cellulose.**

Ingredients added to capsule

Other ingredients can be added to the gelling agent solution like

- Plasticizers such as glycerin and/or sorbitol to decrease the capsule's hardness,
- Coloring Agents,
- Preservatives,
- Disintegrants,
- Lubricants and
- Surface treatment

Since their inception, capsules have been viewed by consumers as the most efficient method of taking medication. For this reason, producers of drugs such as OTC analgesics wanting to emphasize the strength of their product developed the "caplet" or "capsule-shaped tablet" in order to tie this positive association to more efficiently-produced tablet pills. After the 1982 Tylenol tampering murders, capsules experienced a minor fall in popularity as tablets were seen as more resistant to tampering.

Single piece gel encapsulation

In **1834, Mothes and Dublanc were granted a patent** for a method to produce a **single-piece gelatin capsule** that was sealed with a **drop of gelatin solution.** They used individual **iron moulds** for their process, filling the capsules individually with a medicine dropper.

Later on, methods were developed that used **sets of plates with pockets to form the capsules.** Although some companies still use this method, the equipment is not produced commercially any more.

All **modern soft-gel encapsulation** uses variations of a process developed by **R.P. Scherer in 1933.** His innovation was to use a **rotary die** to produce the capsules, with the filling taking place by **blow molding.** This method **reduced wastage**, and was the **first process** to yield **capsules** with **highly repeatable dosage.**

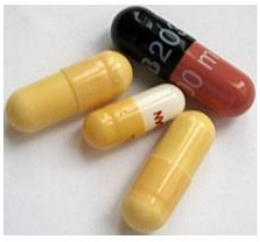
The current owner of the **RPS cherer technology** is **Catalent Pharma Solutions, the world's largest manufacturer of prescription pharmaceutical softgels.**

Softgels

- Softgels can be an effective delivery system for **oral drugs,** especially **poorly soluble drugs.**
- This is because the fill can contain **liquid ingredients** that help **increase solubility or permeability** of the **drug across the membranes** in the **body.**
- Liquid ingredients **are difficult** to include in any **other solid dosage** form such as a tablet. Softgels are also highly suited to **potent drugs** (for example, where the dose is **<100 µg**), where the highly reproducible filling process helps ensure each softgel has the same drug content, and because the **operators** are **not exposed** to any **drug dust** during the manufacturing process.

In **1949,** the **Lederle Laboratories division** of the **American Cyanamid Company** developed the **"Accogel"** process, allowing powders to be **accurately filled** into **soft gelatin capsules.**

Two-piece gel encapsulation



- **James Murdock** of **London patented the two-piece telescoping gelatin capsule in 1847**.
- The capsules are made in **two parts by dipping metal pins** in the **gelling agent solution**.

- Two-piece gelatin capsule machinery is manufactured by **R&J Engineering Corporation of Canada.** The capsules are supplied as closed units to the pharmaceutical manufacturer.
- Before use, the two halves are separated, the capsule is filled with powder or more normally pellets made by the process of **Extrusion & Spheronization** (either by placing a compressed slug of powder into one half of the capsule, or by filling one half of the capsule with loose powder) and the other half of the capsule is pressed on.
- With the compressed slug method, weight varies less between capsules. However, the machinery required to manufacture them is more complex.
- The powder or spheroids inside the capsule contains the active ingredient(s) and any excipients, such as binders, disintegrants, fillers, glidant, and preservatives.

Manufacturing materials

- **Gelatin capsules**, informally called **gel caps** or **gelcaps**, are composed of **gelatin** manufactured from the **collagen** of **animal skin** or **bone.**
- **Vegetable capsules** are composed of **hypromellose,** a **polymer formulated** from **cellulose.**

Manufacturing equipment

- The process of encapsulation of **hard gelatin capsules** could be done on **manual, semi-automatic and automatic machines.**
- **Softgels** are filled at the same time as they are produced and sealed on the **rotary die of fully automatic machine.**

Dosage forms preferred by the public to consume

Dosage Forms	Appears easier to swallow (%)	First choice (%)
Clear oval softgel	89	71
Clear oblong softgel	42	6
Gelatin-coated round tablet	23	5
2-piece hard-shell capsule	19	5
Opaque oblong softgel	18	3
Oblong compressed tablet	8	4
Round compressed tablet	7	5
Gelatin-coated oblong tablet	7	2

Dosage forms

Dosage forms (also called **unit doses**) are essentially pharmaceutical products in the form in which they are marketed for use, typically involving a mixture of active drug components and nondrug components (excipients), along with other non-reusable material that may not be considered either ingredient or packaging (such as a capsule shell, for example).

Parenteral nutrition

Parenteral nutrition (PN) is feeding a person intravenously, bypassing the usual process of eating and digestion. The person receives nutritional formulae that contain nutrients such as glucose, amino acids, lipids and added vitamins and dietary minerals.

It is called **total parenteral nutrition** (TPN) or **total nutrient admixture** (TNA) when no significant nutrition is obtained by other routes. It may be called **peripheral parenteral nutrition** (PPN) when administered through vein access in a limb, rather than through a central vein.

Mechanical pumps to administer TPN

- A mechanical pump under computer control is used to dispense the TPN fluid. Pumps are available that allow TPN administration at home, usually with the preparation and attachment by a family member. These pumps operate on an external dispensing line, part of a single-use dispensing cassette.

- Connection of the dispensing line to the patient is via a valve on a semi-permanent attached venous port whose closure is displaced by a connection on the dispensing line. Preparation, attachment, and valve replacement require care in sanitation and sterile techniques at specific locations.

- The use of a rechargeable battery and a portable component pack allows a convenient household mobility for many patients during administration periods, these being typically from twelve to sixteen hours a day.

Indications

- Total parenteral nutrition (TPN) is provided when the gastrointestinal tract is nonfunctional because of an interruption in its continuity (it is blocked, or has a leak - a fistula) or because its absorptive capacity is impaired.

- It has been used for comatose patients, although enteral feeding is usually preferable, and less prone to complications.
- Parenteral nutrition is used to prevent malnutrition in patients who are unable to obtain adequate nutrients by oral or enteral routes.

Gastrointestinal disorders

TPN may be the only feasible option for providing nutrition to patients who **do not** have a **functioning gastrointestinal tract** or who have **disorders requiring complete bowel rest, including bowel obstruction, short bowel syndrome, Gastroschisis, prolonged diarrhea** regardless of its cause, **high-output fistula, very severe Crohn's disease** or **ulcerative colitis**, and **certain pediatric GI disorders** including congenital **GI anomalies** and **necrotizing enterocolitis.**

Duration

Short-term PN may be used if a person's **digestive system has shut down** (for instance by peritonitis), and they are at a low enough weight to cause concerns about nutrition during an **extended hospital stay.**

Long-term PN is occasionally used to treat people suffering the extended consequences of an **accident, surgery,** or **digestive disorder.** PN has **extended** the **life** of **children born** with **nonexistent** or **severely deformed organs.**

Complications

TPN fully by-passes the GI tract and normal methods of nutrient absorption. Possible complications, which may be significant, are listed below.

Infection

TPN requires a chronic IV access for the solution to run through, and the most common complication is infection of this catheter. Infection is a common cause of death in these patients, with a mortality rate of approximately 15% per infection, and death usually results from septic shock.

Blood clots

Chronic IV access leaves a foreign body in the vascular system, and blood clots on this IV line are common. Death can result from pulmonary embolism wherein a clot that starts on the IV line but breaks off and goes into the lungs.

Fatty liver and liver failure

Fatty liver is usually a more long term complication of TPN, though over a long enough course it is fairly common. The pathogenesis is due to using linoleic acid (an omega-6 fatty acid component of soybean oil) as a major source of calories.

Other complications

Total parenteral nutrition increases the risk of **acute cholecystitis** due to complete disuse of gastrointestinal tract, which may result in bile stasis in the gallbladder. Other potential **hepatobiliary dysfunctions** include **steatosis, steatohepatitis, cholestasis,** and **cholelithiasis.**

Six percent of patients on TPN longer than 3 weeks and 100% of patients on TPN longer than 13 weeks develop biliary sludge. The formation of sludge is the result of stasis due to lack of enteric stimulation and is not due to changes in bile composition.

Gallbladder sludge disappears after 4 weeks of normal oral diet. Administration of exogenous cholecystokinin (CCK) or stimulation of endogenous CCK by periodic pulse of large amounts of amino acids has been shown to help prevent sludge formation. These therapies are not routinely recommended. Such complications are suggested to be the main reason for mortality in people requiring long-term total parenteral nutrition, such as in short bowel syndrome.

In newborn infants with short bowel syndrome with less than 10% of expected intestinal length, thereby being dependent upon total parenteral nutrition, 5 year survival is approximately 20%.

Complications are either related to catheter insertion, or metabolic, including refeeding syndrome. Catheter complications include pneumothorax, accidental arterial puncture, and catheter-related sepsis.

The complication rate at the time of insertion should be less than 5%.[16] Catheter-related infections may be minimised by appropriate choice of catheter and insertion technique. Metabolic complications include the refeeding syndrome characterized by hypokalemia, hypophosphatemia and hypomagnesemia.

Hyperglycemia is common at the start of therapy, but can be treated with insulin added to the TPN solution. Hypoglycaemia is likely to occur with abrupt cessation of TPN. Liver dysfunction can be limited to a reversible cholestatic jaundice and to fatty infiltration (demonstrated by elevated transaminases).

Severe hepatic dysfunction is a rare complication. Overall, patients receiving TPN have a higher rate of infectious complications. This can be related to hyperglycemia.

Solutions

- The nutrient solution consists of **water** and **electrolytes; glucose, amino acids, and lipids; essential vitamins, minerals and trace elements** are added or given separately.
- Previously **lipid emulsions** were given separately but it is becoming more common for a **"three-in-one"** solution of **glucose, proteins,** and **lipids** to be administered.

Emulsifiers

Only a limited number of emulsifiers is commonly regarded as safe to use for parenteral administration, of which the most important is lecithin. **Lecithin** can be **biodegraded** and **metabolized,** since it is an **integral part** of **biological membranes,** making it virtually **non-toxic.**

Other emulsifiers can only be **excreted** via the **kidneys, creating a toxic load.** The emulsifier of choice for most fat emulsions used for parenteral nutrition is a highly purified egg lecithin, due to its **low toxicity** and **complete integration** with **cell membranes.**

Total parenteral nutrition

Examples of total parenteral nutrition solutions			
Substance	**Normal patient**	**High stress**	**Fluid-restricted**
Amino acids	85 g	128 g	75 g
Dextrose	250 g	350 g	250 g
Lipids	100 g	100 g	50 g
Na^+	150 mEq	155 mEq	80 mEq
K^+	80 mEq	80 mEq	40 mEq
Ca^{2+}	360 mg	360 mg	180 mg
Mg^{2+}	240 mg	240 mg	120 mg
Acetate	72 mEq	226 mEq	134 mEq
Cl^-	143 mEq	145 mEq	70 mEq
P	310 mg	465 mg	233 mg
MVI-12	10 mL	10 mL	10 mL
Trace elements	5 mL	5 mL	5 mL

Solutions for total parenteral nutrition may be customized to individual patient requirements, or standardized solutions may be used. The use of standardized parenteral nutrition solutions is cost effective and may provide better control of serum electrolytes.

Ideally each patient is assessed individually before commencing on parenteral nutrition, and a team consisting of specialised doctors, nurses, clinical pharmacists and Registered Dietitians evaluate the patient's individual data and decide what PN formula to use and at what infusion rate.

For **energy only, intravenous sugar solutions** with **dextrose** or **glucose** are generally used. This is **not considered** to be parenteral nutrition as it **does not prevent malnutrition** when used on its own. Standardized solutions may also differ between developers. The solution for normal patients may be given both centrally and peripherally.

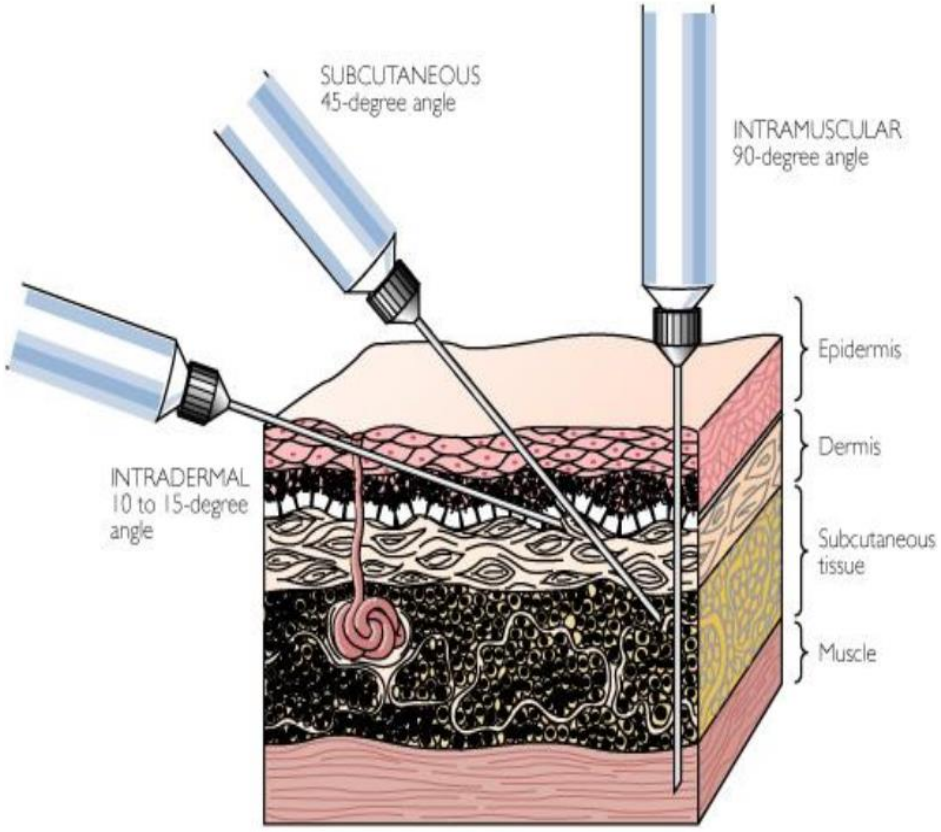
Individual components

Individual nutrient components may be added to more precisely adjust the body contents of it. That individual nutrient may, if possible, **be infused individually**, or it may be **injected** into a **bag** of **nutrient solution** or **intravenous fluids** that is given to the patient.

Administration of individual components may be more hazardous than administration of pre-mixed solutions such as those used in total parenteral nutrition, because the latter are generally already balanced in regard to e.g. osmolarity and ability to infuse peripherally. For example, incorrect **IV administration** of concentrated **potassium** can be **lethal,** but this is **not a danger** if the **potassium** is **mixed** in TPN solution and **diluted.**

Vitamins may be added to a bulk premixed nutrient immediately before administration, typically in two doses, one fat soluble, the other water soluble, this since the additional vitamins can promote spoilage of stored product.

Route of administration of parenteral solutions



1. Intradermal (Id) – into dermis
2. Intramuscular (Im) – into muscle
3. Intraosseous (Io) - injecting directly into the marrow of a bone
4. Intraperitoneal (Ip) – into peritoneum
5. **Intravenous (Iv) – into vein**
6. Subcutaneous (Sc) – into subcutaneous tissue
7. Intrathecal (It) injection into the spinal column