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REVIEW ARTICLE ON CAPSULE & MANUFACTURING OF CAPSULES

Mr. Hrishikesh K. Puri*1, Mr. Abhishek S. Pawar*2, Mr. Sangmeshwar H. Bargal*3

*1,2Student, Department Of Pharmaceutical Chemistry M. Pharm, ICOP, Nanded, Maharashtra, India.

*3Student, Department Of Pharmacology M. Pharm, ICOP, Nanded, Maharashtra, India.

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ABSTRACT

In this review article we study on the capsule (its defined as unit solid dosage form of medicaments available as small containers (shells) made up of gelatin enclosing accurately measured drug substances) manufacturing of capsule, Different types of capsules, components used in formation, test performed, Advantages & Disadvantages etc.

In pharmacology, a drug is a chemical substance, typically of known structure, which, when administered to a living organism, produces a biological effect. A pharmaceutical drug, also called a medication or medicine, is a chemical substance used to treat, cure, prevent, or diagnose a disease or to promote well-being.

Keywords: Capsules, Types, Basic Components, Manufacturing, Quality Control Tests, Size & Dose Chart, Advantages & Disadvantages Of Capsule, Active Pharmaceutical Ingredient (API), Hydroxypropyl Methyl Cellulose (HPMC), Polyvinyl Alcohol (PVA) Capsules, Transmissible Spongiform Encephalopathy (TSE), Good Manufacturing Practice (GMP).

I. INTRODUCTION

Capsules are defined as unit solid dosage form of medicaments available as small containers (shells) made up of gelatin enclosing accurately measured drug substances. The term capsule is derived from the Latin word capsula, meaning a small container. Capsule occupy a significant position in the drug development. They are often believed as the primary oral dosage form because of their manufacturing process compared to other dosage forms. Gelatin has the property of disintegrating when it comes in contact with water, thereby releasing the medicament completely. Instead, of gelatin, denatured gelatin, methyl cellulose and polyvinyl alcohol can also be used to make the capsule shells.There are mainly two types of capsules which are: Hard-shelled capsules, which contain dry, powdered ingredients or miniature pellets made by e.g. processes of extrusion or spheronization. These are made in two halves: a smaller-diameter “body” that is filled and then sealed using a larger-diameter “cap”. Both of these classes of capsules are made from aqueous solutions of gelling agents, such as animal protein (mainly gelatin) or plant polysaccharides or their derivatives (such as carrageenans and modified forms of starch and cellulose). Other ingredients can be added to the gelling agent solution including plasticizers such as glycerin or sorbitol to decrease the capsule's hardness.[1]

Capsules are solid dosage forms in which the drug or a mixture of drugs with or without excipients is enclosed in Hard Gelatin Capsule Shells, in soft, soluble shells of gelatin, or in hard or soft shells of any other suitable material, of various shapes and capacities. They usually contain a single dose of active ingredient(s) and are intended for oral administration.

The use of capsules goes back to the early days of pharmacy, and since these early days capsules have evolved significantly to meet the current needs of the patient and pharmaceutical industry. Some of the early developments in capsule technology occurred as pharmacy evolved from dispensing compounded medication to the dispensing of manufactured products; during this change there were numerous advances in gelatin, capsule shell design and high speed manufacturing equipment. Currently the pharmaceutical industry is undergoing a sea change as the blockbuster drugs become harder and harder to find, more of the value of a drug product comes from a dosage form with advanced delivery capabilities that can improve therapeutic outcomes. For example, capsule filling technologies have been developed for the manufacture of multiparticulate delivery systems, multiple dosage form systems such as a tablet in a capsule, combination products and delivery systems with multiphasic release rates. In addition, capsules have always played an important role in the drug development process because hand filling or semiautomatic filling capsule formulations have minimal requirements and can be quickly developed. Given this context, the chapter will discuss the capsule dosage form in the drug development process starting with a discussion of gelatin, the

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different types of capsules shells, formulation and manufacturing. Also, we will discuss specialty capsules and capsule fills.

Capsules are solid dosage forms in which the drug and such appropriate pharmaceutical adjuncts, such as fillers, antioxidants, flow enhancers, and surfactants are enclosed in a gelatin shell. A "hard" gelatin capsule is composed of gelatin, glycerin, sugar, and water, whereas a "soft" gelatin capsule is composed of only gelatin, glycerin, and water. Capsules vary in size from 000 to 5. As the number increases the capsule size becomes smaller. The sizes provide a convenient container for the amount of drug to be administered and can be of distinctive shapes and colors when produced commercially. Generally drugs are released from capsules faster than from tablets because the powdered drug has not been compressed and can dissolve at faster rates. The gelatin (a protein) is acted upon rapidly by the enzymes of the GI tract, which permits gastric juices to penetrate and reach the contents to promote dissolution.

Traditionally drugs were obtained through extraction from medicinal plants, but more recently also by organic synthesis. Pharmaceutical drugs may be used for a limited duration, or on a regular basis for chronic disorders.

Capsules are a unique dosage form with a long history of use in pharmacy. The original patent was issued in 1834 to a Parisian pharmacist, Joseph Gérard Dublanc, and pharmacy student, François Achille Barnabé Mothès, for the invention and manufacture of gelatin capsules. The term capsule is derived from the Latin word capsula, meaning a small container.

The basic idea of a capsule is to enclose the drug or active pharmaceutical ingredient (API) in an odorless, tasteless, elegant, easy-to-swallow, and easy-to-fill shell. Today there are two main types of capsules: the hard gelatin capsule and the soft gelatin capsule, often called softshells. The hard gelatin capsule can be used for dry fills such as powder, liquids, and semisolids, while the softshell is exclusively used for liquids and semisolids. The typically capsule shell is made of gelatin, but in recent years, there have been a variety of gelatin alternatives introduced to the market. The vast majority of capsule applications are for oral delivery of an API; however, there are specialty applications such as capsules that can be loaded into dry-powdered inhalers, add reagents as part of a diagnostic kit, and occasionally as a suppository base with glycerin.[2] The majority of capsules are filled with a dry powder; however, semisolids, nonaqueous liquids, and other dosage forms such as beads, mini tablets, and even mini capsules can be filled into a capsule shell. These applications will be discussed. In terms of production, capsules are one of the most flexible forms. They can be made one a time in a compounding pharmacy, in small-scale production for clinical studies, and all the way up to commercial production with machines that can make hundreds of thousands of capsules per hour. Given the importance capsules have in the pharmaceutical industry.

From the patient perspective, capsules have many advantages, making them among the most popular dosage forms on the market. Generally speaking, most patients consider capsule shells to be smooth, slippery, and easier to swallow than tablets[2].

II. TYPES OF CAPSULES

There exist various capsule types in scholarly articles, they are; the soft gelatin and hard gelatin capsules, Hydroxypropylmethyl cellulose (HPMC) capsules, polyvinyl chloride (PVC) capsules, starch capsules. These can be summarized as the gelatinous and non gelatinous capsules. Gelatin capsules This category of capsules is basically made from gelatin; they can either be soft or hard gelatin capsules. Soft gelatin capsules General aspects Originally developed in the 19th century to mask unpleasant taste and odour of drug substances, soft gelatin capsules are used in many applications, for pharmaceutical, health and nutrition products, cosmetic applications and even recreational products such as paint balls.

There exist various capsule types in scholarly articles, they are; the soft gelatin and hard gelatin capsules, Hydroxypropylmethyl cellulose (HPMC) capsules, Polyvinyl alcohol (PVA) capsules, starch capsules. These can be summarized as the gelatinous and non gelatinous capsules.

1] Soft gelatin capsule 2] Hard gelatin capsule

2.1 Soft Gelatine Capsule

Originally developed in the 19th century to mask unpleasant taste and odour of drug substances, soft gelatin capsules are used in many applications, for pharmaceutical, health and nutrition products, cosmetic

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applications and even recreational products such as paint balls. In the pharmaceutical field soft gelatin capsules are increasingly being chosen for strategic reasons (line extension), technological issues (high content uniformity of low-dose drugs), safety aspects (reduced operator and environmental contamination with highly potent or cytotoxic compounds) and consumer preference (easy to swallow). The most interesting advances have recently been made in the area of developing liquid and semisolid formulations in a soft gelatin capsule to addr particular bio-performance issues, namely increased bioavailability and decreased plasma variability by improved solubility and absorption-enhancing techniques.[4]

Fig no 1: Soft gelatine capsule.

2.2 Hard gelatine capsule

The majority of capsule products is made of hard gelatine capsules. Hard gelatine capsules are made of two shells: the capsule body and a shorter cap. The cap fits tightly over the open end of the capsule body. The basic hard gelatine capsule shells are made from mixtures of gelatine, sugar, and water. They are clear, colourless, and essentially tasteless.

Hard gelatine capsule shells are fabricated and supplied empty to the pharmaceutical industry by shell suppliers and are then filled in a separate operation. During the capsule filling unit operation, the body is filled with the drug substances and the shell is closed by bringing the body and the cap together [5].

Two-piece capsules have been used for almost a century in the pharmaceutical field, and the gelatine has been adopted as the main material of these capsules due to its excellent characteristic as a gelatinize. However, gelatine is one of the proteins derived from animals; therefore, it is unstable from a chemical viewpoint and has a risk of transmissible spongiform encephalopathy (TSE) [6].

Fig no 2: Hard gelatine capsule

Special types of hard gelatine and soft gelatine capsules-

Altered Release –

The rate of release of capsule contents can be varied according to the nature of the drug and the capsule excipients. If the drug is water-soluble and a fast release is desired, the excipients should be hydrophilic and neutral. If a slow release of water-soluble drug is desired, hydrophobic excipients will reduce the rate of drug dissolution. If the drug is insoluble in water, hydrophilic excipients will provide a faster release; hydrophobic and neutral excipients will slow its release. A very rapid release of the capsule contents can be obtained by piercing holes in the capsule to allow faster penetration by fluids in the gastrointestinal tract, or by adding a small quantity of sodium bicarbonate and citric acid to assist in opening the capsule by the evolution of carbon dioxide.[7]

Coating capsules-

Coatings have been applied extemporaneously to enhance appearance and conceal taste, as well as to prevent release of the medication in the stomach (enteric coated products). Most coatings of capsules require

considerable formulation skill and quality control equipment found in manufacturing facilities. The capsules can be coated to delay the release of the active drug until it reaches a selected portion of the gastrointestinal tract.[8]

Sustained release capsules-

The traditional method of taking a dose three or four times a day leads to periods of excess and deficiency in blood concentration of the medicament. One way of correcting this and, at the same time, reducing the number of doses per day, is to administer a capsule containing numerous coated pellets that release the drug successively over a long period. The finely powdered drug is first converted into pellets, usually by attaching it to sugar granules with an adhesive. The pellets are then treated with protective coatings that delay release of the drug, each batch receiving a different thickness. The batches are mixed thoroughly and suitable doses are filled into capsules. For example, a mixture might contain 30 percent of uncoated pellets, for immediate release of drug, 30 percent each of coated pellets that release at 4 hours and 8 hours, and 10 percent of neutral pellets, used solely to fill the capsule. Each batch may be coloured differently to simplify identification and facilitate control of mixing.[9]

Liquid filled hard gelatine capsules-

It is generally accepted that many of today's NCE‟s (New Chemical Entities) are poorly water soluble and the classical methods, such as reduction in particle size are no longer adequate to achieve satisfactory drug adsorption from a solid oral dosage form. One of the most promising strategies to deliver these insoluble compounds is using dissolved systems like using lipids, liquids or semi-solids to formulate new products. Two-piece hard-shell capsules are one of the most logical approaches when choosing the best dosage form to deliver these new liquid formulations.[9]

Non-Gelatine Capsules-

Traditionally, gelatine has been used almost exclusively as shell-forming material of capsules. In the recent advancements, non-gelatine capsules have been discovered, which do not contain gelatine as its shell forming agent. Under this category of capsules are the HPMC, PVA and starch capsules.

HPMC Capsules-

The commercial and nutraceutical markets have driven the development of alternative forming materials for traditional capsule shell material gelatine according to need. Formulator requires a non-cross-linking capsule that is well characterized, compatible with current excipients and assays, and has a gelatine-like dissolution. Marketing prefers a capsule that meets the dietary and cultural needs of patients. Manufacturing needs a capsule with gelatine-like performance that can run on existing filling equipment. Regulatory wants a capsule polymer that has a proven safety record and wide regulatory acceptance. Clinicians need to be certain that patient compliance is assured.[10]

PVA Capsules-

International Patent Application WO 9 755 3723 describes the preferable use of polyvinyl alcohol (PVA) and optional use of some other materials, all being film forming polymers that lack the gelling properties that are necessary for soft capsule production using the conventional rotary die process. The invention therefore provides the use of preformed rolls of nearly water-free plasticized films that may be fed to a rotary die encapsulation unit for soft capsule production. To render the film material more flexible and to assist the seam formation at temperatures depending on the film composition, the films are partially spray solvated prior to encapsulation. PVA films according to this invention may be composed of 70–75% w/w PVA, 10–15% w/w glycerol and 5–10% w/w starch, with a sealing temperature of 140–180°C, depending on the degree of solvation. PVA as an optional gelatine substitute has the advantage of being less hygroscopic, thus leading to soft capsule shells that are less sensitive to moisture than soft gelatine capsule shell.[11]

Starch Capsules-

It can be formulated with conventional plasticizers such as glycerol, sorbitol, etc. (10–60% w/w of dry shell) and water to form a molten mass that can be extruded to set within less than 20 secs producing mechanically strong, elastic films on temperature-controlled casting drums. Sealing may be performed at temperatures

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between 25 and 80°C, by a fusion process comparable to the one observed with soft gelatine capsules. After drying, mechanically strong and highly elastic products can be achieved.[12]

Prototype capsules with lipophilic fill formulations are shiny with high appearance stability on storage. The capsule shells do not show crosslinking and exhibit a greater mechanical stability than soft gelatine shells when exposed to elevated humidity and temperature, i.e. even under hot and humid storage conditions they may not become sticky. Formulation approaches with hydrophilic fills are expected to be as challenging as for soft gelatine capsules. Oxygen permeability is comparable to gelatinase shells. The dissolution mechanism is completely different to the one of a soft gelatine capsule. On contact with an enzyme-free aqueous medium at 37°C, the capsule shell only swells, at a rate and to an extent depending on the type and concentration of electrolytes present. The capsule content may be released when the shell bursts at its point of lowest resistance, i.e. at the seams. Under in vivo conditions, capsule shell dissolution may be induced by enzymatic degradation. International Patent Application WO 0 137 81730 describes the formation of soft capsules from a potato starch (45–80% w/w), with a specific molecular weight distribution and amylopectin content, together with a conventional plasticizer such as glycerol (12% w/w), a glidant and a disintegrant.[13]

Basic components of capsules.

A] Gelatine:

The capsule shell of both hard and soft capsule is made principally of gelatine blends and may contain plasticizers, water and small number of certified dyes, opacifying agent, flavouring, colouring agents and preservative and medicament to achieve desired effects.

Gelatine's chemical, physical, and physiological properties make it an idea substance for the capsulation of pharmaceutical products.[14]

Gelatine is a heterogeneous product derived by irreversible hydrolytic extraction of treated animal collagen, and as such, it never occurs naturally.

- **Chemical compositions of gelatine-**

Gelatines normally contain about 15% of water & 1-4% of inorganic salts.

Gelatine, like its precursor collogen contains;

Table no 1: Composition of gelatine

1.Carbons	15%
2.Hydrogen	26%
3.Nitrogen	18%
4.Oxygen	25%
5.Sulfer	0.1%
6.Phosphurous	...

- **Properties of gelatine-**

1) Gelling & water binding properties
2) Surface properties
3) Microencapsulation
4) Bioactive properties of hydrolysate
5) Protective colloidal action
6) Amphoteric properties
7) Antimicrobial properties.

- **Sources of gelatine-**

a) Cattle bone
b) Cows
c) Pigs
d) Fish

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e) Mammalian bones & hide

- **Used of gelatine-**

Manufacturing of capsule
Thickener
Source of protein
A great source of dietary collogen
It is good for skin tightening
Benefits hair, nails, joints, digestive system.

B] Plasticizes:

Plasticizers are added to gelatine to reduce the rigidity of the polymer and make it more pliable. Common examples of plasticizers are glycerine and polyhydric alcohol. Water is also a good plasticizer and is naturally present in the gelatine.[15]

C] Water:

Water usually accounts for 30-40% of the wet gel formulation and its presence is important both during the manufacturing process (to facilitate manufacture) and in the finished product to ensure that the capsule is flexible. The desirable water content of the gelatine solution used to produce a soft gelatine capsule shell depends on the viscosity of the specific grade of gelatine used. It usually ranges between 0.7 and 1.3 parts of water to each part of dry gelatine.

D] Colourants:

Most frequently, hard gelatine capsules are coloured to enhance the aesthetic properties and also to act as a means of identifying the product. Colorants used must meet the regulatory requirements of those countries where the product will be sold. Examples of commonly used capsule colourants include synthetic dyes such as azo dyes and xanthene dyes. Iron oxide pigments are also used. The colour of the capsule shell is generally chosen to be darker than that of its contents.

E] Opacifying agents:

Opacifiers (e.g., titanium dioxide) may be included to make clear gelatine opaque. Opaques capsules may be employed to provide protection against light or to conceal the contents. it may add to the shell for visual appeal and/or reducing the penetration of light for the encapsulation of a photosensitive drug.

F] Preservatives:

Preservatives are often added to prevent the growth of bacteria and mould in the gelatine solution during storage. Examples of commonly used as preservatives include potassium sorbate, and methyl, ethyl, and propyl hydroxybenzoate. Preservatives (often parabens esters) were formerly added to hard capsules as an in-process aid in order to prevent microbiological contamination during manufacture. Manufacturers operating their plants to Good Manufacturing Practice (GMP) guidelines no longer use them. In the finished capsules, the moisture levels, 12–16% w/ v, are such that the water activity will not support bacterial growth because the moisture is too strongly bound to the gelatine molecule.

G] Other excipients:

Other, infrequently, used excipients can include flavouring agents and sweeteners to improve palatability. Acid-resistant polymers are used to impart enteric release characteristics. They can also be used to formulate chewable soft gelatine capsules. A chelating agent, such as ethylene diamine tetrameric acid (EDTA), can be added to prevent chemical degradation of oxidation sensitive drugs catalysed by free metals in gelatine, such as iron.

III. MANUFACTURING OF CAPSULES

3.1 Manufacturing of Soft Gelatine Capsule –

Soft gels are manufactured using the following methods

1. Plate process
2. Rotary die process
3. Reciprocating die process

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4. Alcogel process
5. Seamless process.

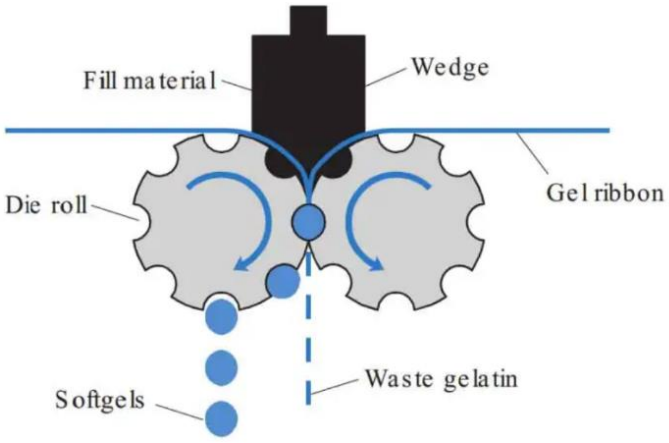
1) Plate process -

This is the oldest commercial process used in the manufacture of soft gelatine capsules. In this process, a warmed sheet of plain or coloured plasticized gelatine is placed over a die plate having a number of depression or moulds or numerous die pockets. By applying vacuum, the sheet is drawn into these depressions or pockets to form capsule wells. The capsule wells are then filled with medication-containing liquid. A second sheet of gelatine is carefully placed on top of the filled wells followed by the top plate of the mould. Pressure is then applied to the combined plate to form, seal and cut the capsules into individual units. This method is used for small scale preparation of soft gelatine capsules and capsules formed generally, had one flat side. The major problems with this method of manufacturing soft gels were the lack of dosage uniformity, high manufacturing losses, and its labour-/cost-intensiveness. This equipment is no longer available.[16]

2) Rotary Die Process –

Most soft gelatine capsules are prepared by the rotary die process, a method developed and perfected in 1933 by Robert P. Scherer. This process almost eliminated all the problems associated with the plate process and produced soft gelatine capsules with improved uniformity and high standards of accuracy.

In this process, two plasticized gelatine ribbons (prepared in the rotary-die machine) are continuously and simultaneously fed with the liquid, semiliquid or paste fill between the rollers of the rotary die mechanism. The forced injection of the feed material between the two ribbons causes the gelatine to swell into the left- and right-hand die pockets which govern the size and shape of the soft gels as they converge. As the die rolls rotate, the convergence of the matching dies pockets hermetically seals and cuts out the filled capsules.



Softgel formation mechanism (rotary die mechanism)

Fig no 3: Soft gel formation mechanism

The precise and extremely low clearance of the rotating parts demands continuous lubrication of the machine to avoid even a slight build-up. The lubrication oil should, therefore, be a GRAS (generally recognized as safe) material. Immediately after manufacture, the formed capsules automatically undergo volatile solvent washing to remove any traces of lubricating oil from the exterior of the capsules. The capsules are then conveyed to a drying station and dried on trays, either in air or under vacuum, to equilibrium moisture content to about 6 – 10 % with forced conditioned air of 20% – 30% relative humidity at 21°C–24°C. The drying technique may proceed with an infrared drying step to speed up the process. After drying is complete, capsules are then be transferred to the inspection station and sampled for release, after performing the required quality control tests for sizes sorting, colour sorting, and packaging. Depending on the manufacturer, additional finishing operations such as off-line print can be performed.[17]

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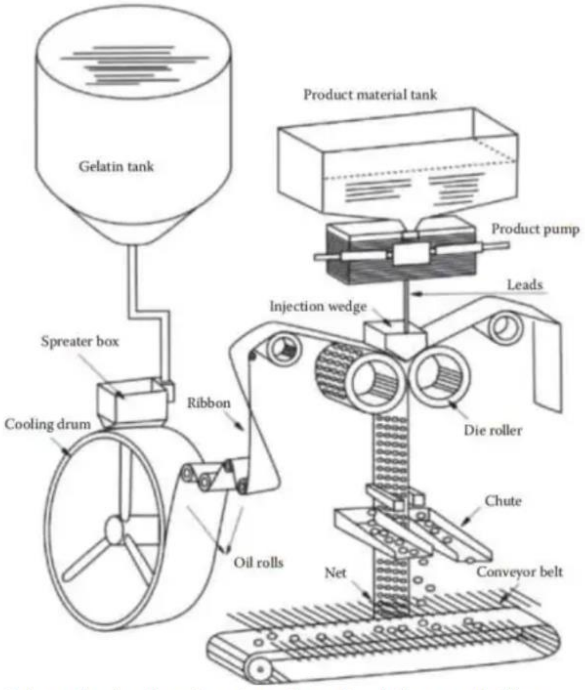

Fig no 4: Soft gelatine capsule filler

3) Reciprocating Die Process (Norton Capsule Machine) -

This continuous soft gelatine capsule processing technology was developed by Norton Company in 1949. This process is similar to rotary process in that ribbons of gelatine are formed and used to encapsulate the fill, but it differs in the actual encapsulating process. The gelatine ribbons are fed between a set of vertical dies that continually open and close to form rows of pockets in the gelatine ribbons. These pockets are filled with the medication and are sealed, shaped, and cut out of the film as they progress through the machinery. As the capsules are cut from the ribbons, they fall into a cooled solvent bath that prevents the capsules from adhering to one another.[18]

4**) Alcogel Process** -

Although the rotary die process and reciprocating die process were capable of producing soft gelatine capsules containing oily liquids and pastes, Lederle Laboratories in 1949 developed alcogel process, a continuous process that produces soft gelatine capsules containing powders and granules. The process involves a measuring roll that holds the fill formulation in its cavities under the vacuum and rotates directly above the elasticized sheet of the gelatine ribbon. The ribbon is drawn into the capsule cavities of the capsule die roll by vacuum. The measuring rolls empty the fill material into the capsule-shaped gelatine cavities on the die roll. The die roll then converges with the rotating sealing roll covered with another sheet of elasticized gelatine. The convergence of two rotary rolls creates pressure to seal and cut the formed capsules

5) Seamless process (Bubble Method) -

The seamless technique produces one-piece soft gelatine capsules without the use of dies. The process is often referred to as a bubble method that creates seamless, spherical soft gelatine capsules called pearl. In this process, a molten gelatine stream flows though the outer nozzle of a concentric tube at a constant rate, and the medicated liquid formulation is dispensed through the inner orifice by means of a precision metering pump. The emerging stream is broken up into an intermittent but steady flow of uniform-sized by a pulsating mechanism, leading to the formation of droplets enveloped in molten gelatine. The formed capsules are quickly removed from the nozzle, slowly congealed, and automatically ejected from the system.[19]

3.2 Manufacturing of Hard Gelatine Capsule -

The process in use today is the same as that described in the original patent of 1846. Hard gelatine capsules are manufactured using a dip-coating method and the various stages involved are as follows:

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Step 1: Preparation of the gelatine solution (dipping solution)

A concentrated solution of gelatine is prepared by dissolving the gelatine in demineralized water which has been heated to 60–70°C in jacketed pressure vessels. This solution contains 30 – 40% w/w of gelatine and is highly viscous, which causes bubbles as a result of air entrapment. The presence of these bubbles in the final solution would yield capsules of inconsistent weight and would also become problematic during capsule filling and upon storage. To remove the air bubbles, a vacuum is applied to the solution; the duration of this process varies with batch size. Following the above steps, colourants and pigments are added to attain the desired final capsule appearance. At this stage, other processing aids may be added, such as sodium lauryl sulphate, to reduce surface tension. The solution viscosity is measured and adjusted as needed with hot demineralized water to achieve the target specification. The viscosity of the gelatine solution is a critical parameter as it affects the downstream manufacturing process and plays a major role in capsule shell wall thickness. After physical, chemical, and microbiological testing, the gelatine is released for capsule production. The gelatine solution is then transferred to temperature-controlled tanks on the dipping machine where it is fed continuously into the dipping dishes.[20]

Step 2: Dip-coating the gelatine solution on to metal pins (moulds)

Capsule shells are manufactured under strict climatic conditions by dipping pairs (body and cap) of standardized steel pins arranged in rows on metal bars into an aqueous gelatine solution (25 – 30% w/w) maintained at about 50 ° C in a jacketed heating pan. Because the moulds are below the gelling temperature, the gelatine begins to form a thin gelatine layer or film on the moulds. The rows of pins are arranged so that caps are formed on one side of the machine while bodies are simultaneously formed on the opposite side of the machine.[21]

Step 3: Rotation of the dip-coated pins

Following adsorption of the gelatine solution on to the surface of the pins, the bar containing the pins is removed and rotated several times to evenly distribute the solution around the pins, correct gelatine distribution being critical to uniform and precise capsule wall thickness and dome strength.

Step 4: Drying of the gelatine-coated pins

Once the gelatine is evenly distributed on the mould, a blast of cool air is used to set the gelatine on the mould. At this point, the gelatine is dried, and the pins are then passed through several drying stages to achieve the target moisture content.

Step 5: Stripping and trimming

After the gelatine is dried, the capsule is stripped off the mould and trimmed to the proper length.

Step 6: Joining of the trimmed capsule shell

Once trimmed, the two halves (the cap and body) are joined to the pre-closed position using a pre lock mechanism. At this point, printing is done if needed before packing in cartons for shipping.

Step 7: Printing

After formation, the capsule shells can be printed to improve identification. Printing can be achieved using one or two colours, containing information such as product name or code number, manufacturer's name or logo and dosage details. Printing reduces the risk of product confusion by the numerous handlers and users of the product including manufacturers, pharmacists, nurses, doctors, caregivers, and patients.[22]

IV. QUALITY CONTROL TEST USED FOR CAPSULE

4.1 In-process quality control tests for capsule drug products-

In-process quality control tests for capsule drug products are carried out at predefined intervals during the product manufacturing, by the manufacturing personnel, and their results recorded on the batch record. Adverse findings in these tests can be used as a guide to altering the manufacturing-process parameters.

During the encapsulation of soft gelatine capsules, the following parameters are usually closely monitored and controlled:

1. Gel ribbon thickness and uniformity across the ribbon
2. Soft gels seal thickness at the time of encapsulation

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3. Weight of the capsule fill and its variation from capsule-to-capsule
4. Weight of the capsule shell and its variation from capsule-to-capsule
5. Moisture level of the capsule shell before and after drying

Visual inspection, fill weight, and fill-weight uniformity are the key in-process tests used for hard gelatine capsules.[16]

4.2 Finished product quality control tests for capsule drug products-

Finished capsules are subjected to a number of tests in accordance with compendial standards and regulatory requirements for unit dose capsule products. These batteries of tests help identify whether the batch is acceptable for marketing or its intended usage.

Finished capsules are evaluated by the following tests:

1) Permeability and sealing

Soft gelatine capsules are tested for physical integrity (absence of leakage) by visual inspection. Similarly, hard gelatine capsules are tested for any breach of physical integrity (breakage or opened cap and body).

2) Potency and impurity content

All capsules are tested for drug content (potency, as a per cent of label claim). In addition, most drug products are tested for related substances or impurities. These must meet predefined specifications for a batch to be acceptable.

3) Weight variation test

The uniformity of dosage units may be demonstrated by determining weight variation or content uniformity. The weight variation method is as follows.

4) Weight variation test for hard gelatine capsules

Ten hard gelatine capsules are usually weighed individually and the contents are removed. The emptied shells are individually weighed and the net weight of the contents is calculated by subtracting the weight of the shell from the respective gross weight. The content of active ingredient in each capsule may be determined by calculation based on the per cent drug content in the formulation.[23]

5) Weight variation test for soft gelatine capsules

For soft gelatine capsules, the gross weight of 10 gelatine capsules is determined individually. Then each capsule is cut open with a suitable clean, dry cutting instrument (e.g., scissors or a sharp open blade), and the contents are removed by washing with a suitable solvent (that dissolves the fill but not the shell). The solvent is allowed to evaporate at room temperature over a period of about 30 minutes, followed by weighing of the individual washed shells. The net contents are calculated by subtraction and the content of active ingredient in each of the capsules can be determined by calculation based on the per cent drug content in the formulation.

Fill-weight variation of capsules is often a function of equipment setup and filling operation. An automated capsule sizing machine and/or weight checker is frequently used to discard over- or underfilled capsules.[23]

6) Uniformity of content

This test is performed only when the content is specified in the individual monographs and when capsules fail weight variation test. If the weight of capsules is completely filled no need of this test. Unless otherwise stated in the monograph for an individual capsule, the amount of drug substance, determined by assay, is within the range of 85.0 % to 115.0 % of the label claim for nine (9) of ten (10) dosage units assayed, with no unit outside the range of 75.0 % to 125.0 % of the labelled drug content. Additional tests are prescribed when two or three dosage units are outside of the desired range but within the stated extremes.[20]

7) Disintegration time test for capsules

Disintegration of hard and soft gelatine capsules is evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. The compendial disintegration test for hard and soft gelatine capsules follows the same procedure and uses the same as quality control test for tablet.

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The capsules are placed in the basket-rack assembly, which is repeatedly lowered 30 times per minute into a thermostatically controlled bath of fluid at 37 ± 2 ˚C and observed over the time described in the individual monograph.

To fully satisfy the test, the capsules disintegrate completely into a soft mass with no firm core and only some fragments of the capsule shell.[17]

8) Dissolution test for capsules

Drug absorption and physiological availability depend on the drug substance being in the dissolved state at the site of drug absorption. The rate and extent of dissolution of the drug from the capsule dosage form is tested by a dissolution test. This test provides means of quality control in ensuring that

1. Different batches of the drug product have similar drug release characteristics and
2. That a given batch has similar dissolution as the batch of capsules that was shown initially to be clinically effective

The compendial dissolution test for capsules uses the same apparatus, dissolution medium, and test as that for uncoated and plain coated tablets. However, in instances in which the capsule shells interfere with the analysis, the contents of a specified number of capsules can be removed and the empty capsule shells dissolved in the dissolution medium before proceeding with the sampling and chemical analysis.

If the capsule floats on the surface of the dissolution fluid, a small, loose piece of nonreactive material, such as a few turns of a wire helix, may be attached to the dosage form to force it to sink to the bottom of the vessel.[23]

9) Moisture content

Water content of the entire capsule or the capsule contents are determined by Karl Fisher titrimetric to enable the correlation of water content with the degradation profile or drug-release characteristics of capsules.

10) Moisture permeation test

The USP requires determination of the moisture-permeation characteristics of single-unit and unit dose containers to assure their suitability for packaging capsules. The degree and rate of moisture penetration is determined by packaging the dosage unit together with a colour-revealing desiccant pellet, exposing the packaged unit to known relative humidity over a specified time, observing the desiccant pellet for colour change (indicating absorption of moisture) and comparing the pre-test and post-test weight of the packaged unit.[18]

11) Microbial content

The capsules are tested to ensure lack of growth of bacteria and mould by microbiological tests. These tests are usually carried out by incubation of the capsule contents in a growth medium and counting the colonies formed after a predefined period of time. Selection of the growth medium and duration of the test, as well as maintenance of aseptic conditions during the testing, are critical to successful assessment of microbial contamination by this method.[22]

Stability testing of capsules-

Stability testing of capsules is performed to determine the physicochemical stability of the drug substance in the finished drug product under specified package and recommended storage conditions intrinsic stability of the active drug molecule and the influence of environmental factors (e.g., temperature, humidity, light), on formulation components, and the container and closure system. The battery of stress-testing, long-term stability and accelerated stability tests help determine the appropriate storage conditions and the product's anticipated shelf life.[23]

Size chart of capsule –

Hard shell capsules are available in a variety of standard sizes and are designated by numbers from 000 to 5. The size of the 000 capsule is the highest and that of the number 5 capsule is the smallest.

1. 000 – Highest
2. 5 – Smallest

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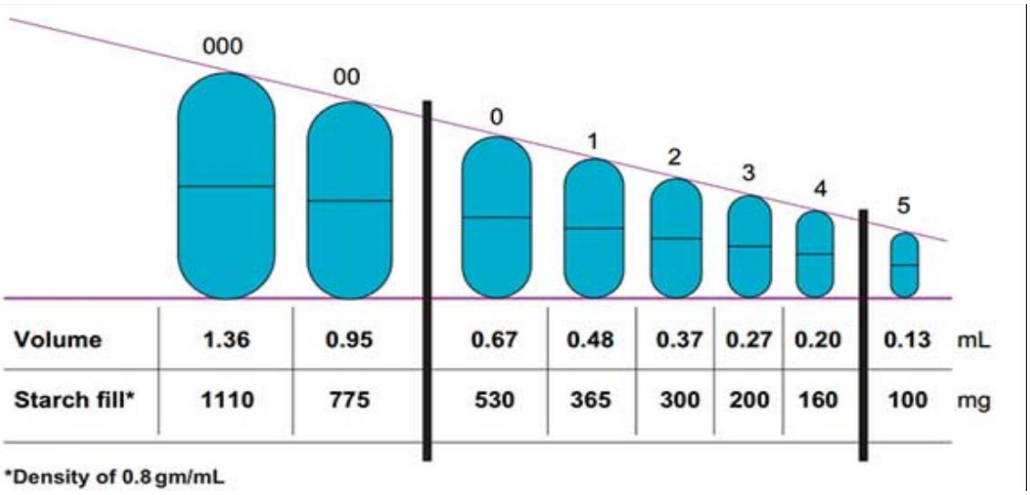

Chart no 1: Size chart of capsule

Dose chart of capsule –

TABLE 1

Capsule volumes and filling capacities

Size Capsule	000	00el	00	0el	0	1el	1	2el	2	3	4	5
volume (ml)	1.37	1.02	0.91	0.78	0.68	0.54	0.5	0.41	0.37	0.3	0.21	0.13
Powder tapped density	Capsule capacity (mg)											
.06 g/ml	822	612	546	468	408	324	300	246	222	180	126	78
.08 g/ml	1096	816	728	624	544	432	400	308	296	240	168	104
1 g/ml	1370	1020	910	780	680	540	500	410	370	300	210	130
1.2 g/ml	1644	1224	1092	936	816	648	600	482	444	360	252	156

Advantages of capsule-

1. Capsules are easy to swallow.
2. The protection of medicament it is possible with capsules
3. Capsules are therapeutically inert & easy to digest
4. It is easy to handle and carry capsules.
5. capsules are available in different sizes
6. Weekend easily identify the product in capsule dosage form
7. No need of complicated machinery
8. Filling of incompatible substance in the same
9. They are smooth, become very slippery when moist and can be easily swallowed.
1. Capsules are easy to swallow.
2. The protection of medicament it is possible with capsules
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Disadvantages of capsule –

1. In comparison to tablets, stability of capsules is low as the material for shell i.e. gelatine is very hygroscopic.
2. Capsules cannot be given to unconscious patient.
3. Highly soluble salts (e.g., iodides, bromides, and chlorides) generally should not be dispensed in hard gelatine capsules
4. Their rapid release may cause gastric irritation.
5. Rate of production of capsule is slower as compared to tablet.
6. Efflorescent substance may cause to capsule too soft.
7. Deliquescent material may dry to the capsule shell to excessive.

V. CONCLUSION

Capsule is the most versatile of all dosage forms. Capsules are solid dosage forms in which one or more medicinal and inert ingredients are enclosed in a small shell or container usually made of gelatine. There are two types of capsules, "hard" and "soft". The hard capsule is also called "two pieces" as it consists of two pieces in the form of small cylinders closed at one end, the shorter piece is called the "cap" which fits over the open end of the longer piece, called the "body". The soft gelatine capsule is also called as "one piece". Capsules are available in many sizes to provide dosing flexibility. Unpleasant drug tastes and Odors can be masked by the tasteless gelatine shell. The administration of liquid and solid drugs enclosed in hard gelatine capsules is one of the most frequently utilized dosage forms.

Depending on the composition of the capsule shell, capsules may be classified as either hard or soft capsule, with soft capsules possessing a flexible, plasticized gelatine film. The shells may be composed of two pieces in the form of cylinders closed at one end; the shorter piece, called the „cap" and the longer piece, called the „body", or they may be composed of a single piece. The two-piece capsules and one-piece capsules are commonly referred to as hard-shell capsules and softshell capsules respectively.

Capsules may be filled with a range of formulation types including dry powders, semisolids, nonaqueous liquids, and other dosage forms such as beads, mini-tablets, and even mini capsules most of which are intended for oral administration. There are also specialty applications such as capsules that can be loaded into dry-powdered inhalers, add reagents as part of a diagnostic kit, and occasionally soft-shell capsules intended for rectal or vaginal insertion as suppositories.

Also, In the recent advancements, non-gelatine capsules have been discovered, which do not contain gelatine as its shell-forming agent. Under this category of capsules are the HPMC, PVA and starch capsules.

Regardless of the type of capsule, the basic components of these capsules include but not limited to; gelatine, plasticizer, colourants, opacifying agents, preservatives, water, thickening agents, flavouring agents, sweetening agents, etc.

Hard gelatine capsules are manufactured using a dip coating method which involves the preparation of the gelatine solution (dipping solution), dip-coating the gelatine solution on to metal pins (moulds), rotation of the dip-coated pins, drying of the gelatine-coated pins, stripping and trimming, joining of the trimmed capsule shell and printing. Also, the basic steps in filling hard gelatine capsules include; rectification of capsules, separation of caps from bodies, dosing of fill material replacement of caps/ closing capsule shells and, ejection of filled capsules, which is then followed by locking and sealing, polishing and brushing among others. On the other hand, soft gels are manufactured using the following methods; plate process, rotary die process, reciprocating die process, alcogel process and, seamless process. The soft gelatine manufacturing and filling occurs simultaneously.

The quality control process s involves the in-process testing, finished product testing and shelf-life testing. The in-process quality control tests for soft gelatine capsule drug products are carried out at predefined intervals during the product manufacturing which involves; gel ribbon thickness and uniformity across the ribbon, soft gels seal thickness at the time of encapsulation, weight of the capsule fill and its variation from capsule-to-capsule, weight of the capsule shell and its variation from capsule-to-capsule and, moisture level of the capsule shell before and after drying. Visual inspection, fill weight, and fill-weight uniformity are the key in-process tests used for hard gelatine capsules. Also, the finished product quality control tests for capsule drug products

include; permeability and sealing, potency and impurity content, weight variation test, weight variation test for hard gelatine capsules, weight variation test for soft gelatine capsules, uniformity of content, disintegration time test for capsules, dissolution test for capsules, moisture content, moisture permeation test and, microbial content. While the shelf-life test involves the stability testing of capsules.

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