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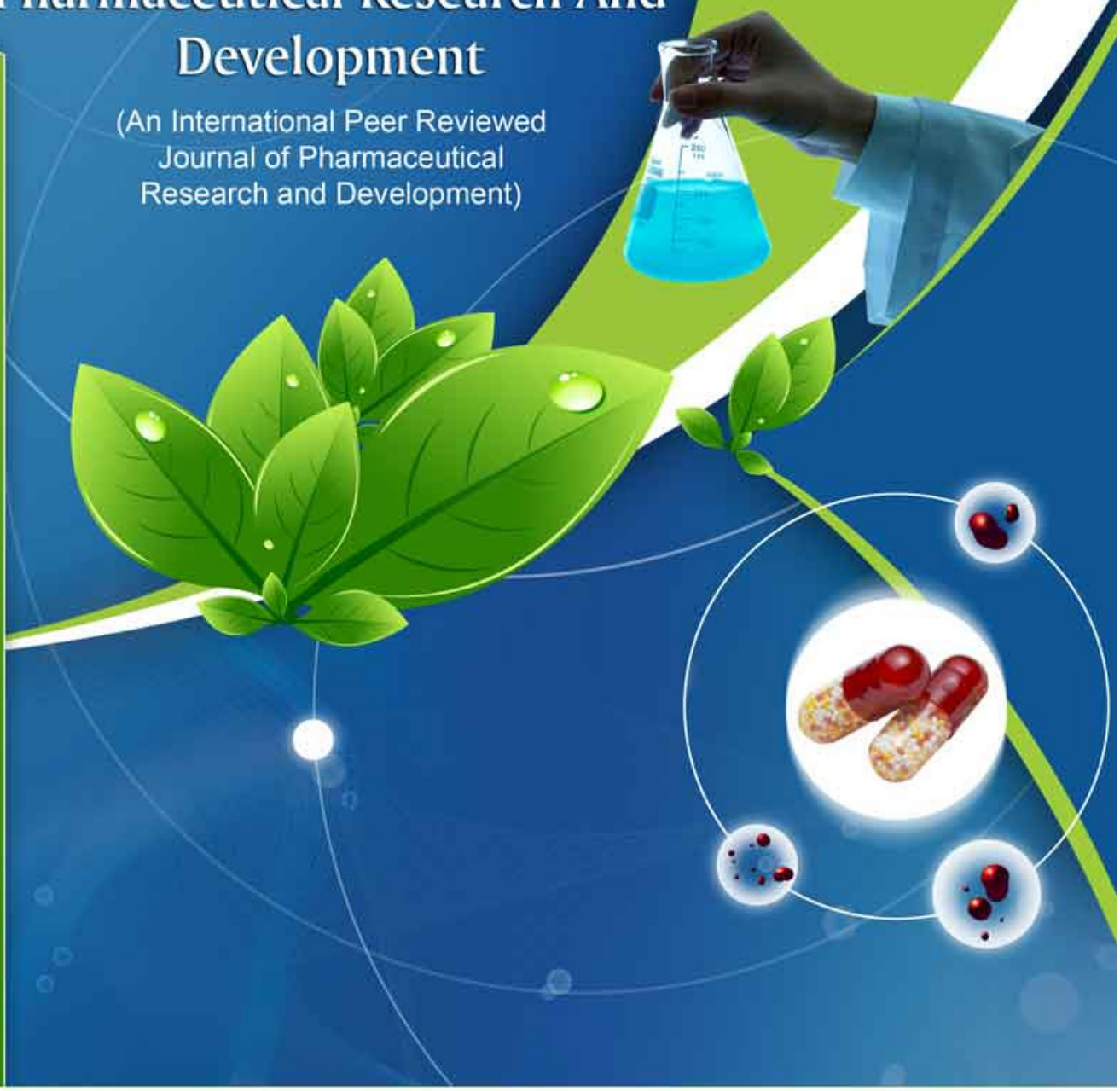

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Review Article

HARD GELATIN CAPSULES (TWO PIECE) – A UNIQUE PHARMACEUTICAL DOSAGE FORM - AN EXHAUSTIVE REVIEW

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ABSTRACT

Pharmaceutical dosage form are the most vulnerable house to hold the medicament(s) along with excipients. From the ancient time to today, number of different dosage form included to pharmaceutical sciences. Every dosage form has distinct character in distributing, releasing & delivery of drug(s). Hence, dosage form play a very vital role for providing therapeutic responses. Capsule is the most popular solid unit dosage form having two types -Hard gelatin and Soft gelatin capsules. Hard gelatin capsules are extensively used as for dispensing many of the active pharmaceutical principles. Specially in case of manufacturing, Hard gelatin shell is required to encapsulate the mixed materials. Most instances, company purchased the shell from supplier. The integrity, thickness, locking quality of empty shell are important for quality capsules. Recently, modified pellets incorporates within shell for upgrading pharmaceutical purposes.

Keywords: *Pharmaceutical dosage form, Drug, Capsule, Hard gelatin capsules, Hard gelatin shell, Pellets.*

INTRODUCTION

The word capsule is derived from the Latin word *'Capsula'* which means a small box or container. The word is used to describe various natural and manmade materials in scientific discipline like in anatomy, as an *enclosing membrane,*in botany for *fruit* and in astrophysics for space *vehicle.* In pharmaceutical sciences, the word *capsule* is usually used to describe a solid dosage form that consists of a container usually made up of gelatin in which the medicinal substance is filled.

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In practice, the term empty capsule is used to describe the capsule containing no drug filled in it, rather, the container as raw material used to fill the drug in it. [1]

Capsules are the solid preparation of hard or soft shell or container that contain mixed ingredients to make unit dose and usually meant for oral administration. They are of two types, hard and soft capsules. First patent was granted in 1834 for a method to produce a single-piece gelatin capsule. [1]

HISTORY OF CAPSULES

Since the inception of capsules, consumers have viewed it as the most efficient method of taking medication. Many tablets are produced by manufacturers in the shape of capsules,

generally called as caplet, combining the manufacturing advantages of tablets with the consumer acceptability of capsules. However, a minor fall in popularity of capsules was experienced due to the famous "Tylenol tampering murders" in 1982 and tablets were seen as more resistant to tampering. Tamper proof designs for capsules were developed later to regain the popularity again. A patent was first granted to Mothes and Dublanc in 1834 for a method to produce a single-piece gelatin capsule that was sealed with a drop of gelatin solution. The method used individual iron moulds for the process, and a dropper to fill the capsules individually. Later on, methods were developed that used sets of plates with pockets to form the capsules. This equipment is not produced commercially any more. This single piece gelatin capsule concept was later on developed as modern soft-gel capsules. The process for soft gelatin capsule was originally developed by R.P. Scherer in 1933 and got modified with time into the present day technology of using 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 concept of preparing gelatin capsules in two parts was first conceived by James Murdock who patented the two-part telescoping gelatin capsule in 1847. The two parts of the capsules are made by dipping metal rods in molten gelatin solution and were supplied as closed units to the pharmaceutical manufacturer. The two halves are separated, and the body part of the capsule is filled with powder (either by placing a compressed slug of powder or by filling with loose powder) and the other half of the capsule (cap) is pressed on. Inserting a slug of compressed powder was found more advantageous in controlling weight variation, but the machinery involved was more complex. Commercial production of the capsule started in the United States during the 1870s and in Europe during the 1950s. [2]

HARD GELATIN CAPSULES

Hard gelatin capsules are the most common & unique form of capsules composed of two parts- cap & body. One end of each section is rounded and closed, and the other is open. The contents of hard capsules are usually in solid form (powder or granules). [3] US Pharmacopeia (USP 24). It defines capsules as solid dosage forms in which the active ingredients are sealed in a hard or soft container or shell. In contrast to the European monograph, the USP also mentions starch and other substances used in the production of the shell. [4]

Body and cap are designed to fit only if the two parts are precisely in line; the slightest sideways movement of the capsule halves during the closing process results in splitting or denting. This problem was solved with the invention of a tapered rim on the body section of the capsule aided by the introduction of fully-automatic filling machines. In a single operation, automatic capsule filling machines line up and rectify the hard gelatin capsules, separate body and cap, fill the body, join cap and body together (for closing), and eject the filled capsule.

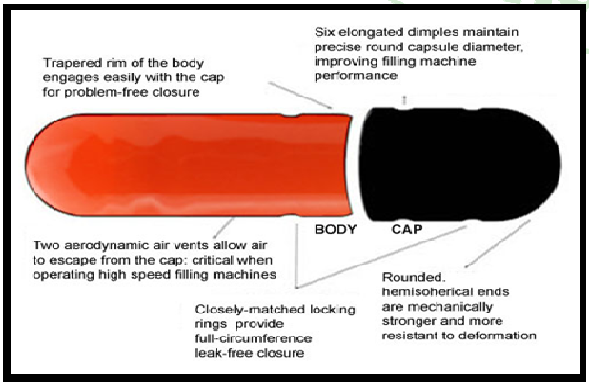


Figure 1: Cap & Body of capsule shell [5]

Figure 2: Empty capsule shell

GELATIN

Gelatin is a product obtained by partial hydrolysis of collagen acquired from the skin, white connective tissue, and bones of animals. Gelatin is a protein which is soluble in warm (or hot) water, but insoluble in cold water. At low temperatures, gelatin dissolved in water becomes a gel (which is insoluble in water). This property is used to prepare Jello® and other gelatin deserts. Gelatin capsules become dissolved in warm gastric fluid and release the contents.

Normally, hard gelatin capsules contain 13–16% of moisture. If additional moisture is absorbed when stored in a high relative humidity environment, hard gelatin capsule shell may lose their rigid shape and become distorted.

SIZE AND SHAPE OF HARD GEL CAPSULES

Empty gelatin capsules for human use are available from manufactures in 8 different sizes ranging from 000 (the largest) to 5 (the smallest). [1]

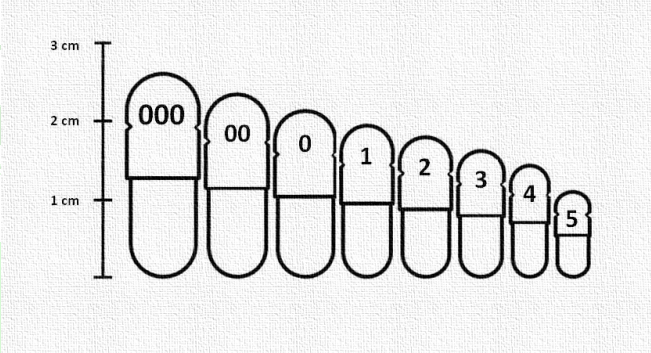


Figure 3: Empty gelatin capsules (000 – 5)

Table 1: Different Capsule sizes in terms of water volume & weight

Capsule Sizes	*Water Volume (ml)*	*Approximate Weight (gm)*
000	1.37	1.00
00	0.95	0.65
0	0.68	0.50
1	0.50	0.32
2	0.37	0.25
3	0.30	0.20
4	0.21	0.15
5	0.13	0.10

ADVANTAGES OF HARD GELATIN CAPSULES [6-7]

- Hard gelatin capsules have often been assumed to have better bioavailability than tablet
- Drug release with a rapid rate due to faster dissolving of gelatin shell.
- Hard gelatin capsules allow for a degree of flexibility of formulation.
- Manufacturing process is very simpler
- Hard gelatin capsules offer less production steps.
- Analytical tests are less in comparing to others.
- The risk of cross- contamination is very less in HGC.
- Granules, powders, liquids, semi-solid formulations and mini tablets can easily be filled alone or in combination.
- Very fewer excipients are required to make ideal formulation.

- Reduces stability problems with sensitive drugs.
- More efficient pharmaceutical development means faster speed to market.
- Unique color and shape configurations enhance product identity.
- Masks tastes and odors thus improves patients compliance.

DISADVANTAGES OF HARD GELATIN CAPSULES [7]

- The drugs having very large unit dose, can't be dispensed as HGC because of ingestion difficulty.
- Drugs that have the tendency to dissolve the capsule shell, are not suitable candidate to dispense in hard gel capsules.
- Hygroscopic and deliquescent materials can't be formulated in hard gel capsules.
- Highly soluble salts (iodides, bromides, chlorides) should not be dispensed in hard gelatin capsules.
- The rapid release may causes gastric irritation due to high drug concentration in localized areas.

MANUFACTURING OF HARD GELATIN CAPSULES

The Manufacturing of hard gelatin capsules in large scale or small scale involves the following steps:

- Development of formulation and selection of capsule size
- Filling the capsule shells
- Sealing capsule shells
- Cleaning and polishing of filled capsules

Development of Formulation and Selection of Capsule Size [1]

Hard capsules are generally filled with dry powders; however, certain capsules are filled with semisolid and liquid compositions also. Following are the objectives set in the formulation of a hard capsule,

- Ease of filling and production
- Accurate dosage
- Stability
- Elegance
- Bio-availability

In dry formulation, the active and the inactive ingredients are required to be blended thoroughly to ensure a uniform powder mix. This is particularly of great importance in dealing with low dose potent drugs, since lack of homogeneity in the powder mix would lead to dosage variations resulting therapeutic consequences. Preformulation study is needed to determine the need for steps to ensure uniform blending like particle size reduction, bulk control, need for glidants, lubrication and proper choice of blending equipment and conditions of blending like sequence of addition, time of mixing, rotation speed and humidity control. Capsule fill mix basically consists of drug, diluents and lubricant/ glidant. However, use of other ingredients like capsule colorant, capsule opaquants is also inevitable to improve the look and elegance of capsules. Coating agents, hardening agents etc., are optional and are used to bring special characteristics and performance to the product when needed.

Diluents

Diluents or fillers are added to the formulation to increase the volume of the fill to produce capsules of a standard size. Generally used diluents include lactose, microcrystalline cellulose, starch etc. Diluents used should have the following properties-

- Provide bulk
- Cohesion to the powder, to ensure smooth filling
- Overcome hygroscopicity of the drug powder, if they are hygroscopic
- Overcome interaction between incompatible ingredients, if any
- Compressibility, in case where pre-compressed compacts are to be filled

Glidants /Lubricants

Industrial scale production of capsules using high speed powder filling machine pose problems of flow of the powder mix leading to non-compliance with content uniformity, weight variation and serious therapeutic implications. Addition of lubricant or glidant such as fumed silicon dioxide, magnesium

stearate, calcium stearate, stearic acid or talc to the powder mix would enhance flow property. When lubricants are added to a powder mass, they form a coat around individual particles which remains more or less intact. Lubricants are mostly hydrophobic and hence the presence of lubricant coating may decrease drug dissolution rate. Glidants are the materials that impart good flow property to the powder blend but provide poor lubrication properties. The uniformity of capsule weights directly depends on how uniformly the capsule are filled. In general many materials commonly referred to as lubricants possess only a minimal lubricating activity and are better glidants or anti-adherents.

Other Ingredients

Many other ingredients like surface active agents, disintegrating agents etc. are used wherever required. Surface active agents like tweens, sodium lauryl sulphate, sodium formaldehyde sulfoxilate etc. are used to improve wetting of hydrophobic drug powder. They are also used to overcome the problem of dissolution of drugs with hydrophobic surface. Disintegrating agents are used in cases where the cohesive powder released after dissolution of capsule shell fails to dissolve due to the lack of wetting or penetration of gastric fluid into it.

MANUFACTURE OF EMPTY GELATIN CAPSULES [11]

Steps involved in making empty gelatin capsules

- **Dipping**
- **Spinning**
- **Drying**
- **Stripping**
- **Trimming**
- **Joining & Ejection**

Hard Capsule Filling (Encapsulation)

Capsules are generally filled with powder blend containing drug and other inactive ingredients. However, in exceptional cases hard capsules are also filled with other forms of materials like mini tablets, smaller capsules, granules, spheroids, semisolids and liquids. Such cases are mostly to prevent incompatibility, provide extraordinary performance like desired dissolution profile, sustained release or to overcome certain specific technical problems.

Usually two types of machine are used for filling of ingredients to capsule shell-

- Hand operated machine
- Semi-automatic / Automatic machine

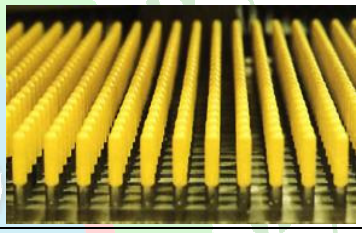
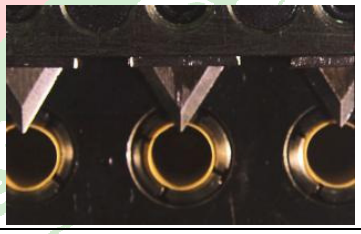
Hand operated, semiautomatic and automatic capsule filling machines are developed for small scale, medium scale and large scale filling operation respectively. Basically any capsule filling operation involve the following steps:

- Loading capsules in the loader tray (Manual or Automatic)
- Separation of caps from the body
- Filling of the powder into the body
- Scraping of the excess powder
- Replacing the cap and seal
- Cleaning the outside of the filled capsule and polishing

Hand operated machine (Manual Filling) [8]

- The powder to be encapsulated is placed on a sheet of clean paper or a glass or porcelain plate.
- With a spatula is formed into a cake having a depth of one fourth the length of the capsule body.
- The cap is removed and the empty capsule body is held between thumb and forefinger and repeatedly punched downward until it is full.
- The cap is replaced and the filled capsule is weighed using an empty capsule of the same size as a tare.

Table 2: Steps involve in Hard Gel Capsule shell production with brief description

Steps	*Description*	*Figures*
Dipping	Pairs of the stainless steel pins (metallic) are dipped into the dipping solution to simultaneously form the caps and bodies. The dipping solution is maintained at a temperature of about 50^0C in a heated, jacketed dipping pan.	
Spinning	The pins are rotated to distribute the gelatin over the pins uniformly and to avoid the formation of a bead at the capsule ends.	
Drying	The gelatin is dried by a blast of cool air to form a hard shells. The pins are moved through a series of air drying kilns to remove water	
Stripping	A series of bronze jaws strip the cap and body portions of the capsules from the pins.	
Trimming	The stripped cap and body portions are trimmed to the required length by stationary knives.	
Joining & Ejection	After trimming, the cap and body sections are aligned and joined, finally ejected from the machine. The entire cycle of the process last for approximately 45 minutes	

Hand operated machine (Manual Filling) [8]

- The powder to be encapsulated is placed on a sheet of clean paper or a glass or porcelain plate.
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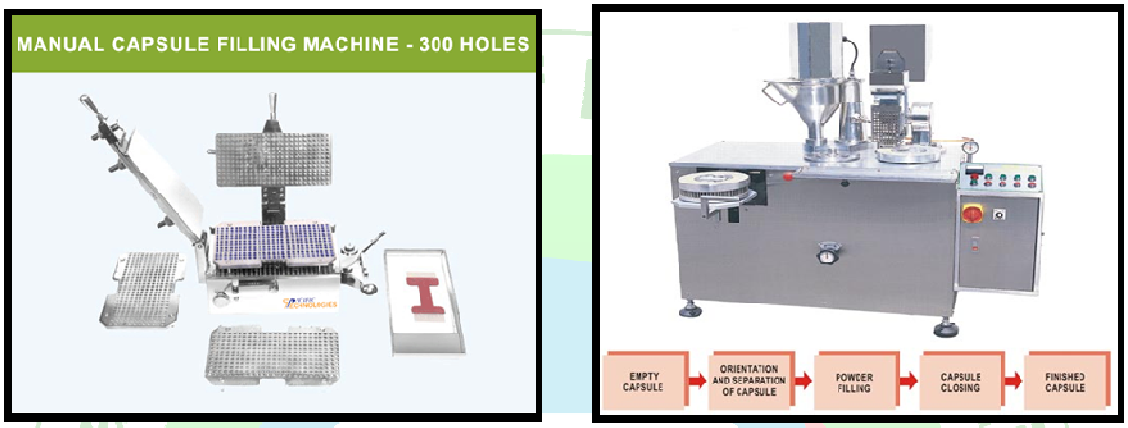

Figure 4: Manual and Semi- automatic filling machine [9]

Semi-automatic Filling

- Capsules are delivered into the perforated capsule filling ring.
- The ring is rotated on a turntable, and a vacuum pulls the bodies into the lower half of the ring, leaving the caps in the upper half of the ring.
- The top & bottom halves of the filling ring are separated manually, and the cap half of the ring is set aside.
- The body half of the ring is then moved to another turntable where it is rotated mechanically under a Powder hopper.
- The hopper contains an auger which feeds the powder into the bodies.
- When the capsule bodies are filled, the Cap and body rings are rejoined.

Automatic Filling

Automatic capsule filling machine usually used for large scale manufacturing of capsules. The machine do four basic jobs for accomplishing the capsule filling (Encapsulation).

- Removal of caps,
- Filling of the bodies,
- Replacement of caps, and
- Ejection of filled capsules.

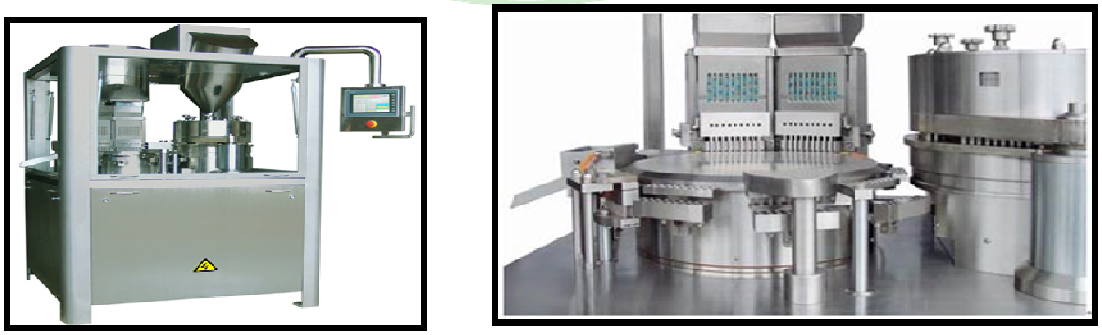

Figure 5: Automatic Capsule Filling Machine (NJP-200)

Polishing of Capsules

After filling of capsule, they are subjected to polishing process. In case of automatic filling polishing machine remain associate to filling machine. Polishing of capsules required -

- To remove trace of powder materials from the surface of the capsule shell.
- Hygroscopic drugs absorb moisture from atmosphere and may deteriorate the product, polishing is required to avoid these types of drugs.
- To remove finger prints from capsule surface.
- To improve the appearance of capsule.

There are number of process involved in polishing of capsules, pan and salt polishing, brushing, cloth dusting.

Pan Polishing : Acela-cota pan is used to dust and polish.

Cloth Dusting : Capsule are rubbed with cloth.

Brushing : Capsule are feed under soft rotating brush.

Figure 6: Capsule polishing machine

Visual inspection [3]

Unpack and inspect at least 20 capsules. They should be smooth and undamaged. Evidence of physical instability is demonstrated by gross changes in physical appearance, including hardening or softening, cracking, swelling, mottling, or discoloration of the shell.

Packaging & Labelling

After production, it is necessary to package capsule immediately. Capsules are capped in air-conditioned area in which the humidity does not exceed 45% of RH (Relative Humidity) at 21-24°C. Capsules may be packaged in the following ways-

- Container package (Glass/ Plastic)
- Strip package
- Blister / See through package

Every pharmaceutical preparation must comply with the labelling requirements established under GMP. **[3]**

The label should include:

- The name of the pharmaceutical product;
- The name(s) of the active ingredient(s); International Nonproprietary Names (INNs) should be used wherever possible.
- The amount of the active ingredient(s) in each capsule and the number of capsules in the container.
- The batch (lot) number assigned by the manufacturer.
- The expiry date and, when required, the date of manufacture.
- Any special storage conditions or handling precautions that may be necessary.
- Directions for use, warnings, and precautions that may be necessary and the name and address of the manufacturer or the person responsible for placing the product on the market.

Storage [3]

Capsules should be kept in well-closed containers. They should be protected from light when required, and from excessive moisture, or dryness, and should not be subjected to temperatures above 30° C.

EVALUATION OF CAPSULES [3], [10]

Disintegration test for capsules

The apparatus consists of a circular basket-rack assembly, a suitable vessel for the

immersion fluid (such as a 1-litre beaker), a thermostatic arrangement for maintaining the fluid at the required temperature (normally 37 ± 2 °C), and a device for raising and lowering the basket-rack in the immersion fluid at a constant frequency of 28-32 cycles/min through a distance of 50-60 mm.

The capsules are placed in the basket-rack assembly, which is repeatedly immersed 30 times per minute into a thermostatically controlled fluid at 37^0C and observed over the time described in the individual monograph.

Dissolution test for capsules

The apparatus, dissolution media and test is the same as that for uncoated and plain coated tablets.

Weight variation

$$W_{capsule} - W_{emptied\ shell} = W_{content}$$

10 capsules labeled amount or average amount, ±10%

Content uniformity

The amount of active ingredient should be within the range of 85% to 115% of the label amount for 9 of 10 capsules, with no unit outside the range of 70% to 125% of label amount

CONCLUSION

Hard gel capsules add a new concentration to the solid pharmaceuticals. The dynamic features of two piece is exist in its shell, which allow the release phenomena of drug with a significant manner to provide an efficient therapeutic response. Modern pharmaceutical science uses pellets (multiple category) in capsule shell. Recently the pellets are coated (film / enteric film) according to drug individual needs. As hard gelatin capsule provides number of benefits to pharmacists, patients and physician it's very sure that the future of capsule technology brings a lot to the realm of pharmaceutical sciences.

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