CHAPTER 1

CAPSULES

1. 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. 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.

There are two types of capsules seen as dosage form, hard capsule and soft capsule. The hard capsule has two parts, the body and the cap which are closed partially to make it in to a near cylindrical form. The body is longer and has slightly smaller diameter, while the cap is shorter and has slightly more in diameter to enable to cap the body part.

2. THE HISTORY OF THE MEDICINAL CAPSULE

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 (1). 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.

### 3. GELATIN: STRUCTURE AND PHYSICO-CHEMICAL PROPERTIES

Gelatin is a translucent, colorless, brittle, nearly tasteless solid substance, derived from the collagen inside animals’ skin and bones. It is commonly used as a gelling agent in food, pharmaceuticals, photography, and cosmetic manufacturing. Gelatin is obtained from the partial hydrolysis of collagen obtained from the skin, white connective tissue and bones of animals. In commerce, it is available as fine powder, shreds, flakes and sheets. Different grades of gelatin are available in the market and are classified as a foodstuff, with E number E441. It is used in almost every “gummy” confectionery as well as other products such as marshmallows and some low-fat yogurt.

Chemically, gelatin is a protein produced by partial hydrolysis of collagen. Different grades of gelatin are available in the market and are classified as a foodstuff.
in water, which sets to a gel on cooling, and its chemical composition is, in many respects, closely similar to that of its parent collagen (4). If gelatin is put into contact with cold water, some of the material dissolves.

Gelatin is a rigid-chain high molecular weight compound which in many respects similar to those of typical rigid-chain synthetic polymers, which is not the case with native collagen. Thus, aqueous solution gelatin macromolecules assume, the conformation of a statistical coil (5) at elevated temperatures. Under specific conditions (temperature, solvent, pH) gelatin macromolecules can display flexibility sufficient to realize a wide variety of conformations. This makes it possible to vary all the gelatin characteristics dependent on its molecular structure. Besides, gelatin shows a rather wide molecular weight distribution (5, 6) a property again similar to synthetic polymers. It is also quite interesting to note the capacity of gelatin to form a large variety of supermolecular structures, from the simplest globular structure (7), typical of amorphous polymers (8), to a well developed fibrillar structure with various intermediate states (9-16).

Clearly this structural diversity of gelatin chain units and supermolecular structures are responsible for wide variations found in the physico-mechanical properties of the gelatin materials.

Gelatin like any other biopolymers contain both acidic and basic functional groups in their macromolecular structure. Some peculiarity observed in gelatin structure are:

1. Gelatin has capacity to form a specific triple-stranded helical structure not observed in synthetic polymers (this structure is formed in solutions at low temperatures). The rate of the formation of a helical structure depends on many factors such as the presence of covalent cross-bonds (5, 16), molecular weight (17), the presence of iminoacids (18) and the gelatin concentration in the solution (19, 20).

2. Gelatin as a biopolymer shows its specific interaction with water which is different to that observed with synthetic hydrophilic polymers. This peculiarity governs the structural and physico-mechanical properties of gelatin in the solid state.

The solubility of the gelatin is determined by the method of manufacture. Gelatin put into contact with cold water, dissolves partially. It can be dispersed in a relatively concentrated acid and such dispersions are stable for 10–15 days with little or no chemical changes. They are suitable for coating purposes or for extrusion into a precipitating bath. Gelatin is also soluble in most polar solvents. Gelatin gels exist over only a small temperature range, the upper limit being the melting point of the gel, which depends on gelatin grade and concentration and the lower limit, the ice point at which ice crystallizes.
The mechanical properties are very sensitive to temperature variations, previous thermal history of the gel, and time. The viscosity of the gelatin/water mixture increases with concentration and when kept cool (≈ 4°C). Gelatin solution show viscoelastic flow and streaming birefringence.

Gelatin is stable in air in dry form but is subjected to microbial decomposition on absorption of moisture. Normally hard gelatin capsules contain 13 to 16% moisture (21). When stored in environment of higher humidity, it absorbs more moisture and become fragile and loses their rigid shape. In the environment of extreme dryness, the capsules may become brittle and crumbles during handling due to loss of moisture. Therefore, it is desirable to maintain hard gelatin capsules in an environment free from excessive humidity or dryness.

### 3.1 Bloom or Gel Strength

In the gelatin world, gel strength is traditionally referred as Bloom. It is the force, expressed in grams, necessary to depress by 4 mm the surface of a gelatine gel (concentration 6.67% kept for 17 hours at 10°C) with a standard plunger (AOAC). Bloom is linked to mechanical elasticity of the gel and is used to classify gelatine types. It generally ranges from 50 to 300 Bloom. We may sometime refer to Low, Medium or High Bloom, with the following limits:

- **Low Bloom:** gel strength below 120 g.
- **Medium Bloom:** gel strength between 120 and 200 g.
- **High Bloom:** gel strength above 200 g.

Gel strength increases with concentration and time as the gel matures. It decreases with temperature.

### 3.2 Gelatin for Capsule Shells Manufacture

The gelatin is marketed in a large number of varieties and a specific quality of gelatin having specified gel strength, viscosity, iron content etc. should be selected for capsules. The variations in gelatin properties arise because of changes in molecular weights and methods followed in conversion into gelatin. The average molecular weight of gelatin, varies between 20,000 and 2,00,000. Two popular grades of gelatin, Pharmagel-A and Pharmagel-B, are acid processed and alkali processed respectively. They have differing isoelectric points (Pharmagel-A: pH 4.8 to 5.2, Pharmagel-B: pH 6.5 to 9.5). For capsule shells generally a mixture derived from pork skin and bones is used. Pork skin gelatin contributes plasticity while bone gelatin gives firmness. However, in using bone gelatin its calcium phosphate content should be check since undue amounts can make capsules hazy. One important reason for the exclusive
use of gelatin for making hard and soft capsules is its solubility characteristics in stomach fluids. It absorbs cold water readily, though the rate of absorption depends upon moisture content of gelatin.

In addition to gelatin, the shell of hard gelatin capsules contains plasticizers and water. Modern day shells may, in addition, consist of preservatives, colours, opacifying agents, flavours, sugars, acids, enteric materials etc. The plasticizers used are glycerin, sorbitol etc. The exact proportions of gelatin and plasticizers have to be determined on the basis of the use of capsules and their storage conditions. Preservatives, if included, are generally a mixture of methylparaben (4 part) and propylparaben (1 part) to the extent of 0.2%. Flavours, if added, should not exceed 2% and are generally ethylvanillin or essential oils. Sugar may be added up to 5% to give the gelatin shell desirable chewable characteristics, if required.

4. MANUFACTURING OF HARD CAPSULE SHELL

The capsule shells are nowadays produced on mass scale by sophisticated machinery. Fundamentally, capsule shell machine contains pairs of pins corresponding to the bodies and the caps of the capsules (Figure 1.1).
They are dipped in heated gelatin solutions containing the necessary additives. The dipping is followed by withdrawal of pins and their rotation a few times to distribute the solutions evenly. Cold air is simultaneously blown on the rotating pins to firm up the gelatin shells. These pins are, thereafter, passed through series of kilns with controlled rates of drying. After drying, the bodies and caps are removed from pins by mechanical jaws and are trimmed to appropriate lengths by rotating blades. Finally the caps are placed on the bodies.

**Special Types of Capsule Shells**

Distinctly looking capsules are also produced by several manufacturers by altering the usually rounded shape of the capsule-making pegs. By tapering the end of the capsule body producing peg while leaving the cap making peg rounded, differentiation is brought about from generally manufactured capsules. Other innovations in capsule designing are Snap-fit, Coni-snap, and Coni-snap supro which are designed to avoid easy separation of the two capsule parts and to provide maximum integrity (Figure 1.2). The original Snapfit design enables the two halves of the capsule shell to get interlocked through the groves present of the shell walls and thus provides reliable closing. However, this design was found to cause splitting or denting of the capsule shell due to slight contraction during joining particularly in any high speed capsule filling machine (operating at capacity more than 1,80,000 capsules per hour). This problem was overcome in **Coni-snap design** where the rim of the capsule body is slightly tapered, which reduces the risk of splitting during high speed filling operations. Coni-snap supro is a modified design of **Coni-snap** to ensure integrity and maximum security against tampering. In this design, the upper capsule part (cap part) extends deep over the lower part (body...
part) where only rounded part of the later is exposed. Opening of such a filled capsule is very difficult because the lower surface offers fewer grips to pull the two surfaces apart.

### 4.1 Specifications

Empty gelatin capsules are manufactured in various lengths, diameters and capacities. The size selected for filling medicaments is decided by the amount of the material to be filled. The density and compressibility of the fill will largely determine to what extent it may be packed into a capsule shell. Following table (Table 1.1) gives the dimensions of the universally manufactured capsule shells and weight capacity of powder of varied density which can be ordinarily filled in various sizes of capsules. External diameter and length of the body part are critical dimensions which enables in designing universal capsule filling machines. Cap part dimensions are critical and match with the dimensions of the body part to see that the capsulation is smooth and the filled capsules are intact.

#### Table 1.1. Technical Specifications for Gelatin Capsules

<table>
<thead>
<tr>
<th>Size</th>
<th>000</th>
<th>00</th>
<th>0E</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average weight (mgs)</td>
<td>158±10</td>
<td>123±7</td>
<td>107±7</td>
<td>99±6</td>
<td>76±5</td>
<td>61±4</td>
<td>48±3</td>
<td>38±3</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>1.37</td>
<td>0.95</td>
<td>0.77</td>
<td>0.68</td>
<td>0.48</td>
<td>0.36</td>
<td>0.27</td>
<td>0.20</td>
</tr>
<tr>
<td>Weight Capacity (mg) of powder of density</td>
<td>0.6</td>
<td>822</td>
<td>570</td>
<td>462</td>
<td>408</td>
<td>288</td>
<td>216</td>
<td>162</td>
</tr>
<tr>
<td>0.8</td>
<td>1096</td>
<td>760</td>
<td>616</td>
<td>544</td>
<td>384</td>
<td>288</td>
<td>216</td>
<td>160</td>
</tr>
<tr>
<td>1.0</td>
<td>1370</td>
<td>950</td>
<td>770</td>
<td>680</td>
<td>480</td>
<td>360</td>
<td>270</td>
<td>200</td>
</tr>
<tr>
<td>1.2</td>
<td>1644</td>
<td>1140</td>
<td>924</td>
<td>816</td>
<td>576</td>
<td>432</td>
<td>324</td>
<td>240</td>
</tr>
<tr>
<td>Overall closed length (mm)</td>
<td>26</td>
<td>23.4</td>
<td>23.4</td>
<td>21.6</td>
<td>19.4</td>
<td>17.6</td>
<td>15.7</td>
<td>14.3</td>
</tr>
<tr>
<td>Individual length (mm)</td>
<td>Cap 12.9</td>
<td>11.8</td>
<td>11.9</td>
<td>10.85</td>
<td>9.85</td>
<td>8.8</td>
<td>8.0</td>
<td>7.2</td>
</tr>
<tr>
<td>Body 21.9</td>
<td>20.1</td>
<td>20.0</td>
<td>18.45</td>
<td>16.4</td>
<td>15.15</td>
<td>13.45</td>
<td>12.1</td>
<td></td>
</tr>
<tr>
<td>External diameter (mm)</td>
<td>Cap 9.94</td>
<td>8.59</td>
<td>7.66</td>
<td>7.65</td>
<td>6.96</td>
<td>6.39</td>
<td>5.85</td>
<td>5.33</td>
</tr>
<tr>
<td>Body 9.55</td>
<td>8.23</td>
<td>7.35</td>
<td>7.35</td>
<td>6.63</td>
<td>6.12</td>
<td>5.60</td>
<td>5.08</td>
<td></td>
</tr>
</tbody>
</table>

(http://www.capscanada.com)

### 5. PREPARATION OF HARD GELATIN CAPSULES

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

1. Development of formulation and selection of capsule size  
2. Filling the capsule shells
3. Sealing capsule shells
4. Cleaning and polishing of filled capsules

5.1 Development of Formulation and Selection of Capsule Size

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 glidents, 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/glident. 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.

(a) 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

Particle size and density of the diluents should match well with the drug for uniform mixing. This can be important criteria for the selection of the diluents for capsule formulation. However, in most of the cases of
wide variation between densities of the drug and diluents, pre-formulation
studies mostly recommends selection of a suitable crystal form of the
drug, granulation etc. Now-a-days, many companies have come out with
unique ready to fill blends in commercial market for problematic drugs
also.

Lactose is a common inert diluents used in capsules. It is available
generally as lactose monohydrate and anhydrous lactose. Monohydrate
variety is supplied in the market as regular and spray dried form. Regular
variety, though has good packing property, is not have good flow property
while; the spray dried lactose monohydrate modified through processing
has excellent flow property. Anhydrous lactose also has good flow
property. Micro crystalline cellulose is other diluent in capsule formulation
having good flow property. Powdered cellulose (Arbocel®) is also used as
an economic and inert diluent in capsule filling. Some granular materials
such as sodium carboxy methyl cellulose also has good flow behavior but
due to it’s property to change dissolution behavior of certain drugs, this
material is not generally recommended in capsule formulation as diluent.

Starch was conventionally used as diluents in capsule formulations
even though it has problem of flow. Recently, modified starch like pharmgel
series has been introduced which has better flow property. All varieties
of pharmgel like PharmGel 03406 (Maize starch), PharmGel 03415 (Low
moisture maize starch), PharmGel 03302 (White maize starch), PharmGel
12012 (Pregelatinised regular maize starch) are recommended for use as
diluent in capsule and powder formulations.

Another diluent used in capsule formulation is di-calcium phosphate.
Augsburger, (1996) suggested the use of unmilled dicalcium phosphate
dihydrate as an efficient diluent for capsules. However, incompatibility
with chelating drugs like tetracycline leading to lowering of bio-availability
was reported with dicalcium phosphate. Hence, diluents selection should
be made carefully as physical-chemical changes might render the product
unstable and might cause problems in manufacturing.

(b) 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

Particle size and density of the diluents should match well with the drug
for uniform mixing. However, in most of the cases of wide variation
between densities of the drug and diluents. Commonly used diluents
include lactose, starch and dicalcium phosphate.

Weight uniformity of powder filled in capsule depends on the flow property
of the powder mix. 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.

Particle size and density of the diluents should match well with the drug
for uniform mixing. However, in most of the cases of wide variation
between densities of the drug and diluents. Commonly used diluents
include lactose, starch and dicalcium phosphate.
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.

**(c) 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.

### 5.2 Hard Capsule Filling

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.

#### 5.2.1 Powder Filling

Hard gelatin capsules are generally filled with 65 to 1000 mgs of powder material in various sizes of capsule from size 5 to size 000.

<table>
<thead>
<tr>
<th>Capsule size</th>
<th>000</th>
<th>00</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximate volume (ml)</td>
<td>1.40</td>
<td>0.95</td>
<td>0.68</td>
<td>0.50</td>
<td>0.37</td>
<td>0.30</td>
<td>0.21</td>
<td>0.13</td>
</tr>
<tr>
<td>Quinine sulphate (mg)</td>
<td>650</td>
<td>390</td>
<td>325</td>
<td>227</td>
<td>195</td>
<td>130</td>
<td>97</td>
<td>65</td>
</tr>
<tr>
<td>Sod. bicarbonate (mg)</td>
<td>1430</td>
<td>975</td>
<td>715</td>
<td>510</td>
<td>390</td>
<td>325</td>
<td>260</td>
<td>130</td>
</tr>
<tr>
<td>Aspirin (mg)</td>
<td>1040</td>
<td>650</td>
<td>520</td>
<td>325</td>
<td>260</td>
<td>195</td>
<td>162</td>
<td>97</td>
</tr>
</tbody>
</table>
Use of smallest size of the capsule properly filled is always preferred. In extemporaneous dispensing, the optimum size of the capsule shell is determined by prior experimentation. In large scale production, the volume of the powder mix filled into the capsule body, in a capsule machine under normal filling pressure is optimized for each powder blend. However, strict control over the property of the powder blend like size and density are to be exercised to avoid inter batch and intra batch weight variation of the capsules prepared.

Simple punch method of filling is used when pharmacist prepare capsules in small numbers over the counter. In this method, the powder to be filled is taken in a glass plate and gently pressed using a spatula to form a cake having depth approximately equal to one third of the length of the body of the capsule. The capsule body is held between thumb and the fore finger and repeatedly pierced/punched vertically into the cake until filled. The body is then capped. Granular materials which are not possible to punch are filled into the capsule body by pouring weighed amount of the powder from a paper fold. These methods do need cross check by weighing the filled capsules individually to ensure uniform filling.

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

(a) Hand Operated Capsule Filling Machine

Hand operated capsule filling machine consists of a loader tray and a filler unit as seen in the figure 1.3. The loader tray is used to load the empty capsules into the filler units and is available with generally 100 holes or in multiples of 100 to load equal number of capsules at once. The filler unit has two plates (Lower and upper plate) both with the same number of holes as the loader tray of the same machine. The lower plate has provision to hold the body of the capsule in position with the help of a key, while the cap is to be separated from the body before filling. The holes in the upper plate has dimension to allow capsule body to go in easily and retain cap with it when lifted. Machine also contains a filling tray which can be fixed above the filler unit to help filling the powder into the capsule body.