Chapter 1

Introduction and objectives
## Chapter 1  Introduction and objectives

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>CONTENTS</th>
<th>Page No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Historical development and role as a dosage form</td>
<td>2</td>
</tr>
<tr>
<td>1.2</td>
<td><strong>Hard gelatin capsules</strong></td>
<td></td>
</tr>
<tr>
<td>1.2.1</td>
<td>Advantages</td>
<td>5</td>
</tr>
<tr>
<td>1.2.2</td>
<td>Disadvantages</td>
<td>6</td>
</tr>
<tr>
<td>1.2.3</td>
<td>Manufacturers and shell composition</td>
<td>7</td>
</tr>
<tr>
<td>1.2.4</td>
<td>Storage, packaging and stability considerations</td>
<td>11</td>
</tr>
<tr>
<td>1.2.5</td>
<td>Cross-linking and dissolution</td>
<td>12</td>
</tr>
<tr>
<td>1.2.6</td>
<td>Official status and standards</td>
<td>18</td>
</tr>
<tr>
<td>1.3</td>
<td><strong>Filling of hard capsules</strong></td>
<td>19</td>
</tr>
<tr>
<td>1.4</td>
<td>Design of hard capsule formulation and choice of excipients</td>
<td>21</td>
</tr>
<tr>
<td>1.5</td>
<td><strong>Objectives of present work</strong></td>
<td>32</td>
</tr>
<tr>
<td>1.6</td>
<td>References</td>
<td>34</td>
</tr>
</tbody>
</table>
1.1 Historical development and role as a dosage form

The word 'capsule' in the English language is derived from the Latin word 'capsula', which means a small box or container. 'Capsule' has been used primarily to describe a solid oral dosage form which consists of a container, usually made of gelatin, filled with a medicinal substance. The word can be used to refer either to the gelatin container itself or to the whole object, container plus drug.

There are many forms of capsule and they can be divided into two main categories which in current usage are described by the adjectives 'hard' and 'soft'. The hard gelatin capsule consists of two separate parts, each a semi-closed cylinder in shape, one part being called the 'cap', having a slightly larger diameter than the other, which is called the 'body' and which is longer. The cap fits closely over the body to form a sealed unit.

Capsules are classified as either hard or soft, depending on the nature of the shell. Soft gelatin capsules (sometimes referred to as "softgels") are made from a more flexible, plasticized gelatin film than hard gelatin capsules. Most capsules of either type are intended to be swallowed whole; however, some soft gelatin capsules are intended for rectal or vaginal insertion as suppositories. Most capsule products manufactured today are of the hard gelatin type. One survey has estimated that the utilization of hard gelatin capsules to prepare solid dosage forms exceeds that of soft gelatin capsules by about tenfold.

The capsule may be considered as a "container" drug delivery system that provides a tasteless and odorless dosage form without need for a secondary coating step, as may be required for tablets. Swallowing is easy for most patients, since the shell is smooth. There availability in a wide variety of colors makes capsules aesthetically
pleasing. There are numerous additional advantages to capsules as a dosage form, depending on the type of capsule employed.

The first capsules prepared from gelatin was a one-piece capsule that was patented in France by Mothes and DuBlanc in 1834. Although the shells of these early capsules were not plasticized, such capsules likely would be classified today as "soft gelatin capsules" on the basis of shape, contents and other features. A wide variety of sizes and shapes are possible, including spherical, oval, oblong, tube and suppository-type; size may range from 1 to 480 minims (16.2 minims = 1 ml.).

Although the patent holders at first sold both filled and empty soft gelatin capsules, the sale of empty shells was discontinued after 1837. However, the demand that had been created for the empty capsules led to several attempts to overcome the patents which, in turn resulted in the development of both the gelatin-coated pill and the hard gelatin capsule. The first hard gelatin capsule was invented by J.C. Lehuby, to whom a French patent was granted in 1846. It resembled the modern hard gelatin capsule in that it consisted of two, telescoping, cap and body pieces. In Lehuby's patent, the capsule shells were made of starch or tapioca sweetened with syrup, although later additions to the patent claimed carrageenan (1847) and mixtures of carrageenan with gelatin (1850). The first person to describe a two-piece gelatin capsule was James Murdock, who was granted a British patent in 1848, and who is often credited as the inventor of the modern hard gelatin capsule. Since Murdock was a patent agent by profession, it has been suggested that he was actually working on behalf of Lehuby.

Unlike soft gelatin capsules, hard gelatin capsules are manufactured in one operation and filled in a completely separate operation. Originally, they were made by hand-dipping greased metal pinlike molds into a molten gelatin mixture, drying the resultant films, stripping them from the pins, and joining the same two pieces
together. Today, they are manufactured in a similar manner by means of a completely automated process. For human use, hard gelatin capsules are supplied in at least eight sizes, ranging in volumetric capacity from 0.13 to 1.37 ml. Typically, they are oblong; however some manufacturers have made modest alterations in that shape to be distinctive.

In further contrast with soft gelatin capsules, hard gelatin capsules typically are filled with powders, granules, or pellets. Modified-released granules or pellets may be filled without crushing or compaction, thereby avoiding disruption of barrier coats or other possible adverse effects on the release mechanism. Although many manufacturers of hard capsule-filling equipment also have developed modifications to their machines that would permit the filling of liquids or semisolid matrices.

Filled hard gelatin capsules are held together by interlocking bumps and grooves molded into the cap and body pieces, and the capsules are usually additionally sealed by a banding process that places a narrow strip of gelatin around the midsection of the capsule where the two pieces are joined.

Recently, hard shell capsules made from starch have become available (Capill; Capsugel, Div. Warner Lambert Co.) They are made by injection molding technique. The glassy mass formed when starch containing 13-14% water is heated, and then dried. Temperatures in the range of 140-190°C reportedly produce masses that flow satisfactorily without degradation. The two parts are formed in separate molds. Unlike hard gelatin capsules that are supplied with the caps and bodies prejoined, the two parts are supplied separately. The caps and bodies do not interlock and must be sealed together at the time of filling to prevent inadvertent separation. Recently hydroxypropyl methylcellulose capsules are introduced in national and international markets.
1.2 Hard gelatin capsules

1.2.1 Advantages

Hard gelatin capsules often have been assumed to have better bioavailability than tablets. Most likely, this assumption derives from the fact the gelatin shell rapidly dissolves and ruptures, which afford at least the potential for rapid release of the drug, together with the lack of utilization of a compaction process comparable with tablet compression in filling the capsules. However, capsules can be just as easily malformulated as tablets. A number of reports of bioavailability problems with capsules have been reported.5-8

Hard shell capsules allow a degree of flexibility of formulation not obtainable with tablets, often they are easier to formulate because there is no requirement that the powders be formed into a coherent compact form. However, the problems of powder blending and homogeneity, powder fluidity, and lubrication in hard capsule filling are similar to those encountered in tablet manufacture. It is still necessary to measure out an accurate and precise volume of powder or pellets, and the ability of such dry solids to uniformly fill into a cavity (often comparable with a tablet die) is the determining factor in weight variation and, to a degree content uniformity.

Modern filling equipment makes possible the multiple filling of diverse systems (e.g., beads or granules, tablets, powders, semisolids) in the same capsule, which offers many possibilities in dosage form design to overcome incompatibilities by separating ingredients within the same capsule, or to create modified or controlled drug delivery. Indeed, capsules are ideally suited to the dispensing of granular or bead-type modified-release products, since they may be filled without a compression process that could rupture the particles or otherwise compromise the integrity of any controlled-release coatings.
Hard gelatin capsules are uniquely suitable for blinded clinical tests and are widely used in preliminary drug studies. Bioequivalence studies of tablet formulations may be conveniently “blinded” by inserting the tablets into opaque capsules, often along with an inert filler powder. Even capsule products may be disguised by inserting them into larger capsules.

1.2.2 Disadvantages

From a manufacturers point of view, there perhaps is some disadvantages in the fact that the number of suppliers of shells is limited. Moreover, filling equipment is slower than tableting, although that gap has narrowed in recent years with the advent of high-speed automatic-filling machines. Generally, hard gelatin capsule products tend to be more costly to produce than tablets; however, the relative cost effectiveness of capsules and tablets must be judged on a case-by-case basis. This cost disadvantage diminishes as the cost of the active ingredient increase or when tablets must be coated.9 Furthermore, it may be possible to avoid the cost of a granulation step by choosing encapsulation in lieu of tableting.

Highly soluble salts (e.g. iodides, bromides or chlorides) generally should not be dispensed in hard gelatin capsules. Their rapid release may cause gastric irritation owing to the formation of a high drug concentration in localized areas. A somewhat related concern is that both hard gelatin capsules and tablets may become lodged in the esophagus, where the resulting localized high concentration of certain drugs (doxycycline, potassium chloride, indomethacin, and others) may cause damage.10

Manufacturers of pharmaceutical products have the responsibility, not only from marketing and ethical standpoints but also from a legal (regulatory) perspective, to ensure that their products meet dissolution specifications during storage conditions described on
the label. This is necessary because dissolution per se is rate determining in terms of the absorption and bioavailability of a drug.

Unfortunately, a few dosage forms exist in which eventual change in the dissolution characteristics is a common problem. Formulations containing gelatin in the outer layer (i.e., hard and soft gelatin capsules) as well as sugar-coated tablets are typical examples. Nevertheless, the material is used widely despite efforts to replace it with other substances.

A major problem with gelatin-based formulations is an apparent fall in dissolution upon aging, which is attributed to the cross-linking of stressed gelatin-containing products. The cross-linking causes the formation of a swollen, very thin, tough, rubbery, water-insoluble membrane, also known as a pellicle. The pellicle acts as a barrier and restricts the release of the drug. It is not disrupted easily by gentle agitation, and the dissolution values (Q values) drop often to the point of rejection.\textsuperscript{11,12}

1.2.3 The Manufacturers and shell composition.

Manufacturers

Empty hard gelatin capsules are manufactured on Colton machines, which were invented about 50 years ago. It has been estimated that there are about 340 such machines worldwide. There are three producers of hard shell capsules in North America (Shionogi Qualicaps, Indianapolis, IN; Capsugel Div. Warner-Lambert Co., Greenwood, SC, and Pharmaphil Corp, Windsor, Ontario).

Shell Composition

Hard capsule shells are manufactured by a process in which stainless steel mold pins are dipped into warm film former/s solutions and the shells are formed on the pin surfaces. Gelatin is the most important constituent of the dipping solutions, but other components
may be present. The film former can be materials other than gelatin also.

_Gelatin_: Gelatin is prepared by the hydrolysis of collagen obtained from animal connective tissue, bone, skin and sinew. This long polypeptide chain yields, on hydrolysis, 18 amino acids, the most prevalent of which are glycine and alanine. Gelatin can vary in its chemical and physical properties, depending on the source of the collagen and the manner of extraction. There are two basic types of gelatin. Type A, which is produced by an acid hydrolysis, is manufactured mainly from pork skin. Type B gelatin, produced by alkaline hydrolysis, is manufactured mainly from animal bones. The two types can be differentiated by their isoelectric points (4.8-5.0 for Type B and 7.0-9.0 for Type A) and by their viscosity-building and film-forming characteristics. Either type of gelatin may be used, but combinations of pork skin and bone gelatin are often used to optimize shell characteristics.\textsuperscript{13,14} Bone Gelatin contributes firmness, whereas pork skin gelatin contributes plasticity and clarity.

_Gelatin Extenders_: These are cheap and readily available materials which can be used to reduce the quality of gelatin needed for capsule and to enable cheaper gelatin, with proper physical properties are to be used.

One natural material now comparatively abundant is starch, and the National Starch and Chemical Corporation has obtained a patent for the use of modified starches in the production of capsules (US patent 3758323, 1953). The suggested material is a product of corn starch and dextrin which is modified by thermal or chemical treatment using succinic anhydride in latter case.

_Gelatin Substitutes_: The preparation of hard capsules from materials other than gelatin have been tried by various researchers.

1. Modified gelatin or combined gelatin:

Crystalline cellulose, high amylose starch (Hylon VII), natural powder of calcium dissolved in sodium metaphosphate, succinylated gelatin,
surface coated gelatin capsule for excellent glide, antistatic and printing qualities during production steps. Above all modified gelatin or combined gelatin does not recover from cross-linking problem.

2. Natural gelatin substitutes obtained from plants are broadly classified as cellulosics, starches, proteins, etc. All these materials have not still produced the characteristics and processing convenience of gelatin and they are of definite range of molecular weight, most of them are covered by patents. Hydroxypropyl starch, whey protein, vegetable protein, starch hydrolysate with or without plasticizer have been studied. Out of all other such materials, hydroxypropyl methyl cellulose has been little more successful than others in producing commercially available capsules. Various gelling agents like polysaccharide and gums (locust, xanthan, gallan), electrolytes (e.g. sodium citrate, potassium chloride), carageenan, pullulan, carboxymethylcellulose, starch and its derivatives, are added in the formulation of HPMC capsules. All such formulations and processing techniques are patented and the capsule shells are atleast 10 times costlier than conventional hard gelatin capsules.

3. Miscellaneous materials other than stated in 1 and 2 are classified as natural or synthetic
   a) Natural materials includes chitosan, agar, algates and dextran. Majority of them have been used for specific targeting of the content but not as substitute for conventional hard gelatin capsules.
   b) Synthetic materials includes polyvinyl alcohol, polyvinyl ester, polyamide, poly -D-L lactic acid, polyglutamic acid and salts, hydroxy ethyl cellulose in combination with polyvinylpyrrolidone, PEG-poly (l-lysine) block copolymer. These materials could not be substitute for conventional hard gelatin capsules.
   The so-called end of gelatin due to BSE (bovine serum encephalopathy) or cross-linking mediated dissolution problem could not have been stopped using people from hard gelatin capsules. Innovation are required in HPMC capsules to address the issues of high
cost, poor gloss and limited colors. All other synthetic materials are useful for coating or microcapsule purposes. Two-piece hard shell capsule which can replace or overcome the problem of gelatin has been extensively thought of in the present study.

Film forming and capsule forming properties should be balanced with above alternative materials. Strength versus resealability, copolymer additives and heat reversible gel formulation are essential properties for converting any film forms into capsule shell. Alternatively, the preformed film technique, injection molding or extrusion techniques are also experimentally developed.

All the patents for capsules produced from synthetic polymers claim that such capsules have improved stability, being less susceptible to bacterial growth and moisture. However, the criteria on which the choice of a material to make capsules is based are the solubility in biological fluids and the oral toxicity. This factor is currently most important because gelatin has universal acceptability despite of cross-linking problems. For any other material to replace it, the cost of performing the required toxicity tests is so high that search is limited to materials those are already, proved safer. Despite numerous patents, there have been no product successfully marketed in synthetic polymer capsules, as yet. Only HPMC has taken place of commercial market but limited because of its cost.

Colorants.

Commonly, various soluble synthetic dyes ("coal tar dyes") and insoluble pigments are used. Commonly used pigments are the iron oxides. Colorants not only play a role in identifying the product, but also may play a role in improving patient compliance. Thus, the color of a capsule may be selected in consideration of the disease state for which it is intended. For example, Buckalew and Coffield\textsuperscript{15} found in a panel test that four colors were significantly associated with
certain treatment groups (white, analgesia; lavender, hallucinogenic effects; orange or yellow, stimulants and antidepressants).

Opacifying Agents.

Titanium dioxide may be included to render the shell opaque. Opaque capsules may be employed to provide protection against light or to conceal the contents.

Preservative.

When preservatives are employed, parabens are often selected.

Water.

Hot, demineralized water is used in the preparation of the dipping solution. Initially, a 30-40% w/w solution of gelatin is prepared in large stainless steel tanks. Vacuum may be applied to assist in the removal of entrapped air from this viscous preparation. Portions of this stock solution are removed and mixed with any other ingredients, as required, to prepare the dipping solution. At this point, the viscosity of the dipping solution is measured and adjusted. The viscosity of this solution is critical to the control of the thickness of the capsule walls.

1.2.4 Storage, Packaging and Stability Considerations

Finished gelatin capsules normally contain an equilibrium moisture content of 13-16%. This moisture is critical to the physical properties of the shells, since at lower moisture contents (<12%) shells become too brittle; at higher moisture contents (>18%) they become too soft.\textsuperscript{16-17} It is best to avoid extremes of temperature and to maintain a relative humidity of 40-60% when handling and storing capsule shells. HPMC capsule shells contain 4-5% moisture.
Chapter 1 Introduction and objectives

The bulk of the moisture in capsule shells is physically bound, and it can readily transfer between the shell and its contents, depending on their relative hygroscopicity.\textsuperscript{18-19} The removal of moisture from the shell could be sufficient to cause splitting or cracking, as has been reported for the deliquescent material, potassium acetate.\textsuperscript{20} Sodium cromoglycate has been reported to act as a "sink" for moisture, in that moisture was continuously removed from hard gelatin shells, especially at higher temperatures.\textsuperscript{21} Conditions that favor the transfer of moisture to powder contents may lead to caking and retarded disintegration or other stability problems. It may be useful to preequilibrate the shell and its contents to the same relative humidity within the acceptable range.\textsuperscript{22-23}

1.2.5 Cross-linking and dissolution

One issue that is receiving current attention is the loss of water solubility of shells, apparently as a result of sufficient exposure to high humidity and temperature or to exposure to trace aldehydes.\textsuperscript{24} Such capsules develop a \textit{"skin" or pellicle} during dissolution testing, exhibit retarded dissolution, and may fail to meet the pharmacopoeial drug dissolution specifications. This insolubilization of gelatin capsules has been attributed to "gelatin cross-linking." In one example, photoinstability compounded by humidity has been suggested as the explanation for the retarded dissolution of model compounds from hard gelatin capsules containing certified dyes, particularly when FD&C Red. No. 3 was incorporated in both the cap and the shell.\textsuperscript{25-26} The problem also has been attributed to the presence of trace aldehydes in excipients,\textsuperscript{27} as well as to the liberation of furfural from the rayon stuffing in bottles.\textsuperscript{24} These results point to the need for appropriate storage conditions and moisture-tight packaging, as well as to the need to exclude aldehydes. The issue is
not new, nor is it a capsule issue per se; rather it is a gelatin issue. The loss of water solubility on exposure of gelatin to elevated temperature and humidity was reported in 1968 to be "particularly disadvantageous in the case of gelatin desserts."28 The phenomenon also has been reported to occur with gelatin-coated acetaminophen tablets.29 The inclusion of gastric enzymes in dissolution media tends to negate these effects,26,29 thus, the phenomenon may have little physiological significance.30,31

The chemistry of the gelatin cross-linking problem

An excellent review by Digenis et al.11 describes the mechanistic rationalizations that explain gelatin cross-linking in stress conditions relevant to pharmaceutical situations.

Postulated chemical events.

The following chemical events are postulated to be involved in the cross-linking process:

> The reactivity of the gelatin arises from the trifunctional amino acid lysine. The lysine residues, which are proximal to each other, are oxidatively deaminated to yield terminal aldehyde groups. One of the aldehyde groups is attacked by a free α-amino group of a neighboring lysine to yield an imine, which subsequently undergoes a series of aldol-type condensation reactions to produce a cross-linked product containing pyridinium ring(s).

> The lysyl α-amino group reacts with aldehyde when it is present as an impurity. The reaction yields a hydroxymethylamino derivative, which loses water to form a cationic imine. The latter reacts with another hydroxymethylamino lysine residue to form dimethylene ether, which eventually rearranges to form a methylene link between two lysyl α-amino groups, resulting in the development of a cross-link.
The third type of gelatin cross-linking is the formation of aminal, the amine form of an acetal, which is produced by a reaction of a cationic imine intermediate (see previous bullet) with a free amino group. The pH of the environment plays an important role in this type of reaction.

A similar type of reaction can occur with glucose or other aldose sugars that are commonly used in pharmaceutical formulations. The imine formed during the interaction of an aldehydic functional group of these saccharides reacts with the free amino group and produces ketose sugar upon rearrangement. The ketose sugar then reacts with another amine through its carbonyl functionality to form cross-linked gelatin. In addition to lysine-lysine cross-linking, lysine-arginine and arginine-arginine crosslinking also are reported. In general, crosslinking of the gelatin polypeptides can occur in the following two ways:

- Bridging can take place within the same polypeptide strand (intrastrand, intramolecular cross-linking).
- Amino acid residues from two neighboring peptide strands can form a bridge (interstrand, intermolecular cross-linking), a process that increases the molecular weight of gelatin.\(^{32}\)

As a result of cross-linking, the interparticulate bonds formed in the original compact are removed and replaced by new bonds, culminating in a dosage form that has a different porosity and pore structure and therefore a different in vitro release pattern as compared with the original.\(^{33}\)

_Causative factors for cross-linking_

The presence of some chemicals, high humidity, high temperature, and exposure to light has been found to play individual or synergistic roles in increasing the in vitro dissolution time of formulations containing gelatin in the outer layer.

In India above causative factors are totally unavoidable throughout the shelf-life. Other formulation excipients containing
trace amounts of aldehydes decomposition products of excipients, sugars, plasticiser, preservatives, fats, PEG, non-ionic surfactants, all are common cause of cross-linking. Meyer et al studied\textsuperscript{34} that the highly stressed acetaminophen capsules were not bioequivalence to the unstressed capsules. They fail in dissolution criteria even in presence of USP simulated gastric fluid. Structural change within the aged capsule shell was responsible for slowed dissolution when enzymes are used in combination with surfactant media. Ionic surfactants (e.g. sodium dodecyl sulfate) can denature enzymes. Capsules should be pre-soaked with enzyme containing media and then surfactant is added. However, cross-linking is a problem, which needs to be solved by any means in order to establish bioequivalency from hard capsule shells.

\textit{Inhibition of gelatin cross-linking}

Efforts have been made to identify the means to protect gelatin-based formulations against changes in dissolution characteristics. Many approaches exist such as using additives and direct inhibitors and controlling humidity and photostabilization.

\textit{Using Type B gelatin}

Type B gelatin is mentioned in the literature to be associated with less cross-linking than is Type A gelatin, but unfortunately no details of the study are reported.\textsuperscript{35}

\textit{Protecting against released aldehydes or preventing the formation of aldehydes.}

Compounds such as lysine, phenylamine, glutamine, hydroxylamine hydrochloride, \textit{p}-amino benzoic acid, glycine, and others function as carbonyl scavengers, preventing the interaction of aldehydes with gelatin shells and thereby inhibiting cross-linking.\textsuperscript{36} It is reported that if the formaldehyde initially present in the capsule fill
is scavenged by the use of glycine, an amino acid, it prevents or reduces the further introduction of aldehyde.\textsuperscript{37} Another approach is to prevent the very formation of aldehydes, a process that can be accomplished by controlling the degradation of the capsule contents through manipulation of pH. Carboxylic acids such as benzoic acid, fumaric acid, maleic acid, and citric acid have been found to be effective for this purpose. Trials have shown that using a combination of an amino acid and a buffer significantly prevents pellicle formation. A typical example is the synergistic use of glycine and citric acid.

\textit{Use of direct inhibitors.}

Some compounds act as direct inhibitors, and they also have been found to protect gelatin-based formulations against changes in dissolution characteristics. Examples include semicarbazide hydrochloride, hydroxylamine hydrochloride, piperazide hydrate, pyridine, piperidine, glycerine, and \textit{p}-aminobenzoic acid.\textsuperscript{36-37}

\textit{Control of humidity.}

The dissolution characteristics of capsules become more seriously affected when they are stored in blister packaging made of PVC, which affords minimal protection against moisture. The best way to overcome this adverse effect is to use water-impermeable packaging systems. An alternate method is to add disintegrants to the hard gelatin capsules fill powder blend. Capsule formulations containing 10\% of disintegrant can withstand the stress of high-humidity storage conditions presumably because of the more-porous nature of the capsule fill.\textsuperscript{38}

\textit{Photostabilization.}

Thoma has reported photostabilization of gelatin capsules using distinct approaches: coloring or pigmentation of the gelatin shell and core and manipulation of the thickness of the shell, size of granules or
powder particles, and the size and height of the core. It has been shown that titanium oxide, iron oxide, and color pigments offer good protection against cross-linking introduced by light. A curcumin content of 0.4% in the capsule shell resulted in a threefold or higher increase in the half-life of the test compounds. Some dyes such as FD&C Yellow No. 5, Blue No. 1, and Red No. 3 also were able to protect dosage forms from light. The same was true of synthetic iron oxides, which are potent absorbers of wavelengths <400 nm.

**Intentional cross linking for specific purposes**

Intentional cross-linking of gelatin before or after drying the capsules allows for sustained release of the drug. Formaldehyde exposure has been exploited to produce enteric hard and soft capsules. Drilling pores in formaldehyde cross-linked gelatin capsules to design a controlled-release dosage form also has been reported. A zero-order release of verapamil was observed with this approach. Several other reports describe the formation of gelatin microspheres and their cross-linking with glutaraldehyde with the objective of sustaining drug release. Cross-linked gelatin gels have been used as biomaterials in living tissues either as bioadhesives or as devices for sustained drug release. A novel system for gene delivery based on the use of DNA-gelatin nanoparticles (nanospheres) formed by salt-induced complex coacervation of gelatin and plasmid DNA has been developed. It consists of spherical particles in sizes ranging from 200 to 700 nm containing 25–30% (w/w) DNA. The particles are stabilized by the cross-linking of gelatin. Therapeutically, gelatin has been used as a plasma substitute and in the preparation of wound dressings. Soft capsules made of gelatin and containing a radiolabeled drug have been used in radioactive tracer studies. Gelatin also is widely used in food products and photographic emulsions. In general, when it is used in an oral formulation, gelatin may be regarded as a nontoxic and nonirritant material. However, rare reports exist of
gelatin capsules adhering to the esophageal lining,\textsuperscript{50-52} which may cause local irritation. Hypersensitivity reactions, including serious anaphylactoid reactions, have been reported following the use of gelatin in parenteral products.\textsuperscript{53}

1.2.6 Official status and standards.

Gelatin is included on the FDA list of inactive ingredients. In the United Kingdom, it appears on the list of licensed medicines. It also is described in most pharmacopoeias. The capsule standards have been extensively reviewed by B.E. Jones.\textsuperscript{41}

They are divided into two categories:
1. Pharmacopoeial standards to control the quality of capsules in relation to their medicinal use.
2. Industrial standards control the quality of capsule shells to ensure the efficacy of the manufacturing process and to produce a product, which is acceptable to consumer.

Pharmacopoeial standards includes raw materials used in shell manufacture, content of active ingredient, uniformity of weight (including that for rectal, vaginal capsules by B.P., uniformity of dosage units or content uniformity, disintegration test for oral empty, filled and enteric capsules simulating in vivo condition, disintegration test for non-oral capsules, dissolution test for capsules. Miscellaneous Pharmacopoeial requirements are formulation of contents, labeling of products, stability, storage conditions and packaging.

Industrial standards are agreed between the capsules producers and users. Standards for empty hard capsules are like dimensions; open, closed, solubility, moisture content, odor, pin-holes, etc. Defects of it are classified as critical, major, minor, or printing defects. Standards for filled hard capsules are reported in American Fed. Std. No. 285A.
1.3 Filling of hard capsules

The several types of filling machines in use in the pharmaceutical industry have in common the following operations:

1. Rectification: The empty capsules are oriented so that all point the same direction (i.e., body-end downward). In general, the capsules pass one-at-a-time through a channel just wide enough to provide a frictional grip at the cap end. A specially designed blade pushes against the capsule and causes it to rotate about its cap end as a fulcrum. After two pushes (one horizontally and one vertically downward), the capsules will always be aligned body-end downward, regardless of which end entered the channel first.

2. Separation of caps from bodies: This process also depends on the difference in diameters between cap and body portions. Here, the rectified capsules are delivered body-end first into the upper portion of split bushings or split filling rings. A vacuum applied from below pulls the bodies down into the lower portion of the split bushing. The diameter of the caps is too large to allow them to follow the bodies into the lower bushing portion. The split bushings are then separated to expose the bodies for filling.

3. Dosing of fill material: Various methods are employed, as mentioned below:

- Powder filling: Auger, Vibrator, Piston-Tamp (slug)- Dosing disk dosator.
  The above mentioned filling patterns were evaluated for successful filling by Stoyle.54 and the characteristics checked were fluidity, compactibility, lubricity and moderate bulk density.
- Nonpowder filling: Modern automatic capsule filling machines of enormous flexibility in terms of beads or pellets, microtablets.
liquids or pasty materials, in addition to powder dosing, immediate release, modified release beads or combinations of tablets, powder plugs and beads into same capsule are also possible by installing different filling stations, closures and ejection in the same machine. Typically tablets are fed to the bodies through a tube and are simply released in the required number as the body passes beneath. Pumpable liquid fills are dosed by conventional liquid dispensing devices.

4. Replacement of caps and ejection of filled capsules: The cap and body bushing portions are rejoined. Pins are used to push the filled bodies up into the caps for closure, and to push the closed capsules out of the bushings. Compressed air also may be used to eject the capsules.
1.4 Design of hard capsule formulations and choice of excipients.

Lubricity, compatibility and fluidity are not only essential to a successful filling operation, but also may be expected to influence drug release from the capsules. Indeed, the various filling principles themselves may be expected to influence drug release. This seems particularly evident for those machines that form compressed plugs. When immersed in a dissolution fluid at 37°C, hard gelatin capsules can be seen to rupture, first at the shoulders of the cap and body where the gelatin shell is the thinnest. As the dissolution fluid penetrates the capsule contents, the powder mass begins to disintegrate and deaggregate from the ends to expose drug particles for dissolution. The efficiency by which the drug will be released will depend on the wettability of the powder mass, how rapidly the dissolution fluid penetrates the powder, the rate of disintegration and deaggregation of the contents, and the nature of the primary drug particles. These processes, in turn, can be significantly affected by the design of the formulation and the mode of filling. Such factors as the amount and choice of fillers and lubricants, the inclusion of disintegrants or surfactants, and the degree of plug compaction can have a profound effect on drug release.

Active Ingredient

The amount and bulk density of active ingredient influences capsule size and the nature and amount of excipients to be used in the formulation. Although there are a growing number of exceptions, drugs having doses less than 10 mg are seldom formulated into capsules. These can usually be as easily formulated into tablets that
are more economical. Thus, the active ingredient often tends to make up a high percentage of the contents of a capsule; much more so than is usual for tablets.

The dissolution of a drug in gastrointestinal fluids must occur before absorption can occur. Drugs having high water solubility generally exhibit few formulation problems. For drugs of low water solubility, the absorption rate may be governed by the dissolution rate. In such circumstances, if dissolution occurs too slowly, absorption efficiency may suffer. Drug stability in gastrointestinal fluids is another concern for slowly dissolving drugs, which can affect their bioavailability. Drugs of low water solubility are usually micronized to increase the dissolution rate. Particle size reduction increases the surface area per unit weight of the drug, thereby increasing the surface area available from which dissolution can occur.

From a manufacturing point of view, a compromise may have to be struck between small particle size and good flow properties. Small particles, in general, are more poorly flowing than larger particles. Surface cohesive and frictional interactions, which oppose flow properties, are more important in smaller particle size powders because of their larger specific surface areas. One possible way to both reduce the effects of aggregation of fine particles and enhance flow properties is granulation. When micronized ethinamate was granulated in a simple moist process with isopropanol, bed permeability and drug dissolution from capsules were greatly enhanced compared with the micronized powder.57

*Dissolution enhancement from Hard Capsules of poorly soluble drugs*

The dissolution of drug at the site of absorption is frequently the rate-limiting factor in the distribution process. It has been established that the formulation of the dosage form and the physico-chemical
characteristics of the drug may have a marked influence on the dissolution process and hence on the pharmacological performance of the drug.

The rate and extent at which, the active ingredient is delivered to the circulation is referred to as the bioavailability. The drug release especially from gelatin capsules have added parameter of decreased bioavailability due to cross-linking under highly stressed conditions. Change in the extent of the absorption will change both the peak height and total area under the curve. Alternatively, the rate and extent of urinary excretion of the drug or its metabolites can be measured. Another approach is in vitro test under simulated in vivo conditions is less time-consuming.

Such tests are based on the ability of a dosage form to disintegrate in a fluid under given conditions (disintegration test) or upon the amount that is released into solution in a specified fluid under given conditions (dissolution test). These tests are used in official standards for certain preparations in B.P. and the USP. Dissolution tests provide reproducible condition for the solution process and can indicate the way in which formulation variables influence the solution rate process. No single test procedure has been devised which can simulate accurately what happens to a dosage form after administration, mainly because individuals vary in their responses. The apparent simplicity of capsule formulation as a blend of powders which will be readily available for dissolution promotes the belief that hard gelatin capsules are a readily bioavailable oral dosage form.

A solution of the drug is considered to be the most useful oral reference preparation as it eliminates the dissolution phase. Hence, comparison with a solution should indicate whether dissolution is the rate-limiting factor.

It is also important to realize that reports of capsule formulations being less bioavailable than other preparations could be
due to a particular drug being poorly absorbed by oral route for various reasons or may be due to cross-linking and pellicle formation of gelatin capsule shell which does not allow subsequent release of the drug even in an enzyme containing media.

In order to ensure adequate bioavailability while formulating hard gelatin capsules, it is necessary to consider various factors viz. solubility, particle size, and wettability of drug, combination with possible additives, requirement to produce granules and filling process. A capsule which does not disintegrate is very unlikely to be less effective. So in addition to formulation and processing factors, insolubilization of shell due to cross-linking is equally important.

*Fill improvement*

Drug solubility: For a wide range of compounds, the intrinsic rate of dissolution is directly proportional to the solubility. Hence the lower drug solubility, the lower will be the rate of dissolution and subsequent absorption. One can anticipate problems when presenting drugs with low water solubility in capsules. Blending of simple additives will not overcome the formulation problems. Modification in capsule shell is another approach.

The most pertinent consequence associated with these interactions is often decreased therapeutic action due to altered stability, dissolution rate and ultimate absorption of the drug. These interactions could be eliminated if no excipients or minimum excipients or only non-interacting excipients were employed. The official compendia demand a plethora of formulation variables in order to meet the specifications of disintegration time, dissolution rate and physiological availability. Hard capsules utilizes minimum number of excipients in the product formulation, there by reduces chances of problems associated with drug excipients interaction. But at the same time gelatin offers cross-linking problem, which results in poor disintegration and dissolution.
of hard gelatin capsule shell. The poor dissolution of relatively insoluble drugs has long been a problem to the pharmaceutical industry. The absorption of such drug is rate limited by dissolution process. The physico-chemical factor controlling the dissolution rate may be described by Noyes-Whitney equation.\textsuperscript{58} The terms in these equations can be modified and the dissolution rate is altered through:

\[ \frac{dc}{dt} = \frac{A^* D (C_s - C)}{h} \]

\( \frac{dc}{dt} \) = Rate of dissolution,  
\( A = \) Surface area,  
\( D = \) Diffusion coefficient,  
\( C_s = \) Solubility in dissolution medium,  
\( C = \) Concentration,  
\( h = \) Thickness of diffusion boundary layers,

\textit{Introduction to solid dispersion}

Chiou and Riegelman.\textsuperscript{59} had defined the term solid dispersion as “a dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by the melting (fusion), solvent or melting-solvent method”. The solid dispersion may also be called solid state dispersions as first used by Mayersohn and Gibaldi.\textsuperscript{60} In practice, these dosage forms have been regarded as being synonymous with systems whereby the in-vitro release of the drug is enhanced compared to conventional dosage forms, with concomitant implications for in vivo release. Furthermore, the carrier used has been a water-soluble or water-miscible polymer such as polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP) or low molecular weight materials such as sugars.
Chapter 1 Introduction and objectives

Classification of solid dispersions

1. Simple eutectic mixtures,
2. Solid solutions,
3. Glass solutions and glass suspensions,
4. Amorphous precipitations in a crystalline carrier,
5. Powdered solutions and liquisolid compacts, and
6. Compound or complex formation.

Mechanism of increased dissolution

The enhancement in dissolution rate by formation of solid dispersion, relative to the pure drug varies from as high as 400 fold to less than two fold. The increase in dissolution rate for solid dispersions can be attributed to a number of factors. It is difficult to demonstrate experimentally that any one particular factor is more important than other.

Selection of carriers

The properties of the carrier have major influence on the dissolution characteristics of the dispersed drug.

Ideal requirement of carrier:

It should be non toxic, pharmacologically inert, heat stable, low melting point, soluble in variety of solvents, chemically compatible with drug, etc.

List of carriers for solid dispersion

<table>
<thead>
<tr>
<th>Sugars</th>
<th>Dextrose, sucrose, sorbitol, maltose, xylitol, mannitol, lactose, etc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acids</td>
<td>Citric acid, succinic acid, etc.</td>
</tr>
<tr>
<td>Polymeric</td>
<td>PVP, PEG, HPMC, MC, HPC, Hydroxyl ethyl cellulose, Cyclodextrins, pectin, etc.</td>
</tr>
<tr>
<td>materials</td>
<td></td>
</tr>
<tr>
<td>PH dependent</td>
<td>Eudragit L, Eudragit RS, Eudragit E-100, etc.</td>
</tr>
<tr>
<td>polymers</td>
<td></td>
</tr>
<tr>
<td>Surfactants</td>
<td>Polyoxyethylene stearate, Poloxamer, Tweens, Spans.</td>
</tr>
</tbody>
</table>
Introduction to inclusion complex.

Here one molecule is enclosed within another molecule or structure of molecules. The combination is characterized by absence of ordinary chemical bonds, the essential criteria is that enclosed molecule or guest be of a suitable size and shape to fit into a cavity within a solid structure formed by a host molecule. The stereochemistry, possibly of both host and guest molecules determine whether the inclusion complex can occur. The inclusion compounds formed with apolar molecules are only slightly soluble in water whereas those formed with polar molecules are moderately soluble.

Dissolution and bioavailability

For Class II category drugs of biopharmaceutical classification, rate of dissolution (kd) is less than rate of absorption (ka). Here dissolution is the rate determining step in drug absorption. In case of cyclodextrin inclusion complex, following oral dose only the drug and practically no cyclodextrin is absorbed. cyclodextrin is only a carrier agent. It transports the lipophilic guest molecule through an aqueous milieu to the lipophilic membrane of cells in the gastro intestinal tract. The dissociation-association reactions of cyclodextrin complexes in solution are very fast and the equilibrium of free-complexed drug is established instantaneously. This may be used also to improve medication through the use of tablets containing both the hydrophobic drug complexed to cyclodextrin and the same drug in the free form. The former would enter the circulation very rapidly, while dissolution of the latter would occur slowly and form a drug depot. The above application is not limited to oral use. Cyclodextrin complexed drugs in suppositories exhibit improved dissolution rate and consequently, higher concentration levels of the drug in circulating blood are obtained.
Fillers

Fillers (diluents) are often needed to increase the bulk of the formulation. The most common capsule diluents are starch, lactose, and dicalcium phosphate. These substances improve flow and compactibility while maintaining the basic properties of the original materials.

Glidants

Glidants are used to improve the fluidity of powders. They are fine particles that appear to coat the particles of the bulk powder and enhance fluidity by one or more of several possible mechanisms. (a) reducing roughness by filling surface irregularities, (b) reducing attractive forces by physically separating the host particles, (c) modifying electrostatic charges, (d) acting as moisture scavengers, and (e) serving as ball bearings between host particles. Usually, there is an optimum concentration for flow, generally less than 1% and typically 0.25-0.50%. The optimum concentration may be related to the concentration just needed to coat the host the particles. Exceeding this concentration usually will result in either no further improvement in flow and, even, a worsening of flow. Glidants include the colloidal silicas, corn starch, talc, and magnesium stearate.

Lubricants

Capsule formulations usually require lubricants just as do tablet formulations. Lubricants ease the ejection of plugs, reduce filming on pistons and adhesion of powder to metal surfaces, and reduce friction between sliding surfaces in contact with powder. The same lubricants are used in both tablet and capsule formulations. Magnesium stearate and stearic acid are typical. The effect of magnesium stearate has been noted in a study of the dissolution of rifampin from hard gelatin capsules.
Disintegrants

Although tablet disintegrants are being used in some capsule formulations, until recently, the role they play in capsules has been a relatively unexplored area. The few studies that have been reported produced only mixed results and usually involved hand-filled capsules. Capsules filled by methods that afford little compression of contents (e.g., auger method) are much looser than tablets, and there is little structure for disintegrants to swell against to effect disintegration. However, the advent in recent years of filling machines that actually compress capsule contents, together with the development of newer disintegrants that have superior swelling or moisture-absorbing properties, appear to warrant serious considerations of disintegrants in modern capsule formulations. These newer disintegrants, which have been called “super disintegrants”, include croscarmellose sodium, type A and crospovidone.

In a later study, the effect of disintegrants on hydrochlorothiazide dissolution from both soluble (anhydrous lactose) and “insoluble” (dicalcium phosphate) fillers was compared for different lubricant levels and tamping forces (instrumented Zanasi LZ-64 machine). Statistical analysis of this multivariable study revealed that all main factors and their interactions were significant. Although the disintegrants were effective in promoting drug dissolution from both fillers, the effect was much less dramatic with lactose. This finding is not surprising, since the lactose-based capsule without disintegrant is already a fast-releasing formulation. Soluble fillers tend to dissolve, rather than to disintegrate. A beneficial effect of increasing the tamping force also was much more evident with the dicalcium phosphate-based capsules. As compression force increases, plug porosity may decrease, possibly making more effective the swelling action of disintegrants. Again, the retardant effect on dissolution of the hydrophobic lubricant is evident; however, it is apparent that the soluble lactose-based formulation is much less profoundly affected.

Surfactants

Surfactants may be included in capsule formulations to increase the wetting of the powder mass and enhance drug dissolution. The "waterproofing" effect of hydrophobic lubricants may be offset by the use of surfactants. Numerous studies have reported the beneficial effect of surfactants on disintegration and deaggregation or drug dissolution.\(^{69,73-75}\)

Hydrophilization

Another approach to improving the wettability of poorly soluble drugs is to treat the drug with a solution of a hydrophilic polymer. Lerk et al.\(^{76}\) reported that both wettability of the powder and the rate of dissolution of hexobarbital from hard gelatin capsules could be greatly enhanced if the drug was treated with methylcellulose or hydroxyethylcellulose. In this process, called hydrophilization, a solution of the hydrophilic polymer was spread onto the drug in a high-shear mixer and the resultant mixture was subsequently dried and screened. No benefit accrued when the drug and polymer were merely dry blended.

Shell improvement

The various researchers have thought to replace conventional gelatin by modifying them or by replacing using other film formers, such gelatin substitutes as discussed in sec.1.2.3 under shell composition.

An European patent (EP 110,052) describes the claims for foam capsule by introducing gas into gelatin dispersion before dip moulding. Various amount of effervescent material can also be entrapped into capsule shell wall.
A Japanese patent (JP 07,262,138) describes use of succinated gelatin in order to produce improved disintegration time of capsule in presence of ammonium and/or ammonium salts.
1.5 Objectives of present work

About 40% of the currently introduced active pharmaceutical ingredients are sparingly soluble in nature. The biopharmaceutical classification system (BCS) classifies the active pharmaceutical ingredients into four classes based on solubility in aqueous medium and permeability of API across gastro-intestinal wall. It is well known fact that an API must first dissolve in body fluids before absorption can occur. Therefore, dissolution is considered as an important factor by R&D scientists. Drug stability in gastrointestinal fluid is also an important factor. Oral route of drug delivery is widely used despite advancements in new drug delivery systems (NDDS). Tablets and capsules are the most widely used solid unit dosage forms. Disintegrations of a dosage form and dissolution of API influences the functionalities of tablets. There is an additional dimension in capsules besides disintegration and dissolution of API, i.e. solubilization of capsule shell wall.

Gelatin undergoes cross-linking reaction under adverse conditions of storage. Therefore, few capsule formulation fail to meet the pharmacopeial standards of disintegration of capsule shell and subsequent dissolution of API on storage.

The problem of dissolution is generally viewed by formulation and development scientist from the view-point of formulation of core (fill). An expertly formulated core formulation may also not release API if cross-linking occurs in gelatin capsules. Pellicle formation is the worst case of cross-linking. Two-tier dissolution test is recommended by USP. However, one should also remember excessively cross-linked capsules fail to meet in vivo in vitro correlation. (IVIVC) Reports of capsule formulation being less bioavailable than other dosage forms could be due to a particular drug being poorly absorbed or it may be...
due to cross-linking and pellicle formation which does not allow subsequent release of API even in enzyme containing media. The time required to reach maximum plasma concentration ($C_{max}$) is delayed but not extent of absorption in presence of enzymes. In case of critical onset required formulation becomes non-bioequivalent in such cases.

If the problem of API dissolution is to be addressed in capsules, equal importance shall be given to the formulation of core (fill) and the characteristics of shells (container). Very few articles are available in pharmaceutical literature wherein both the points have been addressed simultaneously. The main objective of the present investigation was to address the issue of shell insolubilization on storage since it is a pre-requisite before API is released from the expertly formulated core (fine powder of API, solid-dispersion, drug-$\beta$-cyclodextrin complex, etc.) Further object of the present investigation was to study the dissolution from solid dispersion or drug-cyclodextrin complex.

In order to achieve the set objectives, the following studies were carried out.

1. To carry out moisture transmission study in gelatin, HPMC and combination hard capsules.
2. To investigate the effect of type of excipients on moisture transmission and capsule disintegration.
3. To investigate the influence of cross-linking on active pharmaceutical ingredients from gelatin, HPMC and combination hard capsules.
4. Unconventional modifications in hard capsules were done to address the issue of gelatin shell insolubilization on storage.
5. Solid dispersion and API-excipient complexes were prepared to improve the dissolution of model poorly soluble Active Pharmaceutical Ingredients.
1.6 References

Chapter 1 Introduction and objectives


Chapter I Introduction and objectives

54. Stoyle L.E. Jr., A. Ph.A., 113th Annual meeting, Dallas, TX, April 1966.