GENERAL INTRODUCTION

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General Introduction

In the pharmaceutical industry, it is commonly recognized that on average more than 40% of newly discovered drug candidates are poorly water soluble. In turns, this leads to ineffective absorption at the site of administration results in high clinical failure due to poor pharmacokinetics [1, 2].

For poorly water soluble drugs (i.e. biopharmaceutical classification system (BCS) class II, IV), drug absorption throughout the gastrointestinal (GI) tract is primarily limited by the drug dissolution rate[3]. Therefore the conventional formulation work of oral dosage forms for class II, IV compounds was focused on using salt form[4], amorphous form[5], prodrug form[6], nano sizing[7], pre-dissolving the compound in a suitable vehicle to be filled in hard gelatin capsule[8] or by formulating as solid solution using water soluble polymers[9].

Despite of these approaches which can properly resolve the issue related to initial dissolution of drug molecules in aqueous environments within GIT; major limitations face these approaches including poor permeability through GIT especially for class IV drugs, drug precipitation during dispersion of formulation and drug crystallization in the polymer matrix. These problems have been effectively resolved by the use of lipid based drug delivery systems[8, 10].

Lipid based formulations can be used to influence the absorption of active ingredients through different mechanisms:

- Stimulation the lymphatic transport of active ingredients and interaction with enterocyte based transport [11].
- Administration of the drug in solubilized form or suspended in lipid matrix. This, removes any dissolution rate-limiting step in the absorption process[12] to get absorbed better than the conventional solid dosage forms[13] . This is due to the primary role of ingested lipids and their lipolytic products in formation of different colloidal particles with bile components which are able to maintain a larger quantity of poor water soluble drugs in solution via micellar solubilization[14].
- Ability to utilize fill excipients to induce inhibition of P-glycoprotein-mediated drug efflux and enzyme-catalyzed degradation of the compound in the lumen of GIT [15-20].

Although hard gelatin capsule was utilized recently to encapsulate liquid/semisolid formulations [9]; it possesses a multiple process and requires specific capsule filling machines under specific operation conditions that is not available to be used in Egyptian pharmaceutical industry due to economic reasons. From this point of view, application of soft gelatin capsule technology possesses the most convenient route to deliver novel lipid based delivery systems in the form of liquid/semi solid in a solid dosage form.

1. Overview on Soft gelatin capsules "Softgels"

Soft gelatin capsules also referred to "softgels" or soft elastic capsules "SEC". They are single unit solid dosage form, originally developed in 19th century to mask unpleasant taste and odor of drug substances. Then, they were developed to be used in pharmaceutical and nutrition products containing solubilized or suspended drugs in non-aqueous vehicles.

A softgel is a one-piece, hermetically sealed elastic outer shell; mainly composed of a polymer (i.e. gelatin), plasticizers (i.e. glycerin) and opacifiers/colorants and filled with a solution, a suspension, or a semisolid referred to fill formulation.

1.1. Advantages of softgels in the pharmaceutical industry

As an oral solid dosage form, softgels offer several advantages over other conventional oral solid dosage form:

- Improving swallowing ability especially for young and elder patients.
- Masking odor and unpleasant taste.
- Protecting the encapsulated compounds from oxygen and light.
- Ability to be readily dissolves in gastric juices of GIT.
- More suitable to produce pharmaceutical products with high content uniformity of ultra low-dose drugs.(e.g. Cardiac glycosides, vitamin D analogs)
- Reduce operation and environmental contamination with highly potent and cytotoxic compounds.

2. Softgel manufacturing process

As shown in Figure 1, softgel manufacture process is taken place in four successive steps including:

1. Preparation of gel mass for capsule formation
2. Encapsulation process.
3. Drying process
4. Sorting and finishing for the result capsule.

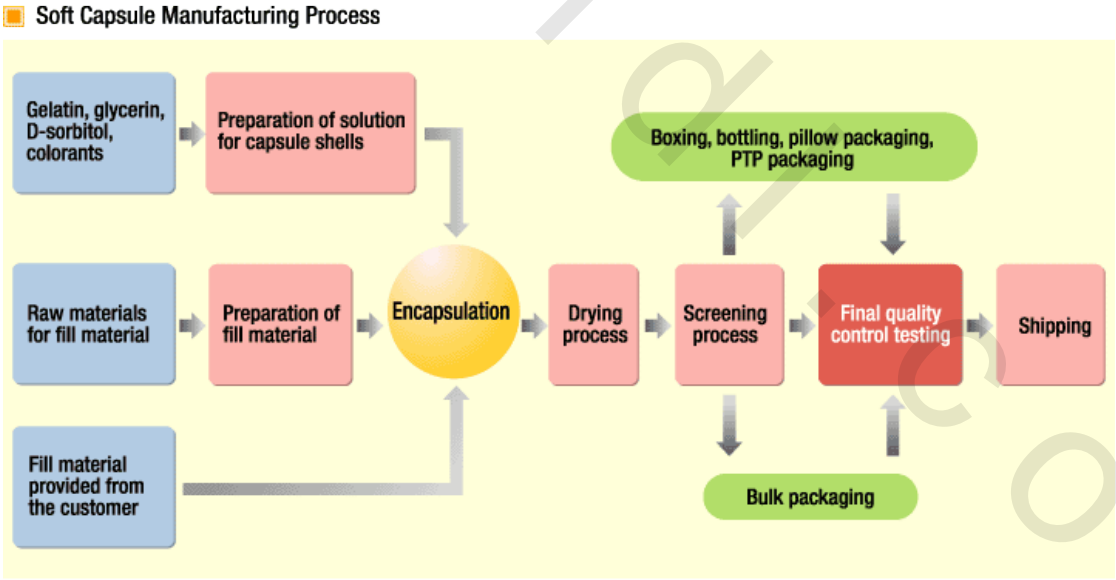

Figure 1: Schematic diagram for soft capsule manufacture process.

2.1. Preparation of gel mass for capsule formation

2.1.1. Gel mass preparation process

Gel mass is used to form the capsule shell for softgels. It is mainly composed of gelatin, plasticizer(s), water and other minor additives such as opacifiers, colorants, flavors and preservatives. It is prepared by mixing water and plasticizer(s) with gelatin granules in a double jacket tank (melter) to form a complete hydrated fluff at room temperature. With the application of steam, it is melted at high temperature under vacuum with slow mixing to remove any air bubble formed during the preparation process. In case of adding opacifiers and/or colorants; it should be dispersed and wetted thoroughly in glycerin/water in a rotating drum for extended periods before the addition to the molten mass[21].

Then the molten gelatin mass is transferred to electrically heating holding tanks and kept at 57-60℃. It should be noticed that gel mass storage temperature must not be stored under high temperature to avoid reduction of the gel strength and viscosity with time[22].

2.1.2. Molten gel mass composition

2.1.2.1. Gelatin

Gelatin is a free-flowing granular material with light amber to light-yellowish tint. It is defined according to USP/NF as a product obtained by partial hydrolysis of collagen derived from skin, white connective tissue and bones of animals as cattle bones, hides, pigskins and fish. It contains a mixture of water soluble proteins (84-90%), mineral salts (1-2%) and water (8-15%). It is a result of thermal denaturation of collagen with aid of either dilute acid (Type A gelatin) or dilute alkali (type B gelatin). Differences between gelatin (Type A) and gelatin (Type B) are illustrated in Table 1.

Table 1 : Differences between gelatin (Type A) and gelatin (Type B).

Point of comparison	Type A (Acid gelatin)	Type B (Alkaline gelatin)
Physical properties	Higher plasticity and elasticity	Higher gel strength
Iso electric point (ISP)	7 - 9	4.7 - 5.3
Dissolution rate	Lower dissolution rate at a given pH	Higher dissolution rate at a given pH
Hydrolysis process	Liable for alkaline hydrolysis	Liable for acid hydrolysis

Quality control testing for gelatin by softgel manufacturers' includes bloom strength, viscosity, iron content and microbial test.

Bloom strength "jelly strength is expressed as the weight in grams that, when applied with 12.7 mm diameter plastic plunger, will produce a depression exactly 4 mm deep in a jelly containing 6.67% w/w gelatin in water matured for 16-18 hour at 10℃. The range of bloom strength of gelatin used in softgel shell is from 150 to 250 grams. Gelatin with high bloom strength possesses more physical stability for softgel so it is reserved only to improve physical stability for large sized softgels which require greater structural strength during manufacture.

Viscosity determination is performed on 6.67% w/w concentration of gelatin in water at 60℃ and usually ranges between 25 and 45 millipoise.

Iron levels present in the gelatin raw material due to use of water in its production and should not exceed 15 ppm as higher levels may potentially result in the color reactions with other softgel components.

Microbial tests should be performed on gelatin raw material as it is considered to be an excellent medium growth for many bacteria. Thus it requires considerable care during its manufacture and handling to avoid contamination.

2.1.2.2. Plasticizers

The high glass transition temperature for anhydrous gelatin (Tg > 100 ℃)[23, 24] prevents the formation of elastic and flexible film readily to be utilized in soft gelatin capsule manufacturing. To lower the glass transition temperature, plasticizer like water was utilized by Coppola *et al*[23] who has reported a decrease in glass transition temperature of gelatin from 160℃ to 20℃. Being a volatile plasticizer, it will be lost during drying process leading to production of a brittle and fragile shell, Thus using non volatile plasticizer as glycerin, sorbitol, partially dehydrated sorbitol (i.e. a blend of D-sorbitol, 1,4-sorbitan, mannitol and water), maltitol (i.e. hydrogenated corn syrup) and low molecular weight polyethylene glycol can be used to improve flexibility and handling of the shell material during its manufacturing and shelf-life.

Non-volatile plasticizer lowers Tg of gelatin by water substitution in the vicinity of the protein chains and reduces the protein-protein interactions with a consequent increase in the mobility of protein chains [23]. In addition, Vanin *et al* [25] considered that the reduction of Tg as a consequence of the total number of moles of all plasticizers (i.e. non-aqueous plasticizers and water) present in the film. Thus, the extent to which a plasticizer could impart flexibility to a gelatin film is determined by its hygroscopicity and ability to interact with the protein chains and to reduce protein-protein interactions within the gelatin film [25, 26].

Typically, plasticizers are used about 15-30% w/w of the total wet mass of shell formulation at time of encapsulation[27] . In case of increasing the plasticizer amounts, this will lead to alter the physical characteristics for the gelatin film resulting in an increase in its flexibility, elongation at break, water retention and water vapor permeability and plus a decrease in tensile strength and elastic modulus [25, 26, 28-30].

Glycerin was reported to be the most practical and effective plasticizer irrespective to the type of gelatin used[25] due to its lower molecular weight and its high hygroscopicity[30]. It must be noticed that the number of moles of a plasticizer for a given concentration would be higher among other plasticizers; hence it tends to reduce the interactions among protein chains

of gelatin. Also Cherian *et al* [31] theorized that glycerin with Tg -93℃ provides more plasticizing effect if compared to sorbitol (- 3℃)[31] due it low glass transition temperature.

Due to extreme hygroscopicity for glycerin, it can influence on gelatin to pick up substantial amount of moisture quickly[23] leading to a soft, tacky and bloated softgel sheath that will ultimately break down or result in softgels sticking together with time. However sorbitol may prone to crystallization from the films on storage at low to intermediate relative humidity conditions due to the insufficient availability of water to keep the plasticizer in solution leading to change in the mechanical properties of gelatin shell[32].Thus it is recommended to blend sorbitol with glycerin that would yield a better control of the overall moisture content of the softgel sheath. Moreover, gelatin films with glycerin are less resistant to moisture and more permeable to oxygen and volatile ingredients than other higher polyols[30, 33]. The oxygen permeability and moisture content increase on increasing the glycerin content in the softgel sheath with an increase of the relative humidity. Based on these observations Hom *et al* [34] theorized that the plasticizer and environmental relative humidity conditions control the equilibrium water content at the gelatin shell and this equilibrium has the greatest effect on the oxygen permeability through the film.

Low molecular PEG pronounced more plasticizing effect over higher molecular weight PEG as it contains a larger number of hydroxyl groups which in turns promote its hygroscopicity. However one of the drawbacks from using PEG is the gelatin film plasticized with PEG that tends to migrate to the outer surface of the film. This phenomena referred to blooming or brushing [28]. It takes place when plasticizer concentration exceeds its compatibility limit in the polymer, leading to phase separation and physical exclusion from the polymer[35].

Partially dehydrated sorbitol tends to influence the gelatin shell to absorb moisture less than glycerin make it not to prone to crystallization like sorbitol. This is due to interactions between 1,4 sorbitan with the gelatin matrix [21].

2.1.2.3. Colorants and opacifiers

Coloring agents are included in softgel shell to provide elegance to a softgel product and to provide a distinctive appearance that may help to differentiate a particular softgel product. The coloring agents could be dyes (water soluble substances) or lakes (insoluble forms of a dye). Coloring agents are subjected to federal regulations and consequently the current regulatory status of a given substance must be determined before it is used. Anionic dyes are known to interact to a greater extent with a cationic type A gelatin than with anionic type B gelatin and this interaction could affect softgel dissolution[21].

Opacifiers are included in a shell formulation to provide light resistance when photosensitive compound is encapsulated in a softgel. Titanium dioxide is the most commonly used as opacifier and is typically used 0.5-1% w/w of a shell formulation. It is supplied as aggregated particles that should be dispersed and wetted before its addition to the molten gel mass to provide maximum light protection to an encapsulated compound.

2.2. Encapsulation process[21]

2.2.1. Fill formulation

Fill formulations are prepared in the form of solution, liquid-in-liquid dispersion, or a solid-in-liquid suspension by application of standard procedures employed in pharmaceutical solution, suspension, and semisolid manufacturing prior the encapsulation process.

Deaeration step is a critical step in the manufacturing of fill formulation as it affects not only the fill viscosity and, content uniformity but also on the physical and chemical stability of the finished softgel product during its shelf-life. It takes place by application of a vacuum to eliminate any of the entrapped air in the formulation. For highly viscous fill formulations deaeration process can be aided by moderate mixing with or without the use of heat.

The temperature of fill formulation may be maintained at 35℃-37℃ at the time of encapsulation and a higher temperature must be avoided to prevent any interference during softgel sealing. In case of fill formulations with high viscosity or solidify during encapsulation process, it could be encapsulated into softgels by continuous heating of the material in its reservoir and in the conveying tubing to higher temperatures until it reaches the dosing pump where it is cooled to lower temperature just before the encapsulation.

2.2.2 Manufacturing process

Encapsulation of soft gelatin capsule is taken place by using rotary die process invented by Scherer at 1933. This was used to eliminate all the problems associated with the plate process and produced softgel dosage forms with improved uniformity and high standards of accuracy.

The gel mass (typically at about 57-60℃) is spread onto a cooling drums which is cooled by using cold air to a temperature about 13-14℃ by aid of a spreader box. The volume of gel mass passes through uniform gap resulting in formation of a ribbon with uniform thickness across its entire width and length. The ribbon thickness may vary from 0.022-0.045 inches, with larger softgel sizes requiring thicker shell to accommodate the higher structural strength required during their manufacture.

The die rollers rotate in an opposite directions and the matching die cavities from each die roller create the capsule pocket as shown in Figure 2. The injected pressure of the formulated content causing the gelatin ribbons to swell in the die cavity and fill with the formulation either in liquid or paste. Figure 3 shows the encapsulation machine for softgels. Different sizes and shapes of the manufactured capsule are illustrated in Figure 4.

2.3. Drying of the manufactured softgels[21]

Due to excessive moisture content of the starting gel mass at the time of encapsulation to reach about 30 to 40% w/w, the formed softgels are highly flexible, thus it undergoes through a drying process. Drying is a dynamic process and continues until the gelatin shell returns to its equilibrium moisture content which is in the range of 10-15% w/w[34]. It isdivided into two stages; primary short time, low intensity drying process which takes place inside a tumble dryer followed by a secondary longer time, high intensity drying process. Tumble dryer is composed of a hollow drum(s) with perforated walls where the dry air is continuously pumped through the rotating drum(s) at an air temperature lower than 35℃. The warm air blown onto the capsule will penetrate the shell and cause it to dry from inside by moving the

water outward to the surface of the softgels. Also the warm temperature keeps the gel in semi-fluid state that promotes further sealing.

By the time, softgels exist the tumble dryer (i.e. primary stage) and proceed to secondary drying stage where they are spread on to trays and keep it under controlled temperature (21-24℃) and low relative humidity (20-30%). The time of secondary stage may vary from hours to days according to the nature of fill formulation, nature of the shell formulation (i.e. type and concentration of plasticizers) and thickness of the softgels.

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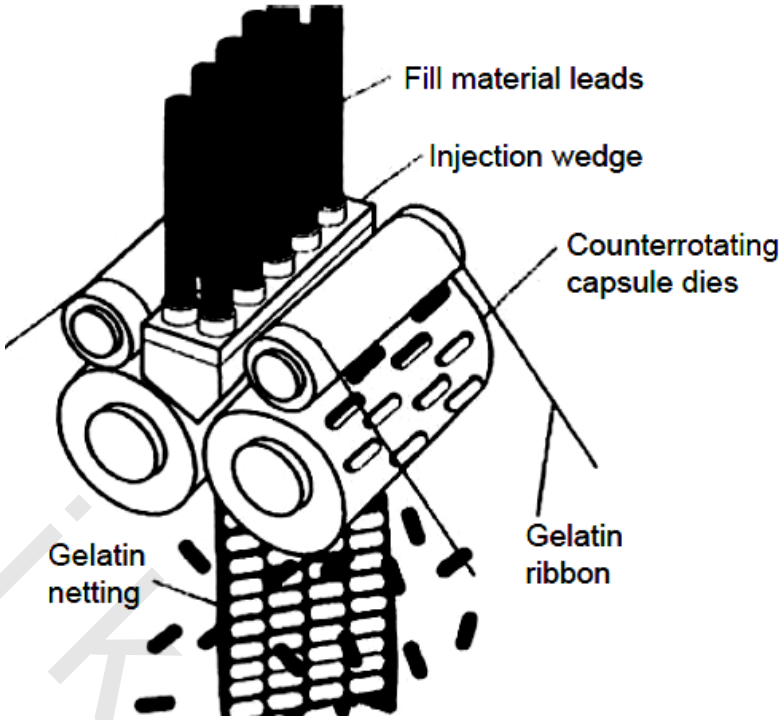

Figure 2: Rotary die encapsulating machine.

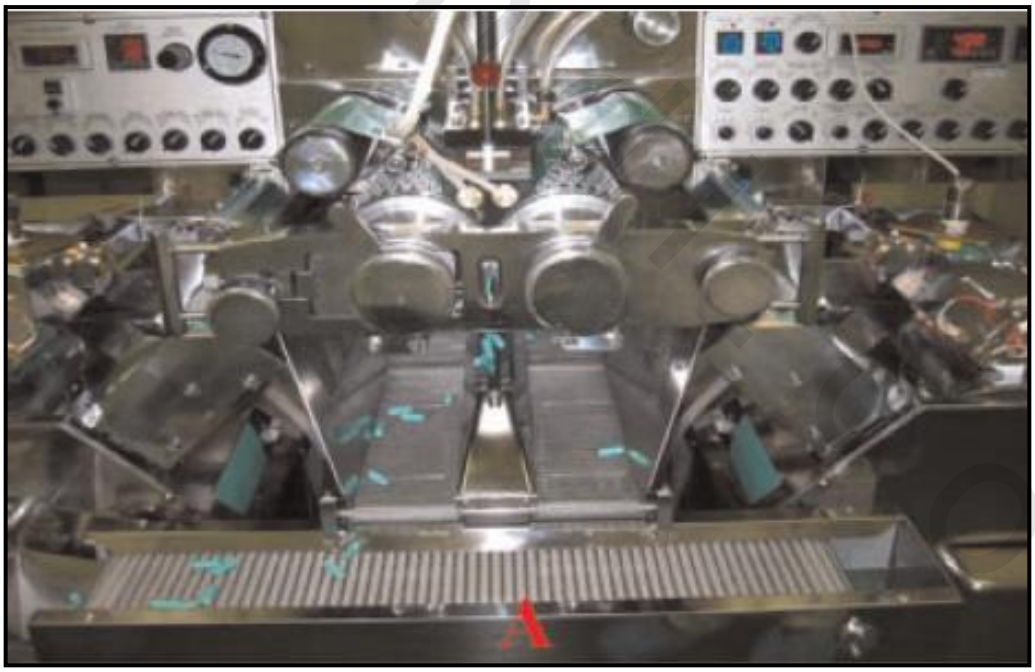

Figure 3: Soft gelatin capsule encapsulating machine.

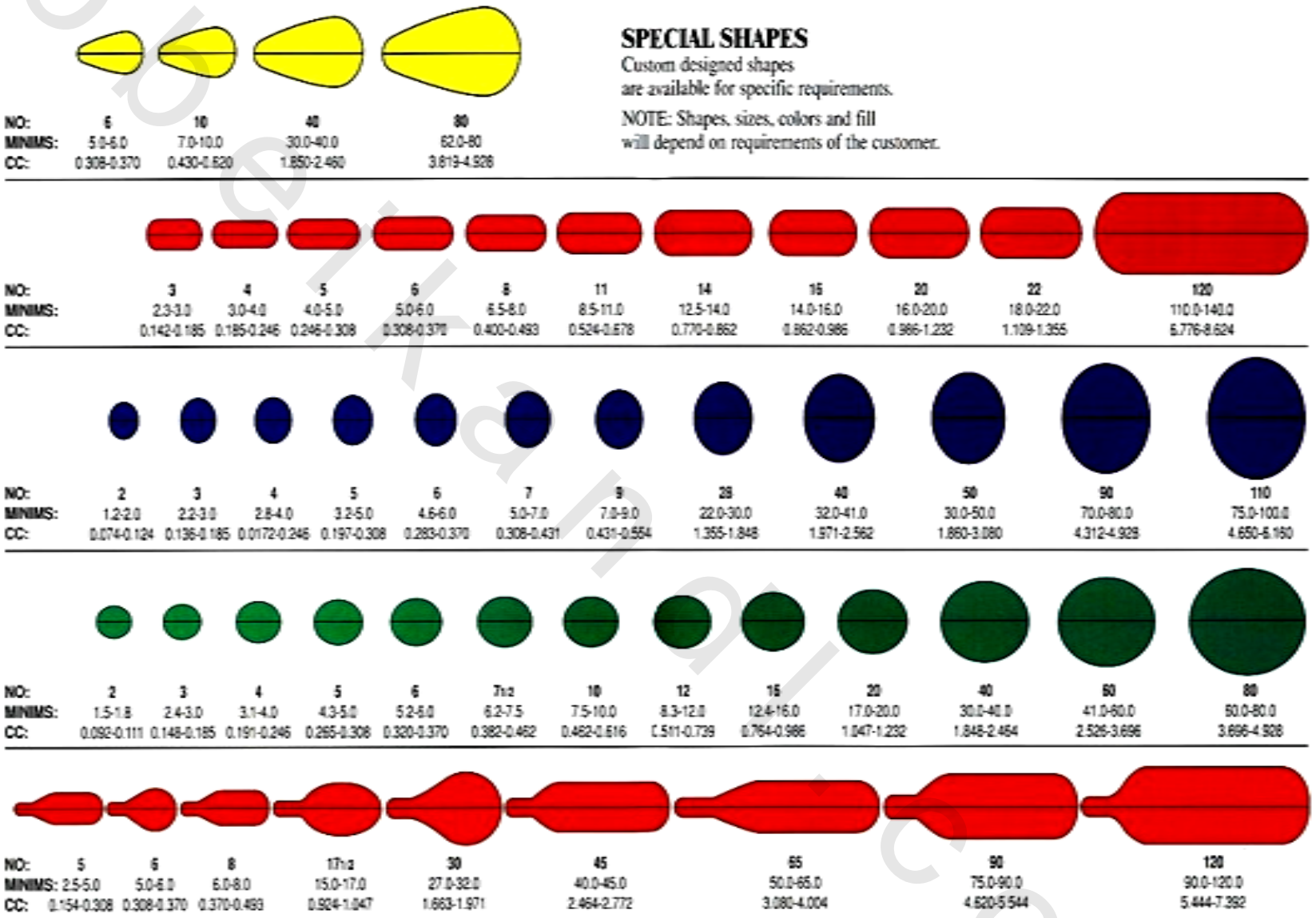

Figure 4: Different size and shapes of soft gelatin capsules (minim=0.0616 ml)[21]

The rate and extent of softgel drying are the critical processing parameters that should be carefully controlled where removal of too much water may result in hard, brittle softgels that have a higher propensity to develop cracked shells. On other hand insufficient dying may result in very tacky softgels and/or tightly stick to each other with time. If the softgels subjected to rapid drying conditions, the product may undergo a phenomenon referred to as "case hardening". It is occurred when the exterior surface of the softgel dries very rapidly and forms a temporary seal that prevents further egress of moisture from the fill and the shell. In such case the hardness of such formulation increases temporarily reaching the acceptance value. However the excess moisture entrapped within the fill and shell migrates slowly during storage, resulting in very tacky softgel product.

2.4. Finishing and sorting[21]

After drying process, softgels are sorted, polished, printed and inspected for their quality. Then, they are packaged into suitable containers, typically of low density polyethylene (LDPE) bags, high density polyethylene (HDPE) bottles, or blisters. The recommended storage conditions for the softgels include a temperature range between 15-30℃ and relative humidity of not more than 50%[34]. When stored under these conditions, the equilibrium moisture content of the shell material and oxygen permeability through the shell will be minimal. Thus, this will improve the physical stability of the produced softgels.

3. Challenges of applying softgels in pharmaceutical industry

- Availability of limited quantities of a compound during the early stages of development may discourage an organization from developing a softgel product for the compound as an early stage clinical form[21].
- High initial water content of the shell formulation at the time of encapsulation and subsequent migration of any amount of water between the shell and the fill formulations could make the softgel dosage form unsuitable for encapsulating compounds prone to water induced crystallization or hydrolytic degradation[21].
- It is essential to keep the apparent pH of the final fill formulation at least between 2.5 and 7.5, where at pH below 2.5 gelatin is hydrolyzed causing leakage of the softgel, whereas at pH values above 7.5, gelatin may be either hydrolyzed or cross-linked resulting in decreasing in the dissolution of softgel[21].
- Caution in the selection of excipients used in the development of softgel product to avoid any interactions with the drug substance and/or with each other and to be free from impurities (e.g. aldehydes, peroxides) that may adversely affect the gelatin shell dissolution process and/or the chemical stability of the drug substance.
- The shell of gelatinous softgels are exposed to be cross-linked on exposure to elevated temperature or aldehydes results in a decrease of its disintegration, dissolution and swelling properties and an increase of its gel strength, a clear indication of the formation of three dimensional networks within the gelatin[36].
- The occurrence of physical and chemical interactions within and between the shell and fill components [37].

OBJECTIVES OF THE WORK

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Our current thesis presents a complete study on the development of soft gelatin capsules encapsulate selected novel lipid based delivery systems used to enhance oral bioavailability for two water insoluble drugs which possess a clinical value in the pharmaceutical industry. The thesis is divided into two parts as following:

Part I: Etodolac Softgels: Feasibility Assessment and Considerations for Lipid-Based /hydrophilic Formulations of a highly hydrophobic drug

The aim of this part is to develop an oral dosage form expressed as soft gelatin capsule for etodolac formulated in lipid vehicle according to LFCS (lipid formulation classification system) and in hydrophilic vehicle as a different attempt to enhance the oral bioavailability of etodolac. In addition, study the effect of these systems on the stability of soft gelatin capsule after encapsulation process. .

Part II: Optimization and development of vesicular delivery systems for curcumin encapsulated in soft gelatin capsule

Due to the biological importance of CUR, its oral bioavailability is optimized by application of selected vesicular delivery systems and is developed to be capable for encapsulation inside soft gelatin capsule as a solid oral dosage form. This part is divided into two chapters represented as following:

Chapter I: Preparation and evaluation of soft gelatin capsule containing curcumin-phospholipid complex.

Due to economical reasons, this chapter aims to develop a locally prepared CUR-Phospholipid complex by local technology similar to Meriva™. On other hand, softgel technology is utilized to provide an advantage in delivering CUR by using semi-solid form of phytosome resulting in enhancing its bioavailability over Convential powder form of phytosome with an ability to increase CUR dose per unit capsule.

Chapter II: Preparation and evaluation of curcumin self phospholipid nano dispersion: As a novel delivery system to enhance curcumin systemic bioavailability.

The aim of this chapter is to prepare a novel delivery system for CUR compromised mainly of liquefied phospholipid "PHOSAL" and to assess its efficiency as a soft gelatin capsule.

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