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KEY CONSIDERATIONS, CHALLENGES, AND SOLUTIONS FOR SOFT GELATIN CAPSULES

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ABSTRACT

It is estimated that new chemical entities resulting of drug discovery process possess poor solubility and/or permeability. It leads to challenges for oral absorption of the molecules. The soft gelatin capsule dosage forms presents a chance to improve the oral bioavailibilty of poorly soluble compounds with a liquid matrix to make solubilize. However, formulation development and manufacturing process has a lot of challanges. The aim of this review is to help a formulator to understand the parameteres should be considered.

INTRODUCTION

One of the oldest dosage forms is capsules among solid oral dosage forms. Class II and/or IV molecules classified based on Biopharmaceutics Classification System have low bioavailability. Soft gelatin capsules are used therefore to increase bioavailability as main reason. Soft gelatin capsule can be defined as a type of capsule containing a liquid or semi-solid composition surrounded by a gelatin and they were originally developed in the 19th century for the drugs having unpleasant taste and odour.[1] They have advantages in terms of easy digestion, increased bioavailability, hermetically sealed, easy swallowing, and gelatin safety.[2] However, it has some diffuculties related to formulation, manufacturing process, and stability. In this review, key considerations, challanges, and possible solutions are mentioned.

KEY CONSIDERATIONS

Several considerations are needed to keep in mind while producing soft gel formulations. To be a good start for soft gelatin capsule product development based on quality by design

(QbD), the following diagram (Figure 1) helps the formulator to track down the reasons for imperfections, variations, defects, or failures. In the pre-development stage, one should carefully evaluate the following parameters separately.

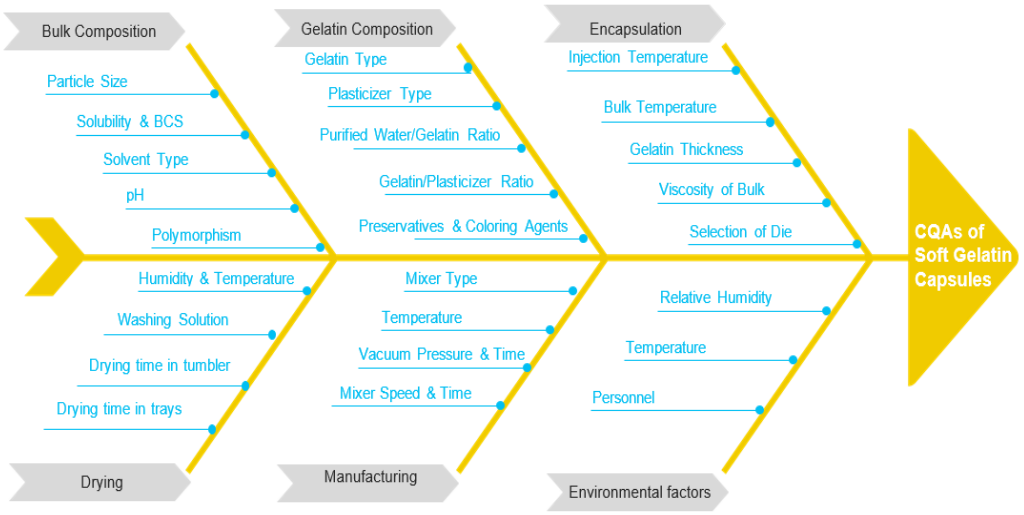

Figure 1: Ishikawa diagram applied to the pre-development of soft gelatin capsules.

1. Bulk Composition

Particle size: Based on ICH Topic Q6 A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, CPMP/ICH/367/96, and Draft guideline on quality and equivalence of topical products, "For some new drug substances intended for use in solid or suspension drug products, particle size can have a significant effect on dissolution rates, bioavailability, and / or stability. In such instances, testing for particle size distribution should be carried out using an appropriate procedure, and acceptance criteria should be provided." Franz diffusion cell aprroach may useful for pre-formulation characterisation of soft gelatin capsule in terms of bioavailabilty to observe particle size effect.[3]

Solubility & Biopharmaceutics Classification System (BCS): The concept of drug absorption in terms of permeability and aqueous solubility can be understood by biopharmaceutics classification system. For the drugs which are Class II (i.e. low solubility and high permeability) or Class IV (i.e. low solubility and low permeability), some solubility enhancement techniques can be used. They are micronization, structural modification, or solid dispersion and so on.

Solvent Type: Soft gelatin capsules dosage forms match with active pharmaceutical ingredient having low solubility. After choosing suitable solvent, pH of the solvent should be taken into consideration. Extreme acidic or basic pH have a risk for encapsulation process and finished product because of hydrolyse gelatin. Another criteria is to prevent migration fill formulation to capsule shell or vice versa. For example, propylene glycol has limited use. Propylene glycol cannot be replaced with medium chain mono- and diglycerides in the generic formulation of Avodart®, GSK Canada containing dutasteride and offering relieve symptomps of bening prostatic hyperplasia for enlarged prostates. Appearance of finished product containing propylene glycol in fill formulation and glycerol in gel shell is like popped ball during drying process. It is necessary to offset induced stresses beacuse of shrinking of the capsules.

Figure 2: "Popped ball" appearence of soft gelatin capsules.

pH: In soft gelatin capsules, bulk composition should be compatible with gelatin shell. It also leads to pH of bulk composition should be applicable for gelatin. Extreme acidic or basic conditions can damage to durabilty and stability of soft gelatin capsules. It should be check isoelectric point of used gelatin in formulation and its compatability with pH of capsule filling.

Polymorphism: It is different arrangment of molecules in crystal for the same material. If API show polymorphism, it has to be monitored any change during stability periods. Changes in solid state affect *in-vitro* performance of finished product (Please check most popular example: Ritonavir-Norvir capsules).[4]

2. Gelatin Composition

Gelatin Type: Gelatin can be derived from different animals which are cows, pigs or fishes. The gelatin derived from different animals does not have different chemical properties rather than their colors. It differs in terms of plasticity/firmness. While bovine bone gelatin improve

the firmness of capsule, porcine gelatin offers softer capsules.[5] It is basically manufactured by extaction of collagen from animal tissues. It is classified based on their manufacturing process. It is called as type A or type B, if the acid process or alkali process is used respectively. They differ in terms of isoelectric point. Isoelectric point of Type A and Type B is can be ordered as 7-9 and 4.7-6.0. A formulator must check viscosity and iron content for choosing optimum gelatin. Viscosity of gelatin is measured by preparing 6.6 % gelatin in water at 60. Optimum viscosity for gelatin is between 25 and 45 millipoise. Raw gelatin used in soft gelatin capsules should have iron content lower than 15 ppm. The values higher than 15 ppm has a risk in terms of possible color reactions with organic compounds.[6]

Plasticizer Type and Gelatin/Plasticizer Ratio: The use of a plasticizer is necessary for achieving elasticity of soft gelatin capsule shells. The plasticizer offers mechanical stability of the shell during and after drying. Glycerol, sorbitol, and sorbitol / sorbitan solutions are the most common plasticizers in the percentage between 15 % and 30 % of the total wet mass of a shell formulation during encapsulation.[7] In addition to them, propylene glycol, and polyethylene glycol such as PEG 200 can be used as alternative. Sorbitol/sorbitan solutions are used for the soft gelatin capsules with PEG fills to prevent migration into fill formulation. Choosing of plasticizer is not only related to fill formulation but also desired capsule strength. According to Venkatachalaiah and Macleod, harder capsules can be obtained when sorbitol is used rather than glycerin.[8] The capsule strength is significant criteria because it leads leakage of filling material. In the general literature, glycerin/gelatin ratio can inform us about soft gelatin capsule strength.

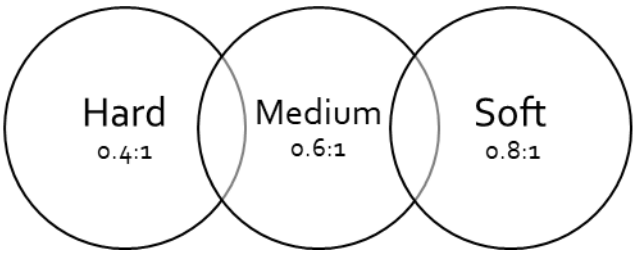

Figure 3: Plasticizer/gelatin ratio for soft gelatin capsules.

Purified Water/Gelatin Ratio: In the previous section, plasticizer: gelatin ratio was mentioned. However, elasticity of soft gelatin capsule is not only depend on plasticizer gelatin ratio but also depends on water content in finished product. Water concentration in finished product should be ideally 8-10 % in the capsule shell.[9] It prevents microbial growth. In addition to low water concentration for preventing microbial growth, hardness and

elasticity depends on how much water left in the capsule shell. If the water concentration is below 8-10 % in capsule shell, it may become risky because it means the capsule become over dried and resulting in brittle capsule and cracking.

Preservatives & Coloring Agents: Although soft gelatin capsule consists of three main components which are gelatin, plasticizer, and water, they have also minor components like preservatives and coloring agents. Methyl paraben and propyl paraben are the most common used for soft gelatin capsules. Soft gelatin capsules contain some water concentration in even dried form. Therefore, it may necessary for preventing microbial growth. Like preservatives, some coloring agents should be added in soft gelatin capsules formulations. For APIs sensitive to light, titanium dioxide should be used for making opaque soft gelatin capsule. Though titanium dioxide is the most common opacifying agent, the other agents which are calcium carbonate, iron oxides, and dioxides can also be used. To obtain opaque soft gelatin capsules, suggested concentration of TiO2 is 0.5-1.0 % w/w.[10]

3. Encapsulation

Bulk Temperature and Viscosity, and Injection Temperature: The highest temperature of capsule fill formulation (injection temperature) should be up to 37 ℃. The temperatures higher than 37 result in melting the gelatin and interfere with the sealing of soft gelatin capsules. In some cases, bulk formulation need to be heated during encapsulation process for especially shear sensitive formulations. At this case, viscosity measurements should be performed at different temperature. Before encapsulation process, required temperature to make sufficient encapsulation should be optimized based on viscosity of filling formulation called as bulk.

Gelatin Thickness: Thickness of capsule shell may differs based on capsule size. It may be between 0.022 inches to 0.045 inches.[9] For soft gelatin capsules having bigger die, such as OVAL-30, OBLONG-16, it is required thicker shell to facilitate higher strength of structure.

Selection of Die: In the stage of choosing die, a formulator must know the density of bulk formulation and weight of capsule filling. In generic formulation developments studies, weight of reference capsule filling should be determined in the reference of USP 905 Uniformity of Dosage Units. After determining the weight and density of capsule filling, one will be ready for choosing a die. For example, the weight and density of capsule filling are

140 mg per capsule and 0.93 mg per ml, respectively. It means that OVAL-3 die can comply with the formulations.

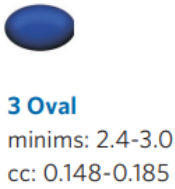

Figure 4: Volume of OVAL-3.

4. Drying

Humidity & Temperature: After encapsulation, drying parameters are critical to prevent brittle and leakage of soft gelatin capsules. Therefore, temperature and humidity should be optimized. Generally, optimum temperature and humidity conditions should be as follows:

Temperature	Humidity
22 ± 3 ℃	Max. 30 RH

Figure 5: Relative Humidity and Temperature in soft gelatin capsule manufacturing area Too little moisture or high moisture are also a major problem in softgel drying process. When you dry your softgel capsules for too long and remove the majority of the moisture, this can cause your capsule to become hard and brittle. A brittle capsule is more prone to breaking and fissures, which will, in turn, cause your filling to leak out of the shell.

Washing Solution: After encapsulation process, some lubricant residues may hold on the surface of soft gelatin capsule. In general, absolute ethanol can be used to remove any residue of lubricant. 96 percent of ethanol should not be used because of degredation possibility. Mineral oil or medium chain triglycerides can be alternative for absolute ethanol.

Drying time in tumbler and trays: For first drying process, tumble dryer is used. The specified amount of soft gelatin capsule is placed into baskets and rotate at constant rpm. After removing from baskets, they is placed on trays and monitor weight and hardness of them. For drying period, following draft table is recommended to use.

Table 1: Draft monitoring table for drying process.

Drying process		1. day		2. day		3. day		4. day		5. day		6. day		7. day		8. day		9. day		10. day	
Total Capsule Weight (… mg/weight±……) Hardness (N)	1																				
	2																				
	3																				
	4																				
	5																				
	6																				
	7																				
	8																				
	9																				
	10																				
Fill Weight (… mg/capsule±……)	1																				
	2																				
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	5																				
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Capsule Shell Weight (… mg/capsule±……)	1																				
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5. Manufacturing

Mixer Type, Speed, and Time: Manufacturing bulk formulation resembles with conventional solution or suspension manufacturing process type. Therefore, mechanical mixer or homogenizator are necessary equipments to produce capsule filling formulations. Speed and time are the parameters should be optimized. Higher rpm may be risky because it leads to produce foam in such formulations. In this cases, bulk formulation should be rested or be applied vacuum to remove foams.

Temperature: Depends on melting point of excipients used in capsule filling formulations, temperature should be optimized. In stage of temperature optimization, a formulator must

check forced degredation studies of APIs, homogenity, and relation between temperature and viscosity if needed.

Vacuum Pressure & Time: In manufacturing of gelatin composition, entrapped air is removed by vacuum. It can be applied up to 0.08 mpa. Duration is depend on batch size of it, therefore, it cannot be said optimum time for vacuum. Removing air in gelatin composition is critical because it leads to problematic sealing procedure and visual defects on soft gelatin capsule.

6. Environmental Factors

Relative Humidity and Temperature: Optimum relative humidity and temperature in soft gelatin manufacturing area are shown in Figure 5. High humidity or high temperature may result in cross-linking for soft gelatin capsules. Capsule shows cross-linking reactions results in slower drug release profile.

Temperature	Relative Humidity
22 ± 3 ℃	Max. 30 RH

Figure 6: Relative Humidity and Temperature in soft gelatin capsule manufacturing area.

Personnel: Like in every dosage forms manufacturing process, experience of operator is one of the criteria for producing capsules having of high quality.

Challenges and Solutions

In order to prevent shell/fill interactions, two types of interactions have to be studied. While studying soft gelatin capsules, fill formulation and the finished product can be evaluated separately. Before encapsulation process, a formulator has to be sure about fill formulation stability. Though fill formulation stability is a big step to achieve a stable product, it is not enough on own. Compatability of fill and gelatin components and physical interactions have to be distunguished. Here is some challenges and solutions one formulator may face.

1. “Black-brown spots”

If black-brown spots is observed the appearance of finished product.

- Iron content should be checked whether it contains lower than 15 ppm or not.
- Thickness of primary package may be increased or used more preservative one in terms of temparature (i.e. PVC- PCTFE (Polychlorotrifluoroethylene) film).
- Maillard reaction may occur. Compatability studies should be performed.

Figure 1: An example of black-brown spots on soft gelatin capsules.

It should be note that iron content criteria is not valid for soft gelatin capsule containing fenticonazole nitrate. Gelatin having 21 ppm and 4 ppm have the same effect for vaginal ovule containing fenticonazole nitrate. This could be explained by a different type of primary package more resistant to temperature.

2. Air bubble

If air bubble may be observed on finished product;

- Fill material or gelatin mass may contain air bubble. Vacuum process should be optimised.
- It may result from filling machine or die. It can be interpreted as not sealing hermetically.

Figure 2: An example of air bubble in soft gelatin capsules.

3. Leakage

Leakage is a typical problem for soft gelatin capsules. One face with leakage problem in encapsulation or drying period, it should be checked encapsulation machine properties or formulation. It is recommended that softgel die roll tooling structure design, injection wedge timing operation, and service life should be checked. Moreover, it could be related to capsule hardness. If the capsule hardness decreases, possibility of brittle may decreases proportionally.

CONCLUSION: Compared to other dosage forms, soft gelatin capsules may have some advantages in terms of bioavailabily or improving solubility. However, it is required to know key consideration, challanges, and solutions during pre-formulation and stability period. The suitable design for a specific softgel capsules leads to appropriate selection of active pharmaceutical ingredient properties, formulation, and process.

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