Soft Gelatin Capsules (Softgels)

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INTRODUCTION

A softgel or soft gelatin capsule is a solid capsule (outer shell) surrounding a liquid or semi-solid center (inner fill). An active ingredient can be incorporated into the outer shell, the inner fill, or both. They are oral dosage form for medicine similar to capsules. Softgel shells are a combination of gelatin, water, opacifier and a plasticizer such as glycerin and/or sorbitol(s).

ADVANTAGES OF SOFTGELS

· Easy to swallow, no taste, unit dose delivery, tamper-proof.
· Wide variety of colors, shapes, and sizes.
· Accommodates a wide variety of compounds filled as a semi-solid, liquid, gel or paste.
· Immediate or delayed drug delivery.
· Can be used to improve bioavailability by delivering drug in solution or other absorption enhancing media.

DISADVANTAGES OF SOFTGELS

· Requires special manufacturing equipment.
· Stability concerns with highly water soluble compounds, and compounds susceptible to hydrolysis.
· Limited choices of excipients/carriers compatible with the gelatin.

OUTER SHELL OF SOFTGELS

The outer shell is composed of a gelatin or potato starch matrix. Gelatin matrix consists of gelatin, plasticizer, solvent and optional ingredients such as flavors and colorants.

Gelatin - bovine, porcine, or piscine (fish) origin. Comes in a variety of bloom strengths, the higher the bloom strength, the more resilient the gel. Most oil based fills are encapsulated using a bloom strength of 150. When polyethylene (PEG) based fills are used, a higher bloom strength is generally used. The limitations of bovine (i.e. bovine-related diseases) and porcine (i.e. not kosher) gelatin may be overcome by piscine (fish) gelatin.

Plasticizer - Glycerin and Sorbitol Special are the two most common plasticizers. Glycerin is generally used with oil based fills. Sorbitol Special is used with PEG based fills. Sorbitol is not soluble in PEG and therefore will not leach out of the shell into the PEG based fill like Glycerin would. Sorbitol Special is formulated to inhibit sorbitol from crystallizing out in the gelatin shell. Do not substitute Sorbitol for Sorbitol Special.

Solvent – Water

Optional Ingredients – Approved colors and flavors.

Potato starch matrix - This is a smooth, transparent substance resembling gelatin, which is neutral in taste and color, easily digestible and of plant origin, and therefore, the concerns of certain bovine related diseases are not an issue, and they offer a gelatin free alternative for vegetarians and vegans. Currently, available from Swiss Caps under the name Vegagels®.

TYPES OF INNER FILL MATERIALS

There are three primary types of inner fill materials.
1. Neat Substance, especially oily liquids.
2. Solution Fills: Active dissolved in a carrier.
· Oils such as soybean oil and Miglyol 812 (neutral oil, triglycerides of medium chain fatty acids).
· Polyethylene Glycols: especially PEG 400 -600.
· Other solvents: Any other solvent which doesn't degrade or solubilize the gelatin shell, i.e., dimethyl isosorbide, surfactants, diethylene glycol monoethly ether.

· Optional Ingredients:
* Water or alcohol: up to 10% w/w, if needed for solubility.
* Glycerin: 1 to 4% w/w to retard the migration of the glycerin out of the shell into the fill.
* Polyvinylpyrrolidone: Up to 10% w/w used in combination with PEG, can increase drug solubility, and also improve stability by inhibiting drug recrystallization.

3. Suspension Fills: Active dispersed in a carrier.
· Suspensions can accommodate about 30% solids before viscosity and filling become a problem.
· Suspensions can be heated up to 35ºC to decrease viscosity during the filling process.
· Suspended solids must be smaller than 80 mesh -- mill or homogenize before filling to prevent needles from clogging during filling.
· Carriers

*** Oily mixtures:**
Soybean Oil with beeswax (4-10% w/w) and lecithin (2-4% w/w). The lecithin improves material flow, and imparts some lubrication during filling. Add enough beeswax to get a good suspension, but avoid creating a non-dispersible plug.

Gelified Oil (e.g. Geloil® SC), a ready to use system composed of soybean oil, a suspending agent, and a wetting agent. Simplifies the manufacturing process, and avoids batch to batch and supplier to supplier variability.

*** Polyethylene glycol:**
PEG 800 -1000 for semi-solid fills.
PEG 10,000 -100,000for solid fills.
Or mixtures of the above.
Heat up to 35ºC to make fluid enough for filling.

*** Glycerides:**
Glycerides of long chain fatty acids (e.g. Gelucire® 33/01). Hydrophobic with surfactant properties.

*** Optional Ingredients:**
I. Surfactant: Sorbitan derivatives such as polysorbate 80 or lecithin.
II. For hydrophobic drugs dissolved or dispersed in an oily matrix, a surfactant of HLB 10 will increase the dispersibility of the product in aqueous fluids and also may improve bioavailability.

INCOMPATIBILITIES

· Avoid aldehydes which can lead to cross linking (pellicle formation) of the gelatin, and poor dissolution of the gelatin capsule in water. This may be overcome by adding enzymes to the dissolution media, (see FDA Guidelines).
· Drugs sensitive to water can degrade (e.g. ranitidine) or undergo polymorphic conversion (e.g. terazosin).
· Compounds (especially those of high water solubility) can migrate from the fill into the shell or get trapped in a hydrophobic matrix resulting in poor dissolution and loss of bioavailability.

SOFT GELATIN ENCAPSULATION PROCESSES AND EQUIPMENT

Rotary Die process: Two ribbons of gelatin are fed continuously into a rotating die assembly and are simultaneously formed into the two halves of a capsule. The ribbons converge adjacent to a fill injector. The fill injector is actuated by a pump which measures and dispenses the appropriate volume of fill material into the capsules. The filled capsules are subsequently sealed as the die assembly rotates. This

process permits accurate and reproducible fill uniformity.

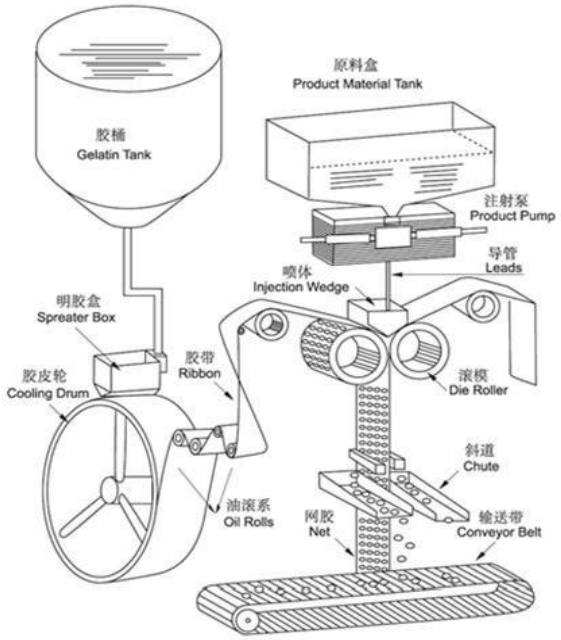
Pump heads are available for fill weights as low as 100 mg. For oral dosage forms, the fill weight ranges from 100 mg up to about 1 gram.

The following should be monitored/controlled:
· Gelatin temperature
· Fill temperature
· Ribbon thickness
· Seal or seam width
· Fill quantity

Following encapsulation, the capsules undergo drying in a tumble drying tunnel with an elevated temperature and a large volume of forced air. From the drying tunnel, the capsules are transferred onto trays and placed into a low humidity drying room.

The following should be monitored:
· Gelatin moisture
· Fill moisture
· Capsule hardness

Drying is a dynamic process, and the goal is to have the gelatin shell return to its equilibrium moisture content in the range of 6 - 8%.



Oil fills dry faster than PEG fills, and typically reaches a shell moisture content of 6 to 8% within 24 hours.

If water migrates into the fill, it needs to migrate back out or at least be in equilibrium with the moisture content of the shell for good stability. This is more typical of the PEG fills. These can take 7 to 10 days to reach acceptable moisture levels, and may still contain up to 10% water after drying.

FINISHING

After drying, the softgels are sorted (sized), polished, printed, and inspected for their quality. The softgels are then packed 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 of 15 – 30^{0}C and a relative humidity of not more than 50%. When stored under these conditions, the equilibrium moisture content of the shell material and oxygen permeability through the material are minimal, thus improving the stability of the softgel products.