

INNOVATIONS IN CAPSULES: SEAMLESS TECHNOLOGY

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ABSTRACT

Hard gelatin Capsules manufacturing requires large amounts of water removal, requiring great amounts of energy and long drying times. Secondly, these shell materials dissolve slowly when the capsules are being consumed, thereby leaving a distasteful plastic film-like residue in the mouth. Seamless capsules formed of a shell material encapsulating a core material have been made by using as the shell material film-forming materials such as gelatin and gums. Seamless capsules have clear and glossy appearance with liquid material encapsulation and showing greater bioavailability and flexible adjustment of the dosage. Shell of seamless capsules is Heat resistance, Acid resistance & Freezing resistance. Different types of seamless capsules available in the market are described in this review. A variety of materials can be encapsulated in seamless capsules.

They are prepared by two methods of manufacturing in use multi component nozzle method and Jet Streams Method/ Drop or Blow Process. Detailed manufacturing method is also described in this review. Seamless capsules are vastly used for Pharmaceutical and Nutraceutical products, Food and confectionary materials & Mouth refreshers, perfumes etc.

Keywords: seamless capsules, Jet Streams Method, Drop or Blow Process, Nutraceutical products.

INTRODUCTION

Seamless Soft Capsules

A soft capsule composed of a plurality of cells coalesced to each other and filling substances encapsulated in the individual cells, the wall of at least one of the cells being formed of a material different from a material forming the wall of at least one of the other cells, and said capsule being seamless. ^[1]

Traditionally, seamless capsules formed of a shell material encapsulating a core material have been made by using as the shell material film-forming materials such as gelatin and gums. These shell materials present two disadvantages. First, they are formed from an aqueous solution. Consequently, when the capsules are formed, large amounts of water must be removed, requiring great amounts of energy and long drying times. Second, these shell materials dissolve slowly when the capsules are being consumed, thereby leaving a distasteful plastic film-like residue in the mouth.

Seamless capsules are usually made by simultaneously extruding the shell material and the core material through concentrically aligned nozzles such that the extruded shell material and the extruded core material exit the nozzles as a coaxial jet with the shell material surrounding the core material into a stream of cooled carrier liquid that is flowing downward. While descending in the cooled carrier liquid, the coaxial jet breaks into droplets with the shell material encapsulating the core material. The droplets then solidify in the cooled carrier liquid to form seamless capsules. Seamless capsules are vastly used for Pharmaceutical and Nutraceutical products, Food and confectionary materials & Mouth refreshers, perfumes etc. ^[2]

DISADVANTAGES OF HARD AND SOFT CAPSULE PRODUCTS (SEAM TYPE) ^[3]

- ✓ Limited range of capsules sizes: difficult to adjust the amount of active ingredients.
- ✓ Observed inferior content uniformity of active drugs.
- ✓ Shorter capsule life.
- ✓ Limited manufacturing site/equipment flexibility.

ADVANTAGES OF SEAMLESS MINI CAPSULES ^[3]

- ✓ Clear and glossy spherical capsules.
- ✓ Direct encapsulation of liquids.

- ✓ Flexible adjustment of the dosage due to its reduced size
- ✓ Provides a vapor barrier to prevent oxidization of the encapsulated substance.
- ✓ Free coloring of the capsules to increase its value added.
- ✓ Flexible control of the capsule size from 1mm to 8mm (diameter).
- ✓ Low shell ratio to the content volume due to the thin shell wall.
- ✓ Versatility in drug dosage forms
- ✓ Increase bioavailability due to liquid dosage
- ✓ Wider ranges of packaging forms are available.
- ✓ Seamless capsules are most suitable as oral quick-dissolving capsules.




WHAT SEAMLESS MINI-CAPSULES CAN DO? ^[4]

- Prevents fish oil and fatty acids from being oxidized.
- Stabilization of volatile materials such as flavors & heat sensitive materials
- Direct encapsulation of oil based drugs, suspensions, hydrophilic materials etc.
- Achieve sustained release effect with the enteric coating of the capsules.
- Combination drugs which are not desired to be mixed can be stably included in a single soft capsule.

DIFFERENCE BETWEEN -SEAMLESS CAPSULES -- SEAM TYPE CAPSULES -- HARD CAPSULES ^[5]

Table 1 shows different parameters and its specifications for seamless, seamtype and hard gelatin capsules.

Table 1: Difference between -seamless capsules -- seam type capsules -- hard capsules ^[5]

Parameters	Seamless soft capsules	Seam type soft capsules	Hard capsules
Appearance			
Manufacturing Method	Dropping Method, Filler Materials and shell are formed simultaneously	Rotary Method, Filler Materials are encapsulated with	Feed contents into the one part of the pre-molded

	in a spherical capsule with a concentric fashion nozzle.	gelatin in sheet using a mold.	shell and joint the other.
Shell Ratio	10%~	30%~	20~50%
Diameter	0.3mm~10mm	5mm~20mm	10mm~21mm
Content	Lipophilic, Hydrophilic, Powder	Lipophilic, Powder in suspension	Powder
Shell Material	Gelatin, Agar, Natural gelling substance	Gelatin, Glycerin	Gelatin, Glycerin
Shell Function	Heat resistance, Acid resistance, Freezing resistance	No function	No function
Characteristics	Functions can be added to the shell. Possible to design multiple layer capsules	Shell thickness is large enough to joint two pcs of gelatin sheets. Use of glycerin can cause blocking.	Only available for powder, not liquid as content. No use for small capsules

TYPES OF SEAMLESS CAPSULES ^[6]

There are five different types of seamless capsules according to their structure. They are made up from different materials and various types of materials and drugs can be incorporated in these types of capsules.

1. Basic type
2. Powder coated capsule
3. Film coated capsule
4. Powder type
5. Multi-layer capsule

1) Basic type seamless capsules

The most commonly used form of seamless capsules. It can produce a variety of products by combining raw materials.

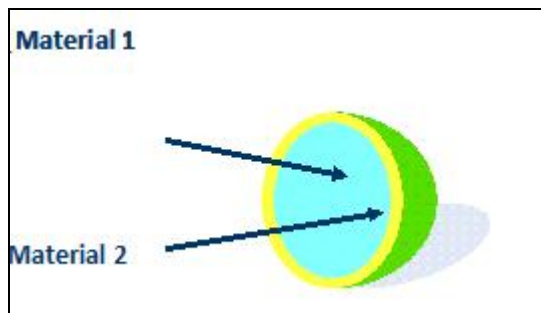


Figure 1: basic type seamless capsule

As a Material -1 Gelatin, Agar-agar, Artificial Coloring, Sweetener etc. can be used.

As a Material -2 Vegetable Oil, Fish Oil, Aroma, Chocolate, Vitamin E, Oil based extract, Menthol, Flavor Oil etc..., Hydrogenated Vegetable Oil can be used.

Flavor, Functional oil type products can be formulated. For example, Refresher, CoQ10.

2) Powder Coated Capsules:

It enables the production of unique products by coating food powders on to the outside of seamless mini-capsules. A flavor can be used as Material 2 to provide improved taste.

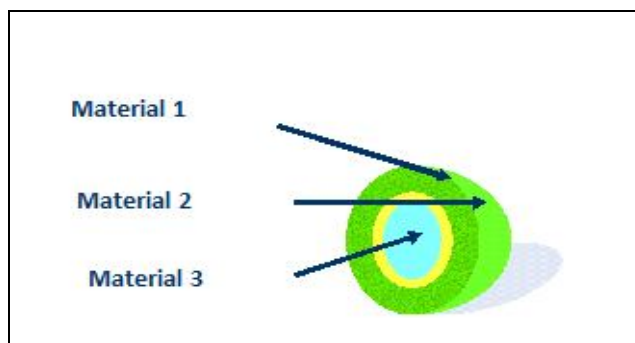


Figure 2: powder coated capsule

As a Material-3 (powder coating) Sugars (Sorbitol, Xylitol, Mannitol, etc.), Vitamin C, Chocolate, Cocoa, Mouth Refreshers, Health Supplement etc. can be used.

3) Film Coated Capsule

A variety of film materials can be applied on to the seamless mini-capsules. Enteric release and higher value added products. A unique product appearance can be produced.

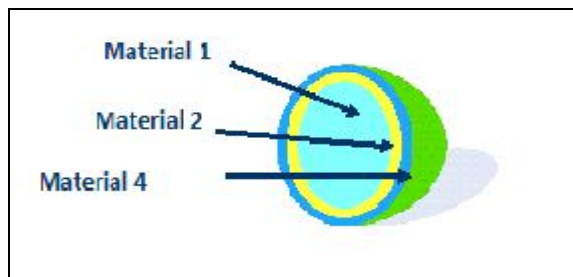


Figure 3: powder coated capsule

As a Material-4 for film coating Water-soluble materials (HPC, HPMC, Hemilose, etc.) and Water-insoluble (enteric) materials (Shellac, Zein) can be used.

Hydrophilic substance & Fruit extract like products can be manufactured for example, Crystal Dew which has functions of Freezing resistance. ^[7]

4) Powder Type

It can produce more effective products by encapsulating powders dispersed into material 2.

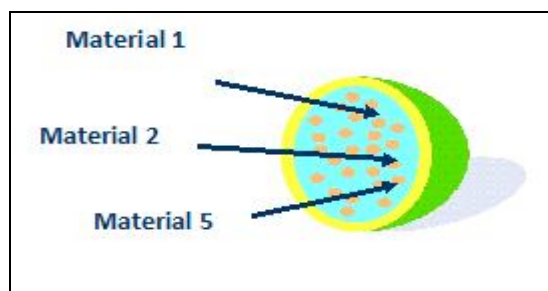


Figure 4: powder type seamless capsule

As a Material 5 (Powders) Lactic Acid Bacterium such as Lactobacillus Bifidus, Minerals such as Calcium, Powder Vitamin (Vitamin C, Vitamin B etc.), Sugars can be incorporated.

Probiotic & Enzymes type products are formulated for example, Bifina, DHA, Blue Berry whose functions are Acid resistance, Control of release. ^[7]

5) Multi-layer capsule

Unique products can be created by using two different ingredients for materials 2 and 6.

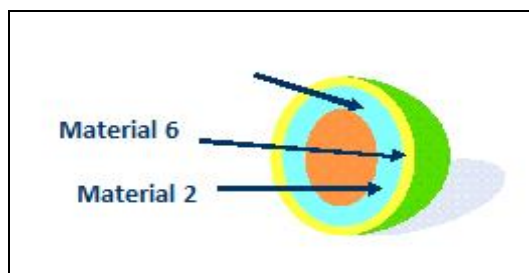


Figure 5: multilayer capsule

As a Material 6 (Inner Solution) Chocolate, Oil base extract, Flavor, Water-soluble solution (Fruit Juice, Herb medicine extract, Hardened Oil, Aroma, Flavor can be much useful to produce Flavor oil, Functional oil for example, Su-Su, Syunkai mint.

MAKING OF SEAMLESS CAPSULES

Seamless capsules mainly contains two parts. Firstly **capsule content** which must be core, and secondly **capsule shell** which is outer coat of capsule.

CAPSULE CONTENT ^[8]

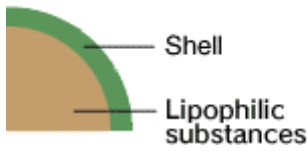
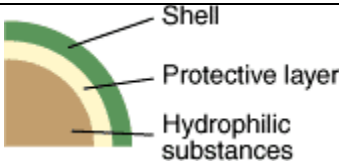
A variety of materials can be encapsulated in seamless capsules. Encapsulations of a broad range of substances are listed in table 2 with examples.

Table 2: capsule content ^[8]

Contents (physical properties)	Adjustment example
Hydrophilic substances	Herb extracts, fruit juices, syrups
Liphphilic substances	Vitamin E, Flavor essences
Amphoteric substances (substances with interfacil activity)	Surfaces active agent
Powders insoluble powders	Suspended in lipophilic solution Suspended in hydrophilic solution

Seamless capsule technology makes it possible to encapsulates hydrophilic substances which were previously thought to be impossible to encapsulate using conventional soft capsules by using some more coating. See table 3. ^[8]

Table 3: coating of hydrophilic and lipophilic substances ^[8]

2 layers for lipophilic substances	3 layers for hydrophilic substances
	

Fill material: ^[9]

- ✓ Drug substances that are naturally in an oil phase.
- ✓ Oil phase drug substances that are diluted and dissolved in an oily base.
- ✓ Water-soluble drug substances that are dissolved in an aqueous base (Macrogol 400).
- ✓ Drug substances that are suspended in an oily base.

Drug substances: ^[9]

Formulation design depends on the drug substance properties of the fill material. However, use of capsules brings common advantages. Table 4 shows some compatibility parameters of filling material and drug substances for filling in seamless capsules.

- ✓ High gas barrier properties of the capsule shell protect stability of drug substances against oxidation.
- ✓ Treatment of the capsule shell with titanium oxide for protection against light supports stability of drug substances.
- ✓ Compounds that cannot be processed into tablet form due to their relatively low melting point can be filled as an oil phase without melting into a soft capsule.
- ✓ Drug substances in oil phase or as suspensions lead to higher bioavailability.
- ✓ Ability to formulate drug substances with strong odor or volatile compounds.
- ✓ Higher cost efficiency by simplified manufacturing processes and high product quality due to accurate and precise encapsulation machinery.

Oily bases:

Oily bases used especially for pharmaceutical products are carefully selected based on multiple studies such as drug substance stability. Vegetable oils such as corn oil, soybean oil, sesame oil, cottonseed oil, safflower oil, wheat germ oil, and middle chain triglycerides have been widely used.

Aqueous bases:

Macrogol 400 is used as an aqueous base. If a drug substance is water soluble, it is either solubilized in water first and mixed with Macrogol 400, or solubilized directly in Macrogol 400. Excess water could lead to problems after the encapsulation process. Drying process conditions must be adjusted accordingly when aqueous bases are used.

Suspensions:

When a drug substance is solubilized in an oily base, it becomes clear. However, when a drug substance is insoluble in an oily base or its low solubility requires a large volume of solution, then it is treated as a suspension. Beeswax or surfactants are used as a suspension agent for oily bases, and Macrogol 4000 or 6000 is used when Macrogol 400 is the base.

Surfactant:

Surfactants are not only used as a suspension agent, but also to enhance solubility and stability. In addition, as an effect on elution and absorption, surfactants are considered to be important in the designing of inner fill material formulation. Polysorbate, glycerin fatty acid esters, and hydrogenated castor oil are mainly used.

Table 4: Compatibility for filling of seamless capsules ^[9]

Parameter	Range
Viscosity (fluidity)	Clear Solublized Solution - 2000 mm ² /s or less (viscosity rate)
Suspension Solution	- 30000 mPa.s or less
<i>Suspension particle</i>	Particle Size - Solid material should pass through 100 mesh
<i>Permission range for content amount</i>	Regular range is 50 to 2000mg; however, amounts beyond this range are also possible

CAPSULE SHELL ^[9]

Capsule shells are mainly compared of gelatin, plasticizer, and excipients such as colorants, titanium oxide, and preservatives may be added accordingly. Table 5 shows ingredients required for capsule shell.

Table 5: Contents of Capsule Shell ^[9]

Name of ingredients	Purpose	Examples
Gelatin	Shell manufacturing	Alkalized gelatin and acidified gelatin. when there is a possibility

		that fill material may cause insolubility, succinated gelatin is used.
Plasticizers	add elasticity to the capsule shell & preventing cracking	Concentrated glycerin and D-Sorbitol
Preservative	To prevent infection during presevation	Ethyl paraben and propyl paraben
Titanium dioxide	prevent light penetration, added to light-sensitive compounds	Titanium dioxide
Colorants	allow easy coloring to make capsules more distinguishable and appealing	FDA approved all colors
Crystallized gelatin	prevents capsules from sticking together or to a container & prevents delayed dissolution of the capsules	Crystallized gelatin

✚ Moisture content:

Moisture content of the capsule shells is reduced to 7-9%. Generally, moisture content that is too low could lead to the tendency for cracking and too high a moisture content could cause problems such as sticking.

✚ Coating:

Enteric coating enables absorption in the intestinal tract.

CAPSULE SHELL QUALITY AND CHARACTERISTICS ^[10]

Following are the characteristics of capsules shell which are required for high quality manufacturing and action in body.

- A. **Solubility:** Capsules that dissolve easily releasing their contents. **Eg.** Seasoning capsules and breath freshening capsules.
- B. **Acid resistance:** Protection and isolation from the action of acids. **Eg.** Enteric capsules for medicinal application and enteric capsules for function food application. Table 6 shows acid resistance of different shell material.

Table 6: Acid resistance criteria of capsule shell material ^[10]

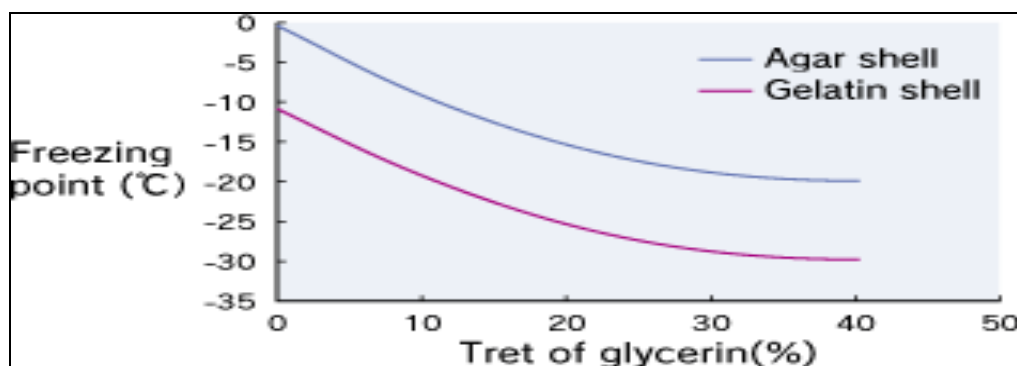
Capsule Shell material	Acid resistance
Agar	Disintegration under pH 4
Gelatin	Dissolve by over body temperature and unrelated pH
Gelatin plus pectin	Un dissolved under pH 4 (37 ⁰ C)

C. Heat resistance: Sterilization by heating is possible using hot water. **Eg.** Health drink capsules and oleastercapsules. Treat of glycerin and freezing resistant of shell. Table 7 shows heat resistance limits of shell material.

Table 7: Heat resistance criteria of capsule shell material ^[10]

Shell material	Dissolving point	Dissolving point in anhydrate
Gelatin	Less than 35 ⁰ C	Less than 100 ⁰ C
Agar	Less than 80 ⁰ C	Less than 100 ⁰ C
Gelatin plus thermostabile gel	Less than 100 ⁰ C	Less than 100 ⁰ C

D. Freezing resistance: Constant shell hardness against low temperature. Tret of glycerin and freezing resistant of shell is described in figure 6.

**Figure 6: freezing resistance of agar & gelatin shell** ^[10]

E. Light resistance: Protection of substances which are reactive to light. Eg. Masking capsules and colored capsules. Light permeability (shell thickness 50~150 μ m). Titanium dioxide should be added with penetration efficiency limits shows in figure 7.

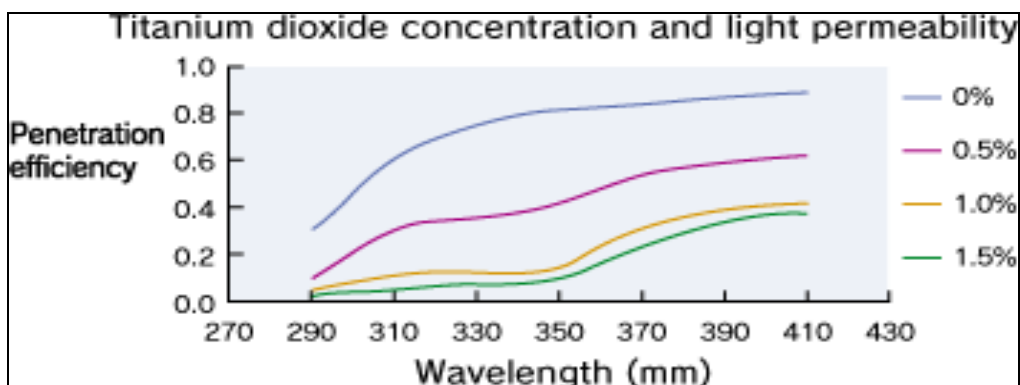


Figure 7: Light resistance with titanium dioxide ^[10]

F. VISUAL SHAPE ^[11]

The seamless capsules shell is extremely **homogeneous and very small** (figure 8). The capsules are extremely homogeneous with almost no variation in size or weight. Reduced chance of variation in fill content is making them suitable for use in medical applications in which accuracy is mandatory. The seamless finish looks neat.

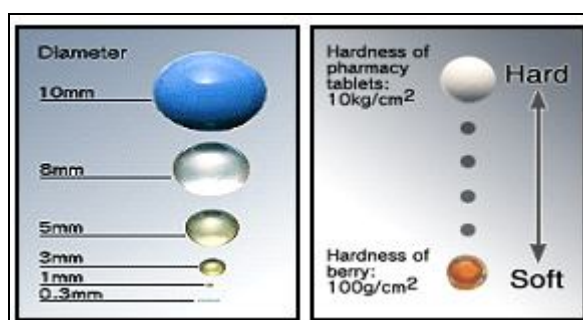


Figure 8: Shape & hardness of seamless capsule ^[11]

The **shell thickness** is controllable and can be made accurately uniform. Medicines can be encapsulated to take advantage of this accuracy. It can be reduced to as little as 30 microns (in the case of a 3mm diameter capsule) which simply cannot be achieved with conventional soft capsules. The capsule dissolves quickly. The thin shell allows a capsule to be filled with 50 percent more substance than conventional soft capsules can hold. The quality of the contents is also assured. The shell is made of a water-soluble polymer such as gelatin or agar.

You can add various kinds of flavor essences while also using a variety of functional additives to meet specific.

The **hardness of capsules** can be freely controlled by changing the material, water content and thickness of the shell (figure 8). It is possible to give the capsule the flexibility of oleaster.

CAPSULE MANUFACTURING TECHNOLOGY ^[12]

Manufacturing of seamless capsules is a great job. It requires skill, expertise persons and qualified equipments with efficient methods and technology. Majorly two methods of manufacturing are in use multi component nozzle method and Jet Streams Method/ Drop or Blow Process.

Multi-component nozzle method ^[6]

Principally, Core solution and shell solution are ejected simultaneously from the nozzle. Mini-capsules are formed due to surface tension effect between different solutions. Shell solution is solidified to form shell in cooling solution. Figure 9 explains construction of multi component nozzle equipment.

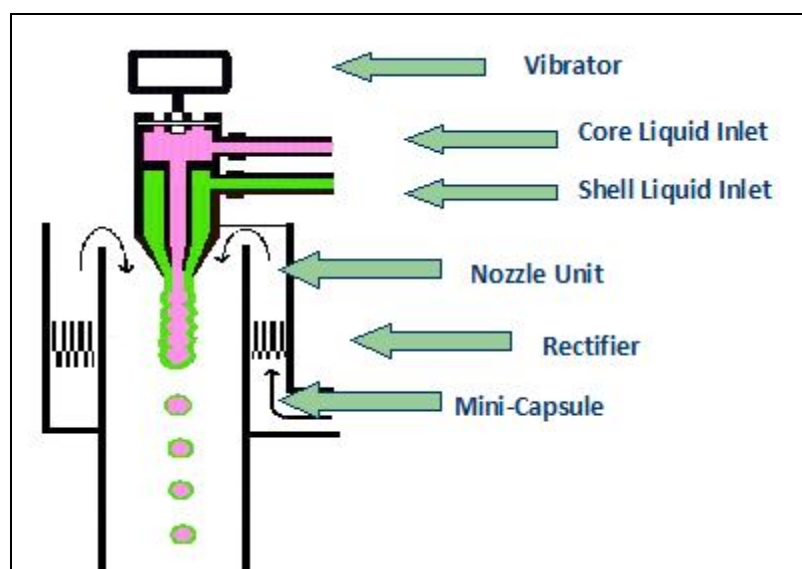


Figure 9: Multi-component nozzle ^[6]

Vibrator: It is used to obtain uniform size & weight of capsule droplet formation. One can produce uniform pressure by using the vibrator. It is on the top of the encapsulation machine.

Core-liquid inlet: Core liquid is stored in vessel & it is introduced in the system through core liquid inlet.

Shell liquid inlet: Shell liquid introduced in the system through the shell liquid inlet, where it cover the internal conical vessel containing core liquid.

Nozzle unit: It is the bottom of the conical vessel at where shell liquid covers core liquid as in spherical shape.

Pump delivers the core & shell liquids simultaneously. These are ejected into cooling liquid forming the seamless mini-capsules.

Rectifier: It is used for obtaining uniform flow of cooling liquid.

Process ^[13]

- A. Before encapsulation process begins, Gelatin mass for out shell and medicine for the capsule fill are prepared. The Gelatin powder is mixed with water and glycerin, heated and stirred under vacuum. The outer layer of this special stainless steel vessel is steam- jacketed. Any required flavors or colors are added using a turbine mixer to molten gelatin and transferred to mobile vessels. The gelatin mass is kept in a steam-jacketed storage vessel at a constant temperature
- B. The medicine fill is prepared using standard procedures used in pharmaceutical liquid, paste or suspension manufacturing.
- C. The encapsulation process begins when molten gel is pumped to the machine. This is entering at the top of the machine. At the same time shell material enter through inlet and surrounding the conical vessel of core material. Vibrator produces appropriate pressure on both of the material towards the nozzle. This pressure is regulated by automatic vibrator monitor.
- D. Shell material covers the core material in spherical shape at nozzle unit. Orifice of nozzle and pressure produce by vibrator can varied according to required size of capsule. These droplets enter into the vessel containing cooling liquid which is regulated by rectifier. After solidification of droplets drying is carried out.

Advances in nozzle method

There is provided a seamless capsule manufacturing device comprising a nozzle for ejecting liquid for forming capsules and a flow passage tube containing hardening liquid for hardening at least a surface part of each liquid drop formed from the liquid, characterized in

that the flow passage tube has an inlet part exposed to the nozzle so as to receive the liquid ejected/supplied from the nozzle and a deformation section having a cross sectional area smaller than the inlet part.

According to the invention, the liquid drops that are ejected from the nozzle into hardening liquid come to show a spherical profile once in a sol state in the inlet part of the flow passage tube. Then, they are introduced into the deformation section from the inlet part while the spherical liquid drops are still held in a sol state. The deformation section has a cross sectional area smaller than the inlet part so that, as hardening liquid is introduced from the inlet part into the deformation section, the flow rate of hardening liquid changes. As the flow rate of hardening liquid changes, the liquid drops are deformed as a function of the change in the flow rate to produce non-spherical *seamless capsules*. Neither a narrow tube nor a mold having a diameter smaller than the diameter of the ejected liquid drops is used to deform the spherical liquid drops by means of a manufacturing device according to the present invention and simply the flow rate of hardening liquid in the deformation section is changed in the molding process. Therefore, the tube or the like is prevented from being clogged and the flow of hardening liquid is prevented from being pulsated to consequently improve the quality of produced capsules and the productivity of manufacturing capsules. ^[14]

Jet Streams Method/ Drop or Blow Process ^[15]

It has been called the Globex process after its developers

Principle:

It is same as multi component nozzle method. Lipophilic filler material is dropped out of a jet while at the same time, warm gelatin solution flows out of a tube surrounding said jet. When dropped into a cooling fluid of predetermined density (for example paraffin oil) surface tension causes these capsules to take up a spherical shape and to solidify. Oily carrier materials are suitable as the filler substance

Procedure:

- A. Preparing a plurality of composite jet streams each consisting of a stream of a film-forming liquid substance for forming a cell wall and within said stream of a film-forming liquid substance a single stream, or a plurality of independent streams, of a filling substance having flowability, the film-forming liquid substance in at least one

of the composite jet streams being different from the film-forming liquid substance in at least one of the other composite jet streams,

- B. Advancing the plurality of composite jet streams in closely spaced relationship into and through a stream of a liquid medium substantially incapable of dissolving the film-forming liquid substance in the flowing direction of the liquid medium stream,
- C. Coalescing the adjacent composite jet streams to each other to form a single composite jet stream in the liquid medium stream,
- D. Cutting the single composite jet stream to a predetermined length successively from its leading end in the liquid medium stream, and
- E. Solidifying the cell walls of the resulting soft capsule.

Disadvantages of blow process

- ✓ Only oily substances can be used as the filling material.
- ✓ The different components required by the process technology such as the oily filling material, the gelatin mass, and the cooled quenching bath (paraffin oil) can be harmonized with each other, only with considerable difficulty, since one is here concerned with a 3-phase system.
- ✓ The residual quenching bath material (paraffin oil) must be removed with a solvent. This gives rise to the same problems as occur under Section (F) of the stamping process.

It is thus clear that the procedures known to the art for the production of soft gelatin capsules are subject to technological and economic problems. The complex requirements of the process technology create considerable difficulties for the pharmaceutical manufacturing companies who wish to install and run a production system for soft gelatin capsules. Additional problems can arise due to the lack of knowledge of the properties of gelatin. Furthermore, problems arise in the cleaning of the residual separation oil or cooling oil from the capsules, to which is added.

FLOW CHART OF PROCESSING STAGES AT LARGE SCALE.^[16]

Table 8 explains detailed steps of seamless capsule manufacturing and testing at large scale production. Refer figure 10 for key manufacturing steps for capsules.

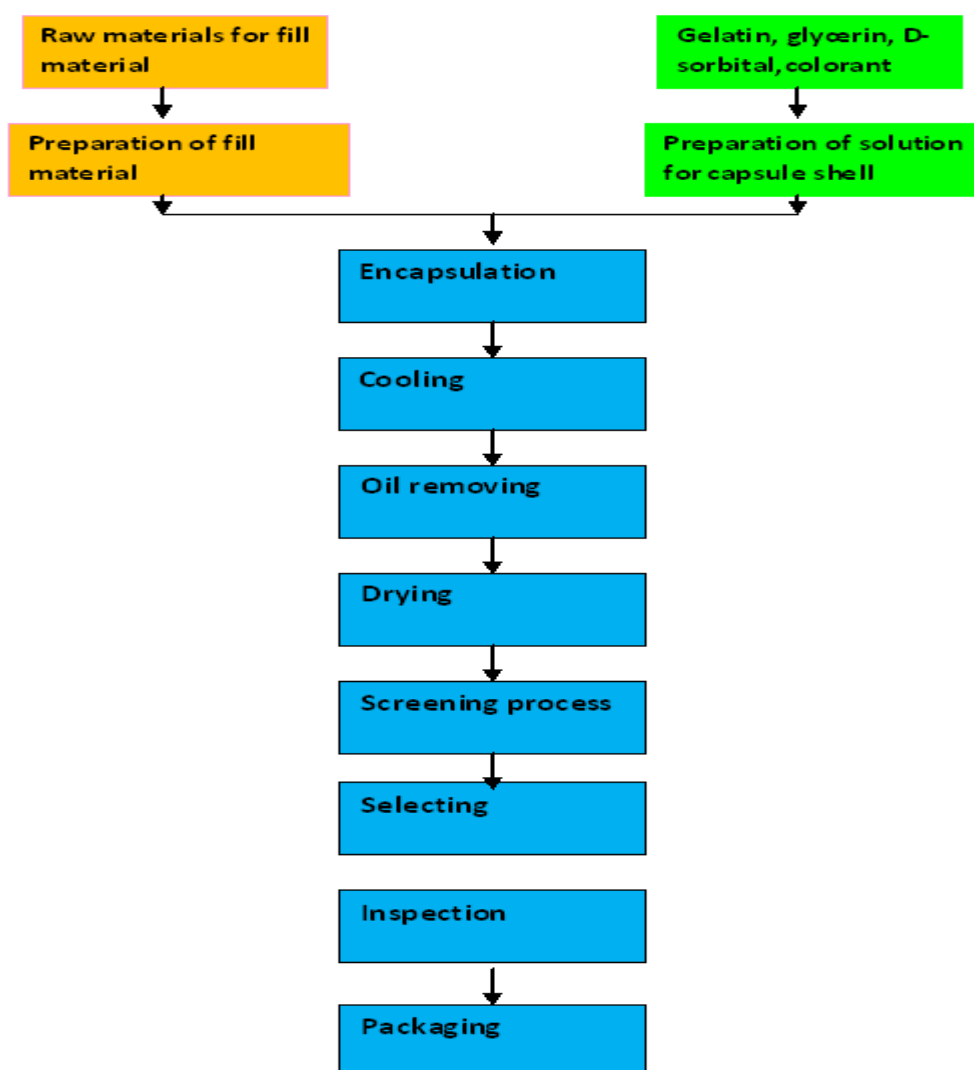














Figure 10: Capsule manufacturing technology ^[16]

Table 8: Seamless capsule manufacturing steps ^[12]

Sr.no.	Manufacturing steps	View in industry
1.	<p>Preparing shell solution</p> <p>According to its intended use, with appropriate caution being used to prevent the gel strength form being reduced.</p>	

<p>2.</p>	<p>Preparation of fill material</p> <p>After raw materials such as active ingredients have been accurately measured, they are subjected to melting and suspension to achieve guaranteed uniformity as a fill material</p>	
<p>3.</p>	<p>Encapsulation</p> <p>Oil is carefully isolated from the surface layer of capsules and undue stress is carefully avoided.</p>	
<p>4.</p>	<p>Cooling</p> <p>During cooling outer layer of capsules get solidify. Cooling process gives sufficient hardness to the capsules. It can be done by using coolant solutions.</p>	
<p>5.</p>	<p>Drying:</p> <p>The soft capsules are carefully dried in a controlled humidity environment. The forced-air drying method (including the fluidized bed drying method), the drum drying method, a reduced pressure drying method, and the like can be used.[15]</p>	

6.	Screening process Capsules are sorted by size using an automatic sizing machine,	
7.	Quality inspection The contents of each capsule are measured according to GMP, and all capsules are visually inspected.	
8.	Quantitative measurement The composition and ingredients of raw materials and the product are quantified to ensure the correct proportions are contained in the product.	
9.	Mass uniformity test By measuring mass of the product, the uniformity of active ingredients is determined.	
10.	Total organic carbon test Carbon atoms composing organic compounds within the tested material are quantified.	

<p>11.</p>	<p>Microbiological test</p> <p>Species and population of microorganisms that exist in the raw materials or product are determined.</p>	
<p>12.</p>	<p>Solubility test</p> <p>Time required for the product to dissolve in test solutions is determined.</p>	
<p>13.</p>	<p>Elution test</p> <p>The rate of the product's active ingredients to elute into test solutions is determined.</p>	

PRACTICAL APPLICATIONS OF SEAMLESS MINI-CAPSULES: [6]

➤ In Food products

1. **Functional food** that contains flavor oils to control mouth odor.
2. Additive **flavor capsules** for chewing gum, chocolate and candy.
3. **Nutraceutical food** such as lactobacillus bijidus.
4. Part of the materials used for **confectionery products**.

➤ Pharmaceutical and Non-pharmaceutical Products

1. Mini-capsules enables divided in **smaller dosages**.
2. Enables the **ingestion of liquid materials and granules** at the same time.
3. Improves the ease of formulating **coated encapsulated drugs**.
4. **Enteric** drug formulation.
5. **Control release** drug formulation.
6. **Stabilization** of drugs with strong odors for unstable drugs such as oral vaccines.

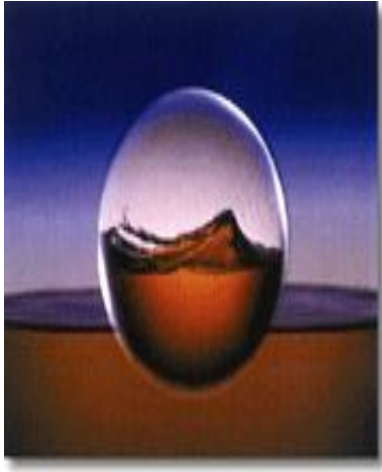
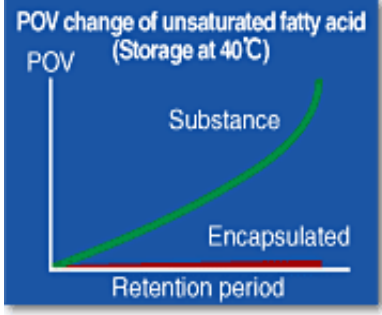
➤ Other industrial application

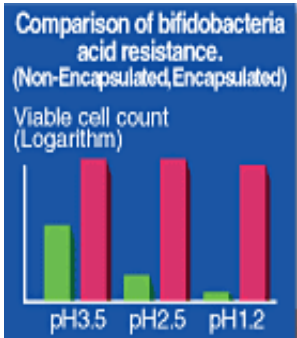

1. **Cosmetics**.
2. **Toiletry** products such as aromatics, Bath oils, detergents, Fertilizer, feed.

IMPORTANCE OF SEAMLESS MINI CAPSULES:^[17]

Some advanced application is described in table 9.

Table 9: Application of seamless capsules ^[17]



Sr.no.	Application	Figure presentation
1.	<p>It is possible to change liquids into solids</p> <p>By encapsulating liquid, you can change liquids into solid particles, or powder. This makes it possible to use substances in applications in which it's difficult to use the liquid form. The better measurability and portability of an encapsulated liquid make it easy to combine with other substances. For example, micro-encapsulation of flavors or fruit juice is possible. This feature has been widely applied in the food and confectionery industries.</p>	
2.	<p>Great improvements in the storage qualities of encapsulated substance</p> <p>It is possible to greatly improve the storage time of substances that would be oxidized if exposed to air or substances whose qualities change when exposed to light or moisture. It also allows low-boiling point substances such as flavors, which evaporate easily, to be stored for long periods. This feature is used to prevent the oxidization of DHA and β-carotene.</p>	

<p>3.</p>	<p>The release of the encapsulated contents is controllable</p> <p>You can freely control the release of encapsulated substances, according to their intended use. Capsules of this type include; an easy-dissolving capsule, which quickly dissolves in the mouth; a capsule which protects its contents against stomach acid and will not dissolve until it reaches the intestine; a time-releases capsule which gradually releases the contents of the capsule to prolong the effect of the encapsulated substances. This feature is used to encapsulate <i>Lactobacillus bifidus</i>.</p>	
<p>4.</p>	<p>Isolation reactive substances</p> <p>Chemically reactive components can be isolated until they are actually needed. For example, this feature is used in cosmetics, when different components need to be mixed just before use.</p>	


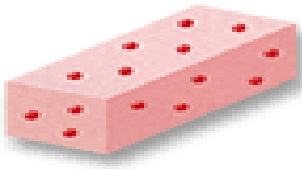
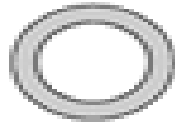
MARKETED PRODUCTS OF SEAMLESS CAPSULES:

A. Confectionery^[18]


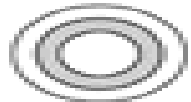
➤ *Herbit*

<p>Eucapsulated flavors, that is easily volatile in high temperature, and blended with candy</p>			
<p>Structure</p>	<p>Shell formulation</p>	<p>Content substance</p>	<p>Application</p>
<p>2LayersΦ1.0mm</p> 	<p>Gelatin</p>	<p>Lipophilic substances</p>	<p>Blended with candy Kneaded in high temperature</p>


➤ *Gum:*


Encapsulated plum flavor and blended with gum. Long lasting flavor every time capsules are burst by chewing.			
Structure	Shell formulation	Content substance	Application
2 Layers Φ 1.0 mm 	Gelatin	Lipophilic substances	Blended with gum differently from liquid flavor, capsules won't lose formability of gum base.

B. Oral care ^[19]➤ *Crystal dew*



Breath Freshener. An ultra-thin shell dissolves quickly in the mouth.			
Structure	Shell formulation	Content substance	Application
3 Layers Φ 1.8 mm 	Gelatin with quick solubility	Hydrophilic substances	capsules

C. Food ^[20]➤ *Noodles*



Encapsulated powdered soup and garlic. Dissolve quickly in hot water and will be appetizing.	
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Structure	Shell formulation	Content substance	Application
3Layers Φ1.8mm 	Gelatin	Lipophilic substances	Flavor capsules blended with graules plus powdered soup



➤ *Beverages*

Encapsulate bad taste substances or lipophilic substances, which hardly melt into base substances. Freshness and functions are visually apparent			
Structure	Shell formulation	Content substance	Application
2Layers 	Agar	Functional oil Lipophilic substances	Blended with beverage




➤ *Yougurt*

The bifidus bacteria capsule which reached intestines while had lived was mixed with the yogurt.			
Structure	Shell formulation	Content substance	Application
3Layers Φ2.0mm 	Gelatin	Powder Suspension hydrog enate oil and fat	Blend with yogurt



➤ *Dressing*

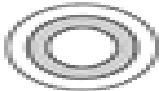
Encapsulated horseradish flavor, and blended with salad dressing.			
Structure	Shell formulation	Content substance	Application
2Layers 	Agar	Lipophilic substances	Mix into lipophilic or hydrophilic liquids

D. Health food ^[21]➤ *Bifina*




Encapsulate bifidobacteria and reach the intestines without being killed by stomach acid.				
Structure	Shell formulation	Content substance	Application	
3Layers Φ 1.8mm 	Gelatin with acid resistance / Enteric	Powder suspended into hardened oil.	Blended with granule(Encapsulated Bifidobacteria + oligosaccharide granule)	

➤ *Bifina Tablet*

Encapsulated bifidobacteria with enteric function. Blended with tablet, which dissolves quickly in mouth				
Structure	Shell formulation	Content substance	Application	




3Layers Φ 1.0mm 	Gelatin with acid resistance / enteric function	bifidobacteria powder	Blended with tablet
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➤ **DHA / EPA:**



Encapsulate mixture of DHA and EPA, adding enteric function. Reduced returning smell.			
Structure	Shell formulation	Content substance	Application
3Layers Φ 2.5mm 	Gelatin with acid resistance / enteric function	Lipophilic substances	Quaffable size Capsule

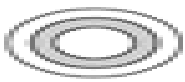
E. **Pharmaceutical product:** ^[22]

➤ **Bifina-Constipation:**

Encapsulate bifidobacteria and reach the intestines without being killed by stomach acid			
Structure	Shell formulation	Content substance	Application
3Layers 	Gelatin with acid resistance / Enteric	Powder suspended in hardened oil	Capsules



➤ **Solmiran**

Encapsulated EPA adding enteric function. Reduced returning smell.			
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Structure	Shell formulation	Content substance	Application
3Layers Φ 1.8mm 	Gelatin with acid resistance / enteric function	Functional oil	Capsules

F. Toiletry products ^[23]

➤ *Tooth paste*

Encapsulate functional oils such as flavor, VitaminE. Blended with tooth paste.			
Structure	Shell formulation	Content substance	Application
2Layers 	Agar	Lipophilic substances Functional oil	Knead into tooth paste

➤ *Body shampoo*

Encapsulated flavor bursts and spreads out, during washing.			
Structure	Shell formulation	Content substance	Application
2Layers Φ 1.8mm 	Agar	Lipophilic substances	Blended with gel

REFERENCES

1. Kraus, Walter, Dr. et. Al., seamless soft capsule, Taisho pharmaceutical co. ltd., Tokyo, japan. European patent application. No. 86117918.2 dated 8/7/1987
United States Patent 6719933, Method for manufacturing seamless capsule. Available at <http://www.freepatentsonline.com/6719933.html>

2. Jesse John Kiefer, Blake Henderson Glenn, Methods and apparatus for making seamless capsules, Patent number: 5888538, Filing date: Mar 28, 1997, Issue date: Mar 30, 1999.
3. Larry L. Augsburger, University of Maryland, Baltimore, MD, Hard and Soft Shell Capsules, Design, Formulation and Manufacture, page no. 8-9.
4. Seamless Mini Capsule, Products, Freund Corporation, Available at http://www.freund.co.jp/english/chemical/trustee/seamless_capsule.html.
5. Noticeable features. Encapsulation technology, Jintan Capsule Technology, Available at <http://www.jintanworld.com/english/capsule/tano.html>
6. Seamless mini capsules, VPS Corporation, A Freund Group company.
7. Different types of seamless capsules and structure of seamless capsules. Available at www.naturalproductsinsider.com/bgpl/NPImitsui2.pdf
8. Capsule contents, Encapsulation Technology, Jintan capsule technology, Available at <http://www.jintanworld.com/english/capsule/naiyo.html>
9. Capsule shell material, fill material, drug content. Available at http://www.tokai-cap.co.jp/e_develop/02.html
10. Capsule shell quality, Encapsulation Technology, Jintan Capsule Technology, Available at <http://www.jintanworld.com/english/capsule/himaku.html>
11. Visual shape, Encapsulation Technology, Jintan Capsule Technology, available at <http://www.jintanworld.com/english/capsule/gaikan.html>
12. Capsule manufacturing technology, Encapsulation Technology, Jintan Capsule Technology, Available at <http://www.jintanworld.com/english/capsule/seisan.html>
13. Gursharan Moonga, Softgel Drug Delivery Systems, innovaro pharmlicensing available at http://pharmlicensing.com/public/articles/view/948454700_3888452c79360/softgel-drug-delivery-systems
14. United States Patent 20060233874, Seamless capsule manufacturing method, seamless capsule manufacturing device and seamless capsule. Available at <http://www.freepatentsonline.com/y2006/0233874.html?query=PN/20060233874%2520OR%252020060233874&stemming=on> as Seamless capsules.
15. United States Patent 5209978, Seamless soft capsule and production thereof. Available at <http://www.freepatentsonline.com/5209978.html>

16. Production line, Tokai Capsule co. Ltd., http://www.tokai-cap.co.jp/e_product/flow.html
17. Capsule function, Encapsulation Technology, Jintan Capsule Technology, Available at <http://www.jintanworld.com/english/capsule/kihon.html>
18. Confectionary, Introduction of commercialized products, Jintan Capsule Technology, available at <http://www.jintanworld.com/english/seihin/confec.html>
19. Oral care, Introduction of commercialized products, Jintan Capsule Technology, available at <http://www.jintanworld.com/english/seihin/confec.html>
20. Food, Introduction of commercialized products, Jintan Capsule Technology, available at <http://www.jintanworld.com/english/seihin/confec.html>
21. Health food, Introduction of commercialized products, Jintan Capsule Technology, available at <http://www.jintanworld.com/english/seihin/confec.html>
22. Pharmaceutical products, Introduction of commercialized products, Jintan Capsule Technology, available at <http://www.jintanworld.com/english/seihin/confec.html>
23. Toiletry products, Introduction of commercialized products, Jintan Capsule Technology, available at <http://www.jintanworld.com/english/seihin/confec.html>