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Liquid Filled Hard Gelatin Capsules: A Novel Revolution in Delivering Liquid Formulations

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Abstract

In the present work is to give innovative information about hard gelatin capsules with liquid filling. The article gives detailed information about advantages of liquid filled hard gelatin capsules over liquid filled soft gelatin capsules. Complete description, manufacturing procedure and marketed products of hard gelatin capsules.

Key words: Liquid Filled, Hard Gelatin, Advantages, Oral Dosage

Contents

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1. Introduction

Drugs discovering now a days are of poorly water soluble category. To increase the solubility of such drugs classical methods, such as reduction in particle size are no longer adequate to achieve satisfactory drug adsorption from a solid oral dosage form. One of the most promising approach to deliver such insoluble drugs is by dissolving it in lipids, liquids or semi-solids to formulate new products. Two piece hard gelatin capsules are one of the most logical approaches when choosing the best dosage form to deliver these new liquid formulations[1].

Types of materials for filling into hard gelatin capsules[2]:

1. Dry solids (Powders, pellets, granules or tablets)
2. Semisolids (Suspensions or pastes)
3. Liquids (Non-aqueous liquids)

Drug categories suitable for filling into capsules:

Drugs with Poor bioavailability

Reports says that the bioavailability of the poorly water soluble drugs can be significantly enhanced when formulated as a liquid in a soft gelatin capsule[3-6]

Drugs with Low melting point:
Materials which have low melting points or are liquid at room temperature present difficulties when formulating as dry powders, often requiring high concentrations of excipient to avoid processing problems [7-10].
Potent drugs:
Drugs in this category present two main challenges; how to achieve acceptable content uniformity and how to control cross-contamination and worker protection [11-13].
Advantages of hard gelatin capsules over soft gelatin capsules Encapsulation
Advantages of hard gelatin capsules over soft gelatin capsules were tabulated in Table 1.

Table 1. Advantages of hard gelatin capsules over soft gelatin capsules

Advantages of hard gelatine capsules	over soft gelatine capsules
Contain 4-5 times less gelatine than soft gelatine capsules	Require 4-5 times more gelatine than the hard gelatine capsules
Require no other additives. Consists of water and gelatine only	Require addition of glycerin for softening purposes
Allow step-by-step filling of 2 different formulations (i.e. 2-stage-release)	Have to be sealed immediately after filling one substance (filling and sealing are one and the same process)
Heat resistant : allow filling of thermo-stable substances up to 75°C	Filling temperature limited to about 35°C : filling of solid substances with higher melting points impossible
Are stable in hot climates	Tend to stick together and become gluey
Will disintegrate faster due to the capsule wall being five times thinner than the walls of soft gelatine capsules	Will disintegrate slower due to the thickness of its gelatine/glycerin wall
Less product migration into the shell, less diffusion of odours	Glycerin acts as a plasticiser by disrupting the gelatine structure - consequently, higher diffusion into and through the walls
Constant external dimensions (easier blistering/packaging)	Dimensions vary according to filling weight and vary throughout a batch

Sustained release drug candidates:
By choosing an appropriate excipient the release rate of an active ingredient can be modified. E.g., soybean oil and glyceryl monostearate [14-17].

2. Compatibility of Fill Materials

The properties of the API dictate whether it is a good candidate for liquid filling. Next, suitable excipients are evaluated, with an understanding that neither the API nor the excipients should cause the gelatin shell to gain or lose excessive moisture, which can cause the shell to lose its mechanical strength. All substances must also be chemically compatible with gelatin [18]. To maintain flexibility, the capsule shell must retain a moisture content of 13-16%. Below that range capsules become brittle and are prone to breakage. Above that range the capsules may deform. To measure the moisture exchange between the fill material and the shell, fill the capsules with the product in question and store them at different levels of relative humidity (RH) (i.e., 2.5, 10, 30, 50 and 60%) for 2 weeks. During that period, the water exchange across the range of RHs should not exceed ±2%.

Fill materials that exchange more than ±2% moisture compared to empty shells stored under the same conditions are not suitable for liquid filling. The capsule's mechanical resistance must be checked in relation to moisture content. This involves storing the filled capsules for 1week at different RHs and then testing them for resistance to breakage and deformation. Chemical compatibility of the fill material with the gelatin shell is also important. For instance, if the fill material causes the protein chains of the gelatin to cross-link, there may be a delay in dissolution. One method of monitoring cross-linking is to first store the fill material inside the hard gelatin capsules under ICH accelerated storage conditions (40°C at 75% RH), and then replace the fill material with acetaminophen. Next, conduct a dissolution test according to USP guidelines to compare the dissolution profiles of the filled and unfilled capsules stored at the accelerated conditions. Lipophilic liquid vehicles, Semisolid lipophilic vehicles, solubilizing agents, surfactants and emulsifying agents that are compatible with hard gelatin capsules are listed in table 2 [19].

Table 2. Excipients for Liquid Filled Hard Gelatin Capsules

Lipophilic liquid vehicles	Refined specially oils	Arachis oil, Castor oil, Cotton seed oil, Olive oil, Soyabean oil, Sesame oil, Maize(corn)oil and sun flower oil
	Medium chain triglycerides	Akomed R (Caprylic/capric triglycerides) Miglyol 810 (actoic acid/capric triglyceride) Miglyol829 (succinic triglyceride) Miglyol840 (propanediol dioctanoate/dicaprate) Softisan645 (bis polyacyladipic diglyceride1) Lauroglycol FCC (Propylene Glycol Laurate), Captex 355
Semisolid lipophilic vehicles	Hydrogenated oils	Arachis oil (Groundnut 36), Castor oil (Cutina HR), Cottonseed oil (Sterotex) and Palm oil (Softisan 154)
	Waxes	Cetosteryl alcohol, Cetyl alcohol and Steryl alcohol
	Gelucires	Gelucires 33/01, 39/01, 43/01
Solubilizing agents, surfactants, emulsifying agents	Emulsifiers- W/O emulsifier, O/W emulsifier	Imwitor 780K(Isostearyl Diglyceryl Succinate) Imwitor 380 (Glyceryl Cocoate/Citrate/Lactate)
	Surfactants	Tween 80, Poloxamer 124 and poloxamer 188
	Liquid solubilizer	Plurol Oleique CC497 (Polyglyceryl Oleate)
	Fatty acid esters	Softigen 701(Glyceryl Ricinoleate) Softigen 767(PEG-6 Caprylic/Capric Glycerides)
	Polyethylene Glycols	PEG>4000
	Gelucires	Gelucire 44/14, 50/13

A capsule from capsugel for filling liquids

Capsugels are capsule specially designed for liquid and semi-solid fillings [20] (Fig.1). This capsule is longer than standard capsules, so that when the capsule body and cap are fully joined, the top of the capsule body's wall contacts the interior of the cap. This provides the primary barrier to prevent the liquid fill from escaping. (It is essential to keep the area of the cap-body interface uncontaminated by fill material. Otherwise, it is virtually impossible to seal the capsule.) To further prevent or reduce leakage and contamination at the cap-body interface, the capsule has no side air vents, which are of typical capsules used in high-speed powder filling. The capsule is normally filled to no more than 90% of its volume to minimize the chance of the liquid fill contaminating the cap-body interface. Capsule dimensions and filling capacities were tabulated [21] in Table 3 and recommended specifications for filling liquids into hard gelatin capsules were shown in Table 4.

Table 3. Capsule dimensions and filling capacities

Capsule Size	Capsule volume (ml)
00	1.37
00el	1.02
00	0.91
0el	078
0	0.68
1	0.50
2	0.37
3	0.30
4	0.21
5	0.10

el: elongated

Table 4. Recommended specifications for filling liquids into hard gelatin capsules

Parameter	Recommendation
Temperature of fill material	Max 70^0C
Viscosity at the pemperature of dosing	0.1 – 1Pa s
Particle size of suspended particle	<50µm
Visco properties	Clean break from dosing nozzle

A brief description of sealing methods:

Once closed, the capsule must be sealed to prevent leaks and tampering. A hydro-alcoholic fusion process (described in the USP's capsule monograph) is one method of sealing (Fig. 2) [22]. This fusion process begins with an application of less than 50µl of sealing solution to the cap-body interface. The solution penetrates the overlapping cap and body by capillary action, while a vacuum removes any excess sealing fluid from the capsule. Next, gentle application of warm (40-60°C) air fuses the gelatin of the cap and body together and evaporates the sealing solution. The entire process takes less than 1 minute and transforms the two-piece hard capsule into a leak-free dosage unit. Once sealed, the capsule meets tamper-evidence guidelines since it cannot be opened without visibly altering it.

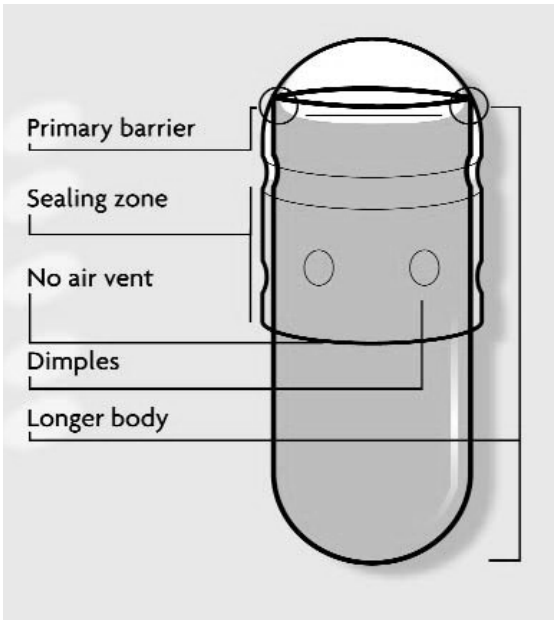

Figure 1. Two-piece capsule for liquid fills

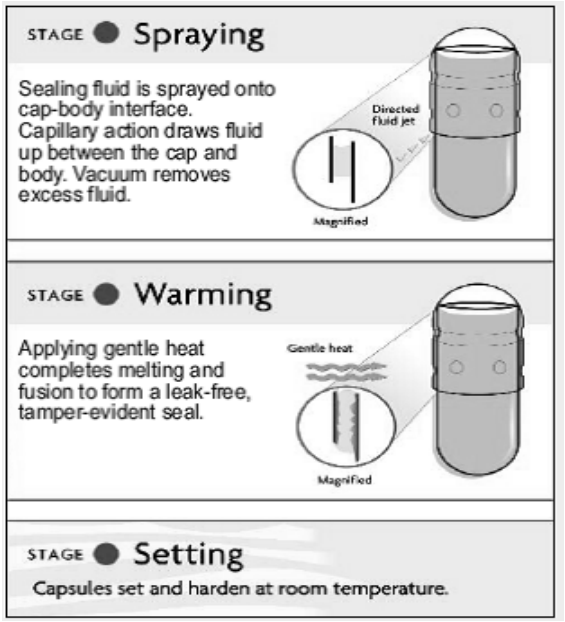

Figure 2. Capsule sealing using a hydro-alcohol solution

Hard gelatin capsule sealing technology by micro spray

The capsule sealing process [23 and 24] uses the principle of lowering of the melting point of gelatin by the application of moisture to the area between the capsule body and cap. The first machine involves dipping the capsules into a bath of liquid and drying in a fluidized bed chamber. During this process the capsules were subjected to considerable stress. In contrast to this, in the redesigned process every capsule is separately sprayed with a micro

amount of sealing fluid at the body and cap junction as shown in Fig. 3. Drying takes place by gently dipping the capsules in a rotating drum. The various stages of the process are outlined in Table 5. Control of the filled and sealed capsules is carried out by inspection on trays after 24 h, inspection after depression test at - 0.8 bar for 20 minutes and inspection after 18 h at 45°C after cooling to room temperature.

By incorporation of a dye tracer into the sealing fluid and observation of the liquid in the overlapping space it could be verified that the sealing liquid does not pass beyond the interlocking rings of a Licaps™ capsule. The machine for industrially sealing hard gelatin capsules, shown in Fig.4, is commercially available and is marketed under the name LEMS™ 30 (Liquid Encapsulation by Micro Spray). The machine is free standing and in practice is connected to the output of a capsule filling machine by means of a conveyor. Numerous companies familiar with the hard gelatin capsule banding operation have evaluated the capsule sealing technology using LEMS™ and over a period of time a neutral comparison of the two processes have been possible. Marketed liquid and semisolid filled Hard Gelatin Capsules [19] were tabulated in Table 6.

Table 5. Stages of the hard gelatin capsule sealing process

Stage	Process
1. Moisturizing	50:50 water/ethanol mixture sprayed onto join and capillary action draws liquid into the space between body and cap. Excess fluid removed by suction. Melting point of gelatin lowered by presence of water.
2. Warming	Application of gentle heat of approx. 45°C completes the melting over a period of about one minute and the two gelatin layers are fused together to form a complete 360° seal.
3. Setting	Gelatin setting or hardening process is completed while the product returns to room temperature. This process is best carried out on trays

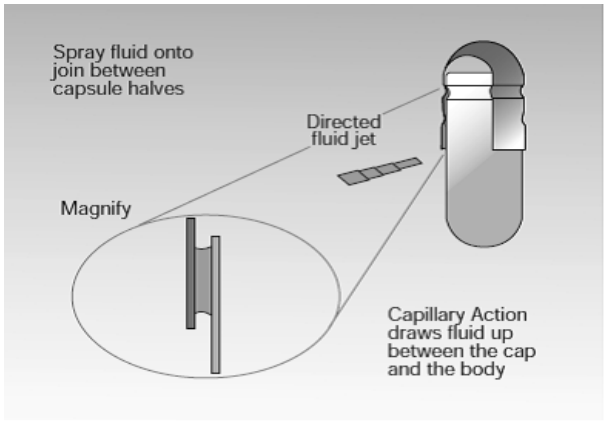

Figure 3. Space between cap and body of the capsule spraying process to moisturize the hard gelatin capsules

Figure 4. LEMS 30 machine for sealing

Table 6. Marketed liquid and semisolid filled Hard Gelatin Capsules

Substance	Brand name	Company	Region
Vancomycin	Vancocin	Lily	USA
Captopril	Captopril-R	Sankyo	Japan
Ibuprofen	Solufen SMB	Ivax	Europe
Fenofibrate	Cil 200mg	Azupharm SMB	Europe
Peppermint oil	Colpermin	Upjohn Pharmacia	Europe
Ethosuximid	Suxilep	Jenapharm	Europe
Phospholipids	Lipostabil 300	Aventis	Europe
Curcuma	Cholagogum	Aventis	Europe
Piroxicam	Solicam	SMB	Europe
nifedipin	Aprical	Rentschler	Europe
Avocado/Soya extract	Piascledine	Pharmascience	Europe

3. Conclusion

The technology potentially provides process to develop drugs which are poorly water soluble, have low melting points, are highly potent or low dosed or have a critical stability issue, into bioavailable, stable and safe dosage forms. One problem which has prevented wider acceptance of this technology was the fact that the capsules had to be banded using a process which is difficult to operate and capital intensive. Development of the LEMS™ technology provides a means to effectively seal hard gelatin capsules using a process which is easy to control. Liquid filling and sealing of hard gelatin capsules thus becomes a much more feasible option. It provides the formulation scientist to rapidly develop products for clinical trials when drug substance is at a premium and also provides an easy route to scale-up and production.

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