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Review Article

Liquid Filled Hard Gelatin Capsule

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ABSTRACT

Novel dosage forms emerge more and more in recent years. One of them is liquid-filled hard gelatin capsules, which have gelatin or the hydroxypropyl methyl cellulose (HPMC) as capsule shell. The liquid-filled hard gelatin capsule is gradually getting attention because of its new-concept dosage form design, which brings liquid drugs by solid form. The paper mostly presents application, pharmaceutical manufacturing, quality assessment, vision of liquid-filled hard gelatin capsules and emphasizes on the application and pharmaceutical manufacturing of liquid-filled capsule. It is recommended that the capsule is suitable for many liquid or semi-solid natural plant extract and achieve different release profiles. The preparation adopted liquid-filled hard capsules technology. The impact factors concluded property of shell and device of filling. The quality was frequently evaluated by moisture content of capsule shell, dissolution rate. At the same time, it was pointed out that the new dosage form has remarkable marketing prospect and brings profits for enterprises.

Keywords: Liquid filled capsule, Capsule Shell, Gelatin, HPMC, Dissolution rate.

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Introduction

Liquid filled hard gelatin capsules are well recognized as a solid dosage form for convenient administration of drugs orally in a liquid form. Liquid filled capsule technology can be used for liquid and semisolid fills in hard gelatin or HPMC capsule with or without banding. This liquid composition available helps the most challenging drug compounds in capsules has increased significantly in recent years. In particular it is possible to solubilize many drug compounds in a micro emulsion pre-concentrate inside the hard gelatin capsules such that on subsequent dispersion in the gastro intestinal tract, the drug remains in solution. It is considered that this technology can make a significant contribution to the development of efficacious pharmaceutical products by providing the flexibility to rapidly develop and test in-house formulation when small quantities of drug are available.

The Hard gelatin capsule has historically been used as a dosage form for pharmaceutical and Nutraceutical products that are formulated as powders or pellets. Liquid-fill hard gelatin capsule technology was established in the early 1980s as an alternative to soft gelatin capsules and offered a number of specific advantages such as lower moisture and gas transmission, use of high melting point excipients, plasticizer- and preservative-free, lower moisture content, ease of coating and choice of capsule composition (gelatin

and hydroxypropyl methylcellulose). This technology is mostly suitable for insoluble compounds, highly potent compounds. Once the capsule is filled, they are sealed by spraying small amount of Water/ethanol mixture at the cap and body interface followed by gentle warming to fuse the two parts of capsule together or by band sealing of capsule with gelatin or cellulose.

Drugs having low melting points or are liquids at room temperatures which have difficulty when formulated as dry powders and often require high concentration of excipients to avoid processing problems. The hard gelatin capsule has been conventionally used for Rx and OTC drugs and herbal products, which are formulated as a powder or pellets. Various categories of drugs, however, demand new and different ways of formulation and the market demands that these products are developed and launched in an ever decreasing time period. This article will review how liquids filled into hard gelatin capsules can achieve some of these difficulties and will review the categories of drugs for which the liquid capsule is particularly suitable and also study the compatibility problems associated with excipients, compare the liquid filled and sealed hard gelatin capsule with soft gelatin capsules and describe a new process for sealing hard gelatin capsules.¹

Drug categories suitable for Liquid filled capsules

1. Drugs with Poor bioavailability: The bioavailability of the poorly water-soluble drugs can be significantly enhanced when formulated as a liquid in a hard gelatin capsule.^(2,3)
2. Drugs with Low melting point: Materials having low melting points or are liquid at room temperature have some problems when formulating as dry powders, often requiring high concentrations of excipient to avoid processing problems.⁽⁴⁾
3. Potent drugs: Drugs in this category present two main challenges; content uniformity and cross-contamination and worker protection.^(5,6)
4. 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.⁽⁷⁾

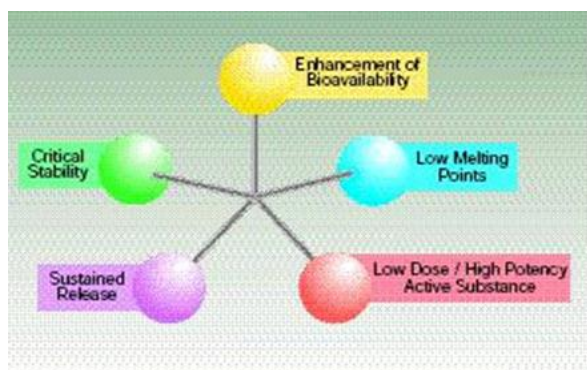


Figure 1: Reasons for Formulating Drugs as Liquid Dosage Forms

Compatibility of Fill Materials

The properties of the API which shows whether it is a good candidate for liquid filling or not. The suitable excipients are evaluated by considering 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. To maintain flexibility, the capsule shell should have the moisture content ranging 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 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 moisture exchange across the range of RHs should not exceed $\pm 2\%$.⁽⁸⁾

Fill materials that exchange more than $\pm 2\%$ moisture compared to empty shells stored under the same conditions as liquid filling. The capsule's mechanical resistance must be checked with relation to moisture content. This involves storing the filled capsules for 1 week at different RHs and then testing them for resistance to breakage and deformation. The chemical compatibility of the fill material with the gelatin shell is also important. If there is a cross linking between fill material and the protein chains of the gelatin may causes 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 substitute the fill material with acetaminophen. And then conduct a dissolution test according to USP guidelines to compare the dissolution profiles of filled and unfilled capsules stored at the accelerated conditions.⁽⁹⁾

Table 1: Excipients for liquid filled hard gelatin capsule

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 (actioic 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 (Glycerol Cocoate/Citrate/Lactate)
	Surfactants	Tween 80, Poloxamer 124 and poloxamer 188 Plurol Oleique CC497 (Polyglyceryl Oleate)
	Fatty acid esters	Softigen 701(Glycerol Ricinoleate)
	Liquid solubilizer	Softigen 767(PEG-6 Caprylic/Capric Glycerides)
	Polyethylene Glycols	PEG>4000
	Gelucires	Gelucire 44/14, 50/13

Table 2: Size and volumes of hard gelatin capsules for liquid filling

Size (ml)	Approx. volume (ml)	Approx. available volume
00el	0.92	0.83
00	0.85	0.77
0	0.61	0.55
1	0.45	0.41
2	0.34	0.31

Capsule filling

Capsugels are capsule especially designed for liquid and semi-solid fillings⁽¹⁰⁾. 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. As 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.⁽¹¹⁾

Recommended specifications for filling liquids into hard gelatin capsules

1. Temperature of fill material: Max 700C
2. Viscosity: 0.1 – 1Pa s
3. Particle size of suspended particle: <50µm
4. Visco properties: Clean break from dosing nozzle

A brief comparison of sealing methods:

Once closed, the capsule must be sealed to avoid leaks and tampering. A hydro-alcoholic fusion process (described in the USP's capsule monograph) is one method of sealing. This fusion procedure starts with an application of less than 50 microliters of sealing solution to the cap-body interface. The solution enters the overlapping cap and body by capillary action while a vacuum removes excess sealing fluid from the capsule. Next is the gentle application of warm (40° to 60°C) air fuses the gelatin of the cap and body together and evaporates the sealing solution. The complete procedure takes less than 1 minute and converts 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.

Another method involves banding the cap-body interface with a thin film of gelatin. Banding involves several added tasks compared with hydroalcoholic sealing. First prepare the gelatin bath and its viscosity must be checked continuously. Care should be taken as there is a risk of microbiological contamination associated with warm liquid gelatin. Furthermore, the gelatin band can cause physical defects in the capsule such as bubbles may form in the gelatin band or the capsules may take on a "banana" shape. The deformation usually occurs when the warm band of gelatin cools and the capsules are subjected to a long drying cycle.⁽¹²⁾

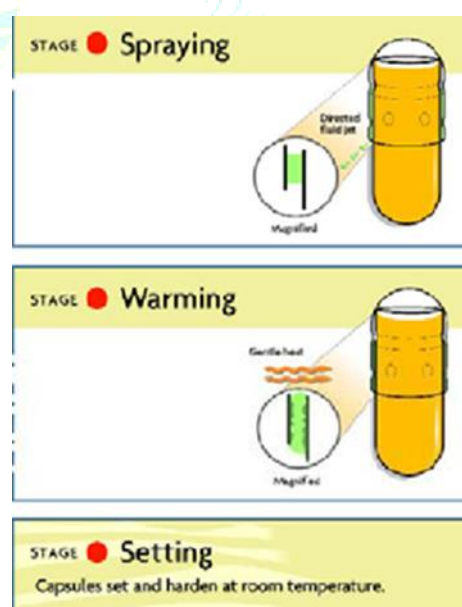


Figure 2: Steps involved in sealing technique

Table 3: Currently marketed products formulated as liquid fill capsules

Sr no:	Active	Brand	Dosage form	License holder
1	Danthron	Co-Danthromer	Hard capsule	Napp
2	Captopril	Captopril-R	Hard capsule	Sankyo
3	Peppermint oil	Colpermin	Hard capsule	J & J
4	Isotretinoin	Claravis	Hard capsule	Teva
5	Mebeverine	Mebeverine	Hard capsule	Mylan
6	Paricalcitol	Zemplar	Soft gel	Abbott
7	Dutasteride	Avodart	Soft gel	GSK

Evaluation parameters of liquid filled capsules

1. Content uniformity of liquid filled capsules:

The content uniformity of optimized formulation filled capsules is performed by assay method. For this test sample of the contents is assayed as described in individual monograph and values calculated comply with prescribed standards. The content uniformity should be in the limit indicating result for assay lay in the range. Content uniformity or assay studies were also done for all capsules at specific intervals showed that drug was uniformly distributed.⁽¹³⁾

2. In vitro dissolution profiles:

Drug release from the liquid filled hard gelatin capsules is evaluated by carrying out dissolution studies in specific solvent using USP II type (paddle type) dissolution tester (Electro Lab, India). The speed of rotations is at 50 RPM. Temperature should maintain at 37°C. The absorbance is measured in UV Spectrophotometry at drug's absorbance maxima. Dissolution study of the formulation should compare with marketed preparation.⁽¹⁴⁾

3. Drug content

The drug content of liquid filled hard Gelatin capsules was determined spectrophotometrically by using UV spectrophotometer. The percentage content of LFHGC: Assay value X 100/ Label claim.⁽¹⁴⁾

4. Sealing integrity / Leak test:

Leak test should perform and all the capsules have to pass the leak test. By repeating the sealing integrity or leak test for all those capsules at specific intervals showed that there was no leakage it conforms that the seal was not broken or disturbed such that the capsules were stable.⁽¹⁴⁾

5. Weight variation test

Fill the capsule shell with formulation. Take 20 capsules and weight of individual capsule should be noted and average weight is calculated. Not more than two individual weight deviates from average weight.⁽¹⁵⁾

6. Disintegration test

For performing disintegration test on capsules, the tablet disintegration test apparatus is used but the guiding disc may not be used except that the capsules float on top of the water. One capsule is placed in each tube which are then suspended in the beakers to move up and down for 30 minutes, unless otherwise stated in the monograph. The capsules pass the test if no residue of drug or other than fragments of shell remains on No. 10 mesh screen of the tubes.⁽¹⁶⁾

7. Stability studies:

Preliminary stability of the best formulation obtained by investigating its Physical characteristics and drug content and drug release after storage at stressed conditions. LFHGC was stored at 40°C & 75% RH for a period of 1 months. The Physical characteristics and drug content and drug release of the fresh (stored at room temperature) and stressed preparations are compared to evaluate the stability and effect of aging. A moisture uptake studies at 75% RH should be conducted to know the stability of empty capsules and the formulation filled capsules. The moisture pickup should not be more than 2% as they were found to split and not acceptable.⁽¹⁶⁾

Conclusion

Liquid formulations filled into two-piece hard capsules is the topic of interest in the pharmaceutical industry over the last decade. Today's challenges in product development due to the poor aqueous solubility and high potency of the new molecules are being addressed by some development groups that are focused on liquid formulations. In-house filling and sealing these formulations into two-piece hard gelatin capsules can be done easily with today's equipment. The processes have also been proven to be commercially viable for in-house manufacturing. Many pharmaceutical products now under development are expected to reach the market within the upcoming years and increasing the number of commercial products using a liquid-filled and sealed capsule. Liquid filling and sealing of hard gelatin capsules thus become a much more possible option. It provides the formulation scientist with an in-house option to rapidly develop products for clinical trials when drug substance is at a premium and also provides an easy way to scale-up and production.

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