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Research Paper

Liquid filled hard gelatin capsule

Akshay dahiya

ABSTRACT
Novel dosage forms emerges more and more in recent years. One of them is liquid-filled hard gelatin capsules, which have gelatin or thehydroxypropyl methyl cellulose (HPMC) as capsule shell. The liquid-filled hard gelatin capsule is gradually getting attention because of its newconceptdosage form design, which bring liquid drugs by solid form.It is recommended that the capsule is suitable for many liquid or semi-solid natural plant extract and achieve different releaseprofiles. 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 newdosage form has remarkable marketing prospect and bring profits for enterprises.
Keywords: *Liquid filled capsule, Capsule Shell, Gelatin, HPMC, Dissolution rate*

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I. Introduction

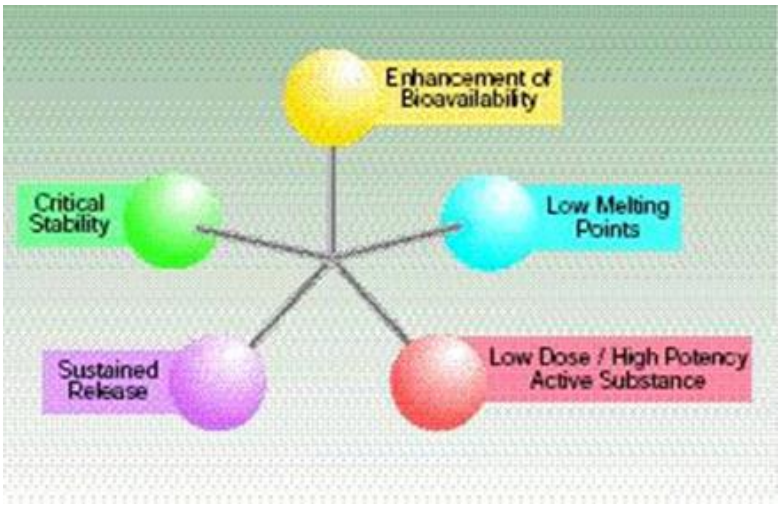
Liquid filled hard gelatin capsule are well recognized as asolid dosage form for convenient administration of drugsorally in a liquid form. Liquid filled capsule technology can beused for liquid and semisolid fills in hard gelatin or HPMCcapsule with or without banding. This liquid compositionavailable help the most challenging drug compounds incapsules has increased significantly in recent years. Inparticular it is possible to solubilize many drug compoundsin a micro emulsion pre-concentrate inside the hard gelatincapsules such that on subsequent dispersion in the gastrointestinal tract, the drug remains in solution. It is consideredthat this technology can make a significant contribution tothe development of efficacious pharmaceutical products byproviding the flexibility to rapidly develop and test in –house formulation when small quantities of drug is available.The Hard gelatin capsule has historically been used as adosage form for pharmaceutical and Nutraceutical productsthat are formulated as powders or pellets. Liquid-fill hardgelatin capsule technology was established in the early1980s as an alternative to soft gelatin capsules and offered anumber of specific advantages such as lower moisture andgas transmission, use of high melting point excipients,plasticizer- and preservative-free, lower moisture content,ease of coating and choice of capsule composition (gelatinand hydroxypropyl methylcellulose). This technology ismostly suitable for insoluble compounds, highly potentcompounds. Once the capsule is filled, they are sealed byspraying small amount of Water/ethanol mixture at the capand body interface followed by gentle warming to fuse thetwo parts of capsule together or by band sealing of capsulewith gelatin or cellulose.Drugs having low melting points or are liquids at roomtemperatures which have difficulty when formulated as drypowders and often requires high concentration of excipientsto avoid processing problems. The hard gelatin capsule hasbeen conventionally used for Rx and OTC drugs and herbalproducts, which are formulated as a powder or pellets.Various categories of drugs, however, demand new anddifferent ways of formulation and the market demands thatthese products are developed and launched in an everdecreasing time period. This article will review how liquidsfilled into hard gelatin capsules can achieve some of thesedifficulties and will review the categories of drugs for which the liquid capsule is particularly suitable and also study thecompatibility problems associated with excipients, compare. the liquid filled and sealed hard gelatin capsule with softgelatin capsules and describe a new process for sealing hardgelatin capsules.

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. 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.
3. Potent drugs: Drugs in this category present two main challenges; content uniformity and cross-contamination and worker protection.
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
Figure : 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 ±2%.

Fill materials that exchange more than ±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 1week 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.

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

Capsules 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.

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

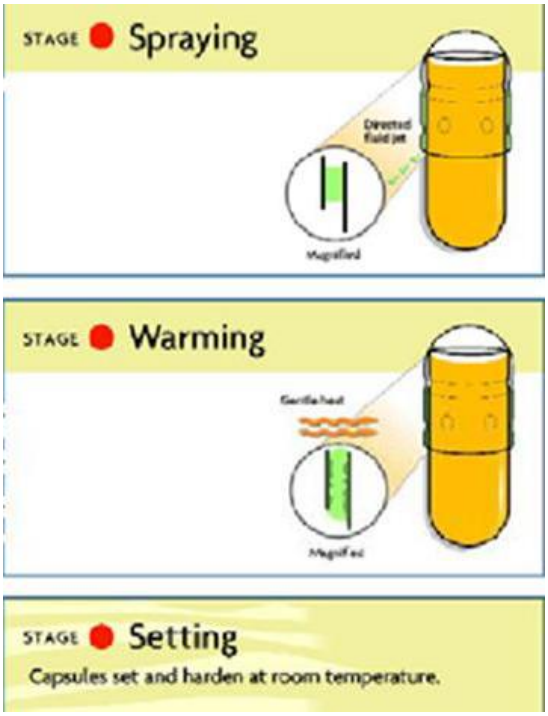


Figure 2: Steps involved in sealing technique

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	Isotretinion	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.

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 370C. The absorbance is measured in UV Spectrophotometry at drug's absorbance maxima. Dissolution study of the formulation should compare with marketed preparation.

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.

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.

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.

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.

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 400C & 75% RH for a period of 1months. 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.

II. 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. 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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