Selecting Excipients for Liquid-Filled Hard Capsules

Thixotropic gels, thermosoftened systems, and self-emulsifying systems have expanded the range of potential excipients.

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Liquid-filled hard capsules (LFHCs) are typically composed of a shell of gelatin or hydroxypropyl methylcellulose (HPMC) and filled with compatible liquids or compositions that can flow below 70 °C. LFHC technology offers several advantages over other solid dosage forms (1). It is crucial, however, to select excipients that are compatible with capsule shell integrity and suitable for the purpose of a formulation.

Excipient considerations

Capsule shell integrity. Hard-gelatin capsules contain 13–16% moisture. Hygroscopic vehicles such as glycerin, propylene glycol, and liquid polyethylene glycols (PEGs), however, cannot be used on their own because they will cause gelatin capsule shell brittleness and fracture. If the moisture content of a filled capsule does not change more than 2% at 65% relative humidity (RH) and 25 °C for six months, then the gelatin capsule will retain its integrity. PEG 400 and 600 can also distort HPMC capsules slightly due to swelling of shell walls caused by PEG diffusion. PEG 900 does not cause this problem. HPMC capsules (moisture content 3–8%) may be useful for moisture-sensitive and hygroscopic products and whenever capsules of vegetable source need to be used (2).

Sizes of capsules. The dose of the drug substance and the quantity of an excipient that can be filled is limited by the capsule size. Commonly available hard capsule sizes for liquid filling along with their filling capacity are listed in Table I. Normally, only 90% of the available volume is used for ensuring proper filling of liquids and sealing of the capsules.

Table I. Hard-capsule sizes and their liquid-filling capacity.

<table>
<thead>
<tr>
<th>Size</th>
<th>00</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (mL)</td>
<td>0.91</td>
<td>0.68</td>
<td>0.5</td>
<td>0.37</td>
<td>0.30</td>
</tr>
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Viscosity. The viscosity of the filled material should be in the range of 0.1–25 Pa•s (100–25000 cps), and filling can be achieved with accuracy and precision so that coefficient of variation (CV) of fill-weight values less than 1% are often achieved. Single components such as dietary supplements (e.g., evening primrose oil), or a two-component formulation where the bioactive substance dissolves in the excipient should fill satisfactorily at ambient temperature. Capsules need sealing if the liquid is flowable at ambient temperatures. Capsule sealing machines have been improved over the years to avoid leakages (2).

Cross-linking potential. Another consideration is the potential for crosslinking. A low concentration of aldehydes may be present in or produced during storage by some of the excipients used in liquid-fill formulations and may cause cross linking of gelatin, which consequently affects dissolution. To check this interaction, filled capsules are stored at 40 °C and 75% RH for six months. The capsules are emptied, cleaned, and then filled with acetaminophen as the dissolution reference material. Comparison of dissolution data for acetaminophen from the stored and reference capsules can provide evidence for interactions between the investigated fill material and the gelatin capsule. If this interaction is the problem, it can be overcome by the use of HPMC capsules that do not undergo these cross-linking reactions (3).

Excipient types

Excipients that have been found to be incompatible with hard-gelatin capsules include ethanol, glycerol, glycerofur 75, medium-chain monoglycerides (e.g., Alkoline MCM, Capmul MCM, Inwitor 308), PEG with a molecular weight (MW) less than 4000, Pharmasolve (N-methyl-2-pyrolidone), propylene glycol, Span 80, and Transcutol P (diethylene glycol monoethyl ether) (4). It may be possible, however, to incorporate small amounts of these excipients into liquid-fill formulations. The maximum tolerable concentration of an excipient should be determined experimentally. Formulations for hard-gelatin capsules that use mixtures containing PEG 200 have been published (5).

The numerous excipients that are compatible with hard-gelatin capsules are classified in three main categories by Cole (4) as follows:

1. Lipophilic liquids (e.g., refined oils, triglycerides, and esters)
2. Semi-solid lipophilics and viscosity modifiers (e.g., hydrogenated oils, cetostearyl/cetyl/stearyl alcohols, glyceryl esters, and Aerosil [fumed silica] for thixotropic gels)
3. Solubilizers, surfactants, emulsifiers, absorption enhancers (e.g., PEGs with MW more than 900 for HPMC capsules and more than 4000 for gelatin capsules, Tween 80, poloxamers).
Liquid filling in hard capsules

The scope of liquid filling has been increased by the use of thixotropic gels, thermosoftened systems, and self-emulsifying systems. In these semi-solid matrices (SSMs), the active substance is present as a particulate disperse phase.

**Thixotropic gels.** A thixotropic gel undergoes shear thinning during filling followed by gel restructuring with an increase in its apparent viscosity in the filled capsule, which reduces tendency to leak from the capsule. For example, Miglyol 95% w/w and silicon dioxide (Aerosil 200) 5% w/w mixture and a liquid paraffin 95% w/wo hydrogenated castor oil (Thixocin R) 3% w/w and Aerosil 200 2% mixture were both filled satisfactorily with a CV of fill weight of 2.8% and 2% respectively (6). The particulate active substance is dispersed uniformly in the gel. Poloxamer/silicon dioxide gels have been also studied (7).

In another example, a highly water-soluble drug, propantheline bromide, was dispersed in Miglyol 829/Aerosil 200 thixotropic gels. The drug release rate was dependent upon the silicon dioxide concentration. An increase in Aerosil percentage increased apparent viscosity of the triglyceride gel, causing a reduction in drug diffusion from the SSM (8).

**Thermosoftened systems.** Thermosoftened formulations are prepared at an elevated temperature to produce a formulation that is sufficiently mobile for satisfactory filling. A typical formulation may be based on a solid excipient (e.g., PEG or poloxamer that will melt below 70°C) in which the active substance will melt, dissolve, or disperse. When cooled to ambient temperature, it will be a solid or semi-solid dispersion in the capsule. The filling process temperature is usually limited up to a maximum of 70°C to avoid thermal damage to the capsule shell and to reduce operational hazards (2). As an example, Merck’s Enterogel capsule, which was approved in the US in 2008, contains alvimopan suspended in PEG 3350.

As another example, a study showed that ibuprofen, which has melting point 75°C, formed clear solutions at 70°C with PEG 6000, 10000, poloxamer, and Dynafill (a palmitic acid derivative of polyoxyethylene-polyoxypropylene block copolymer) (9).

PEGs and poloxamers are stable for several hours at temperatures between 60 and 70°C that are commonly used for liquid-filling thermosoftened SSMs. PEGs of MW 4000–10000 and poloxamers have ideal physical properties for liquid-filling into hard capsules by the thermosoftening process, provided that aging does not adversely affect drug-release properties (2).

Drug release from the SSM formulation could be altered by changing the hydrophilic-lipophilic balance of PEG stearate, the type and concentration of polymer, and the drug loading. This work led to a patent for Opticaps (10).

**Self-emulsifying systems.** This type of formulation is designed to self-emulsify in contact with aqueous media to form a fine dispersion. In each case, the basis of the formulation is a mixture of oil, a surfactant, and a co-surfactant, which can lead to improved drug delivery and bioavailability. A self-emulsifying drug delivery system (SEDDS) was formulated for Coenzyme Q10 using Myvacet 9-45 (diacetylated monoglyceride) (40% w/w) as oil, Lebrasol (50%) w/w) as surfactant, and lauroglycol 10% w/w as co-surfactant. It showed a two-fold increase in bioavailability compared to a powder formulation, when tested in dogs. A self-nanoemulsified system (SNEDDS) based on a mixture of an essential oil, polyoxyl 35 castor oil (Cremophor EL), and a medium-chain mono- and diglyceride mixture (Capmul MCM-O8) overcame some of the problems, such as low solubility and irreversible precipitation of active drug, associated with the SEDDS formulations (11).
Applications of LFHC for particular drug formulations

Hygroscopic drugs. Vancomycin HCl is a highly hygroscopic drug, and it was first available only as a dry powder in sealed ampoules. The problem of hygroscopicity was solved using an SSM formulation (12). The SSM formulation was prepared by a thermosoftening technique with PEG 6000 that protected the drug from moisture uptake and produced a stable and effective preparation in a liquid-filled hard-gelatin capsule. A similar approach was used to solve a problem with the hygroscopic and very unpalatable drug mercaptoacetone hydrochloride (13). An SSM formulation with PEG 6000 protected the drug from moisture uptake and masked the taste and smell of mercaptoacetone hydrochloride, which resulted in excellent compliance and the successful treatment of cystinosis in the children (2).

Sustained release. Sustained-release formulations have been prepared by using excipients that influence the hydrophilic-lipophilic balance of the SSM (2). Phenylpropanolamine was formulated as an SSM of arachis oil, beeswax, and silicon dioxide (14), and captopril is an SSM consisting of soybean oil and glycerol monostearate (15).

Propranolol capsules contained a rapid-release phase of propranolol in oleic acid and a sustained-release phase of an erodible matrix of the same drug. The mixing of two phases was prevented by either inserting a hydrophobic Gelucire barrier between the two phases or by adding a hydrophobic Gelucire to the rapid-release phase to solidify it at temperatures less than 37°C (16). For example, isosorbide dinitrate retard capsules (Tilots Pharma) contain 40% lactose and 60% Gelucire 50/02 as excipients.

Potent drugs. Micronization of the drugs in oil and filling the suspension in oil will minimize exposure to the potent drug. Agglomeration results in reduced solubility and hence reduced bioavailability, but filling the oily suspension instead of powder reduce the chances of agglomeration. Triamterene dosed at 20 mcg in a PEG mixture as a semi-solid filled in capsules shows a standard variation at 1.8%, compared to 3.1% for powder-fill capsules. The main reason for the improved standard deviation lies in volumetric filling, which does not show differences in density and homogeneity for semi-solids as it does for powders (17). The highest in-vitrodissolution was when it was formulated with PEG 1000 and Gelucire 44/14; it was lower with PEG 1500 and lowest with PEG 6000 and PEG 4000 (18).

Bioavailability enhancement. Biphenyl dimethyl dicarboxylate dissolved in a centrate prepared from Tween 80, Neobee M-5, and tricaprin provided improved bioavailability (19). Isotretinoin in sorbitan monoleate, soybean oil, and stearylpolyoxy glycerides is approved as 505(b)(2) product against a softgel product (20). Another marketed product contains hydrogenated soybean oil, polysorbate 80, soybean oil, and white wax.

Avoiding hepatic metabolic pathway for higher bioavailability. The undecanoyl ester of testosterone exhibits much lower aqueous solubility than the native form, yet demonstrates higher oral bioavailability due to a greater lipophilicity and a greater propensity to enter the systemic circulation via the lymph, particularly when formulated as a lipid solution (Andriol Testocaps). It is dissolved in castor oil and propylene glycol monolaurate and filled as a soft-gelatin capsule (21) or LFHC.

Formulating drug compounds in liquid or semi-solid excipients is used to target lymphatic transport (22) or to circumvent the impact of transporters (23) and metabolizing enzymes (24) in the gastrointestinal tract.

Abuse-resistant formulations. Liquid or semisolid filled capsules by their nature are resistant to crushing and powdering, and a drug is difficult to extract from waxes. For example, Oradur (Durect) uses a high-viscosity base matrix of sucrose acetate isobutyrate.

Conclusion

Large varieties of excipients are available for use in LFHCs based on the purpose of the formulation. Compatibility with the capsule shell and viscosity at the temperature of filling up to 70°C are most important considerations. With the advancements in machinery for sealing of hard capsules, more products could be developed as LFHCs.

References


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