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# APPLICATIONS OF LIQUID-FILLED HARD-SHELL CAPSULES IN DRUG DEVELOPMENT

Liquid-filled hard-shell capsules (LFHCs) are a popular formulation for oral solid delivery of chemical drugs and nutraceuticals. Often selected for drugs with poor solubility/bioavailability, LFHCs also have applications in a number of other situations, including specific benefits during early phase clinical development.

In this issue of **The Altascientist,** you will find:

- Applications of LFHCs
- The process for developing an LFHC formulation
- The role of excipients
- Other advantages of LFHCs
- CASE STUDY—Rapid Development of an LFHC Formulation of Cannabidiol

# APPLICATIONS OF LFHCs

The use of modern drug discovery approaches, such as combinatorial chemistry and high-throughput screening, as well as structural understanding of drug-target binding by X-ray diffraction and molecular modelling, has resulted in an increasing percentage of highly potent lead compounds.

The majority of these compounds have high-melting points and poor aqueous solubility, which directly impact their dissolution and bioavailability. In an LFHC, readily metabolized lipid-based solutions are used as liquid carriers, providing for optimized absorption of the active pharmaceutical ingredient (API).

Many formulations can be challenging to produce for oral delivery, see Table 1.

**Table 1.**

| CHALLENGING APIs ARE THOSE WITH THE FOLLOWING CHARACTERISTICS: | |
|---|---|
| Low bioavailability | High toxicity |
| High potency | High levels of hygroscopicity |
| Sensitivity to degradation from light/heat | Abrasiveness |

LFHCs offer several advantages for handling these challenging APIs.

## Improved Safety in Processing and Administration of Potent Drugs

Compounds in the low dose/high potency category include Schedule I drugs, hormones, oncology drugs, and cytotoxic APIs, and present two main challenges for the manufacture of solid dosage forms:

1. **Containment of potent drug material during processing.** Highly potent APIs (HPAPIs) are not uncommon in modern drug development, with more classes of molecules and new chemical entities being formulated for a broad range of conditions. Liquid-filled capsules provide a safer production process, in that the HPAPI powder is dissolved in the confines of a closed system, and operators are not exposed to airborne particles during manufacturing.
2. **Content uniformity.** When working with low dose APIs in solid format, ensuring that each tablet has the same quantity of active ingredient is challenging. By dissolving the active ingredient and creating a homogenous solution, capsules can be filled with equal dosage of API, time after time.

## Ease of Administration

Some APIs have abrasive properties, and can damage or cause pain to a patient's throat or esophagus while swallowing. Encapsulation of such chemicals facilitates administration. Drugs with unpleasant taste or odor can also be effectively encapsulated, for a better patient experience. Drugs that benefit from slow or extended release are also excellent candidates for LFHCs.

## Flexible Application

Drug formulation and polymer composition of the capsule can be customized to accommodate APIs with many different properties and desired dissolution profiles. For example, drugs with high levels of hygroscopicity can be formulated in capsules with a low water content to avoid clumping of the contents. Opaque capsule shells protect the API and filling from light intrusion. The final formulation, including the drug substance, must be screened for compatibility before the formulation is finalized.

LFHCs are a practical option for developing fixed-dose combinations, as they provide for improved homogeneity between low and high potency API formulations. There are patient centricity benefits to combining drugs within one delivery system, rather than prescribing two different drugs or increasing the dose of a single drug. Synergistic drug combinations have shown benefits compared with single-drug therapies, including increased efficacy, decreased dosage with equal efficacy, and reduced side-effects. Drug developers can also benefit; a 505(b)(2) application for an improved formulation can extend the market life of an existing drug.

Existing molecules that have failed development in the past due to formulation challenges may be suitable candidates for LFHCs. And finally, LFHCs provide marketing differentiation opportunities for sponsors, as they come in a wide range of colors, banding, and print options.

## Abuse Resistant Benefits

Liquid-filled capsules provide an excellent basis for abuse-resistant formulations as the capsules are resistant to crushing and powdering due their wax-like substance filling.

# PRODUCTION PROCESS

The encapsulation of drugs as liquid-filled capsules is a relatively simple and efficient process. Gelatin, largely sourced from collagen, is the base material for the shell matrix of liquid-filled capsules. Capsules may also contain plasticizer, colorants, opacifying agents, and preservatives, depending on the specific formulation requirements. Hard-shell capsules also typically contain 12 to 16% water, depending on the storage conditions. Vegetarian options include a polymer, such as hydroxypropyl methylcellulose (HPMC), potato starch, and carrageenan from seaweed.

A typical high-level production workflow is presented in Image 1.

Each of the steps in the above flowchart has a more detailed process behind it. The general process happens as follows:

The API is suspended or dissolved inside a heated, jacketed kettle via mixing with excipients as needed. The excipients are chosen based on the properties of the API, and typically include triglycerides, mixed glycerides, pharmaceutically acceptable co-solvents, such as polyethylene glycol, and propylene glycol, water-soluble and water-insoluble surfactants, solubility enhancers, and other additives such as α-tocopherol. These excipients can help improve bioavailability, ensure equal distribution of the active ingredient throughout the mixture, and keep the drug substance contained.

The formulation is delivered to filling machinery through heated hoses, if necessary, to maintain optimal temperature, and is used to fill two-piece, hard-shell capsules. The capsules come in a variety of sizes, see Image 2, depending on the mixture and API concentration being developed. Once filled, the capsules are sealed to prevent leaking, usually with a colored band. When cooled to room temperature, the mixture solidifies to a wax-like consistency, except in the case of vitamin E oil or other fully liquid products.

**Image 1. High-level production workflow**

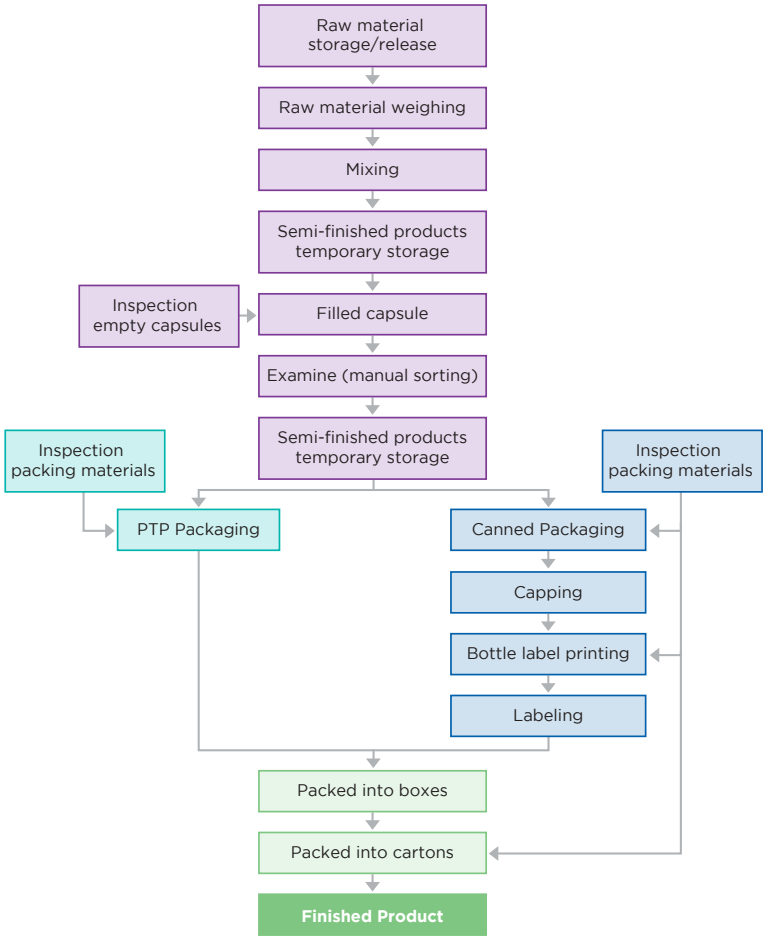
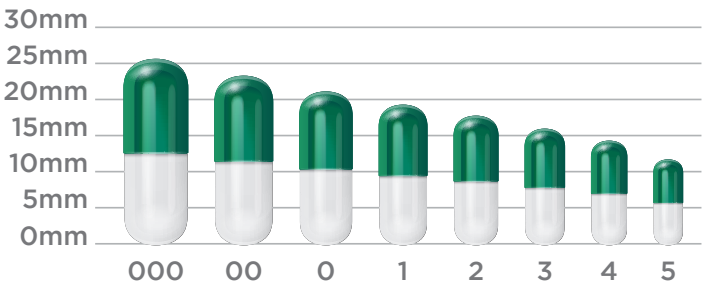



**Image 2. Capsule sizes**



The key considerations for a liquid-filling operation are temperature, viscosity of the fill material, and, in the case of a suspension, the particle size of the suspended drug. If the viscosity is too low, there may be splashing of the bushings, which could prevent a good seal from being formed. Absence of a clean break during dosing ("stringing") can have the same effect. The guidelines for optimal filling are given in Table 2.

**Table 2.**

| OPTIMAL FILLING CONDITIONS FOR LFHCs[1] | |
|---|---|
| Temperature of fill material | Maximum 70 °C |
| Viscosity at dosing temperature | 0.1 to 1 Pa·s |
| Particle size of suspended API | < 50 µm |

Images courtesy of Qualicaps

# THE ROLE OF EXCIPIENTS

Excipients are generally defined as an ingredient other than the active substance contained in a dosage form. Excipients play a central role in the drug development process, in the formulation of stable dosage forms, and their administration[2].

The materials listed below have been tested for use in drug manufacturing. Compatible excipients suitable for formulation of drugs into LFHCs are shown in Tables 3, 4, and 5, classified into three groups:

- Lipophilic liquid vehicles
- Semi-solid lipophilic vehicles/viscosity modifiers for lipophilic liquid vehicles
- Solubilizing agents, surfactants, emulsifying agents, and adsorption enhancers

**Table 3.**

| COMPATIBLE LIPOPHILIC LIQUID VEHICLES | |
|---|---|
| **Refined Specialty Oils** | **MCTs* and Related Esters** |
| • Arachis oil<br>• Castor oil<br>• Cottonseed oil<br>• Maize (corn) oil<br>• Sesame oil<br>• Soybean oil<br>• Sunflower oil | • Akomed E<br>• Akomed R<br>• Captex 355<br>• Labrafac CC<br>• Lauroglycol FCC<br>• Miglyol 810<br>• Miglyol 812<br>• Miglyol 829<br>• Miglyol 840<br>• Softisan 645 |

*MCT=medium chain triglyceride

**Table 4.**

| COMPATIBLE SEMI-SOLID LIPOPHILIC VEHICLES/VISCOSITY MODIFIERS FOR LIPOPHILIC LIQUID VEHICLES | |
|---|---|
| **Hydrogenated Specialty Oils** | **Other** |
| • Arachis oil: Groundnut 36<br>• Castor oil: Cutina HR<br>• Cottonseed oil: Sterotex<br>• Palm oil: Softisan 154<br>• Soybean oil: Akosol 407 | • Aerosil<br>• Celosteryl alcohol<br>• Cetyl alcohol<br>• Gelucires 33/01, 39/01, 43/01<br>• Glyceryl behenate (Compritol 888 ATO)<br>• Glyceryl palmitostereate (Preciril ATO 5)<br>• Softisans 100m 142, 378, 649<br>• Steryl alcohol |

**Table 5.**

| COMPATIBLE SOLUBILIZING AGENTS, SURFACTANTS, EMULSIFYING AGENTS, AND ADSORPTION ENHANCERS | |
|---|---|
| **Hydrogenated Specialty Oils** | **Other** |
| • Capryol 90<br>• Cremophor RH 40<br>• Labrafil M 1944 CS, M 2125 CS<br>• PEG MW > 4000<br>• Poloxamer 124 and 188<br>• Tagat TO | • Gelicure 44/14, 50/13<br>• Imwitor 191, 308**, 380, 742, 780K, 928, 988<br>• Lauroglycol 90<br>• Plurol Oleique CC 497<br>• Softigen 701, 767<br>• Tween 80 |

**glycerin content < 5%

The quality of excipients is routinely verified to ensure batch-to-batch consistency, and the thermal history of the excipients during manufacture is recorded to ensure they have remained within acceptable range.

Excipients shown in Table 6 are considered to be incompatible with LFHCs and are not used at high concentrations. They may have applicability in mixed systems, in which case the critical concentration compatibility limit must be determined experimentally. It seems that the incompatibility of the medium chain monoglycerides (MCMs) is related to the presence of glycerol remaining from their synthesis—this level must be < 5% if the MCMs are being considered as excipients (see **).

**Table 6.**

| INCOMPATIBLE EXCIPIENTS FOR LIQUID/SEMI-SOLID FORMULATION (AT 100% LEVEL) | |
|---|---|
| • Ethanol<br>• Glycerin<br>• Glycofurol 75<br>• MCMs – Akoline MCM, Capmul MCM, Imwitor 308** | • PEGs of MW < 4000<br>• Pharmasolve<br>• Propylene glycol<br>• Span 80<br>• Transcutol P |

**glycerin content < 5%

# OTHER ADVANTAGES OF LFHCs

The simplicity of the process offers many advantages during the different phases of drug development.

### Early-Phase Testing

- Speed of development – fewer excipients, simpler process, rapid delivery to clinical site
- Flexibility of manufacture – small batches can be filled by hand
- Ease of dosage adjustment – modify the amount of API in the mixture, or use a different size capsule for the new dosage

### Late-Phase Testing

- Ease of scale-up – small to large batches can be filled via the same efficient process
- Rapid availability for clinical trial site
- Ease of dosage adjustment
- Range of dosage options easily produced for different trial arms

### Commercialization

- Ease of scale-up without significant change in equipment or process
- Range of dosage options can be manufactured for commercial use
- Variety of band colors offer customized marketing opportunities

# ALTASCIENCES' CASE STUDY

## Rapid Development of a Liquid-filled, Hard-Shell Capsule Formulation of Cannabidiol

### Introduction

Cannabidiol (CBD) has shown promise for addressing a number of ailments, including epilepsy, anxiety, pain, and inflammation. The pharmaceutical industry is now working toward developing reliable products that will deliver the best outcomes for patients, and solve the many unmet health needs within the population.

### Objective

Altasciences' client presented the challenge of developing several oral formulation candidates for CBD from scratch for a new over-the-counter product in Australia. The goal was to create alternative oral formulations that may match or improve upon the PK profile of oral CBD in the fastest and most cost-effective manner possible.

### Methods

Nine LFHC formulations were designed, manufactured, and compared in vitro via a standard dissolution assay at Altasciences' manufacturing site in Philadelphia, PA. The assay was able to distinguish the speed and completeness of dissolution among the nine early formulations. Based on these results and other factors, such as cost and availability of excipients, the client selected three formulations for their crossover PK studies in eight beagle dogs at Altasciences' preclinical testing facility in Scranton, PA, for which 3,000 capsules of each formulation containing 50 mg of CBD were manufactured.

Epidiolex (100 mg/mL solution in sesame oil/ethanol, GW Pharma) was included in the study for comparison. The research animals were allocated to four different treatment groups receiving 50 mg of CBD in four different formulations. All animals that were administered 50 mg of CBD in four different treatment groups were systematically exposed to CBD following a single oral administration, with variability between the individual animals within each treatment group being observed. The same eight research animals were used for each

treatment, and treatments were separated by a minimum seven-day washout period.

Twelve serial blood samples (~3 mL per sample timepoint) per treatment were obtained from each dog via direct venipuncture of a jugular vein using blood collection tubes containing $K_2$-EDTA as the anticoagulant at pre-dose and at 10 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 2.5 hours, 3 hours, 4 hours, 8 hours, 12 hours, and 24 hours post-dose.

Plasma was separated and analyzed for CBD using a qualified LC-MS/MS bioanalytical method developed by Altasciences' laboratories in Laval, Québec. Non-compartmental analysis (NCA) of plasma concentration data was conducted using Phoenix® WinNonlin®, version 8.0.

### Results

PK analysis confirmed good correlation between **in vitro** dissolution and **in vivo** PK data. The best formulation developed dramatically outperformed the commercial product Epidiolex in both $C_{max}$ and AUC. The mean CBD $C_{max}$ and $AUC_{last}$ observed in Treatment 4 were 2.5- and 4.1-fold higher than the mean values observed following the oral administration of CBD oil (Epidiolex) in Treatment 1. The mean CBD $C_{max}$ observed in Treatments 2 and 3 were generally similar to the mean $C_{max}$ in Treatment 1, while the mean $AUC_{last}$ values were approximately two-fold higher than the mean $AUC_{last}$ of Treatment 1.

The timeline, from the design of formulations through development of analytical methods, prototype manufacturing and characterization, test article manufacturing of three candidates, design of animal study and testing protocols, bioanalytical method development and analysis, and reporting of data **was completed in just over three months**.

### Conclusion

The results of the study confirmed expectations that an improved formulation with potentially better pharmacodynamics was possible using suitable, FDA-acceptable excipients in a capsule format.

## ALTASCIENCES' CAPABILITIES

Altasciences has a proven track record and thorough expertise with LFHCs, having completed numerous projects over the years, for a wide range of clients. Our highly knowledgeable experts will assist you in determining the most appropriate and efficient program parameters, from batch size to excipient selection and capsule composition, color, and banding options.

Our skilled operators use state-of-the-art machinery for every step of the process. We perform comprehensive process validation prior to manufacture, identifying and correcting any potential issue before it becomes a problem. We provide 100% manual inspection of the finished capsules and take pride in doing the job right the first time, every time.

## REFERENCE


1 Cole, E. Liquid Filled and Sealed Hard Gelatin Capsules. Capsugel Library. https://cpsl-web.s3.amazonaws.com/kc/library/liquid-filled-and-sealed-hard-gelatin-capsules.pdf?mtime=20170701121846. Accessed Sept. 14, 2022.

2 The Purpose of an Excipient. https://novonordiskpharmatech.com/the-purpose-of-an-excipient/ Accessed Sept. 14, 2022.


# ALTASCIENCES' RESOURCES

### Webinar

Manufacturing Solutions—Liquid-filled Capsules

### White Paper

Applications of Liquid-Filled Capsules for Challenging APIs

### Videos/Quick Chats

Ben Reed, Benefits of Liquid Filled Capsules

Andrew Buis, Complex and Customized Formulation Development

### Brochure

Getting Your Drug to the Clinic Fast with Liquid-filled Capsules

### Webpage

Liquid-filled Capsules

### Infographic

Benefits of Liquid-Filled Capsules

## ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.