THE GROWTH OF LIQUID-FILL ENCAPSULATION:
A FOCUS ON ITS BROAD VERSATILITY & APPLICATIONS IN ORAL DRUG DELIVERY

This article, from Joseph V Carey, PhD, Head of Contract Services & Business Development, Hansueli Schaub, Head of Tillotts Services, and Claudio Scialdone, Senior Manager, all of Tillotts Services (a business unit of Tillotts Pharma AG), presents an overview of the key benefits and recent developments in liquid-fill encapsulation with a focus on practical applications and case studies from the company’s own product portfolio. The three variable components, coating technologies, capsule format and formulation design, are also discussed with respect to engineering a dosage form that can be targeted to a specific region of the gastro-intestinal tract and provide a specific drug delivery profile.

INTRODUCTION

Pioneering developments in manufacturing equipment, capsule design, excipients and coating technologies have propelled liquid-fill encapsulation up the list of oral drug delivery options for the formulation development scientist. Together with an increasing number of poorly water soluble drugs, highly potent APIs, probiotics and biologicals within drug company pipelines, the potential applications for liquid-fill encapsulation has grown substantially in recent years. These drivers have served to reduce costs such that liquid-fill encapsulation is able to compete economically with soft gelatine capsule manufacturing.

Advantages of hard gelatine capsules over soft gelatine capsules

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<tr>
<th>Advantages of hard gelatine capsules</th>
<th>over soft gelatine capsules</th>
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<tbody>
<tr>
<td>Contain 4-5 times less gelatine than soft gelatine capsules</td>
<td>Require 4-5 times more gelatine than the hard gelatine capsules</td>
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<tr>
<td>Require no other additives, Consists of water and gelatine only</td>
<td>Require addition of glycerin for softening purposes</td>
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<td>Allow step-by-step filing of 2 different formulations (i.e. 2-stage-release)</td>
<td>Have to be sealed immediately after filing one substance (filing and sealing are one and the same process)</td>
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<td>Heat resistant: allow filing of thermo-stable substances up to 75°C</td>
<td>Filling temperature limited to about 35°C: filing of solid substances with higher melting points impossible</td>
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<td>Are stable in hot climates</td>
<td>Tend to stick together and become gluey</td>
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<td>Will disintegrate faster due to the capsule wall being five times thinner than the walls of soft gelatine capsules</td>
<td>Will disintegrate slower due to the thickness of its gelatine/glycerin wall</td>
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<td>Less product migration into the shell, less diffusion of odours</td>
<td>Glycerin acts as a plasticiser by disrupting the gelatine structure; consequently, higher diffusion into and through the wall</td>
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<tr>
<td>Constant external dimensions (easier blistering/packaging)</td>
<td>Dimensions vary according to filling weight and vary throughout a batch</td>
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Figure 1: Advantages of liquid-filled, hard-shell capsules over soft gelatine capsules.
Figure 2: Tillotts Services’ milestone-based approach to formulation design and scale-up.

**UNIQUE BENEFITS**

Two-piece hard-shell capsules offer formulators several unique benefits over soft gelatine capsules (Figure 1), particularly for more challenging APIs.

Capsules made from hydroxypropylmethylcellulose (HPMC) also provide a source of non-animal-derived alternatives to gelatine but with the added benefits of liquid-fill encapsulation.

**INNOVATIONS IN TWO-PIECE, HARD-SHELL CAPSULES**

During the last decade, an increasing number of suppliers of gelatine and HPMC capsules have emerged. This increased competition has served to drive down costs as economies of scale have also improved together with a shift in production to low-cost countries such as China and others within Eastern Europe. Capsugel (Morristown, NJ, US), Qualicaps (Irvine, TX, US), ACG (Mumbai, India) and Suheung Capsule Co (Seoul, South Korea) are also developing modified capsule formats using new (GRAS listed) ingredients to provide broader end-user applications. For example, ACG has recently developed an enteric capsule that has the potential to remove the need for a final coating step and thereby reducing time and costs.

Two-piece, hard-shell capsules provide further advantages with respect to addressing other challenges currently facing the pharmaceutical industry such as the threat from counterfeit products. Barcode printing, hologram inclusion and the addition of markers in the coating or capsule shell can serve to provide additional anti-counterfeit barriers. In this way, individual capsule batches can potentially be uniquely tagged at the dosage form level and provide easy verification at key stages in the distribution chain.

**A STARTING POINT IN FORMULATION DESIGN USING LIQUID-FILL ENCAPSULATION**

Understanding the physicochemical properties of the drug substance is a key starting point with regards to pre-formulation design since molecules with poor solubility, hygroscopic, polymorphic, air/moisture sensitive or highly potent properties will need careful management with regards to their development and scale-up. However, liquid-fill encapsulation is highly applicable to such challenging molecules and commercial manufacturing can be effectively implemented with comparable cost economics to other technologies.

Tillotts Services’ starting point is to review the available API data with our customer which allows the pre-formulation strategy to be defined and in doing so minimise development costs and time (Figure 2).

![Figure 3: The Biopharmaceutical Classification System (BCS).](image-url)

Tillotts Services has recently established a co-operation agreement with Solid Form Solutions (Penicuik, Scotland, UK), a world-leading CRO providing the pharmaceutical industry with chemical development services covering:

- Salt Screening
- Co-Crystal Screening
- Crystallisation Screening
- Polymorph Screening
- Batch Process Development (API)
- Physical Properties and Developability Testing

It is well established that there is an increasing number of highly potent molecules within drug development pipelines that require a high containment strategy.\(^1\) Defining the Occupational Exposure Level (OEL) at the pre-clinical stage can sometimes be challenging where minimal toxicity data may be available. In such cases it is possible to utilise external experts (SafeBridge Consultants, for example) in toxicology and occupational hygiene who are able to use comparative structural or compound class data in order to assess such risk.

Additional challenges include poor solubility where currently around 70% of new chemical entities entering drug discovery and development programmes exhibit inferior aqueous solubility and consequently have poor or variable bioavailability. These BCS Class II drugs (see Figure 3) can now be formulated through the utilisation of an increasing number of lipid-based systems such as self-micro-emulsifying drug delivery systems (SMEDDS) where a range of excipients with different hydrophobic lipophilic balance (HLB) values can be screened and subsequently optimised to maximise solubility.

Lipid-based formulations range from simple oily solutions to complex mixtures of oils, surfactants, co-surfactants and co-solvents, classi-
fied as lipid self-emulsifying (SEDDS) or SMEDDS. Due to their ability to maintain the active molecule dissolved and/or to prevent precipitation in vivo, self-dispersing lipid formulations are of high pharmaceutical interest for improving the biopharmaceutical properties of active molecules.

An additional and important testing programme involves the performance of the drug product in bio-relevant in vitro tests which are now increasingly able to predict the in vivo behaviour and fate of the drug product more accurately. Within Tillotts Services, we have established state-of-the-art instruments and equipment for both development projects and up to large-scale industrial manufacturing.

Excipient choice and formulation approach is also critical in terms of controlling polymorphism where subtle solvent changes can cause polymorphic transformation and thereby present substantial difficulties in process control and compliance, again undertaking the appropriate solid state API screens are important.

A good understanding of these and other physico-chemical properties (see Figure 2, left column) place the formulator in a strong position with respect to developing a liquid-fill capsule dosage form for further optimisation. In some cases a formulation will consist of two or more excipients and compatibility experiments will be undertaken in order to support the provision of regulatory data.

Following excipient selection, phase diagrams will be used to demonstrate the effectiveness of the chosen formulation. Liquid-fill encapsulation is also applicable to high melting point excipients such as beeswax and polyethylene glycols since capsules can be filled up to 75°C (Figure 1).

**FAST INTO MAN APPLICATIONS**

Given the above benefits, liquid-fill encapsulation using two-piece, hard-shell capsules is now being more widely utilised within clinical development where drug product can be quickly produced in small batches and validated for first in man studies. Within Tillotts, we have over 26 years’ experience in the development of gastro-intestinal (GI) therapies and can modify the capsule coating for delivery to specific areas of the GI tract as well as modify the formulation for a tailored release profile. Such optimised and tailored targeting and release profiles can be easily optimised during early development in order to identify the optimal drug product characteristics.

**SCALE-UP ADVANTAGES**

Liquid-fill encapsulation is also amenable to expedient scale-up once key process parameters are defined during the development phase. Within Tillotts Services, we have successfully scaled-up from laboratory scale to commercial scale within one day and achieved un-optimised filling speeds of 30,000 capsules/hour. Further optimisation of the production process can quickly achieve the maximum filling speed of 50,000 capsules/hour using one of our two Bosch GKF 1500 commercial liquid-filling machines (Figure 4) that is configured in a linear fashion with a Shionogi S100 banding and drying machine.

The key parameter for liquid-fill encapsulation is the formulation viscosity and for it is important to define and fix the range of this parameter very early in the development process. Viscosity is also monitored at key stages prior to capsule filling through in-process controls (IPCs). Hygroscopic and sensitive APIs can also be handled within production and an increasing number of biological, probiotic and sensitive materials are being produced using this technology.

**COLPERMIN® CASE STUDY**

Twenty six years ago, Colpermin®, a pioneering liquid-fill product was launched by Tillotts Pharma AG as a health-food supplement and is now sold throughout most of Europe as an OTC therapy for Irritable Bowel Syndrome (IBS). Colpermin® consists of 0.2 ml of Peppermint Oil (PO) formulated as a semi-solid oleo gel and contained within an enteric coated, two-piece, hard-shell gelatine capsule. The formulation and manufacturing process for Colpermin® was developed by Tillotts Services and we currently produce the finished and packaged product exclusively within our state-of-the-art liquid-fill encapsulation facility in Ziefen, near Basel, Switzerland.

The GI clinical pharmacology of PO has been reviewed in an article by Grigoleit et al who have qualified its benefits in treating the severe symptoms of IBS. They concluded that the adverse effects of PO, such as heartburn, which occur if it is released in the upper GI tract. They further conclude the importance of a sustained-release PO formulation, as used in Colpermin®, having an optimal peak release at about four hours after ingestion with a release time of PO of up to 24 hours.

Peppermint oil (Mentha piperita aetheroleum) is obtained from the fresh leaves of peppermint, Mentha piperita L, by steam distillation. The plant, indigenous to Europe, is now widespread in cultivation throughout all regions of the world. The major constituents of the oil

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**Figure 4:** One of two Tillotts Services Bosch GKF 1500 and Shionogi S100 production lines.

**Figure 5:** Mechanism of action for (-)-menthol.

**Figure 6:** Pharmacokinetic profile for Colpermin® capsules.
include the terpenes (-)-menthol (30-55%), (-)-menthone (14-32%), (-)-isomenthone (1.5-10%), (-)-menthyl acetate (2.8-10%), (+)-menthofuran (1.0-9.0%), 1,8-cineole (3.5-14%) and limonene (1-3.5%).

Hawthorn et al have attributed the calcium antagonistic properties of (-)-menthol to the anti-spasmodic effects of PO (Figure 5). However it is likely that the additional terpene components of PO also positively contribute to, or enhance its clinical effects in treating IBS.

The pharmacokinetics of Colpermin® have been optimised to provide a sustained release of PO over 12 hours along the distal small intestine and colon (Figure 6). The enteric coating of the capsule enables survival in the acid environment of the stomach. However on reaching a pH of 6.8 the coating begins to disintegrate along with the capsule shell to release the oleo gel formulation containing PO. The sustained-release profile provides active over 12 hours within the region of the distal small intestine and colon.

**COLPERMIN® MANUFACTURING PROCESS**

Tillotts have manufactured Colpermin® capsules for over 26 years and is a pioneer in the development and commercialisation of this technology. Tillotts Services’ SwissMedic-approved GMP facility is dedicated to liquid-fill development and manufacturing such that all the necessary development, analytical and production equipment is housed under one roof along with a highly experienced team of scientists, project managers, engineers and production staff. During the next year we plan to begin production of products for the US market and expect to be the subject of a US FDA inspection in the near future.

**A. Preparation of the filling mixture**

The first step is mixing Arachis oil and Beeswax from a mixing vessel and PO from a second vessel, colloidal silica is also added during the mixing and blending process. The viscosity of the homogenised mixture is tested and is a key IPC (Figure 7, Stages 1-4).

**B. Filling Process**

A precise quantity of the blended formulation mixture is injected into one half of an empty, two-piece, hard-shell capsule of size 0.

**C. Banding and Drying Process**

Rectification rollers rotate the capsules into the correct orientation and transfer them onto a stainless steel belt with embedding for size 0 capsules; formats are also available for other capsule sizes. Gelatine is applied by using two spinning discs that are in contact with a gelatine bath, and then the capsules are fed into the drying chamber and placed afterwards onto drying trays. It is also possible to modify the drying chamber to decrease the drying time if this is required. The last step of the process is the visual inspection of the capsules for any defects or leaks (Figure 7, Stages 7-9).

**D. Coating Process**

A proprietary coating mixture is evenly applied using a pan coater which provides a gastro-resistant barrier. The enteric coat is resistant to low pH and only starts to dissolve around pH 6.8 (Figure 6). For confidentiality reasons, we are unable to disclose the exact nature of the coating mixture. Tillotts Services’ capabilities include the development of new coatings for our customers who may require targeted delivery to the lower digestive tract or colon (Figure 8).

This step is followed by a final drying stage and the capsules are sent for blistering and final packaging (Figure 9).

**COLPERMIN® CAPSULE FEATURES**

- Each Colpermin® capsule contains 187 mg (0.2 ml) of peppermint oil.
- Oleo-gel formulation – ensures sustained delivery (>12 hrs).

**Figure 7: Colpermin® manufacturing process.**

**Figure 8: Colpermin® Coating Process.**

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www.ondrugdelivery.com
• Gastro-resistant, hard-shell capsule – avoids release in the stomach.
• Optimal delivery profile for prolonged & effective relief of symptoms.
• Global liquid-fill GMP manufacturing production process.

**CONCLUSIONS**

Liquid-fill encapsulation using two-piece hard-shell capsules has matured considerably during the last decade as witnessed by the increasing number of commercial products and development stage projects that utilise this technology. The primary drivers have been a decrease in the cost of capsules, innovation in their design and performance together with the introduction of new excipients and coating technologies.

A continued increase in the number of poorly water soluble drugs, probiotics and biological molecules within drug development pipelines means that this technology will have an increasing number of applications.

**ACKNOWLEDGEMENT**

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**REFERENCES**

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