Liquid-Fill Based Formulation: Advances and Challenges

Liquid-fill hard capsule technology is becoming increasingly accepted by the pharmaceutical industry and – while it can hardly be expected to replace more conventional dosage forms such as tablets and powder-filled capsules – it will become a mainstream alternative for those products with particular processing or clinical needs.

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, plasticiser- and preservative-free, lower moisture content, ease of coating and choice of capsule composition (gelatin and hydroxypropyl methylcellulose, HPMC) (1-3).

Liquid-fill formulations – whether in soft gelatin or hard shell capsules – offer an important oral dosage strategy for drugs with low aqueous solubility and/or permeability, and low dose drugs that can cause content homogeneity issues when formulated as powders into capsules or tablets. In addition, this technology offers an inherently safer process than powder filled capsules and tablets for highly potent or cytotoxic drugs, as dust generation does not occur with liquid-fill formulations.

The liquid-fill capsule dosage form (soft and hard) has gained increased acceptance over the last 30 years in an industry that has historically been dominated by tablets; a selection of current commercial products formulated in this way are listed in Table 1. The remainder of this article will focus primarily on recent developments as they relate to liquid-fill hard capsules.

TECHNOLOGY DEVELOPMENTS

Process

The liquid-filled hard capsule process is relatively straightforward and now well established in a number of pharmaceutical companies and contract development and manufacturing organisations (CDMOs). The process involves the addition and mixing of the active substance in a liquid or molten vehicle (which could be a single excipient or a multi-component mix). The drug formulation is then filled into capsules, which can be sealed if necessary to prevent leakage.

The fundamental process has not changed significantly in the last few years. Liquid-fill encapsulation machines are available from a number of equipment manufacturers that are regularly upgrading machines to increase filling speeds and provide more in-line process checking (temperature, speed, fill weight), as well as automatic feedback in line with process analytical technology (PAT) requirements of the industry.

Certain formulations filled into liquid-filled capsules may remain fluid during their shelf life and, as such, require sealing; here, seal integrity is critical to product success. The process itself may be implemented through two commercial systems – banding or microspray (liquid encapsulation microspray sealing, LEMS). In both cases,
Seal integrity is a function of detailed process control and operator training. At Encap Drug Delivery, we have over 20 years’ experience of banding with gelatin and more recently with HPMC, and have developed the banding formulations and process to a point where routine batch leak testing is only conducted on QC samples. This demonstrates a high degree of confidence in the robustness and repeatability of the banding process that can be achieved. Nevertheless, there is limited published data on the factors affecting seal integrity and leak potential, and this is currently an area of research.

Capsule Shells
Gelatin (bovine, porcine and fish) continues to be the main capsule-forming material, with ongoing activity in developing alternatives. HPMC shells are an established alternative to gelatin where there is a market preference and for products where cross-linking or other compatibility issue is a problem with gelatin. There are slight differences between capsules from different suppliers in terms of shell components, dissolution characteristics and shell design, and these can be important for certain products. Pullulan is listed as a new authorised Food Additive, “E 1204 Pullulan” via EEC Directive 2006/52/EC. A naturally occurring water-soluble polysaccharide, it has film-forming properties suited to capsule formation and is the subject of ongoing development for non-gelatin hard-shell capsule manufacture by a number of manufacturers. It has not, however, yet entered mainstream use.

Excipients
There is a very wide range of non-aqueous excipients that are available to the formulator. New novel excipients are rare due to the cost of development (toxicology and regulatory studies) and hence most research interest is focused on understanding how the currently available materials behave in vivo.

TECHNOLOGY APPLICATIONS

Accelerated Clinical Development
Liquid-fill encapsulation can provide a valuable tool to enable drug developers to more rapidly progress clinical candidates through the development process. The use of powder fill capsules without formulation using equipment such as the Xcelodose (Capsugel) has been very well accepted by the industry for first-in-man studies. This has been a valuable innovation; however, a drawback is that the capsule output makes it difficult to support larger scale trials without the need for long manufacturing campaigns running into many days for a single batch. Liquid-fill encapsulation provides an alternative route to rapidly progress simple formulations of actives into the clinic and is capable of accommodating batch-to-batch variations in API (particle size, shape, density and flow characteristics); the process can also scale easily from bench to high speed machines, thus enabling rapid progression through the clinical development process.

High Potency Products
Liquid-fill hard-capsule technology is becoming an increasingly attractive approach for both high-potency products and anti-cancer agents. Technically, it offers processing convenience in minimising the hazards of cross-contamination, reduces the need for complex and expensive engineering controls, and assures product uniformity. The approach has also become more attractive commercially with the availability of contract facilities with the relevant specialised full-scale GMP plant.

Coatings
For many years, capsule coating has been only a low-volume manufacturing process with restricted market opportunities. It has been aimed primarily at pharmaceuticals that require protection of the active against gastric acid. Commercial exploitation has been partly restricted by technological difficulties in assuring robust processing and in adopting non-aqueous systems. For example, it is difficult to coat ‘softgels’ due to the low coat adhesion on the plasticised capsule shell surface, and hence coating is carried out using solvent systems. The use of ‘hard shells’ minimises this problem since there is no plasticiser present and the capsule surface provides for good shell/coat adhesion.

The cap/body edge can represent a mechanical weak-point for the coat but this can be minimised by capsule banding (Qualicaps ‘Hicapseal’ system). It provides a non-stepped surface for coat adhesion and is suited to use with industry-standard aqueous-coat materials. Coating can be enteric (copolymers of methacrylic acid and methyl methacrylate); these are standard for the pharmaceutical industry but are not allowed in nutritional supplements. An alternative approach using shellac in an aqueous-based system is available (Sensient Pharmaceutical Technology’s Protect™ enteric coating system); this meets pharmacopoeial standards of enteric-coat performance while meeting the acceptability requirements for non-pharmaceuticals. The system can be used on industry-standard coating equipment, for example, in ‘Accelacota’ systems.

Another interesting development is the coating of liquid-filled capsules to deliver drugs to the colon for the
local treatment of disease (cancer, IBD, Crohn’s) or for systemic absorption. The combination of liquid-filled formulations with coatings that will reliably deliver the capsule contents to the colon (for example, Encap’s EN CODE colonic coating technology) where there is minimal water for dissolution of conventional powder filled capsules or tablets could be a major advance for the delivery of many drugs including proteins and peptides - a growing area of interest to the pharmaceutical industry.

Abuse Resistant Formulations

There is an increasing interest from pharmaceutical companies and regulators in the development of abuse resistant formulations. The FDA now requests that companies manage any potential abuse risks through their approved Risk Evaluation and Mitigation Strategy (REMS) programmes. The main therapeutic area of interest is in pain management products, but there is also interest for other drugs of abuse such as methylphenidate. There are a number of strategies that have been employed, such as creating an inactive pro-drug, inclusion of sequestered antagonist molecules and agents that would produce some other unwanted side effect (for example, facial flushing). Liquid and semi-solid filled capsules by their nature are resistant to crushing and powdering, and therefore provide a good basis for developing an abuse resistant formulation. This has been exploited by Duirect with their Oradur™ high viscosity base matrix (Sucrose Acetate Isobutrate, SAIB) and by our own company with our Abusolve™ technology.

DuoCap Technology

Single oral capsule dosage units comprising capsule-in-a-capsule technology such as Duocap (see Figure 1) offer a broad range of therapeutic applications. The inner and outer capsules may contain the same active drug, providing multiple release profiles from the dosage unit - for example, an immediate release formulation from the outer capsule and a controlled release formulation from the inner capsule. In addition to modifying release profiles, it is also possible to target the inner and outer capsule to different areas of the GI tract (small intestine or colon) with an appropriate coating. Alternatively, the inner and outer capsules may contain different actives for use with combination therapies or actives that are incompatible.

Combination therapies are currently of significant interest, as demonstrated by the recent launches of Combodart™ (GSK) and Vimovo™ (Pozen, AstraZeneca). This interest in combination therapies is being driven by an increasing acceptance by regulators, and a desire on the part of pharmaceutical companies to develop life cycle products that provide increased patient convenience and compliance. Currently only nutraceutical companies have progressed this technology to a commercial product; however,
various pharmaceutical companies have products in development.

**FUTURE CHALLENGES**

Liquid-fill hard capsule technology is becoming increasingly accepted by the pharmaceutical industry, and while the dosage form can hardly be expected to replace the more conventional dosage forms (tablets and powder filled capsules), it will become a mainstream alternative for those products for which it provides a processing or clinical benefit.

Capsule seal integrity and leaking potential is a concern within the industry, particularly for those companies that have had poor experiences in this regard - either within their own organisations or at CDMOs. In our experience, with appropriate process controls, careful machine set-up and trained operators, leak-free products can be manufactured. Nevertheless proponents of the technology will need to do more to demonstrate and make known the robustness of the process. It is likely that there will be further developments in the area of sealing technology, and this is an active area of interest at our company.

Although there are a number of very successful commercial products demonstrating the robustness of the technology, the development of any new product requires a thorough understanding of the analytical and stability challenges, in addition to those of formulation and processing. Analytical challenges are going to occur with regard to greater characterisation of the products, and modelling for potential in vivo behaviour; including digestion and specific site release. Where the active ingredient has been presented in a specific form (amorphous, nano-particulate, single polymorph and so on), physical chemistry is also becoming more critical, proving that the drug substance has been maintained in a stable state. Similarly, for formulations such as self-emulsifying drug delivery systems (SEDDS), self-microemulsifying drug delivery system (SMEDDS), self-nanomulsifying drug delivery system (SNEDDS), solutions or solid-state solutions, it is important to ensure that these formulation approaches continue to perform as well throughout their shelf life as they do during the development stages.

**Acknowledgement**

The authors acknowledge the input and assistance of other Encap Drug Delivery colleagues in the preparation of this paper: Dr Jane Fraser (R&D Director), Dr Robbie Stewart (Sales and Marketing Director) and Bill Bowtle (Technical Director).

**References**

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