A Hard Act to Follow

Two-piece, hard shell capsules remain a popular oral dosage form, their flexibility proving particularly useful in early-stage clinical trials. But assessing the range of options, from drug-in-capsule to liquid formulations, demands attention – especially in light of new advances.

For first-in-human clinical trials for new drugs, the emphasis is very much on choosing a means of administration which is fit-for-purpose. For oral delivery, the dosage form is often drug-in-bottle (for reconstitution prior to administration) or a capsule. This article focuses on the latter, discussing the key considerations in developing a drug presentation for administration in capsules, particularly hard shell varieties.

The familiar two-piece, hard shell capsules have been used in the pharmaceutical industry since the 1930s and were first produced by Parke, Davis & Co. Traditionally, they have been gelatin-based. However, in recent years there has been an increase in popularity for capsules composed of non-animal-derived materials, such as hydroxypropyl methyl cellulose (HPMC), which are culturally more widely accepted.

HPMC capsules may also offer advantages over gelatin capsules where the drug substance is hygroscopic (HPMC capsules contain less water, compared with gelatin capsules), or if there is the possibility of an interaction between the drug and gelatin.

**Pros and Cons**

Two-piece, hard shell capsules are a very convenient presentation for oral administration of new drugs in early clinical trials. At this stage of the drug development programme, often little is known about how the drug will be absorbed or what dose range will be appropriate for clinical effect and to avoid significant side-effects. Flexibility in dosage options is of prime importance during early studies, and capsules are a suitably adept oral dosage form.

The advantages of capsules for oral administration include:

- Rapid drug release achievable on rupture of the shell
- Flexibility in fill composition:
  - Drug only
  - Powder blends
  - Granules
  - Liquids/semi-solids
  - Spheroids
  - Mini-tablets
- Flexibility in dose adjustability:
  - Different size capsules
  - Different fill weights
- Good atmospheric barrier for sensitive drugs, especially when sealed – for example, banded capsules
- Wide range of batch size capabilities:
  - A few capsules (hand-filled) to several thousand (automated filling)

However, due consideration needs to be given to some of the limitations of using capsules:

- Low bulk density compositions can have difficulty achieving the required fill weight in a suitable capsule size
- The drug or excipient may not be fully compatible with the capsule shell for the following reasons:
  - Hygroscopic materials can absorb water from gelatin shells, leading to embrittlement of the shell
  - Moisture-sensitive compounds may be susceptible to degradation from contact with water from the shell (typically there will be 13-16% water present in hard gelatin capsule shells)
  - Impurities in fill materials (for example, trace amounts of aldehydes) can cause cross-linking of gelatin shells, resulting in deterioration of the *in vitro* dissolution properties of the capsule shell. However, it has been demonstrated that cross-linking of gelatin has no physiological relevance (1)

**Formulation Types**

The types of formulation that can be incorporated into two-piece, hard shell capsules are shown in Figure 1. It is not common practice to consider the more complicated multiparticulate options – for example, coated beads or mini-tabs – for early clinical trials, unless there is a very good reason. Considerations for the development of multi-particulate systems are substantial and not covered in this article.

The simplest approach for first-in-human clinical trials is to administer only the drug substance – with no excipients involved. If only a small
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Drug absorption is very likely to be poor and/or variable. What if the drug substance is micronised?

Poorly soluble compounds are often micronised – typically to achieve a particle size <10μm – to enhance the dissolution rate of the drug. But the resulting hydrophobic, fine particle mass will not wet easily, and will tend to form agglomerates that are slow to disperse; this conflicts with the objective of micronising the drug – to improve the rate of dissolution. Micronised powders should be blended with dispersants/wetting agents to ensure the particles disperse efficiently in the stomach.

Drug-in-Capsule

In considering the drug-in-capsule approach, there are several points to take into account:

What is the bulk density of the drug and what capsule size is required?
For low bulk density drug substances – particularly relevant for a micronised drug – it might not be possible to fill the required amount of drug into a capsule shell without applying a degree of powder compression.

If the volume of the intended dose exceeds the volume of the capsule shell, automated capsule filling using a precision powder dispenser becomes impractical due to the mode of operation of the equipment (similar to shaking a pepper pot). The only viable option here is to increase the size of the capsule to be used.

What is known about the aqueous solubility of the drug?
A simple drug-in-capsule approach should be considered with care for all new drugs. If the drug substance is a freely soluble compound, this simple approach is adequate for initial Phase 1 studies, and possibly Phase 2 if the increased capsule numbers required can be produced economically. However, if the compound exhibits poor aqueous solubility then, without the addition of excipients to improve wetting, dispersion and dissolution of the

quantity of capsules is required, this can be achieved through hand-filling or frame-filling. For larger quantities of capsules, filling may be performed using automated precision powder dispensers, such as the Xcelodose® (Capsugel®) – see Figure 2. Xcelodose is also capable of filling sub-milligram doses of drug into capsules, which is of particular interest for potent compounds.

Powder Blends and Granules

For clinical trials, a basic powder blend of the drug with a minimal number of excipients is often fit-for-purpose. In many circumstances, a simple binary blend of drug/excipient will be suitable to satisfy the product’s functional requirements. Partial pre-gelatinised starch (for example, Starch 1500®, Colorcon®)

Figure 1: Types of early development formulations for two-piece, hard shell capsules

Figure 2: Xcelodose precision powder dispenser

Drug only
Powder blend/granule
Multi-particulates (such as coated beads and mini-tabs)
Liquid/semi-solid
Typical excipients used in capsule powder blends are:

- Bulking agent/filler: lactose, microcrystalline cellulose, partially pre-gelatinised starch
- Disintegrant: sodium starch glycolate, croscarmellose sodium
- Glidant/powder flow aid: colloidal silicon dioxide
- Wetting agents: sodium lauryl sulphate, sodium docusate
- Lubricant: magnesium stearate, stearic acid

For powder blends, it is preferable to match particle sizes of the ingredients as closely as possible, to reduce the potential for de-mixing of the components during powder transfer activities. When a micronised drug is used, the particle size will obviously not be matched with that of the excipients; but, due to the adhesive nature of micron-sized particles, they will adhere to carrier particles in the powder blend, so segregation is not generally a concern. For poorly soluble drugs, soluble fillers – for instance, lactose – are often used to maximise dispersion of the drug particles.

**Low Dose Compositions**

For formulations where the drug content is low (<5mg per unit dose), uniformity can be a challenge. An ordered mixing approach, involving the repeated passage of the blend through a sieve – for example, 250μm mesh size – is often used to evenly distribute the drug throughout the powder mix. Some excipients are claimed to be particularly well-suited for low dose drug formulations: for instance, pre-gelatinised starch (such as Starch 1500, Colorcon) or low particle size microcrystalline cellulose (Avicel® PH-105, particle size 20μm; and Avicel PH-101, particle size 50μm, FMC BioPolymer). The small particle size for these grades of Avicel means that powder flow is poor. However, the incorporation of a small quantity of colloidal silicon dioxide – usually <2% weight/weight – can aid powder flow.

For very low dose formulations (drug content <1mg per unit dose), good drug content uniformity can be achieved by pre-dissolving the drug in a suitable solvent and spraying the solution onto all or part of the chosen filler, while mixing in a high-shear mixer/granulator. The solvent is then removed by an appropriate drying process, such as tray drying. Including a small quantity of a binding agent (2-5% weight/volume), such as polyvinylpyrrolidone, in the drug solution will strengthen the adhesion of the precipitated drug particles to the surface of the filler particles, since the binding agent acts as a ‘glue’.

An alternative formulation approach for consideration for very low drug doses is liquid-fill capsules.

**High Dose Compositions**

For preparations containing a high concentration of drug (for example, ≥250mg per unit dose), drug content uniformity should not be a concern, but powder flow could be an issue – particularly if the drug substance exhibits poor flow properties.

Some excipient suppliers lay claim to certain excipients being well-suited for high drug load formulations. For instance, the co-processed, starch-based excipient StarCap 1500® (Colorcon) has been shown to aid the processing of gabapentin capsules (300mg, with good powder flow and fill weight control), and the resulting product demonstrated satisfactory dissolution behaviour (2). Alternatively, the use of traditional wet or dry granulation techniques can be employed to provide granular product with good flow characteristics.

**Liquid or Semi-Solid Fill**

Two-piece, hard shell capsules can also be used to contain liquid and semi-solid formulations. There are two main reasons for considering this type of formulation strategy:

- To improve the bioavailability of a poorly water-soluble drug through use of a lipidic or self-emulsifying formulation
- To address issues of drug content uniformity for very low drug doses, such as μg doses, by pre-dissolving the drug in a suitable vehicle prior to encapsulation

Manufacturers now provide capsule shells specifically intended for liquid fill formulations (for example, Licaps®, Capsugel), though there is still a need to seal the capsules to prevent leakage. This can be achieved through application of a band of gel around the cap/body junction of the capsule using banding equipment (such as BD3000 banding machine, Dott. Bonapace), or through fusion of the cap/body interface of the capsule using LEMS® technology (for instance, CFS1200™ capsule filling/sealing machine, Capsugel).

When considering use of a liquid/semi-solid fill for hard shell capsules, the following are necessary:

- Compatibility check of the formulation vehicle with the capsule shells:
  - High concentrations of hydrophilic solvents and surfactants tend to cause embrittlement of capsules

is an effective multi-functional excipient often used to provide binary capsule blends.
If considering a semi-solid capsules can only be attributed to then dose variability between is fully dissolved in the formulation, suitable for encapsulation. If a drug by dissolving the drug in a solvent as hormones and cytotoxic drugs, dose/high potency products, such drug content uniformity for very low encapsulation can provide good Liquid formulations for this field (4-6).

There are also several formulations characterised by Table 1 summarises the types of formulations for oral delivery (3).

Devised by Pouton, the lipid formulation classification system (LFCS) is a useful guide for formulation scientists considering the use of lipid/self-emulsifying formulations for oral delivery (3). Table 1 summarises the types of formulations characterised by the LFCS. There are also several recommended reviews covering this field (4-6).

Liquid formulations for encapsulation can provide good drug content uniformity for very low dose/high solubility products, such as hormones and cytotoxic drugs, by dissolving the drug in a solvent suitable for encapsulation. If a drug is fully dissolved in the formulation, then dose variability between capsules can only be attributed to the capsule filling accuracy and reproducibility. In addition, liquid fill formulations provide a means for safer handling of highly potent/cytotoxic compounds as, once the drug is in solution, there is less risk of harmful exposure to the drug during production operations.

Future Outlook

Alternative materials for hard shell capsule shells are continually being investigated. In recent years, HPMC capsules have become a popular alternative to gelatin due to greater cultural acceptance; and also because, in certain respects, they can be considered more chemically inert ‘containers’, compared with gelatin capsules. For drug substances sensitive to acid, it will soon be possible to use capsules made from an enteric polymer, HPMC (ARCaps®, produced by CapsCanada®), expected to be commercially available in 2015. Capsugel has also announced the availability of a new enteric polymer-based capsule for acid-sensitive products.

Advances in formulation science will continue to yield new excipients and technologies for improving oral drug delivery, and it is inevitable that administration in hard shell capsules will continue to be a well-used, reliable dosage form for pharmaceuticals for many years to come, especially in clinical trials.

References

2. StarCap 1500® utilised in a direct-fill capsule formulation of a high dose/high solubility active drug – Gabapentin capsules 300mg, Colorcon® Product Application Data Sheet

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