



Unmasking the Blind of Over-Encapsulation

A study conducted by the Tufts Center for the Study of Drug Development it is estimated that the cost of bring a novel compound to market is in excess of \$800m, so the need to prove superior efficacy and safety when compared to an already marketed product is of critical importance. When developing protocol designs, blinding or masking of clinical supplies is an integral part of many studies. This can help remove both investigator and patient bias due to the visibility of the marketed product, and can limit any potential placebo effect. One of the extensively used mechanisms available to sponsor companies to promote blinding is over-encapsulation of tablets or capsules.

Over-encapsulation is now a widely accepted mechanism used throughout the clinical supplies industry, and the while the process itself, may appear to be relatively straightforward, packaging for clinical supplies in a complex process and is strictly controlled by Good Manufacturing Practice (GMP). The principle of over-encapsulation is simply the addition of a product or products to a hard gelatin capsule, which may or may not be backfilled with an inactive bulk agent or excipient. This process can be used for comparator products, investigational medicinal products (IMP) and/or placebos providing the output of visually identical capsules for each product or strength, thus maintaining the blind and removing any potential bias.

This article we will review the mechanisms and techniques currently available to promote successful over-encapsulation. However, there are a number of key GMP challenges that need to be addressed to ensure product and study result integrity. Annex 13 defines the data that should be available (for example stability, comparative dissolution, bioavailability) to show that there has been no significant quality change within the product and also clarifies how expiry dates should be justified and assigned¹. In addition, there is a need to tightly control and scrutinise the manufacturing process, not only ensuring that product is blinded appropriately but also to allow rapid identification of the product in the case of any possible emergency¹. Allied with this is the visible branding of commercial products either via the placement of product/sponsor logos directly onto products, or patented shapes/designs meaning that encapsulation is not as easy as it may initially appear.

Manufacturing of clinical supplies when compared with commercial operations – whether it be over-encapsulation, bottling, blistering or labelling poses its own set of specific challenges. It is not simply a case of the variation of batch size, multiple set-ups or the required in-process checks but also variations in capsule size, flow of excipients used as backfill and the shape or dimensions of input product which pose further challenges. Also evident within clinical trials is the need to produce strengths of product not currently available on the market as a single tablet or capsule. This practice serves to promote adherence to the prescribed dosing regimen, therefore capsules may not necessarily contain only one marketed product, but could contain two or three depending on the required dosage, input product size and capsule size selected.

Excipients and Blending

Excipients are added to capsules in addition to the product being over-encapsulated in order to prevent rattling. When selecting an excipient, it is important to select something that will remain inactive, have no effect on the quality of the product (as detailed within Annex 13) and that will flow efficiently during the over-encapsulation process. It may be worth while considering the bulk excipient used during the manufacturing process of the commercial product or IMP, as the excipient of choice. There are currently “off the shelf” products that



lend themselves to over-encapsulation without the need for additional blending, however, on occasion it may be necessary to add a lubricant such as Magnesium Stearate. The addition of lubricants, as the name suggests, ensures that the excipient does not clog equipment during over-encapsulation, causing unnecessary down time due to equipment cleaning requirements. In these cases Magnesium Stearate would be blended with a bulk excipient (for example, Lactose) prior to the over-encapsulation process.

Choosing Capsule Shells

There is now a wide range of hard gelatin capsules available that are specifically aimed at the clinical supplies market. Supplier's can provide consistent stocks of hard gelatine capsules where the range of diameters and lengths allow many products to be over-encapsulated, inter-locking shells make it difficult for capsules to be opened without causing damaging, and opaque colourations promote blinding by ensuring that input products are not visible. Colouring agents used within capsule shells vary, with some being more universally accepted than others so it is worthwhile reviewing their acceptability and lead-time to purchase in advance.

Over-Encapsulation Process

Depending on the quantity of material to be over-encapsulated, shape of the product and the number of input components there are a series of processes that may used, ranging from manual to semi-automated to automated.

Manual and semi-automated processes are similar as they require the separation of the capsule shells followed by placement of the tablet or capsule into one half of the capsule shell. Whether the product is placed in by hand or by semi-automated method, a second verification check should be performed to ensure the presence of product within the shell. This process lends itself to irregular shaped tablets or to the addition of multiple products to a single capsule shell. In the instance where multiple products are added to single capsule it is feasible to not only place two or three products of the same strength within a single capsule but also products of different strengths for example a 5mg tablet and 10mg tablet may be placed into a single capsule to produce a 15mg capsule.

Once the product has been placed into the capsule it is then volume-fed with excipient, prior to replacing the lid of the capsule shell and closing it securely. To ensure the quality of the shells, it is important to conduct an initial sample batch so that a fill weight range may be established, to be used as part of the in-process checks and later during check weighing. Check weighing is a high speed, automated system utilised to verify the weights of the capsules produced during any over-encapsulation operation. Capsules will be automatically checked against a defined set of weight parameters (established above), any capsules falling outside this range will be automatically rejected and placed securely with in a reject bin, which is physically segregated from acceptable capsules. During this process capsules will also be de-dusted and polished to remove any excess excipient from the outside of the capsule shell.

The automated approach for over-encapsulation provides a higher throughput of material, and removes the need for manual verification steps. The product will be loaded into a hopper where tablets or capsules will be fed into lanes, these will correctly orient the product prior to addition to the body of the capsule shell. The addition of the product to the capsule shell is control by a vision system thus ensuring that the product has been correctly added to the capsule shell, and that any miss-fed capsules will be automatically rejected. One of the key



differences between the automated and manual/semi-automated approach is the addition a controlled dose of excipient to each capsule, instead of simply flood volume filling. A controlled dose is the addition of a predetermined, consistent volume of excipient to each capsule during the manufacturing process. This allows strict weight variation parameters to be set during the check weighing process, and provides further assurance regarding the integrity and quality of the over-encapsulated product.

Modular systems are now available that allow a high degree of flexibility with regards to the products that can be handled with a single set of tooling. Typically with many high-speed, automated lines, tooling must be sourced and designed specifically for the input product, which can have cost and lead-time implications. With the Modular systems, specific tooling is not necessarily required for each input product providing faster start-up times and no additional tooling design and purchase costs. These systems also provide flexibility when considering which excipient should be used, as magnesium stearate does not necessarily need to be added as a lubricant. An added benefit with these systems is that they also provide the capability to manufacture capsules with microdoses of excipient. Micro-doses are typically required for capsules involving inhalation of material - in these instances a dose of 30µg, can be consistently and accurately added to a capsule shells.

Manufacture of Match Placebos

A further link in this process is the supply of matching placebo capsules for use within placebo-controlled trials. Due to legal and ethical implications it is generally not possible to manufacture placebos to branded products- another reason why over-encapsulation is a useful procedure. Two of the most common methods used for placebo product manufacture are:

- Manufacture of Placebo capsules to contain excipient only
- Manufacture of Placebo capsules to contain a placebo tablet or capsule and excipient

The placebos will, of course, be manufactured to similar specifications as those utilised during the active over-encapsulation process to maintain the blind.

Conclusion

Blinded studies are required to provide the evidence necessary to prove safety and efficacy of any new IMPs where compared to the current market leader. This article has focused on blinding of solid oral doses, as this is currently the most common manufacturing practice. Blinding techniques are not only required for solid oral doses but are used on vials, injectables, metered dose inhalers, dry powder inhalers and secondary packaging operations to name a few other examples.

Over-encapsulation, while a simple process to comprehend does pose challenges which in most cases are surmountable. Planning and initial research are crucial to successfully negotiating over-encapsulation requirements and ultimately ensuring accuracy and integrity of study results, while maintaining the quality of the over-encapsulated product.

Table

Listed below are other techniques that may be used instead of over-encapsulation, although they too come with their own set of specific challenges that need to be carefully considered.

Technique	Concept	Pros	Cons
Mill and Fill	Grinding of tablets prior to placing a controlled volume of ground tablets into a capsule.	<ul style="list-style-type: none"> Allows selection of smaller capsule shell Blinding method for tablets that would not fit into available capsule shells 	<ul style="list-style-type: none"> Content uniformity analysis required Substantial analytical support needed to confirm product quality Cannot be used in conjunction with enteric coated tablets Rarely used within the industry
Tablet Splitting	Split tablets into two halves, prior to placing into a capsule	<ul style="list-style-type: none"> Allows selection of smaller capsule shell Blinding method for tablets that would not fit into available capsule shells 	<ul style="list-style-type: none"> Analytical support required to confirm quality i.e. comparative dissolution, stability testing and bioavailability Cannot be used in conjunction with enteric coated tablets
Film coating	Coating tablets with a film to obscure commercial markings	<ul style="list-style-type: none"> No over-encapsulation required 	<ul style="list-style-type: none"> May have an effect on dissolution profile Will not hide embossed or de-bossed markings May need several coats to completely obscure marking Not suitable for friable products
Removal of markings	Use of a solvent to remove commercial markings or logos from tablets or capsules	<ul style="list-style-type: none"> No over-encapsulation required 	<ul style="list-style-type: none"> Analytical testing required to confirm absence of solvent following processing Not suitable for enteric coated product May see colour variations between areas where solvents have and have not been used

1. Annex 13 Manufacture of Medicinal Products, Rules and Guidance for Pharmaceutical Distributors 2007, Compiled by the Inspection and Standards Division of the Medicines and Healthcare products Regulatory Agency.

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