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White Paper

Unmasking the blind of over-encapsulation

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Unmasking the blind of over-encapsulation

A recent analysis conducted by the Tufts Center for the study of Drug Development[1] estimated that the average cost to develop and gain marketing approval for a new drug is in excess of $2.55 billion (based upon out of pocket and time costs), 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 the over-encapsulation of tablets or capsules.

Over-encapsulation is a widely accepted mechanism used throughout the clinical supplies industry, and while the process itself may appear relatively straightforward, packaging for clinical supplies is a complex process that 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 gelatine capsule (although use of non-gelatine capsules is increasing), which may or may not be backfilled with an inactive bulking agent or excipient. This process can be used for comparator products, Investigational Medicinal Products (IMPs) and/or placebos, providing an output of visually identical capsules for each product or strength, thus maintaining the blind and removing any potential bias.

This article 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 in order to ensure product and study result integrity. Annex 13 defines the data that should be available (for example stability, comparative dissolution and bioavailability) to show that there has been no significant quality change within the product, and also clarifies how expiry dates should be justified and assigned[2]. In addition, there is a need to tightly control and scrutinise the manufacturing process, not only to ensure that the product is blinded appropriately, but also to allow rapid identification of the product in the case of any possible emergency[2]. 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 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 variation in batch size, multiple operational 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 take into account their source, manufacturing process, supply chain complexity and the final use of the Investigational Medicinal Product (IMP). This is to ensure a proportionate level of oversight to the risks posed by the excipient in accordance with the requirements in EudraLex Chapter 5[3]. Furthermore, it is important to select something that will remain inactive, have no affect on the quality of the product, as detailed within Annex 13[2], and that will flow efficiently during the over-encapsulation process. It may be worthwhile 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

[1] Tufts CSDD Assessment of Cost to Develop and Win Marketing Approval for a New Drug Now Published, 10 March 2016

[2] Eudralex, The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice, Medicinal Products of Human and Veterinary Use, Annex 13, Investigational Medicinal Products

[3] Eudralex, The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice, Medicinal Products of Human and Veterinary Use, Chapter 5, Production

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 as well as later during check weighing.

cases magnesium stearate would be blended with a bulk excipient (for example, lactose) prior to the over-encapsulation process.

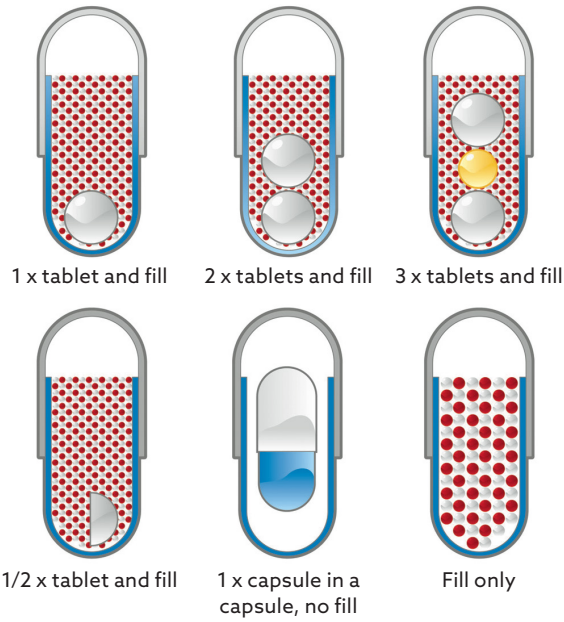
Choosing capsule shells

There is a wide range of hard gelatine capsules available that are specifically aimed at the clinical supplies market. Suppliers can provide consistent stocks of gelatine and non-gelatine capsules where the range of diameters and lengths allow many products to be over-encapsulated; an inter-locking "Cap" and "Body" make it difficult for capsules to be opened without causing damage; 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, the shape of the product and the number of input components, there are a series of processes that may be 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 into the cap and body followed by the placement of the tablet or capsule into the body 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 the 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 a 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, assuming that the appropriate verification steps are in place – for example a 5mg tablet and 10mg tablet may be placed into a single capsule to produce a 15mg capsule. It is critical in this scenario that adequate separation of the filling stations is conducted to prevent any possibility of incorrect filling.

Figure 1: Potential encapsulation scenarios



Once the product has been placed into the capsule body it is then volume-fed with excipient, prior to replacing the cap 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 as well as 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 within a reject bin, which is physically segregated from the acceptable capsules. Check weighing is a critical part of the GMP process; it is essential to have processes in place to ensure the correct information is programmed into the check weigher. A robust data governance system should be integral to the Pharmaceutical Quality System to maintain the integrity of the data.

During this process filled capsules must also be metal checked to mitigate against the risk of contamination, along with being dedusted 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, and these will correctly orient the product prior to its addition to the body of the capsule shell. The addition of the product to the capsule shell is controlled by a vision system, thus ensuring that the product has been correctly added to the capsule shell, and that any misfed capsules will be automatically rejected. One of the key differences between automated and semi-automated/manual approach is the addition of 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 micro-doses of excipient. Micro-doses are typically required for capsules involving inhalation of material – in these instances a dose of 30µg, for example, can be consistently and accurately added to capsule shells.

Manufacture of matching placebo capsules

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 not generally possible to manufacture placebos to branded products – another reason why over-encapsulation is a useful procedure. Two of the most common methods used for manufacturing placebo products 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 the safety and efficacy of any new IMPs when compared to the current market leader. This article has focused on the 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 being a simple process to comprehend, does pose challenges which, in most cases, are surmountable. Planning and initial research is crucial to successfully negotiating over-encapsulation requirements and ultimately ensuring the accuracy and integrity of study results, while maintaining the quality of the over-encapsulated product.

Richard has over 17 years clinical trial experience in both clinical conduct and clinical supply management. A majority of this time has been spent working within Almac (since 1999) where he has served in various Business Development roles as an individual contributor, manager and leader. Richard is currently part of the Executive Management team within Almac Clinical Services, within the role of Vice President of Business Development for Europe and Asia.