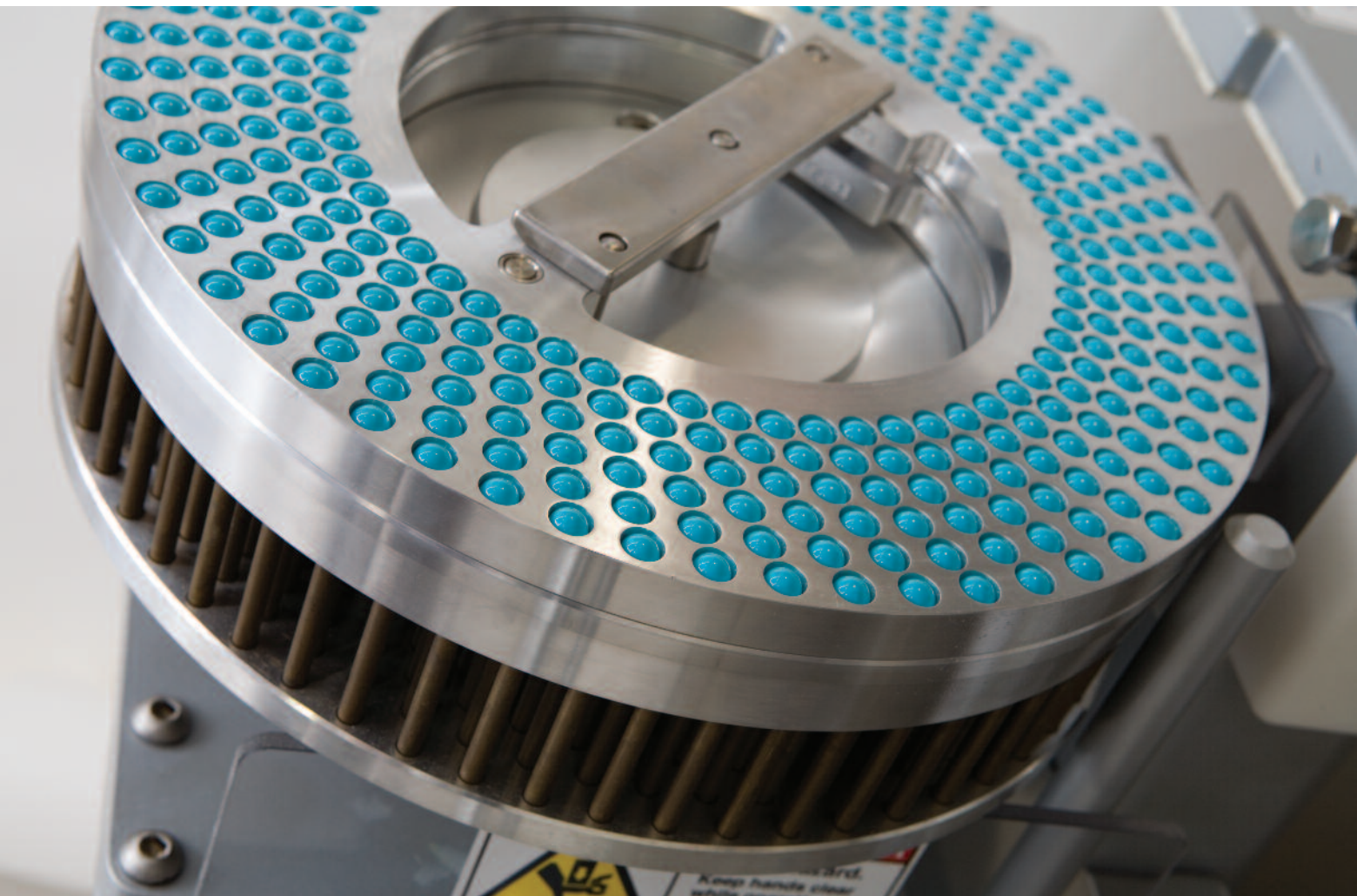


clinical trial materials

OVER-ENCAPSULATION: TECHNIQUES AND CHALLENGES OF BLINDING CLINICAL TRIAL MATERIALS

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Over-encapsulation is the most widely used method of blinding supplies in clinical studies, which are larger, more complex, and spread through more countries than ever before. This article reviews techniques for successful over-encapsulation and suggests solutions to common problems.

Between 2006 and 2008, the number of registered clinical trials increased 156 percent in the USA and 133 percent in Europe [1], due in part to greater regulatory emphasis on drug safety and a growing demand for com-

parative effectiveness research. Meanwhile, scientists are seeking more efficient and cost-effective ways to produce high-quality clinical trial materials (CTMs).

Methods of blinding the dosage forms used in CTMs range from deprinting or debossing the comparator or manufacturing an identical placebo to milling the tablets and filling them into capsules. But over-encapsulation is the most common approach. Over-encapsulation places the product or products (e.g., tablets, caplets, capsules) into an opaque capsule that prevents investigators and subjects from identifying which capsules hold the active medication and which hold the placebo or comparator

product. The method removes bias and allows you to perform comparator studies without manufacturing matching placebo samples.

Manufacturing CTMs is a complex process that is regulated by good manufacturing practice (GMP) as outlined in 21 CFR Part 211 in the USA and Annex 13 in Europe [2]. All over-encapsulation must conform to these regulations.

GMP compliance poses challenges to over-encapsulation because it requires

- Provision of data to show that product quality has not been altered;
- Justification of expiry dating;
- Blinding that resists tampering and clearly reveals when tampering has occurred; and
- Rapid unblinding to identify the product in case of emergency.

In addition to following regulatory requirements, you should also consider the components of your CTMs, namely the capsule shell and backfill.

Selecting materials

Capsule shell. Gelatin is the most commonly used material for over-encapsulation because it has a history of good performance and safety. Two-piece gelatin capsules come in a range of sizes and shapes, and it's best to select the smallest shell that fully encapsulates the product without breaking or grinding it. (Breaking or grinding tablets may allow some tablet fragments to be lost before or during over-encapsulation.) A small shell minimizes the need for backfill, which simplifies manufacturing and reduces the risk of dissolution and bioequivalence problems [3]. In addition, a small shell can improve patient compliance in study populations that may have difficulty swallowing, such as children and the elderly.

Some two-piece gelatin capsules are intended specifically for double-blind clinical trials. One such capsule features an extended cap that creates a double-layer shell along the body, completely opacifying the contents and making the capsule nearly impossible to open [4]. In fact, pulling the capsule apart creates obvious damage, just as regulations require. And because it is shorter and slightly larger in diameter than a standard capsule shell, it accommodates a variety of shapes and sizes of intact tablets and can eliminate the need for backfill and its concomitant time-consuming dissolution testing. Standard capsule shells, typically size 0 or 00, are also commonly used (Figure 1).

Shell color is another consideration. The color should fully blind the enclosed product, including all printing and shadowing or air pockets caused by backfill. It must also remain consistent between lots and between comparator and reference products, especially for long trials and crossover studies. Lastly, be sure that the dyes and pigments used in the blinding capsule are accepted in the countries where the study will occur.

Also check for the availability of the capsule shells. Not all manufacturers maintain a large stock of globally accepted colored capsules, and long lead times can poten-

tially delay the clinical study. Once you have the capsules, store them according to the manufacturer's recommendations, generally for not more than 2 years. If you expect the study to last longer than 2 years, monitor the temperature and humidity of your supplies to ensure their integrity, or order new supplies with enough lead time. In addition, order size-change parts for your capsule filling machinery in advance because they also have long lead times. It's best to order them when you order the capsules.

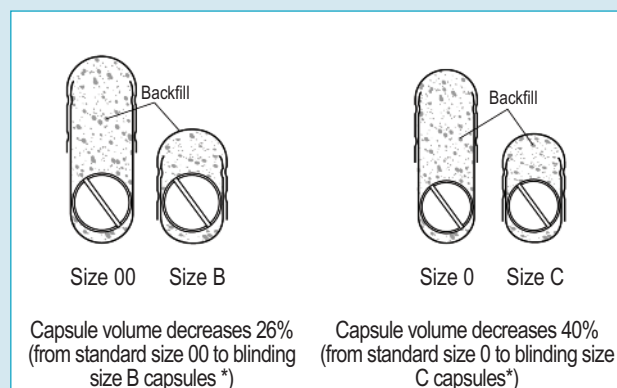
Backfill. Backfill refers to the excipients added to the blinding capsule to help eliminate rattling and decrease the likelihood of breaking the blind. When possible, use the same excipients that were used to manufacture the comparator. Backfill excipients should be compatible with both the over-encapsulated product and the capsule shell to avoid dissolution problems (as discussed in the next section). Select an excipient that remains inactive, flows efficiently during over-encapsulation, and has no effect on product quality.

In some cases, backfill excipients interact with the gelatin capsule. To prevent that, avoid hygroscopic excipients, since they require low-moisture containment and can result in brittle gelatin capsules. Also avoid excipients that contain traces of aldehydes or peroxides, since they can affect dissolution and promote gelatin cross-linking. According to Lai, some sources of spray-dried and anhydrous lactose contain the impurity 5-(hydroxymethyl)-2-furfuraldehyde [3]. Polysorbate 80, a common wetting agent, can undergo autoxidation to produce aldehyde. Polyethylene glycol, such as PEG 6000, can also undergo autoxidation to form formaldehyde. Cornstarch may contain trace quantities of formaldehyde. Also look closely at film-coated tablets because the film may contain some or all of these incompatible excipients [5].

Two common backfill excipients—used separately or blended—are microcrystalline cellulose (MCC) and lac-

FIGURE 1

Blinding capsules that are shorter and slightly larger in diameter than standard capsules accommodate a wide variety of shapes and sizes and can eliminate the need for backfill.



* Coni-Snap vs. DBcaps

Over-encapsulation checklist

- Perform gross inspection of the drug to be over-encapsulated to look for broken tablets, crushed capsules, broken or missing induction seals, and foreign materials.
- Inspect empty capsules for pinholes.
- Verify that the correct number of products is in each capsule body.
- Test for movement inside the capsule after backfilling to determine final filling requirements.
- Check the weight of the filled capsules.
- Inspect filled capsules for visual defects.

tose monohydrate. Both are relatively stable. MCC is hygroscopic, has good disintegration properties, and is incompatible with strong oxidizing agents. Lactose monohydrate is incompatible with primary and some secondary amines, amino acids, aminophyllines, and amphetamines. Naturally, you'll want to limit the amount of lactose monohydrate used if the study population is lactose intolerant. A lubricant (such as magnesium stearate) is sometimes added to the backfill to ensure that capsule filling goes smoothly.

Common challenges

For scientists, the most common challenges of over-encapsulation are its possible effect on dissolution, disintegration, and bioequivalence in clinical trials, as well as the interaction between the backfill and the gelatin capsules.

According to the GMP regulations for manufacturing CTMs, study sponsors must provide data (e.g., about dissolution, disintegration, and bioequivalence) demonstrating that over-encapsulation will not alter product quality. The use of backfill requires additional compatibility and preformulation studies.

The dissolution profile of an over-encapsulated product largely depends on the properties of the API, the characteristics of the over-encapsulated unit, and the backfill. An article by Wilding et al. compared the *in vitro* dissolution, bioequivalence, clinical validation studies, and gamma scintigraphic data of encapsulated and nonencapsulated sumatriptan tablets (Figure 2) [6]. The authors found no significant difference, in any test they performed, between encapsulated and nonencapsulated sumatriptan tablets. The encapsulated tablets dissolved *in vitro* in 17 minutes; the nonencapsulated tablets dissolved *in vitro* in 15 minutes. Bioequivalence testing demonstrated that the encapsulated and nonencapsulated tablets were equally effective. Clinical validation studies showed an identical therapeutic gain (drug response less the placebo response), and gamma scintigraphic studies provided similar results, with no differences in mean time for initial or complete disintegration. A similar study performed by Esseku et al. on rofecoxib (a poorly soluble API) and propranolol (a highly soluble API) drug products showed that while both had a small lag time (2 to 3 minutes) in dissolution for their respective over-encapsulated forms, overall disintegration and dissolution times were not significantly affected, no matter whether the drug products were over-encapsulated in standard gelatin capsules or specialty CTM capsules (figures 3 and 4) [7].

While blinding the drug product or placebo in a capsule might not affect dissolution, the choice of backfill may. A study by Faust showed that different varieties of

FIGURE 2

In vivo disintegration profiles of encapsulated and nonencapsulated sumatriptan using gamma scintigraphy in healthy volunteers

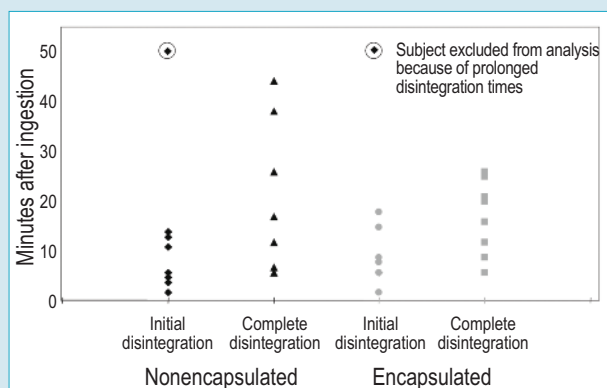


FIGURE 3

Effect of capsule type on dissolution profile of rofecoxib tablets

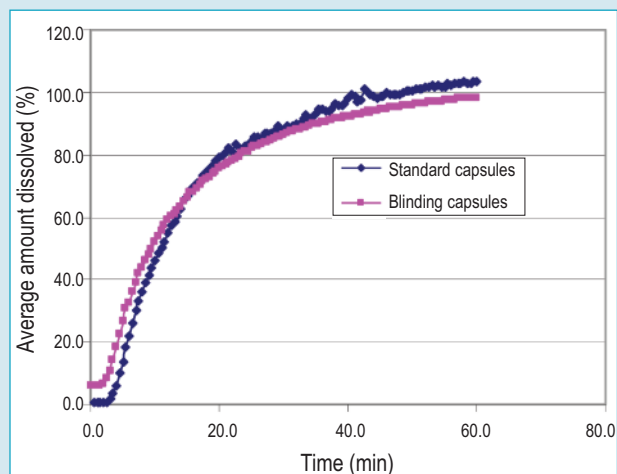
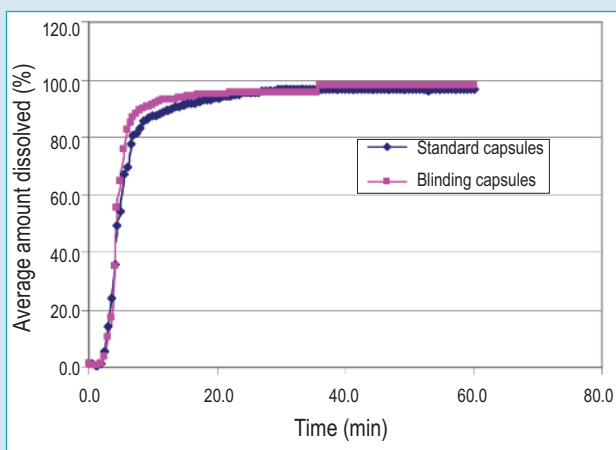


FIGURE 4**Effect of capsule type on dissolution profile of propranolol tablets**

MCC have different effects on the dissolution of over-encapsulated products [8]. To reduce the effect of backfill on dissolution, make sure to formulate it properly and minimize the amount used.

Typically, gelatin capsules disintegrate within 3 minutes in media of pH 1.2 to 11 and disintegrate in less than 15 minutes in water between 36° and 38° C. Using a stereoscopic microscope, Ludwig et al. observed the disintegration of two-piece gelatin capsules. After the shell ruptured, the contents began to empty and, after 10 minutes, the capsule wall had completely dissolved. The authors evaluated drugs with different hydrophilicities and observed that a drug's hydrophilicity did not seem to affect how quickly the liquid penetrated the wall [9].

If hygroscopic or gelatin crosslinking-promoting backfill cannot be avoided, you can use a hydroxypropyl methylcellulose (HPMC) capsule with a dissolution profile similar to that of a gelatin capsule. This capsule can be formed without gelling agents, thus eliminating the delay that had kept HPMC with gelling agents from being used as an acceptable over-encapsulating polymer. Furthermore, because HPMC is derived from plants, using capsules made from it eliminates the paperwork required for animal-based products. HPMC capsules also conform to most dietary requirements of customers worldwide.

Manufacturing CTMs

How you manufacture blinded CTMs depends on the quantity of material to be over-encapsulated, the product shape, the number of components, and the equipment. While you can use manual, semi-automatic, or fully automatic machines, reducing or eliminating manual processes will help you streamline the over-encapsulation process so that you reach the next milestone faster.

For semi-automatic machines, the use of a tablet or capsule loading ring has been shown to increase efficiency of the process and ensure that only one drug product unit is placed in each capsule at a time. Placing a light

table underneath a capsule filling ring containing capsule bodies will highlight any cavity missing a capsule shell and magnify capsule defects, such as pinholes. The operator floods the loading ring with drug product and works each product unit into separate cavities in the ring. (Make sure the ring's cavities fit your product perfectly and accommodate only one product unit at a time.) The filled loading ring is then placed over the capsule filling ring. After the capsules are filled, the light will show through any capsules missing the comparator (Figure 5). To fill additional products into the capsules, repeat the loading process [10]. Even different-strength products can be added to a single capsule. The filling machine adds a controlled dose of backfill, if needed, to each capsule. Then the capsules are closed and locked. Throughout over-encapsulation, make sure to incorporate quality checks at integral points.

FIGURE 5

Light from beneath the capsule ring shows through any shell that does not contain the drug product to be encapsulated. Here, the unit being encapsulated is another capsule.



Courtesy of Fisher Clinical Services, Allentown, PA

Conclusion

Over-encapsulation is a widely used, highly effective technique for blinding solid oral dosages in comparative clinical trials. If you understand and control every step of over-encapsulation—from material selection to manufacture—you will gain an efficient means to ensure the integrity of your study and avoid bias. T&C

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