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Blinding Clinical Supplies Utilizing Overencapsulation

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During the preparation of clinical studies, the method for visually blinding the dosage form is a decision that needs to be made early on in the process. While there are many blinding options available today, i.e., deprinting, mill & fill, manufacture of generic drug, and overencapsulation to name a few, the overencapsulation method still seems to be the most popular method. Perhaps overencapsulation is not the least complex, but it is the most commonly chosen option for blinding clinical supplies today.

The following paragraphs detail some of the items that need to be taken into consideration when utilizing the overencapsulation process as a blinding option. There are many items that need to be addressed to ensure that the operation runs smoothly, from component selection and comparator purchase to the availability of trained personnel.

Overencapsulation is basically hiding another dosage form, tablet or capsule, inside a capsule shell. It is important to select the appropriate components that will be needed to support the overencapsulation of the tablet or capsule unit. Once the unit has been identified, the first thing to determine is what size capsule shell will need to be utilized to properly blind each unit. Although it is not completely necessary, it is recommended that the unit that is being encapsulated does not protrude above the body of the capsule shell when inserted. If the unit does not "sit" properly inside the body shell, and backfilling is required, it may become necessary to backfill the capsule in a manner that will produce a considerable amount of backfill as waste.

There are various size capsule shells available for blinding and perhaps the most popular is the DB CAPS™ capsule shell.1 This style shell is typically shorter and larger in diameter than the standard capsule shell sizes. An additional feature of this style is the double layer of shell that is created upon closing the capsule. This is due to the walls of each piece of the shell being almost identical in length. There is little area for the patient to grab a hold of at either end of the capsule, making it very difficult for the patient to pull the capsule apart. These two features not only make the capsule more user friendly from a manufacturing stand point, but assist in keeping the drug blinded at the patient level.

While the DB CAPS™ style shell is the most frequently used, it is not unusual to see the standard size capsule shells used as well. Size 0 and size 00 capsules are most commonly used for overencapsulation in this case. In some instances, the larger size 000, and smaller size 1, 2 and 3 capsules are also chosen for blinding. Generally, a study will involve the breaking of tablets to fit them into the smaller capsule sizes. When tablets are broken, it is critical to ensure that all of the tablet fragments are collected and accurately placed into each associated capsule shell. If all of the fragments are not collected, the final dose of the blinded tablet could be altered. Other matters to consider when choosing a capsule size is your study population. Is the study geared towards children or the geriatric population both of whom may have difficulty swallowing larger size capsule shells?

Besides the appropriate capsule size, capsule color is an extremely important detail that requires a lot of insight. It is critical to choose a color that will completely hide your enclosed unit. One that does not show any shadowing or air pockets due to the backfill encompassing the unit, or allow for any printing or coloring of the encapsulated tablet or capsule to be seen, is the color that should be utilized. These are generally opaque capsules in nature and are usually not the same color or shade of the unit being blinded, but rather slightly darker or more opaque in color.

Not only do we need to ensure that the capsule color will effectively blind the enclosed unit, but also that the color dyes and pigments used in the color formulation are accepted wherever the study is being conducted. Many countries have restrictions on particular colors. This needs to be researched prior to selecting a color. There are several colors that are accepted worldwide and capsule vendors should be able to provide any information with these selections. Capsule vendors are capable of producing capsule colors in any imaginable shade.

Once the color and size of the capsule shell have been selected, one must be aware of the lead times involved with ordering capsule shells. It is possible to have lead times of two to three months depending on size and color requirements. Vendors normally stock a few colors in quantities of a few million, however it would be impossible for them to stock every color and size combination conceivable. This is usually the main obstacle, which can delay the start of most studies. Upon receiving the capsule shells, storage becomes an important issue as well. Be sure that the capsules are stored under the manufacturer's recommended conditions. Generally, if capsules are stored for more than 2 years, it is not a bad practice to replace them with a fresh supply, especially if one cannot store them at the recommended temperature and humidity conditions. Extended periods of storage can create brittle and distorted capsules. This creates it's own difficulties once encapsulation begins.

Now that capsule details have been determined, the selection of backfill material becomes the next critical step in the overencapsulation process. Backfilling the capsules is required to eliminate the rattle of the unit inside the capsule shell so that the patient is not able to determine the presence of another dose inside the capsule. If the rattle is not eliminated, the patient can possibly break the blind. In rare cases, backfill may not be used and both the placebo and the active doses contain overencapsulated tablets for similar rattle between the doses.

When selecting a backfill material, it is best, but not required, to choose an excipient that is present in the dosage form of which you are blinding. This information can usually be found on the package insert as well as in the Physicians' Desk Reference.2 Dissolution profiles and stability work should be conducted to verify that the material selected does not interfere with or create any bioavailability issues in the overencapsulated dosage form. The most commonly used excipients for backfilling are Microcrystalline Cellulose and Lactose Monohydrate. These materials are used both independently of one another as well as combined in a blend. In some cases, research has shown that the combination of the two may improve the dissolution results.3 Depending on the grade of the material chosen, a lubricant, usually, Magnesium Stearate, present usually less than 0.5%, is added as part of the backfill formulation. Not all grades of these two materials require such lubrication and the choice of adding the Magnesium Stearate is usually based on its presence in the formulation of the unit being encapsulated. Lead times are usually not an issue with regards to backfill when compared to those that may be encountered with ordering capsule shells.

When running a trial and overencapsulating a commercial product, there are additional things to consider besides what capsule size the unit will fit in or what backfill formulation should be utilized. Perhaps the most important thing you need to keep in mind is who is going to order the comparator. It is important to protect the confidentiality of the company doing the study, and therefore consideration needs to be taken, as suppliers may become aware of what compounds the company has involved in such trials. When the company conducting the trial orders the comparator, this can create the potential for various outside parties to know which compounds are being considered. If a second party orders the comparator, the potential for the manufacturer of the compound to know that a study is being conducted against their compound, as well as confidentiality issues can practically be eliminated.

In conjunction with ordering supplies, be sure that the proper size change parts to run the capsule size on the equipment are on hand. Change part availability could become an issue. Typically there are long lead times and the parts can become rather costly. It is advantageous to have an adequate supply of parts on hand for the machinery. If you are in the middle of a run and the equipment fails, the down time that can be saved by having items on hand is immeasurable. In this article, a semi-automated capsule filling machine is utilized for the encapsulation process. Additional equipment such as a loading ring and a light table will enhance the process making it easy for operators to determine and eliminate defects in the drug as well as the capsule shells. These items are discussed in more details within the actual process below.

Personnel can also be an issue during the overencapsulation process. One must ensure that there are an adequate number of trained operators available to support the project(s). The overencapsulation process can be quite complex when performed properly, and requires a dedicated team of trained personnel that are familiar with the common issues that occur during the process, from equipment problems to recognizing issues created with the materials being used.

From this point forward we will assume that the equipment, room, and personnel are adequately prepared for manufacturing, the components for the project are released accordingly, and all production records have been written and approved. With everything in place, we can start to remove the drug from its commercial package. As the drug is removed, it is important to perform a 100% gross inspection on the drug that is being overencapsulated. Although these products are commercially manufactured, packaged, and released, there are occasions where you may need to reject entire lots of product due to anomalies found in the product. Examples of these anomalies include everything from broken tablets, crushed capsules, and broken or missing induction seals, to foreign materials compressed directly into tablets. Once these units are eliminated from the commercial lot, the overencapsulation process is ready to begin.

When overencapsulating any drug product, the use of a tablet or capsule loading ring will enhance the efficiency of the process and assist in ensuring that only one unit is placed into each capsule shell at a time. There are a number of different style loading systems available. However, the design of the loading ring must be carefully chosen. The loading ring is utilized by flooding the ring with product and then manually working one unit into each cavity of the loading ring. This ring is then placed on top of the lower portion of the capsule ring that contains the bodies of the capsule shells. The drug product is then released into the bodies. If additional units are required in each capsule shell, the process is then repeated as required.

There are several things to consider when selecting the proper loading ring:

1. The ring should not be made of aluminum. Aluminum has the potential to leave black markings on tablets when traveling across the surface of the ring.
2. The ring should be designed so that each cavity of the ring is size specific to the shape of the tablet or capsule. Each cavity should also accommodate only one unit at a time.
3. If the loading ring utilizes offset holes to load the units into the capsule shells, be cautious when working with caplet or oval shaped tablets. The ends of the units can get stuck in the cavities and when the spring mechanism is triggered to align the holes, the ends of the tablets can be broken and/or chipped. It is extremely difficult to tell if the entire single unit went into the same capsule shell. You may not even know that the tablet has been damaged.
4. Outsourcing of loading rings can sometimes take several weeks, leading to delays in starting the project.

Prior to placing the loading ring onto the capsule bodies, utilizing a light table underneath the bodies can have many benefits. The first advantage is that the light will draw immediate attention to any cavity that is missing a capsule shell. Second, if the capsule bodies contain any defects such as pinholes due to a thin gelatin area, usually found on the capsule ends, the light magnifies these holes and the capsules can be removed prior to filling. This capsule defect is extremely difficult to detect otherwise. If this defect is not detected prior to filling, it could result in capsules leaking powder out of the ends of the capsule shell. If this defect is present, it is usually not noticed until the

product is packaged and/or distributed, long after the capsules are filled and closed. Third, once the capsules are filled with the drug product, the light will illuminate any empty capsules without the product (see Figure 1). Even though the loading ring will release a unit into each shell, human error can still result in an empty capsule. It is highly recommended to perform an additional 200% visual, documented inspection, with the final check being completed by the operator responsible for backfilling the capsules, totaling a 300% inspection.

Figure 1. Light from beneath the capsule ring illuminates the shell that does not contain the unit to be encapsulated. Here the unit being encapsulated is another capsule.

With the units loaded into the capsule shell bodies, the capsule ring is then transferred to the filling machine. Upon completion of filling the first set of capsules, several capsules should be checked prior to formally closing the capsules. This is to determine if any "rattle" or movement can be felt or heard from the encapsulated drug inside the capsule shell. To do this, remove several capsules by hand, closing them as they are removed from the ring. If there is noticeable movement, there are several routes to take to "lock" the drug in the capsule shell. Be aware, however, that depending on the backfill and the shape of the unit being overencapsulated, there is a possibility that the movement will not be completely eliminated. If this point is reached, a decision needs to be made on how to proceed. Two options for increasing the amount of backfill present in the capsule are as follows:

1. The ring of capsules may be tapped to settle the backfill around the drug and a second filling can be done to add more backfill to the capsule.
2. The auger on the capsule filling equipment can be changed to assist in forcing additional backfill into the capsule shell, as well as altering the fill settings on the equipment.

Once the capsules are filled, it is typically necessary to polish the capsules to remove any residual backfill material from the outside of the capsule. Having an empty capsule eliminator attached to the discharge area on the polisher will eliminate any possibility of an empty shell making it's way into the finished product container. An empty capsule can occur if a capsule is crushed during closing or if a capsule does not close properly and opens during the polishing process. This is possible due to the turbulence created inside the polisher.

In low humidity conditions, the residual backfill may become difficult to remove due to static. If this situation arises, determine the relative humidity in the room and, if possible, raise the humidity to at least 25%, or move the operation into a room at a higher relative humidity without jeopardizing operating conditions.

At this point, the overencapsulation process is basically complete. A final weight check and inspection to assure proper closure and no visual defects are the closing segments of production. During the entire overencapsulation operation, there are many quality checks at integral parts of the process:

- gross inspection of the drug to be encapsulated
- inspection of empty capsules for pinholes
- three, documented, visual checks for the presence of the proper number of units in each capsule body
- a formal check for drug movement inside the capsule at the initiation of powder filling to determine the final filling requirements.

A final confirmation in the process is weighing a minimum of 10 capsules from every ring to ensure that they are within the desired range and that the operators are in control of the filling operation. Samples may be

pulled from each ring to create a mini-batch of the entire process. Retains and release samples are then pulled from this composite.

The finished product upon final inspection should be placed into a properly lined, tared and labeled container. Labels should be present on the inside as well as the outside of the containers for identification purposes. Pre-numbered tamper seals should be placed on the containers and the number recorded within the batch documentation. The manufacturing operation is now complete and the material can be released for further processing.

Overencapsulation involves many individual operations that can create a variety of complex situations. Additional complexities arise when tablets need to be broken to fit into capsule shells, or half of a tablet needs to be placed into a capsule shell. Even different doses may be combined into the same capsule to meet specified dose requirements. Analytical support becomes extremely important when creating a new dose or altering the original form.

With the potential of using any of these different scenarios, overencapsulation remains the most sought after method of blinding drugs for clinical trials. The key to success during each of these operations is to remember that each segment of the process is extremely important. Each requires proper planning and careful execution. From capsule color and size selection to having a well-trained team dedicated to the manufacturing process, taking the time to make sure each segment is managed properly will result in minimal problems related to the encapsulation portion of the study, as well as curtail problems that could occur once the patient receives the supplies.

References

1. DB CAPS™ is a registered trademark of CAPSUGEL.
2. Physicians' Desk Reference. Medical Economics Company, Inc. Montvale, New Jersey.
3. Faust, Mary Beth, "Effect of Variations in Backfill on Dissolution for an Over-Encapsulated Comparator Product," *Pharmaceutical Engineering*, May/June 1999, pp. 48-54

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