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Formulation Considerations for Over-Encapsulation of Clinical Trial Materials in DBcaps® Capsules

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BAS 251 E 2003

DBcaps® capsules are often specified for over-encapsulation of active comparators in double-blind clinical trials. The complete line of these specially-designed capsules offer increased patient compliance. In addition, they feature a patented locking mechanism, providing unsurpassed protection from bias caused by breaking the blind.*

This paper provides a technical review of formulation considerations relating to the use of gelatin DBcaps capsules for clinical trials, as well as a list of published references.

**DBcaps US Patent: 4,893,721*

Design Differences of DBcaps Capsules vs. Standard Capsules

DBcaps capsules are made in a wide variety of unique sizes and shapes (from very small Size E to very large Size AA elongated - see Figure 1) allowing comparators to be over-encapsulated in the smallest possible dosage form, increasing patient compliance. DBcaps accommodate the over-encapsulation of a wide range of sizes and shapes of dosage forms, typically tablets or other capsules. In addition to this difference in sizing, DBcaps capsules differ from standard size capsules (e.g. 00, 0, 1, 2, etc.) in that the length of the cap portion of the capsule is extended. The extended cap completely covers the side wall of the body portion of the capsule, making it difficult to grasp or pull the body without visibly damaging the capsules (See Figure 2).

As is the case with standard capsules, DBcaps capsules have dual locking rings to keep the cap and body securely connected. Utilizing DBcaps capsules allows clinicians to demonstrate that adequate measures have been taken to minimize bias by the subjects, observers, and analysts of the data.

Also, the thickness of the walls of both DBcaps capsules and standard capsules are similar; and size change parts are available to allow DBcaps capsules to run on most commercially-available capsule filling machines (see Figure 3).

Disintegration of DBcaps Capsules

Gelatin remains the capsule material of choice for most DBcaps capsules applications today, owing to gelatin's long history of safety and performance. Capsugel manufactures DBcaps capsules using the same gelatin formulation as standard size Coni-snap® capsules. Consequently, the disintegration data of standard size gelatin capsules are shown (see Figure 4) as an indication of the disintegration for DBcaps capsules. Typically, gelatin capsules disintegrate within 3 minutes in medium between pH 1.2-11. Capsugel Quality Assurance specifications indicate that capsules should disintegrate in less than 15 minutes in water at 36-38°C.

By using a stereoscopic microscope, Ludwig and Van Ooteghem[1] showed, in detail, the mechanism of disintegration of hard gelatin capsules. It was described that the capsule opened within 1-2 minutes at the shoulders after immersion in the liquid. By measuring the thickness of the capsule wall at the cylinder, the shoulder and the pole areas, it was shown that the shoulder portion of the capsule was thinner than the other areas.[2] This explained the observations made by the stereoscopic microscope. In this study, the media used was 100ml 0.1N HCl with 0.001% Tween 80, at 37°C. The surface tension and pH of the medium were similar to the gastric fluid. After the rupture of the shell, air bubbles escaped and the contents began to be wetted and started to empty. After 10 minutes, the capsule wall was completely dissolved. By evaluating drugs of different hydrophilicity (aminophenazone, phenacetin and cupric sulphate anhydrate), the authors observed that the hydrophilicity of the drug did not seem to affect the penetration rate of the liquid through the wall. However, the penetration of the liquid through the powder mass was more rapid for hydrophilic than hydrophobic drug due to better wettability of the hydrophilic material.[1]

In terms of in vivo disintegration, Brown et al[3] showed that unstressed gelatin capsules, filled with acetaminophen, disintegrated in 8 +/- 2 minutes; and the complete in-vivo disintegration occurred at 12 +/- 3 minutes, as measured by gamma scintigraphy, with healthy human volunteers.

Dissolution of DBcaps Capsules

The dissolution profile of a tablet encapsulated in a DBcaps capsules will largely depend on the properties of the drug, the characteristics of the over-encapsulated tablet, and the overfill excipient(s) which are used. In many cases, the dissolution curves between non-encapsulated and over-encapsulated tablets have been shown to be comparable. On occasion, a lag time of 5-10 minutes has been observed. This lag time is associated with the opening of the capsule,[4] and may not necessarily affect the dissolution end point.

Factors Affecting Dissolution

As discussed below, there are three key parameters that can affect dissolution of active comparators that are encapsulated in gelatin capsules.

1) Active Ingredient
   It is important that the drug does not contain or transform to chemical structures related to aldehydes which may cross-link with gelatin capsules.

2) Overfill Excipients
   Diluents are often used to overfill the capsules when over-encapsulating a tablet, in order to eliminate the potential rattling of the content. These excipients may affect dissolution performance.

   - Insoluble/hydrophobic excipients may delay dissolution. For example, a hydrophilic or soluble overfill excipient such as lactose or microcrystalline cellulose is often preferred.

- Excipients should be compatible with the over-encapsulated tablets. In fact, excipients used in the manufacture of the tablet are often used as overfill to reduce chances of incompatibilities.[5]
- Excipients should be compatible with gelatin capsules; excipients containing aldehyde should be avoided. For example:
  - Some sources of spray dried and anhydrous lactoses contains 5-(hydroxymethyl)-2 furfuraldehyde, as an impurity.[6]
  - Polysorbate 80, a common wetting agent, can undergo autoxidation to produce aldehyde.[6]
  - Polyethylene glycol such as PEG 6000 which can also undergo autoxidation to form formaldehyde.[6]
  - Corn starch which may contains trace quantities of formaldehyde.[6]
  - Film coated tablets which may contain some or all of the above mentioned excipients.
- Faust[5] showed that the dissolution profile of the over-encapsulated product could be affected by the ratio of microcrystalline cellulose and lactose monohydrate used. In this case, a 50/50 blend of microcrystalline cellulose/lactose provided the most comparable dissolution profile to the particular comparator product studied (see Figure 5).
- Huynh-Ba and Aubry[7] also showed that the dissolution profiles of two encapsulated forms of the same tablet with different overfill excipient gave significant different results in dissolution (see Figure 6).[7] The specific overfill excipients and comparator tablet used were not discussed.

In order to reduce the amount of overfill excipients required and minimize any potential negative effects on dissolution,[5] the smallest appropriately sized capsule for the over-encapsulated tablet should be selected. For example, the use of the appropriate size DBcaps capsule results in 26% - 40% less enclosed capsule volume in comparison to standard sized capsules (see Figure 7).

3) Storage Conditions
At 40°C/75% RH, which is considered a very stressed condition for gelatin capsules, a delay in dissolution may be observed. This observation may not occur at normal storage conditions of 30°C or below. It is prudent to be able to identify the real cause of any dissolution delays.

Recommendations for Compatibility Programs

Given the multiple factors that could contribute to dissolution performance, the following compatibility tests are suggested as a way to generate some baseline data:

– DBcaps capsules with overfill excipients

– DBcaps capsules with tablet only

– DBcaps capsules with tablet, and overfill excipients

One additional suggestion is to store empty DBcaps capsules under the same storage conditions as the above tests in order to establish a control.

Also, note that according to USP 25/NF 20, Method <711>, for hard gelatin capsules that fail a non-enzymatic dissolution test, it is allowable to repeat the dissolution testing using pepsin or pancreatin in the dissolution medium.[8]

Dissolution Test Method

If a compendial dissolution test method exists for the comparator tablet, it is often used for dissolution testing of the over-encapsulated tablet. If a compendial method is not available for the comparator tablet, an in-house dissolution method is often developed. Sometimes, information may be obtained through FOI (Freedom of Information) Act but often, this takes a long time. In some instances, the dissolution test method developed for the tablets is not always suitable for the over-encapsulated version of the same product.

In addition to dissolution, other general analytical development strategies for comparator products were also discussed by Huynh-Ba & Aubry.[7]

Evaluation of Dissolution Test Data

Dissolution tests are often used as one of the release testings to determine whether or not the over-encapsulated products pass the specification for use in the clinical trials. In addition, by comparison between dissolution curves that are generated for both non-encapsulated and over-encapsulated product, one can consider using the Similarity Factor (f_2) or Difference Factor (f_1) as an indicator of bioequivalence between the two products, as described in the FDA guideline "Dissolution Testing of Immediate Release Solid Oral Dosage Forms".[9] The f_2 or f_1 values can be calculated using the mean dissolution values of both curves at each time interval (e.g. 15, 30, 45, 60 minutes). Generally, the acceptance range of f_2 is when values are greater than 50 (i.e. 50-100); and the acceptance range for f_1 is when values are up to 15 (i.e. 0-15). It is desirable that f_1 should be close to 0; and f_2 should be close to 100.[4] Note that for products with

	AAel	AA	A	B	C	D	E
Length of Capsule Body							
Inches	0.750	0.540	0.594	0.441	0.433	0.406	0.370
mm	19.05	13.72	15.10	11.20	11.00	10.30	9.40
Tolerance in inches is ± .018"; Tolerance in mm is ± .46mm							
Internal Diameter of Capsule Body							
Inches	0.3573	0.3573	0.3075	0.3075	0.2748	0.2480	0.2260
mm	9.07	9.07	7.81	7.81	6.98	6.30	5.74
Tolerance in inches is ± .002"; Tolerance in mm is ± .051mm							
Capsule volume ml	0.97	0.80	0.68	0.50	0.37	0.30	0.21
Powder Density	Capsule Capacity mg						
0.6 g/ml	582	480	408	300	222	180	126
0.8 g/ml	776	640	544	400	296	240	168
1 g/ml	970	800	680	500	370	300	210
1.2 g/ml	1164	960	816	600	444	360	252

Figure 1: DBcaps capsules specifications*

Note: For best encapsulation, the dimensions of the dosage form to be over-encapsulated should be less than both the length and the internal diameter of the body portion of the DBcaps capsule. Capsugel publishes a Clinical Trials Over-Encapsulation Size Guide that enables you to select the most appropriate DBcaps capsule based on the dimensions of the comparator product. Order your free guide today by going to www.capsugel.com and click on the Clinical Trial Materials icon.

**As specifications are under continuous review, be sure to contact Capsugel for the most up-to-date technical information.*

Figure 2: DBcaps capsules patented* locking mechanism

The extended cap completely covers the side wall of the body portion of the capsule, making it difficult to grasp the body without visibly damaging the capsule.

*US Patent #4,893,721

a) Manual Scale: ProFill Capsule Filling System – Available through Capsugel.
Bonapace Minicap

b) Semi-Automatic / Automatic Scale:

Examples of Manufacturers / Encapsulator	Machine Speed Range
Capsugel / Ultra 8 II	9,000 - 28,000 capsules per hour
Bosch / GKF series	7,800 - 150,000 capsules per hour
IMA / Zanasi series	6,000 - 200,000 capsules per hour
MG / MG series	6000 - 200,000 capsules per hour

Figure 3: Capsule filling machines for DBcaps capsules

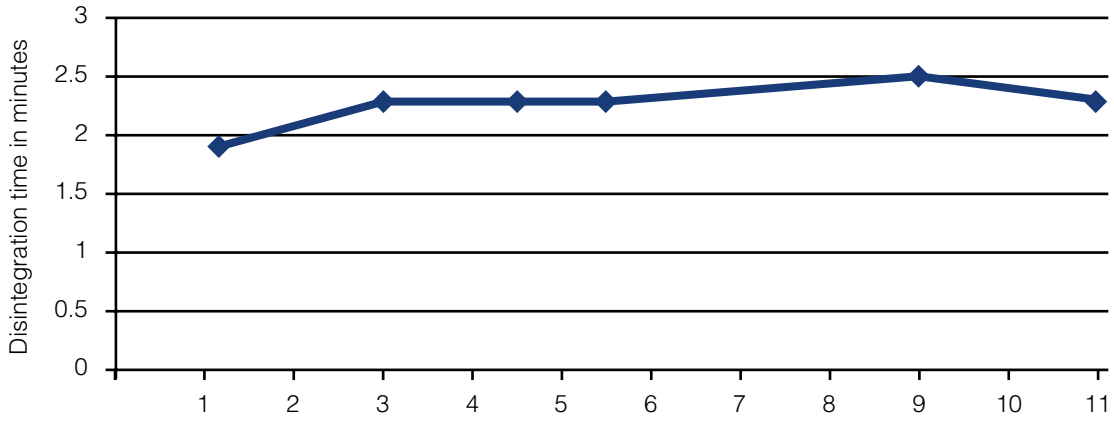

Figure 4: Disintegration time of gelatin capsules in a medium over pH range of 1.2 – 11

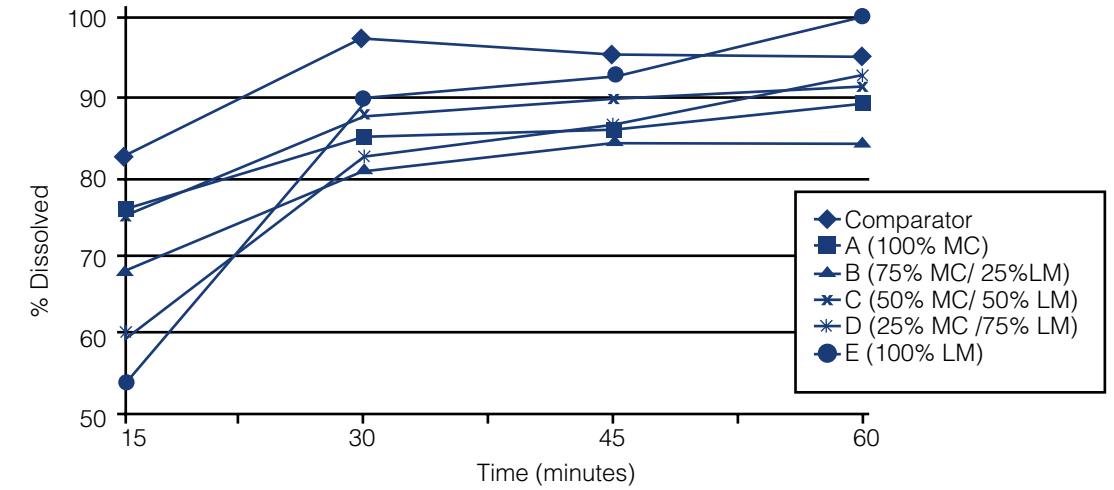

Figure 5: Dissolution profiles of a comparator product and five lots of over-encapsulated comparator product containing various combinations fo microcrystalline cellulose (MC) and lactose monohydrate (LM)[4]

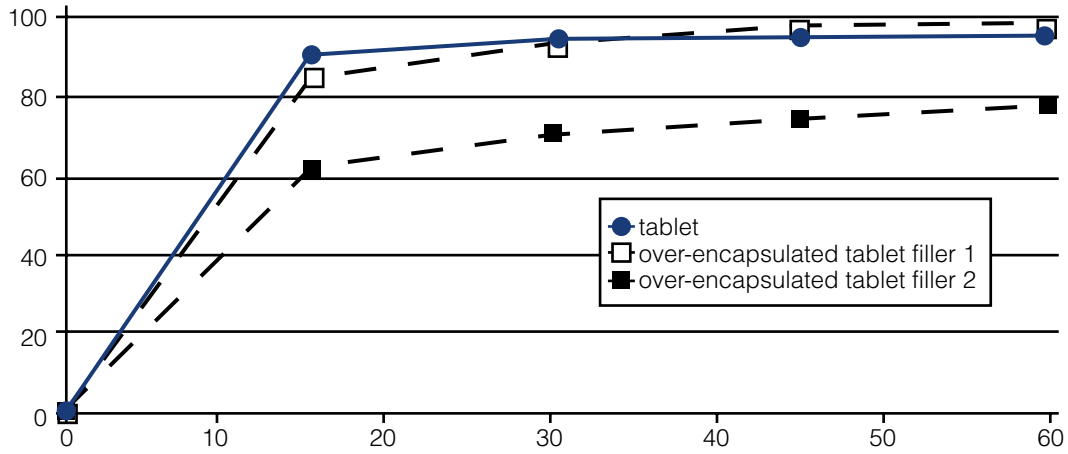

Figure 6: Comparison of dissolution profiles of innovator's tablet and two over-encapsulated formulations[7]

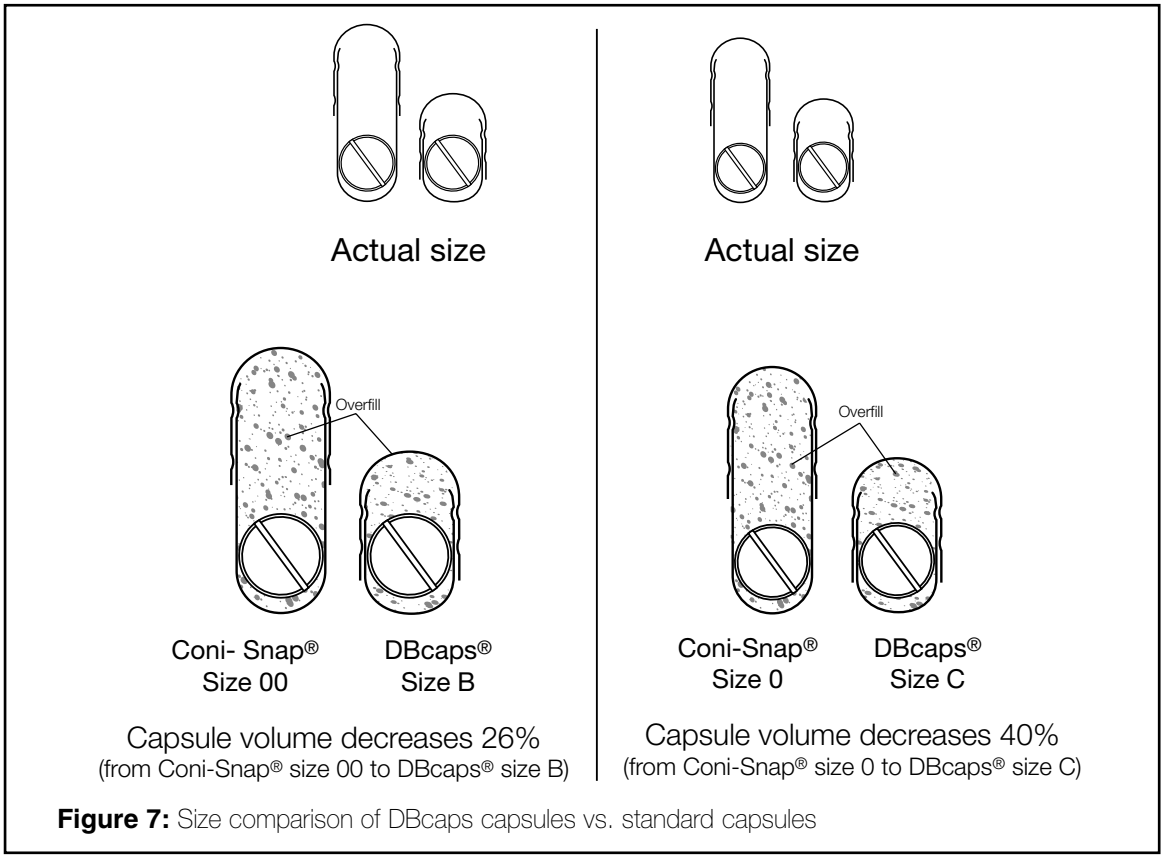

Figure 7: Size comparison of DBcaps capsules vs. standard capsules

a rapid dissolution specification (e.g. >85% release in 15 minutes), the dissolution profile comparison using an f_2 test is probably unnecessary, as suggested in the FDA guideline for "Waiver of in vivo bioavailability and bioequivalence studies of IR solid oral dosage forms based on a biopharmaceutics classification system".[10]

In those instances when one needs to optimize the dissolution performance of the over-encapsulated formulation, one possible approach would be to conduct experiments with differing levels and/or types of overfill excipients, as these have been shown to impact dissolution rate.[5] Also, the capsule size itself should also be minimized in order to decrease the overall amount of overfill excipients used.

Crosslinking with the gelatin shell could also be the cause of poor dissolution. If this is suspected, repeating the dissolution test with a medium which contains pepsin/ pancreatin may provide an indication as to whether the in-vivo performance of the encapsulated products would be affected.[11] Of course, a bioequivalence study can be performed to show that the over-encapsulated product is equivalent to the unblinded product, although this is usually not the preferred approach due to cost and time involved.

Ultimately, in cases where there is a dissolution problem, a few questions need to be asked:

a) Is there an artifact in the dissolution method?
b) Is the tablet stable in presence of the capsule shell and the overfill excipient(s)?
c) Based on pharmacokinetic requirement, is the dissolution data acceptable?
d) Is the therapeutic effect of the product compromised?

Pharmacokinetics Considerations

In some cases, when similar in vitro dissolution profiles are obtained, and even when similar overall bioequivalence data (C_{max}, AUC) are achieved between non-encapsulated and over-encapsulated tablets, it may not necessarily reflect the drug absorption during the interval from 0 to 2 hours after dosing.[12] For clinical conditions in which early exposure to the drug is a critical determinant of efficacy, and when encapsulation is used as a blinding method, it is strongly suggested that both the investigational and the reference drug are encapsulated so that appropriate comparisons and conclusions can be drawn.[12]

Conclusion

Of the many blinding options available (for example, deprinting, mill and fill), the over-encapsulation method using DBcaps capsules is probably the most commonly chosen option for blinding clinical supplies today,[13] and in many cases, also the most efficient.

Acknowledgement

I would like to thank my industrial colleagues for the experience and insight they shared in this specific area and to my Capsugel colleagues for the support they provided.

The Capsugel Library contains a wide array of technical documents relating to the formulation and handling of two-piece capsules. Contact Capsugel at any of our worldwide locations, or visit us on the web at www.capsugel.com.

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