

Effect of Variations
in Backfill on
Dissolution
for an
Over-Encapsulated
Comparator
Product

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The dissolutions are compared by examining the % dissolved vs. time, the % RSD vs. time, the published specification, and two fit factors. A 50/50 blend of lactose monohydrate and microcrystalline cellulose best fit the dissolution profile of the non-encapsulated comparator product.

Pharmaceutical companies often sponsor clinical studies in which the control is a comparator product. These studies are often required in NDA product filings and in support of product marketing. There are many options for performing these studies, ranging from using open label comparator product to the less favored physical modification of the dosage form (i.e. mill and fill).¹ One of these options is to visually blind the dosage form. A popular technique for visually blinding is to over-encapsulate the comparator product.

Purpose

This article concerns the blinding of the comparator product by placing the product (tablet or capsule) into a capsule and backfilling the remaining capsule void space with excipients. Backfilling is required for over-encapsulation to eliminate the potential rattling of the comparator product in the capsule, and also eliminate the ability of the patient to feel the comparator product if the capsule were squeezed. Either of these instances would eliminate the blinding of the study. Backfilling is not general considered invasive to the product, but can affect the dissolution of the product. This article examines the effect of the backfill ingredients on the dissolution of the product.

Rationale

In August 1997, the FDA published the "Guidance for Industry - Dissolution Testing of Immediate Release Solid Oral Dosage Forms".² This guidance contains information for setting dissolution specifications and making dissolution profile comparisons. Included in a section for Scale-Up and Post Approval Changes Immediate Release (SUPAC-IR) to provide guidance as to the type of supportive data required for changes to the process or site. The guidance states, "For manufacturing site changes, scale-up equipment changes and minor process changes, only dissolution testing should be sufficient to ensure unchanged product quality and performance." The guidance goes on to include "[SUPAC-IR guidance] recommends dissolution profile comparisons using a model independent approach and the similarity factor (f_2)."

The model independent approach uses two factors for determining sameness/equivalence between the performance of test and reference products: the difference factor f_1 and the similarity factor f_2 . These fit factors provide criteria for determining sameness/equivalence of dissolution profiles comparing test and reference samples.

The difference factor, F_1 , is defined as:
$$F_1 = \{[\sum_{t=1}^n |R_t - T_t|] / [\sum_{t=1}^n (R_t)]\} \times 100$$

The similarity factor, f_2 , is defined as:
$$F_2 = 50 \log \{[1 + (1/n) \sum_{t=1}^n (R_t - T_t)^2]^{-0.5} \times 100\}$$

Where:

n = number of sampling points

$\sum^n_{t=1}$ = summation over all time points

R_t = assay value of reference sample at time 't'
(comparator product)

T_t = assay value of test sample at time 't'
(over-encapsulated comparator product)

In addition:

- Dissolution time points should be the same for both profiles.
- Zero time point is not included in the comparison

f_1 values should be close to 0 (0-15) and f_2 values should be close to 100 (50-100) for dissolution profiles to be considered same/equivalent.

The same fit factors will be used in this discussion to determine the sameness/equivalence between dissolution profiles between the non-encapsulated comparator product and over-encapsulated comparator product. Over-encapsulated products with a f_1 below 15 and a f_2 value above 50 and which also meet the stated dissolution acceptance criteria will be judged to be the same or equivalent to the comparator product and will be considered acceptable for use in clinical trial.

Excipients

When possible, the excipients used for the backfill should be excipients used in the manufacture of the comparator product. This will reduce any incompatibilities between the comparator product and the backfill and should result in stable over-encapsulated product. The inactive ingredients used in the manufacture of the comparator product are usually listed in the product label insert and also in the Physicians' Desk Reference.³

Two commonly used materials are microcrystalline cellulose and lactose monohydrate. Both are relatively stable excipients. Microcrystalline cellulose is hygroscopic and also possesses some disintegration properties. However, it is incompatible with strong oxidizing agents. Lactose monohydrate is incompatible with primary and some secondary amines, amino acids, aminophylling and amphetamines, and the quantity used should be evaluated for patient populations that are lactose intolerant.⁴

Given the above noted restrictions, microcrystalline cellulose and lactose monohydrate are both commonly used diluents, or fillers, in the manufacture of pharma-

ceutical oral solid dosage forms and thus were chosen to determine their effect on the dissolution of over-encapsulated products.

Manufacturing

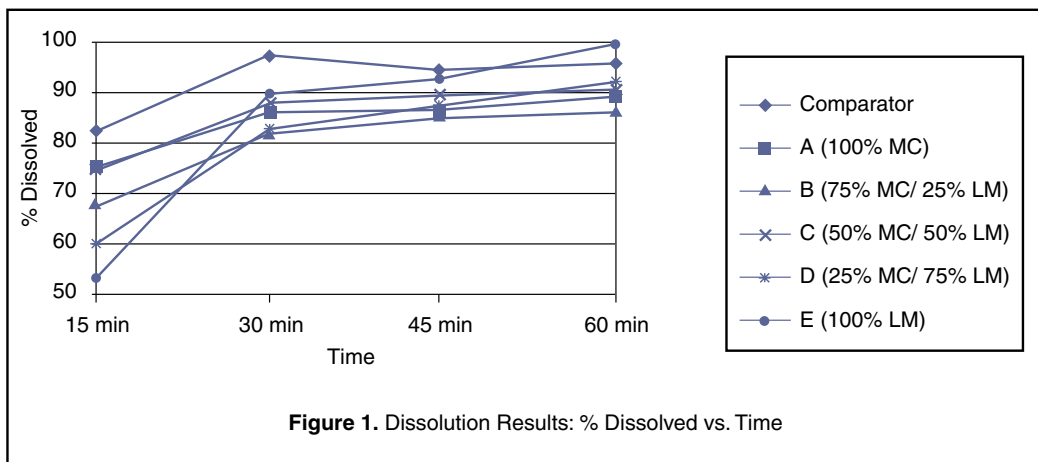
Five experimental batches were manufactured to determine the effect of different combinations of microcrystalline cellulose and lactose monohydrate on the dissolution of the over-encapsulated comparator product. The five lots were filled as follows:

Lot	Fill Material
A	100% microcrystalline cellulose
B	75% microcrystalline cellulose and 25% lactose monohydrate
C	50% microcrystalline cellulose and 50% lactose monohydrate
D	25% microcrystalline cellulose and 75% lactose monohydrate
E	100% lactose monohydrate

The microcrystalline cellulose used for these experiments was FMC Corporation Avicel® Microcrystalline Cellulose NF, Type PH-102. The lactose monohydrate used was Foremost Lactose - 316 Fast Flo, NJ Monohydrate, Modified Spray Dried, Number 8598062661.

Each lot consisted of the comparator product being over-encapsulated using a PD-8 capsule filling machine. Set-up was performed to ensure that the proper amount of backfill was delivered to properly blind the comparator product. Following set-up, one ring was filled for each lot. The comparator product that was evaluated for this experiment fit into a Size 1 capsule. However, the over-encapsulation was performed using Size 0 capsules. The use of a Size 0 capsule maximizes the amount of backfill being delivered to each capsule, and should maximize the effect of backfill on dissolution rate. Thus, these results could be considered a worst case scenario. Selecting the smallest appropriately sized capsule for a comparator product can reduce the amount of backfill materials required and minimize negative effects on dissolution.

Machine settings and auger were held constant. For lots B, C, and D, the microcrystalline cellulose and lactose monohydrate were preblended for three minutes in a two quart twin shell blender. After each lot was over-



encapsulated, the capsules were cleaned with salt and a representative sample of capsules was analyzed for dissolution and compared to the original comparator product.

Analytical

Dissolution testing was performed on the comparator product and the five lots of over-encapsulated comparator product using the dissolution parameters and media for the comparator product obtained from published literature. USP Apparatus II (paddle) was used with the standard paddle speed of 50 rpm. With paddles at 50 rpm, excipient mounding may have a significant effect on dissolution rate. Better results could be anticipated for dissolutions performed at higher paddle speeds. The purpose of the testing was to determine which of the over-encapsulated lots' dissolution profiles best matched the dissolution profile of the comparator product. The data was treated as described in the "Guidance for Industry - Dissolution Testing of Immediate Release Solid Oral Dosage Forms" SUPAC-Immediate Release August 1997, with the fit factor being calculated and evaluated for each backfill lot. For each test, dissolution was performed on n=6 units.

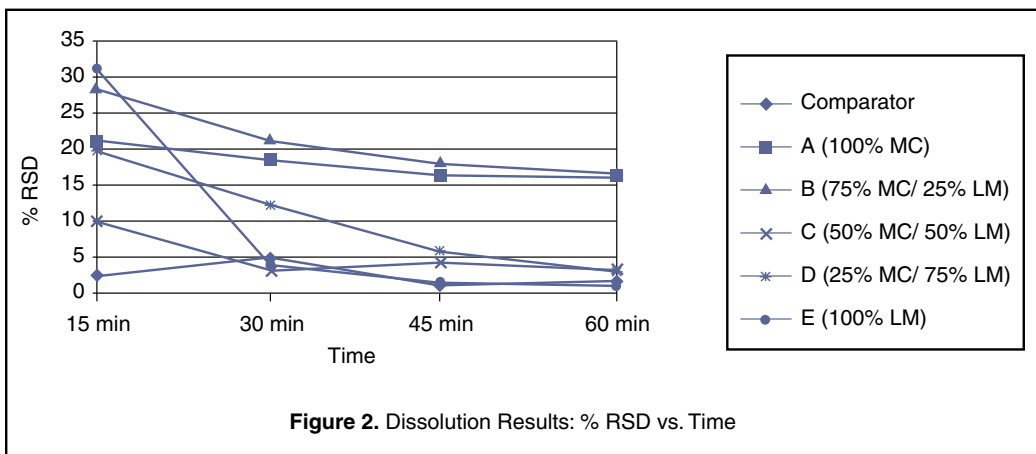
Dissolution of an over-encapsulated product occurs in several distinct steps. First, there is the disintegration of the capsule shell. If the backfill material does not readily dissolve in the dissolution media, mounding can occur around the comparator product. If mounding occurs, disintegration of this excipient mass must occur before the comparator product and begin to disintegrate.

Finally, once the comparator product disintegrates, it must dissolve into the media. The capsule shell disintegration and effect of mounding can delay the onset of dissolution of the comparator product.

Results and Discussion

Dissolution results are summarized in Figure 1 (% Dissolved vs. Time) and Figure 2 (% RSD vs. Time). The comparator product eroded as opposed to disintegrating in the vessel within 2 to 2.5 minutes.

- For Lot A (100% microcrystalline cellulose), the capsule shell dissolves within 1-1.5 minutes. Microcrystalline cellulose covered part to all of comparator product after the capsule shell dissolved.
- For Lot B (75% microcrystalline cellulose and 25% lactose monohydrate), the capsules began to break apart after about two minutes. The comparator product was exposed after about four minutes. The comparator product was partly covered and mounding occurred after capsule shell disintegration.
- For lot C (50% microcrystalline cellulose and 50% lactose monohydrate), the capsules began to dissolve and break apart within 1.5 minutes. The comparator product was slightly covered by excipients but less so than for Lot B. Mounding occurred after capsule shell disintegration.
- For Lot D (25% microcrystalline cellulose and 75% lactose monohydrate), capsules began to break apart after two minutes and comparator product



exposed within four to five minutes. The comparator product was partly covered. Mounding occurred after capsule shell disintegration, similar to Lot B.

- For Lot E (100% lactose monohydrate), capsules began to dissolve after 2.5 minutes, but did not completely disintegrate until after about five minutes. Comparator product was completely exposed after capsule shell disintegration and eroded in the same manner as the comparator product alone.

The % dissolved vs. time for each of the five lots appear similar at the 30 minute time point and beyond. Prior to this, variations are seen in dissolution due to the effects of mounding (lots with high microcrystalline cellulose) and slow capsule shell disintegration (lots with high lactose monohydrate). Lot E most closely mimics the comparator product alone after the initial capsule disintegration.

Looking at the percent relative standard deviation gives a different picture of the dissolution results. Lots A, B, and D show a wide variation in results and appear to be unacceptable. While Lot E is closest to the comparator after the 30-minute time point, but has wide variation at the 15-minute time point. Lot C has the lowest variation and is most similar to the comparator product overall.

Finally, evaluating the data versus the published specification of not less than 75% (Q) dissolved in 30 minutes and versus the fit factors, f_1 and f_2 , gives the results listed in Table A.

The increase in the net backfill weight for the blends was due to the difference in densities of the blends used. In all cases, the comparator product was suitably blinded.

Although both Lots C and E meet the specification of not less than 75% (Q), lot E has an acceptable f_2 value.

Table A

Blend	Net Backfill Weight (mg)	Specification met at S_1 , level (Q-75% in 30 minutes)	F_1 Value (difference factor)	F_2 Value (similarity factor)
A	228.4	No	9.19	52.63
B	268.7	No	13.24	44.98
C	301.0	Yes	7.30	56.54
D	328.0	No	12.43	43.59
E	366.1	Yes	9.46	40.97

Because of the time delay for capsule shell disintegration, none of the over-encapsulated lots, A through E, unequivocally mimics the dissolution profile of the comparator product alone. Treating the data as described in the "Guidance for Industry - Dissolution Testing of Immediate Release Solid Oral Dosage Forms" SUPAC-Immediate Release August 1997, Lot C, the 50% microcrystalline cellulose and 50% lactose monohydrate blend, meets the criteria for sameness/equivalence as compared to the comparator product alone. Lot C also has the lowest % RSD vs. time profile and also meets the published specification of not less than 75% (Q) met at the S_1 level.

Conclusions

Although the capsule shell disintegration occurred more rapidly for lots with a larger percentage of microcrystalline cellulose, mounding occurred thus interfering with the dissolution of the comparator product. The capsule shell disintegration occurred more slowly for lots with larger percentages of lactose monohydrate, thus delaying the onset of disintegration of the comparator product. The difference in the rate of capsule shell disintegration is probably due to the hygroscopic nature of microcrystalline cellulose. Backfills with high percentages of microcrystalline cellulose would pull water into the capsule shell, causing it to expand and break apart faster than backfills with high percentages of lactose monohydrate. The best fit of the data occurred with a 50/50 blend of microcrystalline cellulose and lactose monohydrate, where the effect of the two excipients seemed to counterbalance. This blend met the SUPAC-IR Guidance criteria for sameness/equivalence as compared to the comparator product alone, and also met all other specifications as well.

If the dissolution parameters for a comparator product allow for a higher paddle speed, the mounding effects of microcrystalline cellulose should be reduced. It is anticipated that results can be improved by selecting the smallest appropriately sized capsule for a comparator product, thus reducing the amount of backfill materials required. Care also can be taken to minimize the amount of backfill materials used in over-encapsulating, i.e. do not tightly pack the void space in the capsule shell. However, care must be taken to have enough backfill to properly blind the comparator product, i.e. prevent rattling.

Finally, when choosing excipients for over-encapsulating, be sure to select those which are compatible with the comparator product. If possible, choose materials that are present in the comparator product to reduce any potential incompatibilities.

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Mary Beth Faust is currently a Research Associate for the Clinical Manufacturing Department of Pfizer Research and Development. She has previously held positions in the Consumer Product R&D Process Engineering and Consumer Product R&D Process Development Groups. Her experience is in the areas of solid dosage forms, clinical manufacturing, process control, and process development. Faust holds a BS in chemical engineering from Rensselaer Polytechnic Institute and is a licensed PE in the State of New Jersey.