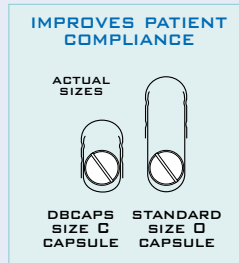


# DBcaps® Capsules – Uniquely Designed for Double-Blind Clinical Trials

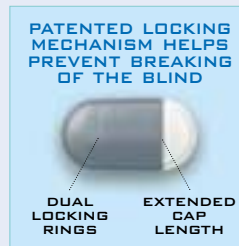
## Smaller Size Improves Compliance

DBcaps® are shorter than standard size capsules, making them easier to swallow. This contributes to increased patient adherence levels, particularly when multiple daily doses are required. Another benefit of the shorter size is that less powder backfill is required to secure the tablet within the capsule, reducing any potential negative impact of the backfill material on dissolution performance.



## Patented Design\* and Locking Mechanism Minimize Bias

The extended length cap of DBcaps capsules completely covers the side wall of the capsule body, making it virtually impossible to open the capsule without causing clearly visible damage. And the dual locking ring design provides a full-circumference, leak-free closure.



\*US Patent #4,893,721

## Wide Array of Capsule Sizes Enables Blinding Without Altering

DBcaps are available in eight different sizes, to best accommodate a wide range of comparator shapes and sizes without having to grind or alter the active comparator. With no need to modify the comparator, the clinical materials manufacturing process is simpler, and the risk of bioequivalence issues is significantly reduced.

## Globally Approved Color Selection

DBcaps can be custom formulated in a wide array of colors. For convenience, five standard color formulations have been developed which utilize globally accepted colorants, and which provide sufficient opacity to ensure blinding.

## High-Speed Production Capability

DBcaps can be filled on most automatic and semi-automatic capsule filling machines, as well as on selected manual filling machines. Capsugel's staff of field engineers are always available to provide technical assistance for filling DBcaps.

## Now Available in a New AAA Size

- DBcaps new AAA size capsule is designed to make over-encapsulation of larger active comparators easier and more convenient, eliminating the need to split or grind.



- With the addition of the new larger AAA, 90% of the top 200 drugs can now be over encapsulated compared to the previous 78%.

## Swallowability Study for DBcaps® AAA

### Background and Purpose

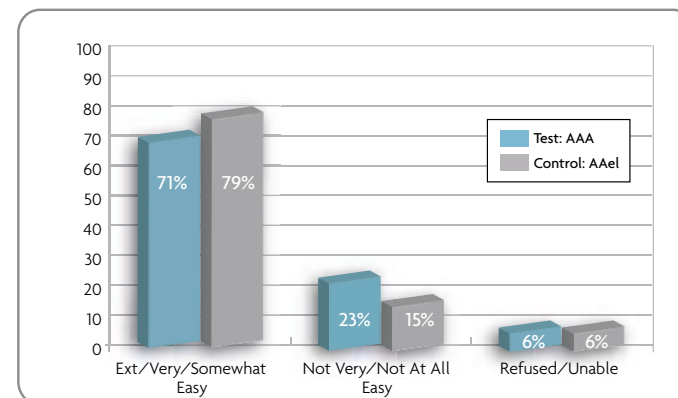
- Confirm that the new AAA DBcaps will be acceptably easy to swallow.
- Compare the performance of the DBcaps AAA to the AAel capsule, which has been successfully used in double-blind studies for several years.

### Methodology

Conducted 250 in-person, one-on-one interviews in May 2005 with adults age 18 - 64 who at least sometimes swallow capsules, tablets or gelcaps and have no medical condition that compromises swallowing.

### Conclusion

A strong majority found the AAA at least somewhat easy to swallow, which was similar to the AAel.



## Overencapsulation and Drug Product Performance of Selected Drugs Using DBcaps Capsules

### Background and Purpose

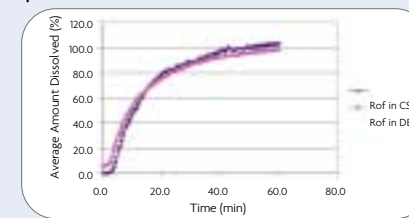
Conducted by Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, PA to study the effect of disintegration and dissolution of propranolol and rofecoxib (BCS classes I and II respectively) when overencapsulated by DBcaps (double walled) capsules and Coni-Snap® capsules (conventional) as a reference.

### Methodology

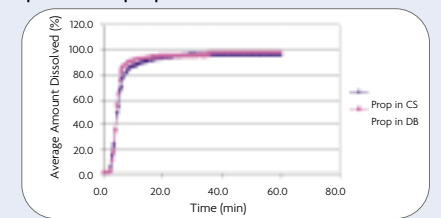
Two blocks of 2x2 randomized full factorial design were used to determine the effect of three independent parameters at two levels [2 drug types (propranolol and rofecoxib), 2 capsule types (DBcaps and Coni-Snap), 2 filler levels (microcrystalline cellulose/lactose 1:1 mixture and no filler)].

### Results and Discussion

Effect of capsule type on the dissolution profiles of rofecoxib tablets



Effect of capsule type on the dissolution profiles of propranolol tablets



### Conclusion

- Disintegration time was not significantly affected by the solubility of the drug; propranolol (high solubility) and rofecoxib (low solubility) had comparable D-times. The presence or absence of filler, and capsule type did not have effect on disintegration.
- Neither the capsule type nor the absence or presence of filler had a significant effect on dissolution. However, there was an interaction effect of the capsule and drug type that was significant. The BCS solubility class of the drug influenced the dissolution significantly with rofecoxib (Class II drug) being slower than propranolol (Class I drug). There was a 2-3 min lag time for the over-encapsulated products compared to the plain tablets.
- The use of double walled DBcaps capsules for blinding drug candidates should not affect the performance of the dosage form in a clinical trial study.

## In Vivo Disintegration Profiles of Encapsulated and Nonencapsulated Sumatriptan: Gamma Scintigraphy in Healthy Volunteers

### Background and Purpose

Conducted by Ian R. Wilding, PhD, Darren Clark, PhD, Heather Wray, MD, Jeff Alderman, PhD, Nancy Muirhead, MS, and Carolyn R. Sikes, PhD, the goal of this pilot study was to use gamma scintigraphy to evaluate, under physiological conditions, disintegration profiles of encapsulated and nonencapsulated formulations of 100 mg sumatriptan.

### Methodology

Healthy volunteers (n = 10) ingested 100-mg doses of sumatriptan tablets radiolabeled with <sup>111</sup>Indium, as well as encapsulated sumatriptan tablets that were prepared similarly, then placed within a gelatin capsule and backfilled with an excipient blend radiolabeled with <sup>99m</sup>Technetium. A gamma camera recorded scintigraphic images until 5 hours postdose.

### Results and Discussion

Summary of Laboratory and Clinical Data Demonstrating the Equivalence of Nonencapsulated Versus Encapsulated Formulations of Sumatriptan 100 mg		
Preclinical and Clinical Data Category	Nonencapsulated Sumatriptan	Encapsulated Sumatriptan
Time to complete in vitro tablet dissolution in deionized water, min	15	17
Time to complete in vivo tablet dissolution by gamma scintigraphy, min	18	16
Meets full bioequivalence criteria		
Standard (Food and Drug Administration, C <sub>max</sub> /AUC <sub>0-∞</sub> )	NA	Yes
Early (AUC <sub>0-2 h</sub> ) <sup>a</sup>	NA	Yes
Headache response at 2 hours (mean)		
Sumatriptan 100 mg, %	59 <sup>c</sup>	56 <sup>c</sup>
Therapeutic gain (over placebo), %	29 <sup>c</sup>	29 <sup>c</sup>

a. Because the bioequivalence studies were powered to examine standard criteria, and AUC<sub>0-2</sub> was more variable than AUC<sub>0-∞</sub>, pooling of the data post hoc from the studies was done to provide sufficient power to test AUC<sub>0-2</sub>.  
 b. Results based on meta-analysis. [see full paper for references]  
 c. Results based on 3 placebo-controlled trials using encapsulated sumatriptan 100 mg. [see full paper for references]

### Conclusion

Results of this study demonstrate that encapsulated and nonencapsulated sumatriptan have equivalent in vivo dissolution rates.