# Assessment of Low Dose Content Uniformity of Indomethacin in Excipient Blends Using FT-Raman Mapping Spectroscopy

## OBJECTIVE

To characterize the physical uniformity and chemical content uniformity of a very low dose of indomethacin (0.5%) within Starch 1500®, partially pregelatinized maize starch, in comparison with spray dried lactose (FastFlo) and dibasic calcium phosphate, dihydrate (Emcompress) using a novel Raman spectroscopy mapping technique.

To identify key excipient properties that promotes blend uniformity and explains why Starch 1500 improves content uniformity of low dose drugs.

## BACKGROUND

Starch 1500 is a multifunctional excipient with bulking, binding and disintegrating capability. It has been previously shown that Starch 1500, when pre-mixed with an active pharmaceutical ingredient (API), yielded excellent content uniformity on a production scale of 4 million tablets. The average assay of the tablets was 99% of label claim with a variation of 2% RSD, even though the API dose was only 0.07% (w/w) of the formulation[1].

The work presented here confirms the ability of Starch 1500 to promote content uniformity and provides insights into the reasons for this performance. Using a mapping technique in conjunction with chemical assay enabled the visualization of the physical/spatial and actual distribution of the API in the blend sample.

## METHODOLOGY

**Blending:**

Blends of indomethacin [m.w. 357.79, calculated log P 4.18, D (v, 4,3) 0.749 µm)] and pregelatinized starch (Starch 1500, Colorcon) spray dried lactose (FastFlo, Foremost) or dibasic calcium phosphate, dihydrate (Emcompress, JRS Pharma) were dry blended in an Apex double cone blender for 10 minutes. Samples (200 mg) were removed in triplicate from different locations of the powder bed in the blender using a stratified sampling technique.

**Scanning Electron Microscopy (SEM):**

SEM micrographs were obtained for indomethacin, Starch 1500, FastFlo and Emcompress, and the blends thereof with a Cambridge Instruments Stereoscan S-360 Scanning electron microscope (Cambridge Instruments, Cambridge, UK). Samples were gold coated using an Edwards S150 b sputter coater. The images were used to approximate particle size and investigate the nature of the interaction between the excipients and the API.

**Laser Diffraction:**

The particle size distributions of the excipients and the API were determined in a dry state by laser diffraction, using a Malvern Mastersizer 2000 fitted with a Sirrocco dry powder flow accessory (Malvern Instruments, Worcs, UK). The results were compared to those obtained by SEM to confirm particle size.

**FT-Raman Spectroscopy mapping:**

FT-Raman spectra of indomethacin in the excipient blends were obtained between 0 and 4000 $cm^{-1}$ using a Thermo-Nicolet NXR FT-Raman Spectrometer, equipped with an NXR Genie detector (liquid nitrogen cooled) and a computer controlled mapping stage. Vibrational bands at 1698 $cm^{-1}$ (indomethacin), 363 $cm^{-1}$ (FastFlo), 478 $cm^{-1}$ (Starch 1500) and 988 $cm^{-1}$ (Emcompress) were used for analyses. Initial data acquisition was by Smart ARK and OMNIC software. The data were subsequently analyzed using the InSight chemometrics software package. A standard configuration was used to obtain a Raman spectrum from different small areas of the active blend from which FT-Raman spectroscopic spatial maps were obtained.

**Chemical Assay:**

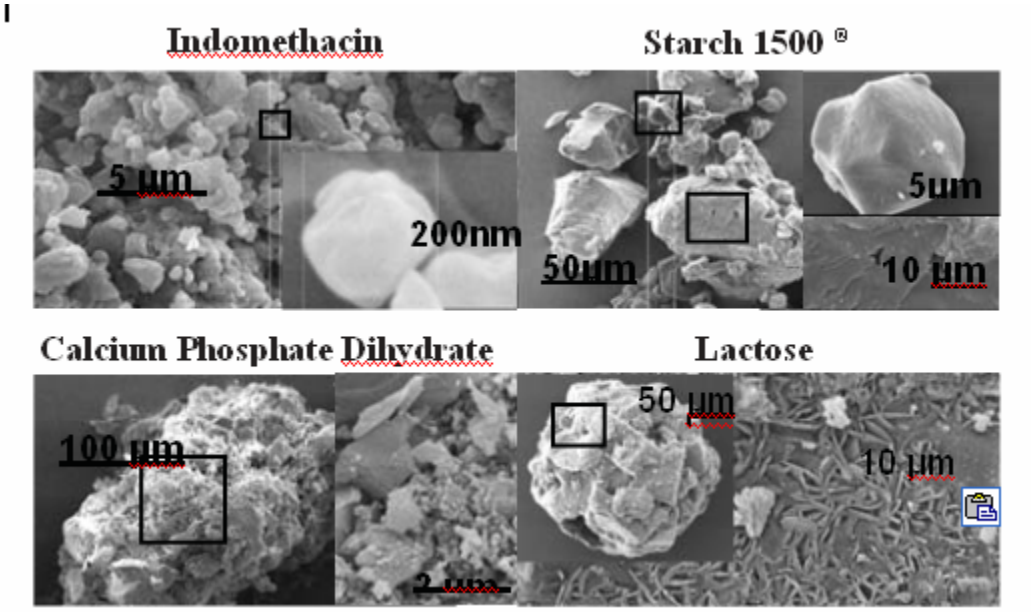
The chemical content of indomethacin in the sampled blends was analyzed with the aid of a Waters Acquity UPLC System (Waters Corporation, MA, USA) at 254 nm using a 0.1 M phosphate buffer in acetonitrile/ water mobile phase. The % RSD for replicate standard injections were not more than 2.0 %, and the USP plate count was not less than 1488.

## RESULTS & DISCUSSION

**Particle Characteristics by Laser Sizing and SEM**

The particle sizes (in microns) of the materials obtained by laser sizing are given in the table below.
The particle characteristics of the materials as obtained by SEM are given in the table below. Some of the surface features, which are expected to affect the interaction between the active and the excipient, are also presented.

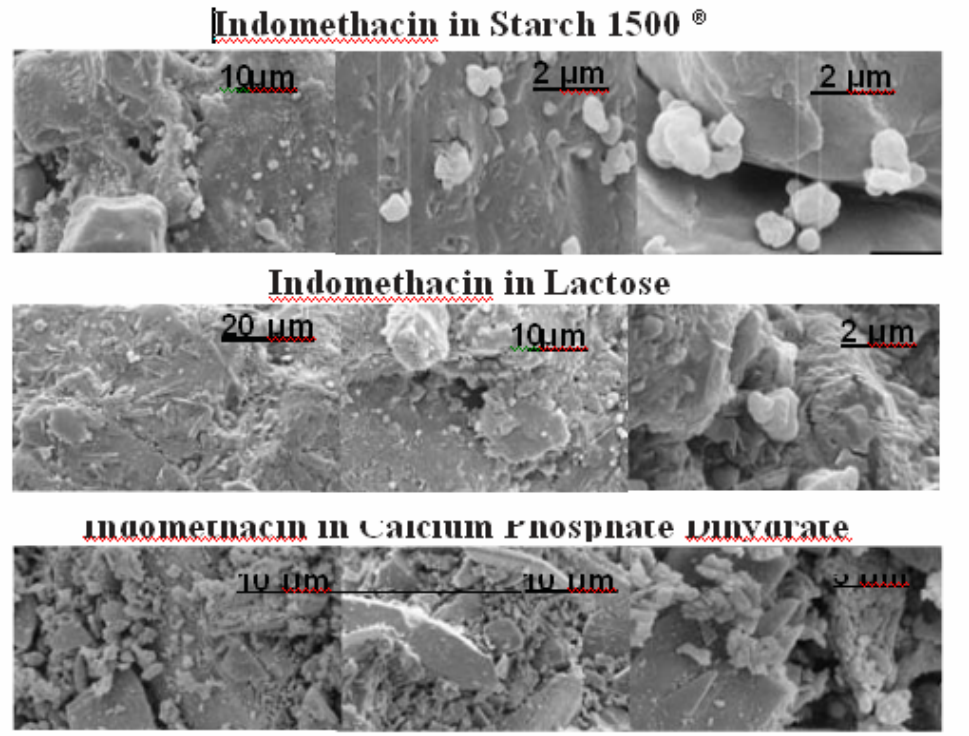
| Material | D10 | D50 | D90 |
|---|---|---|---|
| Indomethacin | 0.64 (0.03) | 1.664 (0.18) | 5.407 (2.21) |
| Starch 1500 | 12.25 (0.55) | 24.26 (6.65) | 53.17 (23.88) |
| FastFlo | 16.1 (9.63) | 40.29 (29.79) | 72.12 (46.77) |
| Emcompress | 49.08 (5.57) | 261.8 (36.03) | 591.63 (61.77) |




| Material | Size (µm) | Comments |
|---|---|---|
| Indomethacin | 0.5–1 | Glassy, Crystalline clusters, large crystals |
| Starch 1500 | 10–70 | Plate-like surface, irregular |
| FastFlo | 10–100 | Porous, Crystalline deep surface folds |
| Emcompress | 10–150 | Crystalline clusters, irregular, aggregates |

The particle sizes obtained from both techniques are in very good agreement. There are some larger particles of indomethacin than were observed by SEM. However, with the analysis of a larger sample size, the particle size range determined by laser diffraction is more representative than the size range by SEM.

The micrographs below show what is believed to be the interaction between indomethacin and the different excipients:




It can be seen that the indomethacin particles are attached to the surface and 'nestling' in the crevices of Starch 1500 particles. There are more discrete fine particles of indomethacin observed in the case of Starch 1500 as compared to agglomerates of indomethacin in the FastFlo and Emcompress samples.

**Chemical Assay of Indomethacin:**

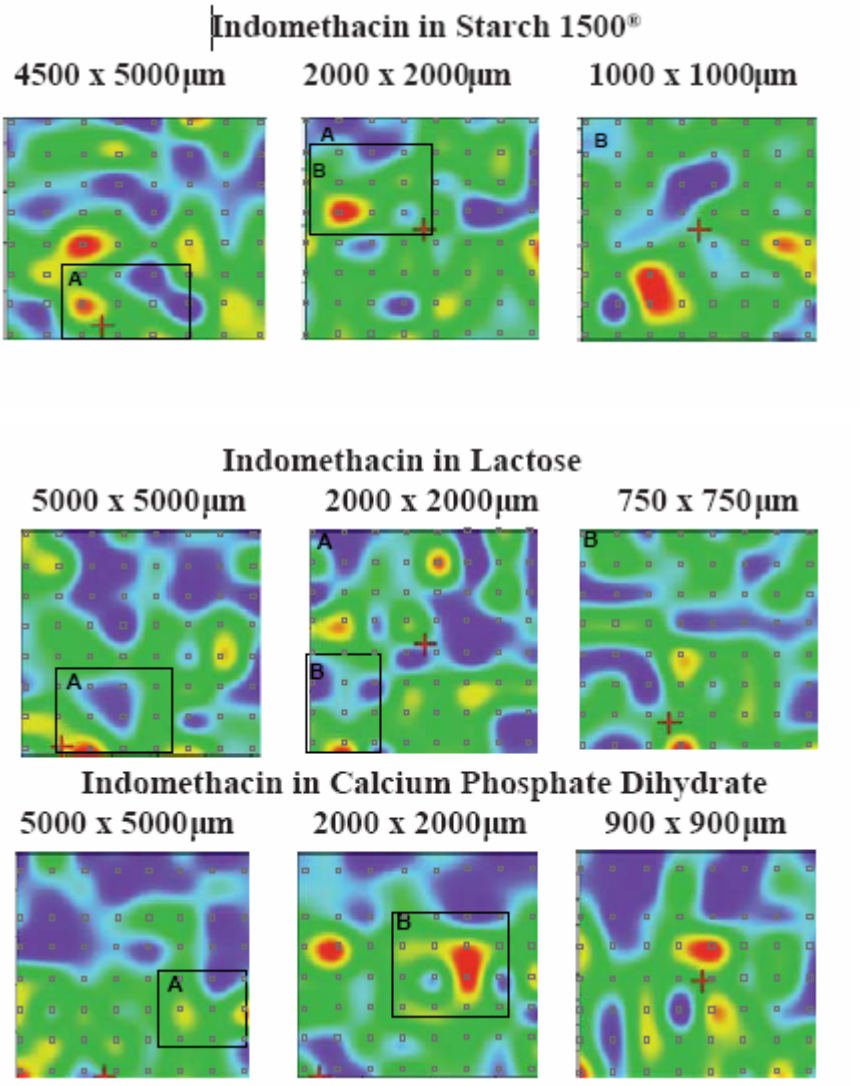
Data for the blend uniformity assay (n=6 positions within the blender) of indomethacin in Starch 1500, FastFlo and Emcompress are summarized in the table below:

| Material | Avg % of Label Claim | % RSD |
|---|---|---|
| Starch 1500 | 90.85 | 1.64 |
| FastFlo | 88.15 | 1.83 |
| Emcompress | 79.97 | 2.53 |

The blend with Starch 1500 had the highest uniformity of indomethacin distribution followed by FastFlo and Emcompress. The high average assay and low %RSD for the blend containing Starch 1500, at a very short mixing time (10 min.), have confirmed the postulations above.

**Spatial Distribution of Indomethacin by Raman Mapping:**

The physical distribution of indomethacin in the blend is shown in typical Raman maps below.




In each of the Raman maps, the marker chosen was indomethacin. The red and yellow regions indicate the presence of indomethacin, while green and blue indicate the lack of indomethacin. It is postulated that the yellow is indicative of indomethacin further from the surface.

Nine Raman maps were plotted for each of the three excipient-indomethacin blends. These maps showed the following trends:

- indomethacin was most uniformly dispersed in the Starch 1500 blends
- lactose blends exhibited good uniformity; however, the level of agglomeration was much higher
- calcium phosphate blends had the poorest uniformity and the highest level of agglomeration

## CONCLUSIONS

The content uniformity of very low doses of indomethacin in three excipient blends can be characterized by FT-Raman mapping, SEM and chemical assay.

It was demonstrated via all three methods that Starch 1500 consistently yielded blends with significantly better homogeneity and minimal API agglomeration compared with lactose (FastFlo) and dibasic calcium phosphate dihydrate (Emcompress).

The ability for Starch 1500 to achieve good homogeneity of the API was ascribed to a uniform distribution of fine particles of API “nestling” into crevices of Starch 1500 substrate. The moisture contained within Starch 1500 may mediate strong adsorption of active within the crevices via a hydrogen bonding mechanism.


## ACKNOWLEDGEMENT

The authors wish to thank Jennifer Payne and David Ferrizzi of Colorcon for the chemical assay work.


## REFERENCES


1. Ahmed H, Shah N 2000. Amer. Pharm. Rev. 3(3):1-5.