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# Evaluation of the internal and external structure of directly compressed polyethylene oxide (PEO) based matrix tablets before and after curing using X-ray micro-computed tomography

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## PURPOSE

Polyethylene oxide is frequently used in the formulation of extended release tablets. Polyox based matrix tablet exhibit increased tablet resistance to crushing when cured above the melting temperature. Increased crush resistance induced by curing may result in changes in the internal structure of the tablets which in turn lead to increased binding. Therefore, the purpose of this study is to examine the internal structure of the PEO based directly compressed matrix tablets before and after curing using micro-computed tomography (µCT) as a non-destructive technique.

## METHODS

### Experimental Design

In this study, Metoprolol Succinate was selected as model drug. Two grades of PEO (100K and 7M) and two grades of MCC (Avicel PH-101 and PH-105) were used (Table 1, formulation F1-F8). Magnesium stearate was used as a lubricant. The tablets were prepared per the formulation designs in Table 1. Another part of this study included evaluation of PEO compacts prepared per the formulations P1 – P5 shown in Table 1. The tablets and PEO compacts were also cured at temperatures ranging from 70 $^{o}$C – 95 $^{o}$C. The selection of the range was based on the glass transition temperature of PEO. The cured tablets were cooled for NLT 2 hours before subjecting them to X-ray Micro-Computed Tomography Scanner.

### Tablet Preparation

All ingredients were passed through USP sieve 270 to break lumps and remove larger particles. The ingredients were then mixed in Turbula mixer for 10 minutes. Finally, magnesium stearate was added to the mixture and mixed for additional 5 minutes. Powder blends were then directly compressed into 200 mg tablet, 8mm diameter, using rotary tablet press (Riva-Piccola rotary tablet press, SMI, NJ). The compression parameters were set at 8 – 10 kN compression force and 12 – 14 rpm.

### X-ray Micro-Computed Tomography (µCT)

The cured and uncured tablets were placed in a 14mm diameter sample holder and were scanned using X-ray µCT. The X-ray µCT scans and records the images of the samples in several hundred layers of a pre-defined thickness and also generates a 3D structure using the scans. Using this instrument, solid volume fraction and the images of cross section slices of the tablets were evaluated. The solid volume fraction represents the ratio of volume of solid mass of the table to the total volume (solid mass + void) volume of the tablet. A placebo formulation containing either PEO 100K or 7M was also evaluated similarly (Table 1, formulations P1 – P5). The outcome of placebo study will serve as control to discriminate the effect of drug on overall changes in the internal structure and void volume of the tablets before and after curing.

| | Formulations | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | P1 | P2 | P3 | P4 | P5 |
| Metoprolol Succinate (%w/w) | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | - | - | - | - | - |
| PEO 100K (%w/w) | 54.2 | 50.2 | - | - | 48.3 | 39.4 | - | - | 100 | - | 75 | 50 | 25 |
| PEO 7M (%w/w) | - | - | 48.3 | 44.6 | - | - | 56.8 | 39.4 | - | 100 | 25 | 50 | 75 |
| MCC 101 (%w/w) | 14.8 | 18.8 | 20.7 | 24.4 | - | - | - | - | - | - | - | - | - |
| MCC 105 (%w/w) | - | - | - | - | 20.7 | 29.6 | 12.2 | 29.6 | - | - | - | - | - |
| Mg-Stearate (%w/w) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | - | - | - | - | - |

Table 1. Formulation design

## RESULTS

- Some of the formulations exhibited change in shape after curing. It was observed that tablets containing PEO expands during the curing process and then contracts after cooling which leads to the development of fissures and cracks. Fissures and cracks were also previously observed on the tablet surface in a similar study using SEM.
- Figure 1 shows 3D images of the uncured and cured Polyox compacts. The compacts of low molecular weight PEO showed shape deformation and development of relatively large fissures and cracks. The compacts of high molecular weight PEO did not show shape deformation but showed coarse surface with smaller fissures.
- The images in figure 2 shows the internal view of the cross section of the Polyox compacts. The images of the uncured samples showed almost no voids. However, the images revealed voids formation inside the compacts after curing.
- The tablets containing PEO 100K showed formation of more number of voids after curing as compared to tablets containing PEO 7M. The presence of MCC in the formulations showed smaller voids after curing. This is also reflected in the solid volume fraction data.
- The solid volume fraction data obtained from µCT can be seen in table 2. The percent change in the solid volume fraction of polyox compacts ranged from 14.1% - 46.7% and the same for metoprolol succinate tablets ranged from 6.8% - 13.8%. The change in solid volume fraction among tablets and compacts at different temperatures was relatively insignificant.

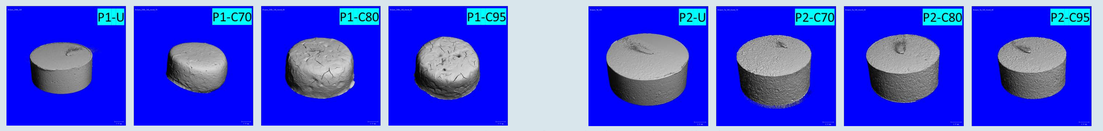


Figure 1. Micro-Computed Tomography 3D images of uncured and cured Polyox (100k and 7M) compacts

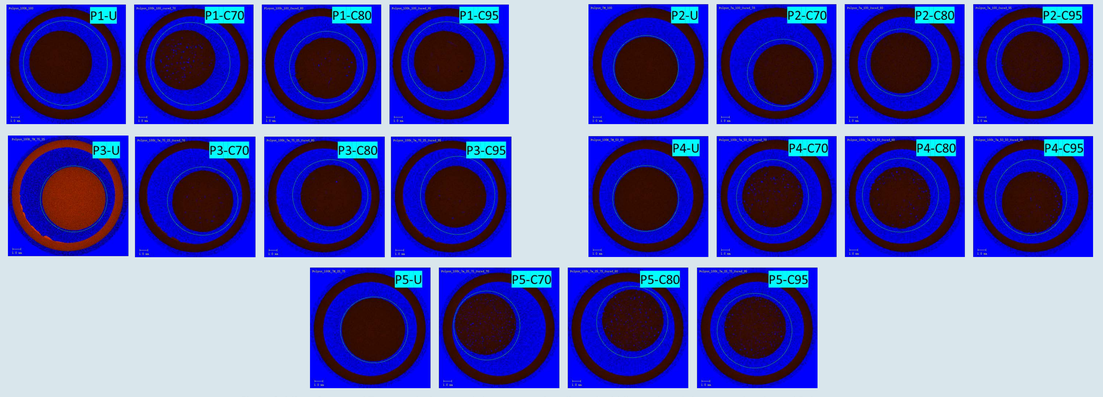


Figure 2. Micro-Computed Tomography images of the cross-section slices of middle portion of the uncured and cured Polyox compacts

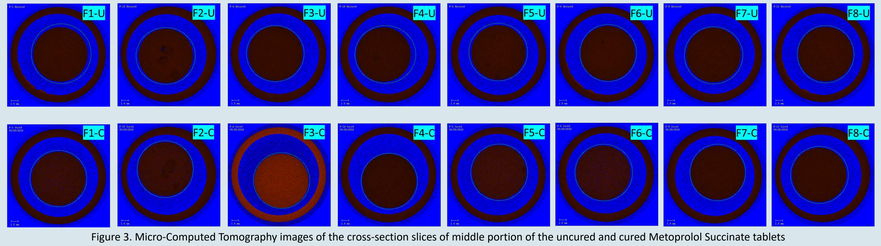


Figure 3. Micro-Computed Tomography images of the cross-section slices of middle portion of the uncured and cured Metoprolol Succinate tablets

## RESULTS

| Formulation | Uncured | Cured at 70 | Cured at 80 | Cured at 95 |
|---|---|---|---|---|
| P1 | 0.5288 | 0.4544 | 0.6429 | 0.5343 |
| P2 | 0.9169 | 0.7051 | 0.7093 | 0.6016 |
| P3 | 0.8585 | 0.7525 | 0.6504 | 0.5837 |
| P4 | 0.87 | 0.6387 | 0.6134 | 0.6361 |
| P5 | 0.8898 | 0.7234 | 0.6651 | 0.6065 |
| F1 | 0.7867 | - | 0.8727 | - |
| F2 | 0.8229 | 0.8874 | - | - |
| F3 | 0.8558 | - | - | 0.9242 |
| F4 | 0.7878 | 0.9136 | - | - |
| F5 | 0.8072 | 0.8771 | - | - |
| F6 | 0.8866 | - | - | 0.8302 |
| F7 | 0.8431 | - | - | 0.9081 |
| F8 | 0.8816 | - | 0.8796 | - |

Table 2. Solid Volume Fraction of the uncured and cured tables

## CONCLUSIONS

- X-ray Micro-Computed Tomography is a non-destructive technique to visualize entire tablet structure.
- Nondestructive nature of the µCT method can be used as a tool to visualize structural changes of same tablet before and after curing. This approach therefore could explain changes in crush resistance of PEO based cured matrix tablets.
- Changes in solid volume fraction of the uncured and cured tablet indicates level of molecular interaction between polymer strands. It needs further verification using alternative techniques or approaches.
- X-ray µCT can also be used to assess the internal structural changes in a tablet due to the addition of other ingredients. Also, it allows to visually examine distribution of ingredients, based on different densities, inside a tablet.
- Additionally, it is important to investigate if any correlation exists between change in solid volume fraction with quantifiable mechanical properties of PEO or PEO mixtures based tablets.
- Changes in the internal structure of tablets due to formulation, process and impact of drug product processing can be quantitatively studied using X-ray µCT. This can significantly help in identification of formulation and process design space for a better drug product development.

## ACKNOWLEDGEMENTS

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