

Examples of Technical Challenges in Drug Projects with Titanium Dioxide Alternatives

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PQRI Workshop:

TiO₂ Use in Pharmaceuticals

Global Regulatory and Technical Challenges

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Presentation Objectives

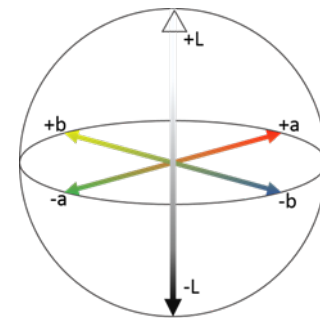
- Why is the industry evaluating alternatives
- Alternatives and known technical hurdles
- Tablet examples
- Capsule examples
- Conclusions

Why Evaluate Alternatives

- Not evaluating alternatives due to TiO₂ safety concerns
- Commission Regulation (EU) 2022/63 requests evaluation
- Evaluating alternatives inform product risk assessments
- TiO₂ plays an important role beyond just a colorant
 - Enables product differentiation, prevents counterfeiting
 - Affords protection of drug substances from light
 - Aids in swallowability, mouth feel, taste masking, etc
 - Results in pharmaceutical elegance, reflection of quality

Known Technical Hurdles of Alternatives

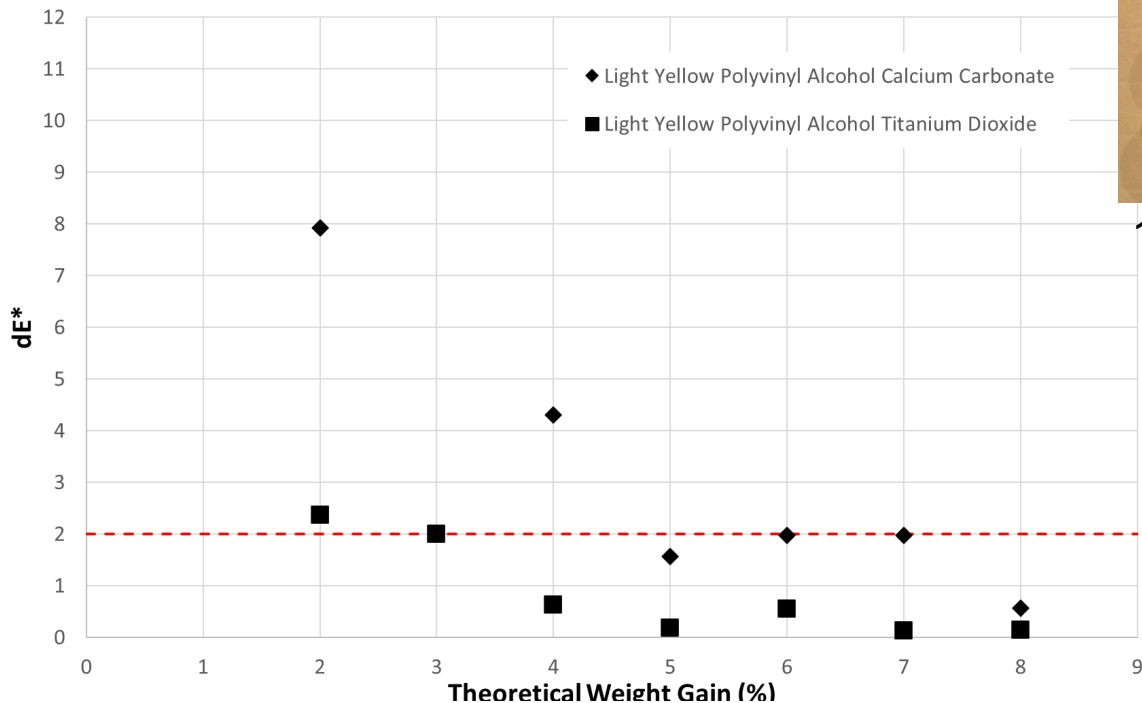
- Global acceptability of alternative
- Safety of alternatives in comparison to TiO_2
- Opacity of alternatives are inferior to TiO_2
- Ability to color match an existing product
 - dE^* value of ≤ 1 not perceptible to human eye**
 - dE^* value of 1-2 perceptible with close observation
 - dE^* value of >2 perceptible



$$dE^* = \sqrt{(L - L_{standard})^2 + (A - A_{standard})^2 + (B - B_{standard})^2}$$

**<https://www.viewsonic.com/library/creative-work/what-is-delta-e-and-why-is-it-important-for-color-accuracy/>

Color Matching – Light Yellow Example



↑
 $dE^* = 31$

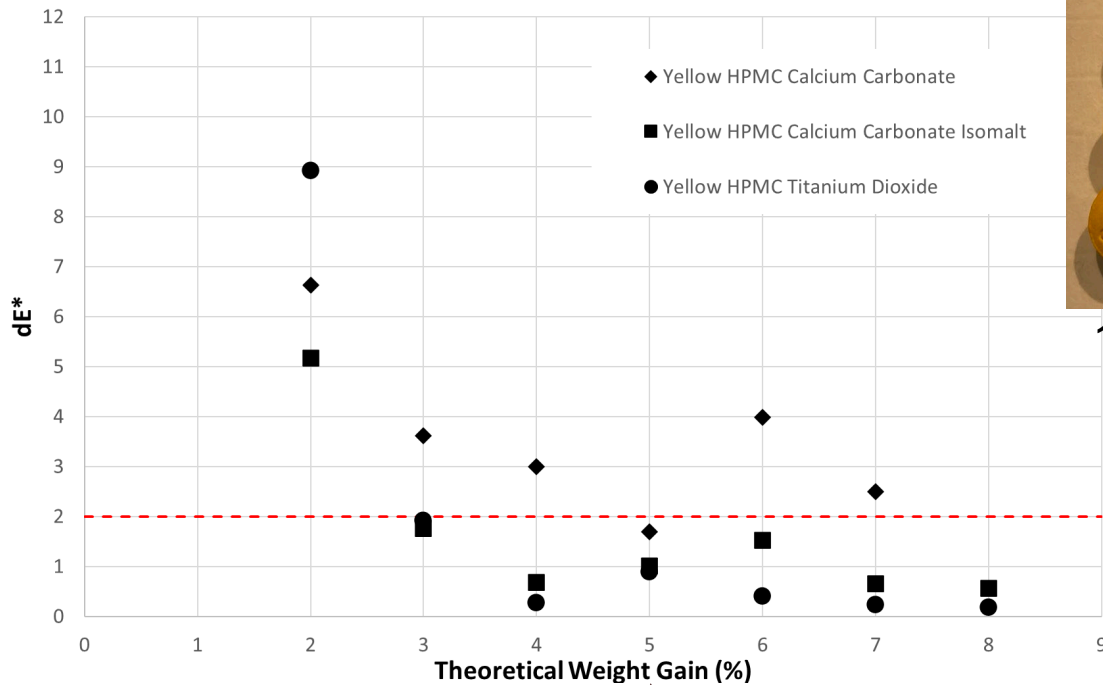


1% 2% 3% 4% 5% 6% 7% 8%

Observations:

- Higher weight gains to obtain lack of color change
- Bolder color compared to TiO_2 containing
- Debossment infilling at higher weight gains

Color Matching – Yellow Example



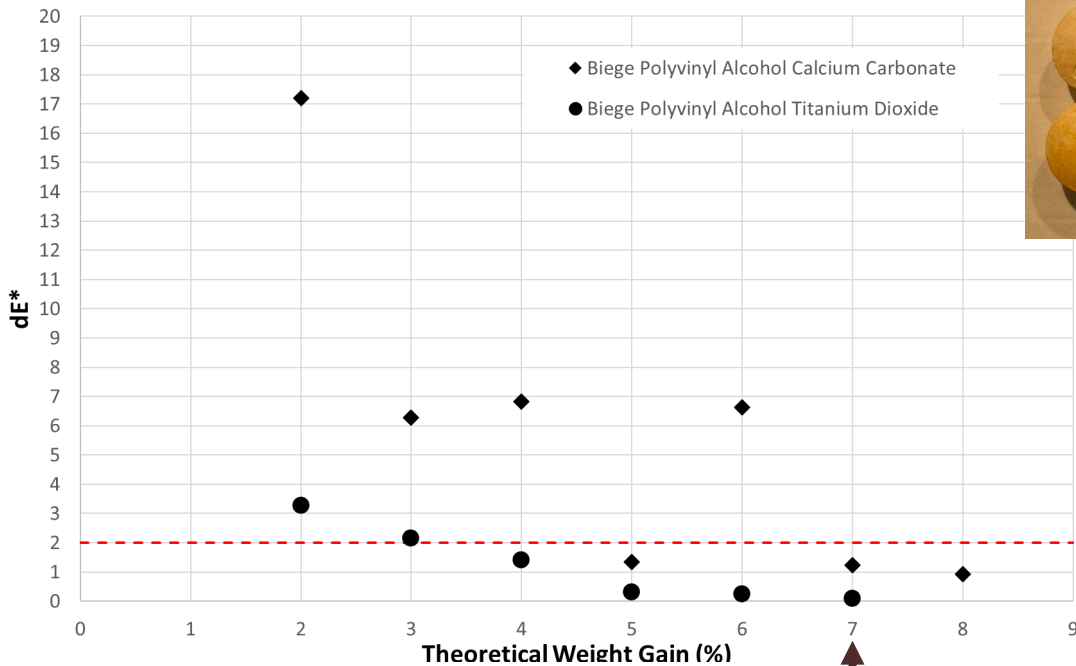
1% 2% 3% 4% 5% 6% 7% 8%

Observations:

- CaCO₃ higher weight gains to obtain lack of color change
- CaCO₃ / Isomalt similar weight gains to obtain lack of color change
- CaCO₃ / Isomalt results in speckled appearance

CaCO₃ dE* = 8
 CaCO₃ / Isomalt dE* = 11

Color Matching – Beige Example

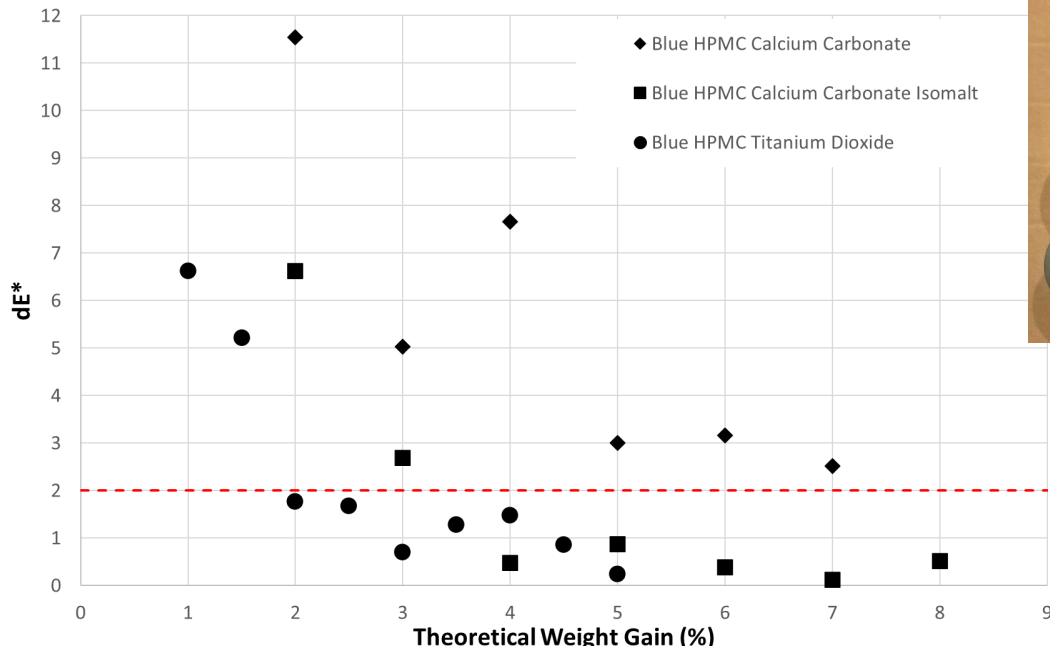


1% 2% 3% 4% 5% 6% 7% 8%

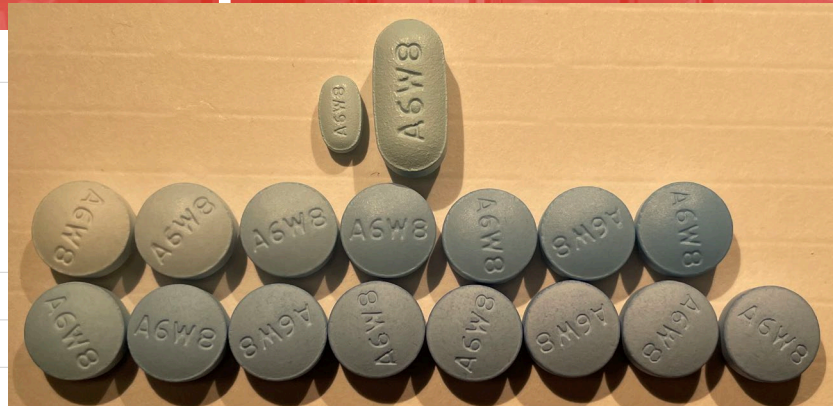
Observations:

- Higher weight gains to obtain lack of color change
- Bolder color compared to TiO₂ containing
- Belly band appearance difference
- Non-uniform appearance

Color Matching – Blue Example



CaCO_3 dE* = 7
 $\text{CaCO}_3 / \text{Isomalt}$ dE* = 8



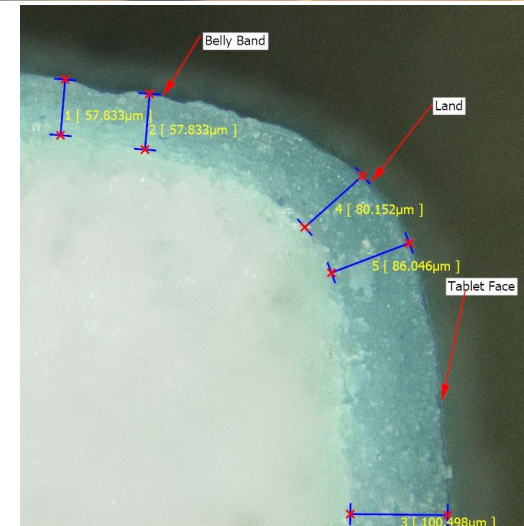
1% 2% 3% 4% 5% 6% 7% 8%

Observations:

- CaCO_3 never reached $dE^* < 2$
- Belly band appearance difference
- $\text{CaCO}_3 / \text{Isomalt}$ results in speckled appearance

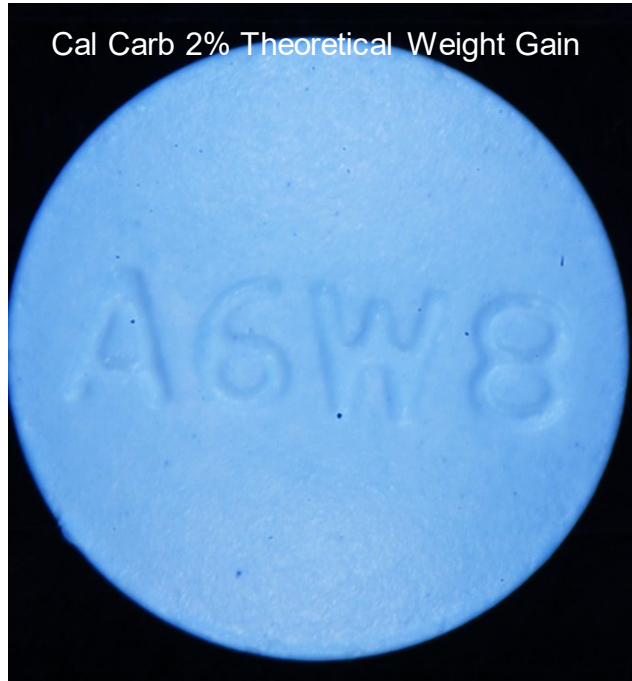
Tablet Appearance

- Different colors within a single tablet with CaCO_3
 - Caused by opacity difference
 - Doesn't appear to go away as weight gains increased
 - Tablet shape interactions
 - Better tablet design for coating process
 - Not pharmaceutically elegant

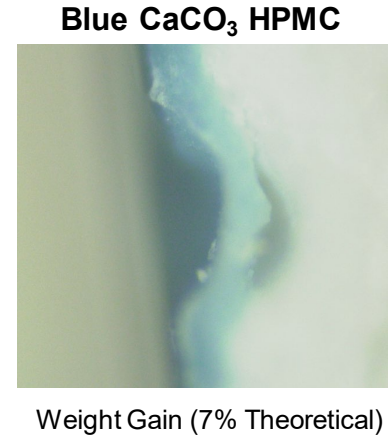
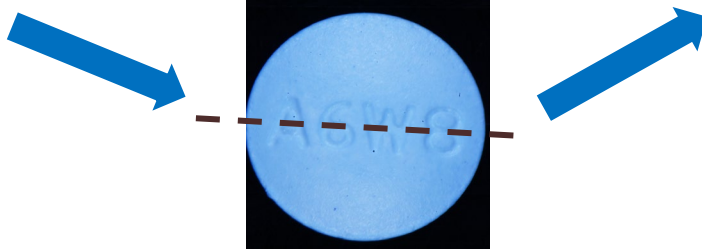
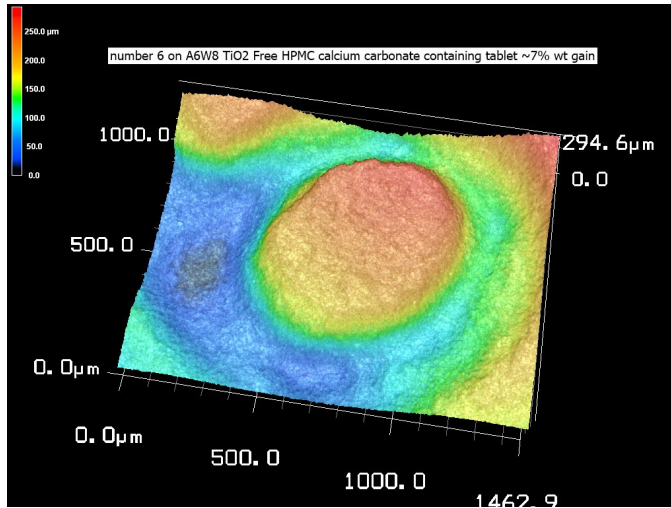


Tablet Appearance CaCO₃ / Isomalt

- Isomalt results in speckled appearance



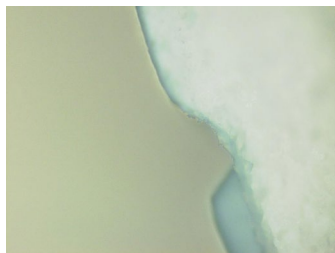
Infilling of Tablet Debossment



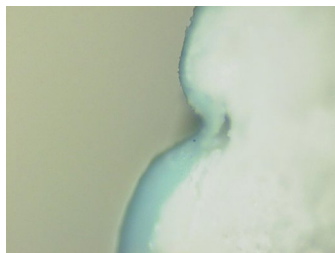
- Observed in debossment at higher weight gains, >6%
- Coating observed to be pulling away from the debossment
- Calcium carbonate hypromellose coating system only

Tablet Debossment

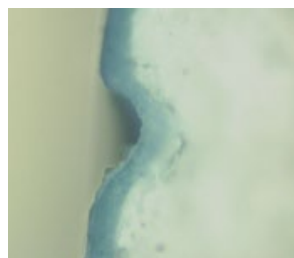
Blue CaCO₃ HPMC



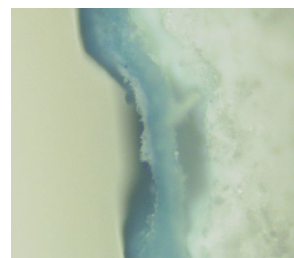
Weight Gain
(1% Theoretical)



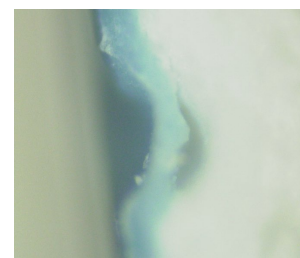
Weight Gain
(3% Theoretical)



Weight Gain
(5% Theoretical)

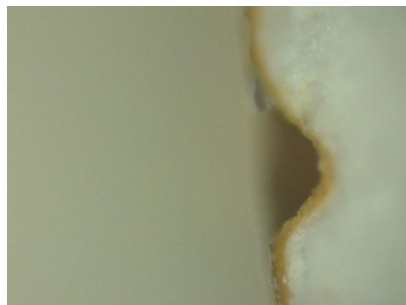


Weight Gain
(6% Theoretical)

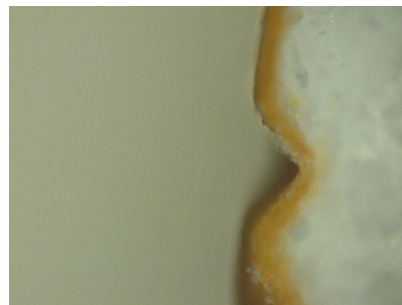


Weight Gain
(7% Theoretical)

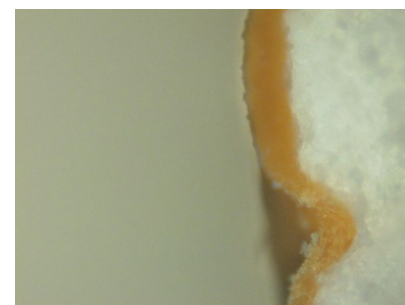
Beige CaCO₃ PVA



Weight Gain
(3% Theoretical)

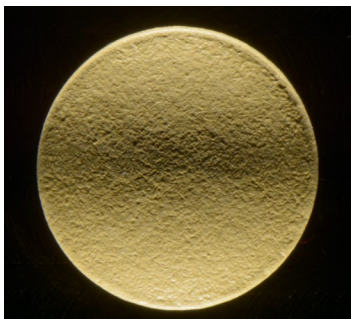


Weight Gain
(5% Theoretical)

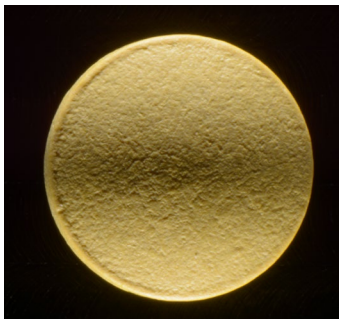


Weight Gain
(8% Theoretical)

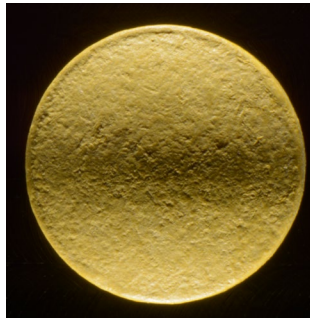
Surface Texture



TiO₂
~5% Weight Gain



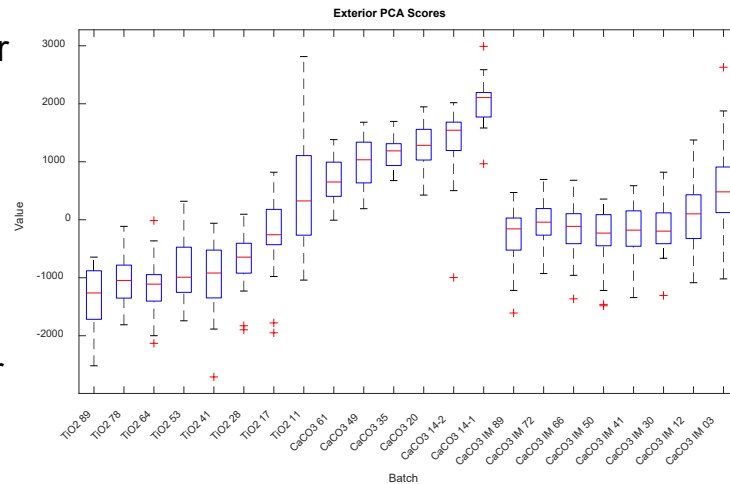
CaCO₃
~5% Weight Gain



CaCO₃ / Isomalt
~5% Weight Gain

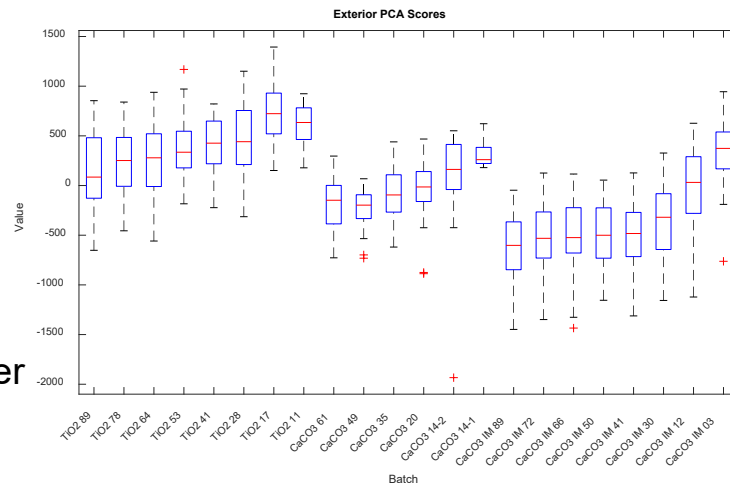
Smoother

Rougher



Finer

Coarser



Tablet Disintegration

	TiO ₂	Calcium Carbonate	Calcium Carbonate / Isomalt
Time (sec)	100-128	104-168	104-152

- Yellow hypromellose based coating system with 4% weight gain
- More variability in disintegration times for alternatives
- Could be more than just coating weight gain resulting in variability in performance

Ready-Made Color Mixture Conclusions

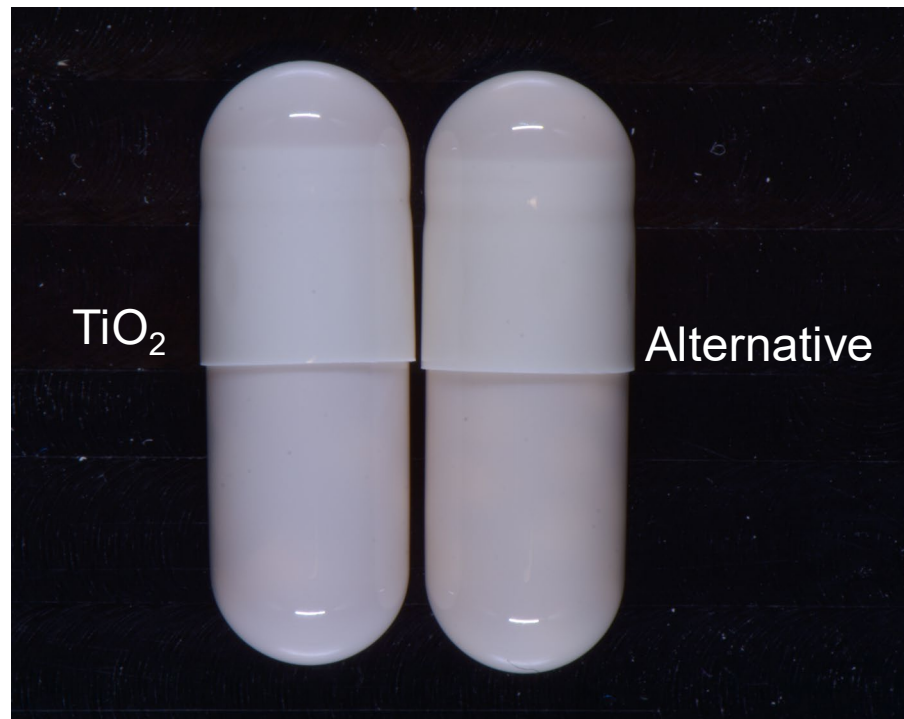
- Ready-made color mixtures
 - Alternatives may need higher weight gains to get color uniformity
 - Risk of logo bridging at higher weight gains
 - Explanation for HPMC coating lifting from debossment unknown
 - Tablet modifications may be needed to afford a pharmaceutically elegant product with alternatives

Hard Capsule Shells

- Evaluated multiple suppliers of empty capsules
 - Hypromellose
 - Gelatin
- Current solutions lacking global acceptability
 - not meeting pharmacopeial monographs
 - Some alternatives not approved for use as a colorant
- Opacity difference when calcium carbonate use by itself
- Coloring capability with alternatives is under development at not well understood

Capsule Opacity - Gelatin

- Challenges for Alternative:
 - Coloring capability unknown (white only)
 - Photolabile drugs stability unknown but similar opacity
 - Slightly more yellow appearance
 - Encapsulation performance unknown



Capsule Opacity - Hypromellose

- Challenges for Alternatives:
 - Blinding for CTs
 - Photolabile drug risk
 - Surface appearance slightly rougher
 - Imprinting performance
 - Encapsulation performance unknown

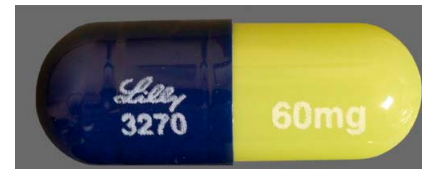
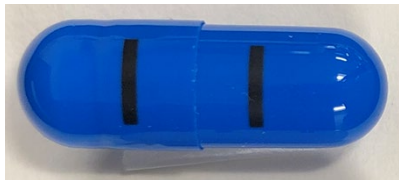


Hard Capsule Conclusions

- Alternatives have different level of opacity
- Currently used alternatives may not be globally acceptable
- Surface differences result in difficulty in imprinting quality
- Blinding clinical materials may be difficult
- Iron oxides help with opacity
 - Make it quite difficult to color match existing products
 - Iron levels allowing for opacity can result in additional labelling for iron content

Dosage Form Marking Technologies

- Without TiO₂:
 - No UV Laser marking
 - No white imprinting
 - Reduces ability to have light imprinting
- Dark inks will not allow for desired contrast difference



Conclusions

- Proven safe alternatives are not currently available
- Difficulty matching marketed or late-stage development products with current solutions
 - Patient impact to changes in appearance beyond just color
- Differences in surface attributes could impact mouth feel or swallowability of the tablets
- Colors available for markings of dosage forms will become limited

Acknowledgements

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Thank You

