Technical challenges substituting TiO_2 from different coating producers' point of view

PQRI Workshop 13-14 June 2023

PQRI Workshop:
TiO2 Use in Pharmaceuticals
Global Regulatory and Technical Challenges
June 13-14, 2023

Previously presented at APV conference

The future Role of Titanium dioxide as an excipient in Pharmaceuticals - Exploring the current and future situation worldwide

With much appreciation to our Film Coating industry colleagues

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Alternative Opacifiers

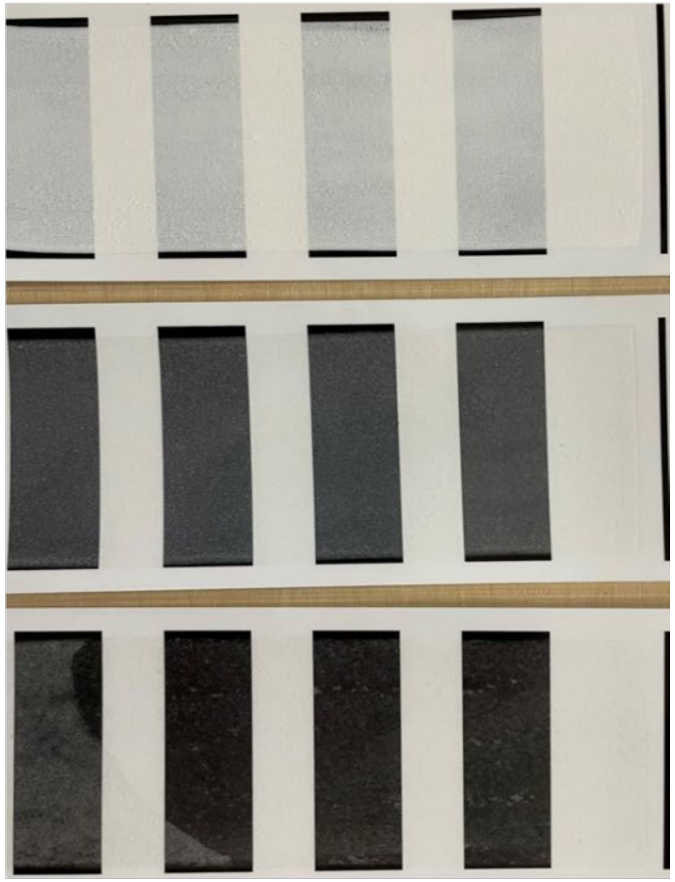
Titanium dioxide a critical excipient ?

- **E171** – a specified food-grade form, one of the most important food additive in nutraceuticals / pharmaceuticals, widely used as a whitening agent *(e.g., in tablets or tablet film coating)*

- **the white pigment with highest refractive index and brightness.** The whitening is best achieved with TiO_2 particles within a size range of 200–300 nm, due to their light scattering effects.

- An excipient with unique properties (attractiveness) – even a low content of titanium dioxide provides a significant influence on appearance of products (capsules: appr. 1-5%)

But: *EFSA* has updated its safety assessment of TiO_2 as 'no longer safe when used as a food additive'



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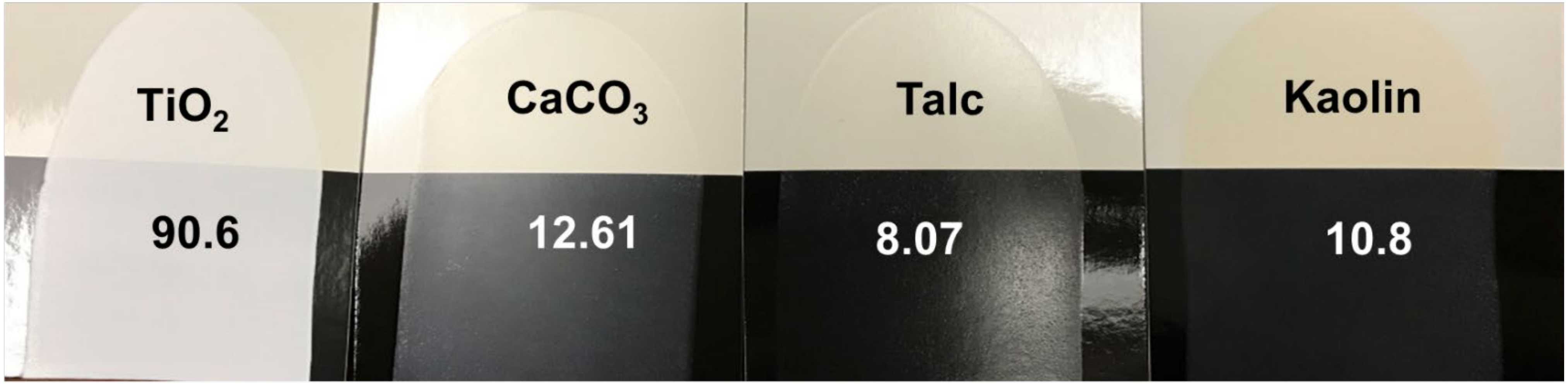
Contrast ratio examples - Opacifiers

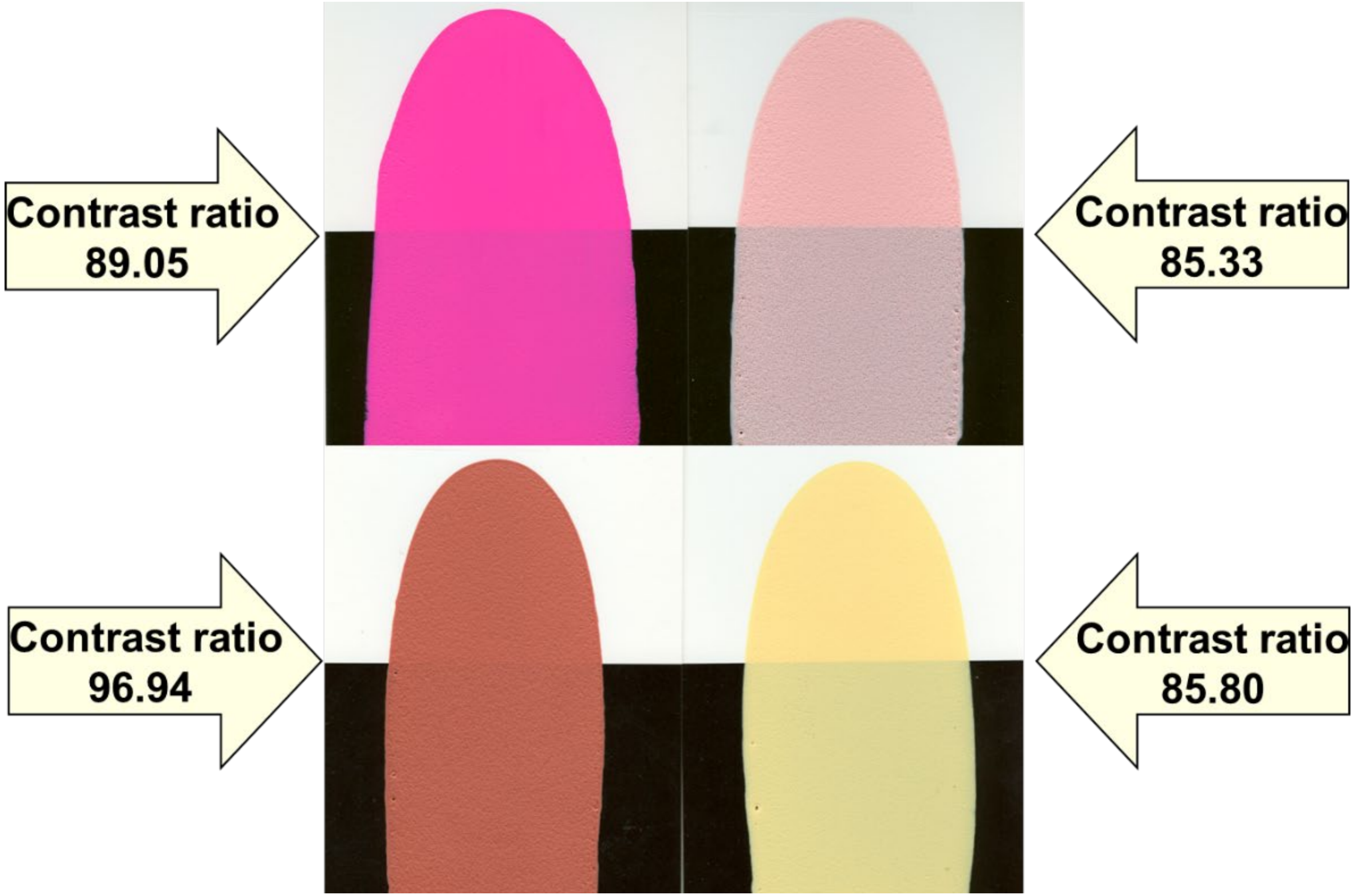
HPMC films with 20% filler



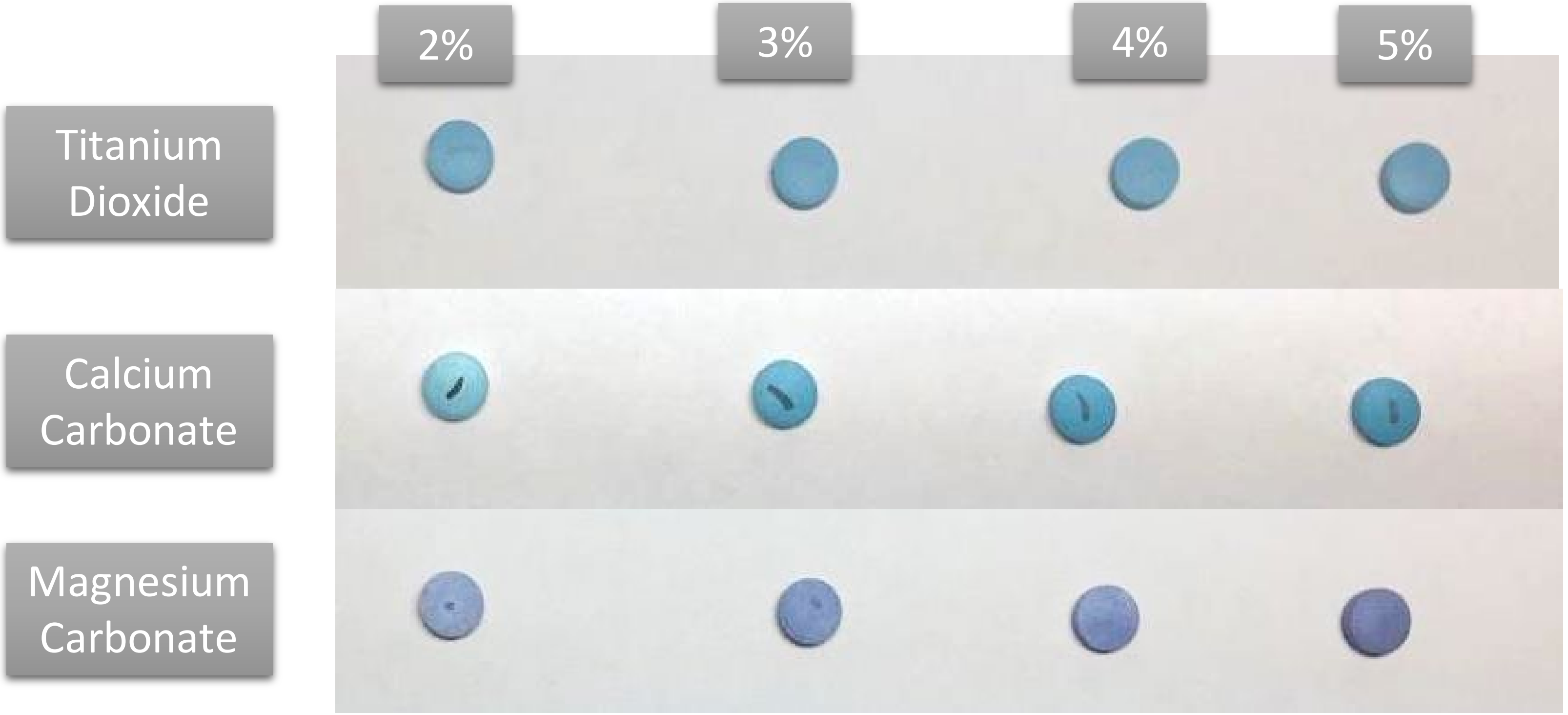
$$Contrast\ ratio = \frac{Yb}{Yw} X\ 100$$

Where Y_b is the Y tristimulus value measured against a black substrate, and Y_w is the similar value measured against a white background

Contrast ratio examples - pigments



Alternative Opacifiers



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Challenges associated with the alternatives

Challenges of TiO_2-free film coatings – Selection of Polymers

Commonly used polymers in TiO_2 coatings:

- HPMC
- PVA
- PVA-PEG
- HPMC/HPC
- Copovidone
- Polymethacrylates

Recent experience indicates that Polyols are helpful to „stabilize“ $CaCO_3$ and thus improve tablet aesthetics

Effect of different plasticizers on opacity

Plasticizer 1 Plasticizer 2 Plasticizer 3

Challenges of TiO_2-free film coatings – Addition of stabilizer

Comparison of results

TiO_2-free formulations

- 1. AquaPolish® 014.32 MS
- 2. AquaPolish® 019.XXX MS
- 3. AquaPolish® 00002

- Formulation containing titanium dioxide shows the best results
- AquaPolish® 019.XXX MS shows suitable results in comparison with titanium dioxide at 4 % weight gain level, edges are covered well
- Visible improvement through usage of the right amount of stabilizers compared to formulation AquaPolish® 00002

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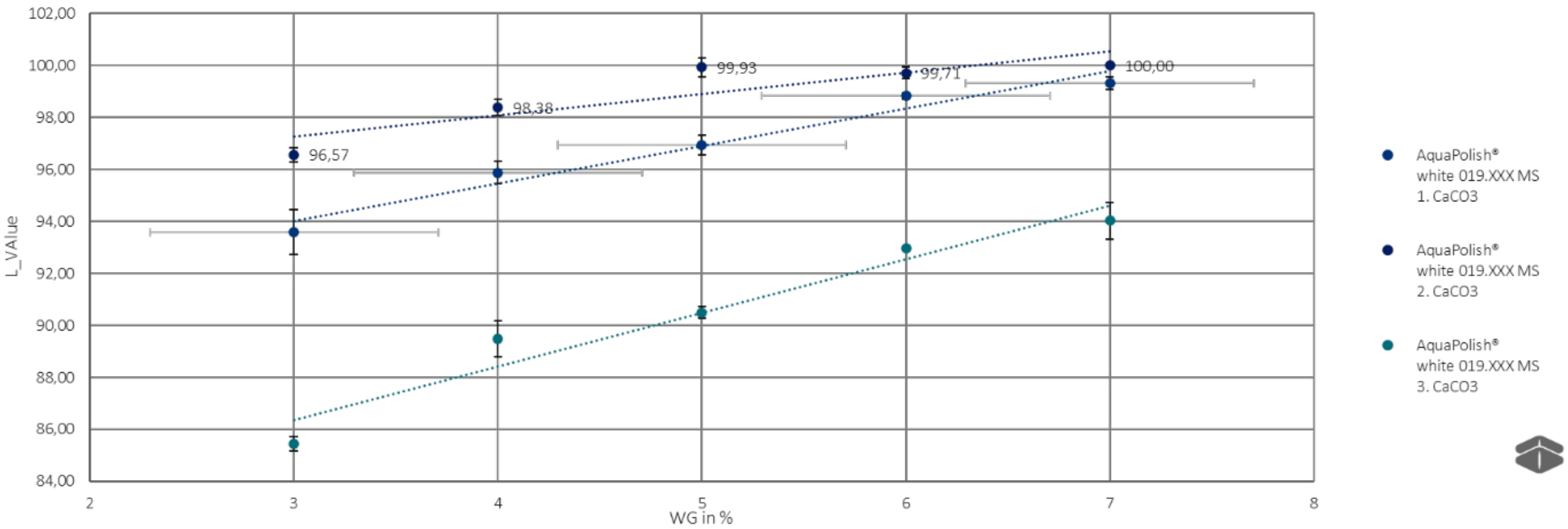
Challenges of TiO_2-free film coatings – Selection of $CaCO_3$

Comparison of L-Value – three different pigment manufacturers

TiO_2-free formulations

- L-Value of the coating can depend strongly on the used form of pigment, which differs by the selection of manufacturers
- The L-Value of the Formulation AquaPolish® white 019.XXX MS shown in the previous slide can still be increased that way
- By that, even the L-Value of the TiO_2 containing coating can be reached with the same weight gain level (at 3%: 96,87 / 96,57)



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Challenges of TiO_2-free film coatings – process related challenges

- switching from a TiO_2-based traditional coating to a titanium dioxide free coating system might negatively effect process time and economics
  - even at a similar viscosity and spray rate, a higher coating weight gain requires longer process times
- final film coating appearance will be impacted by the tablet core color, it's shape and size
  - lighter cores see less change and a weight gain of 3-5% might achieve good results
  - darker cores may need higher coating weight gain (up to 7%)
  - effect of substrate diminishes with increasing weight gain

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Film coating with FD&C Blue #2 pigment



Reference with TiO_2 — 28.54% TiO_2, 3.4% FD&C Blue #2

Direct $CaCO_3$ Replacement — 28.54% $CaCO_3$, 3.4% Blue #2

Pigment Reduction (1/3) — 30.81% $CaCO_3$, 1.13% Blue #2


Mixed Substrate


White core


Dark core


White core


Dark core

- All coatings shown at 3.0% weight gain
- Color will be brighter and darker color with replacement of TiO_2 with $CaCO_3$.
- Pigment level needs to be significantly reduced to approach same color as reference and may require higher coating weight gain to build opacity.

Color Matching

Different between TiO2 and its alternative with the same pigments

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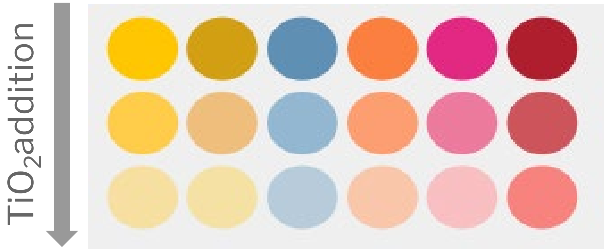
Challenges - Shift in color/ appearance

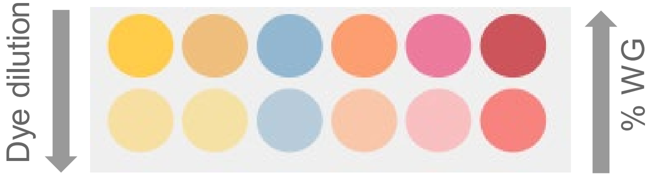
Replacement of TiO2 in colored film-coatings
→ What are the difficulties when trying to obtain a colored coating without TiO2?

TiO2: unique whitening agent with opacifying properties



vs

Dilution with dyes without TiO2



- ★ Lighter shades obtained with TiO2 increase
- ★ High covering power, at low % WG

- ★ Less color intensity of starting shades
- ★ Lower covering power => % WG impacted

With TiO_2

Without TiO_2

Spotted nude cores

Color matching – challenges and limitations

2% Purple Carmine

TiO_2

Cal Carb

- Color development is basically made by the combination of pigment(s) and TiO_2 ratio : wide range of color shade
- Without TiO_2, the color development is only driven by the quantity of pigment(s)
- Darker color edges may occur depending on tablet shape
  - Edge design / radius
  - Pigment inclusion levels
  - Coating weight gain

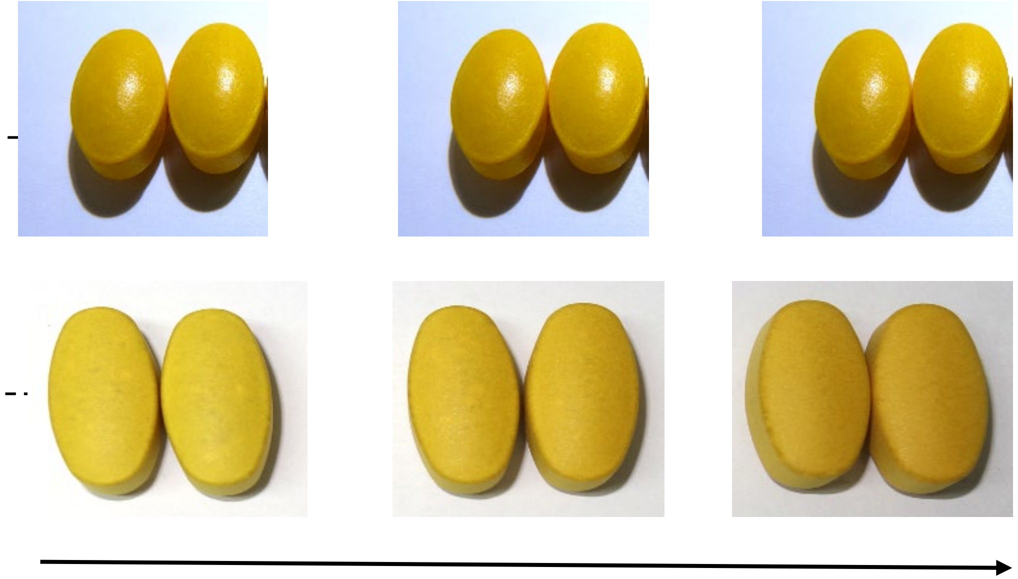
Challenges - Shift in color/ appearance

Color homogeneity - *Example:*

Dye: Natural Yellow colorant

With TiO_2

Without TiO_2



3% **5%** **8%** weight gain

Same color whatever the WG

Starting with a translucent shade.. with the increase of WG, color intensification (darker) and better covering effect

→ Select a color taking into account the appearance of the core

→ Adapt the WG

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Color Stability

Challenges of using $CaCO_3$ (Alkaline pH)

Coating with $CaCO_3$

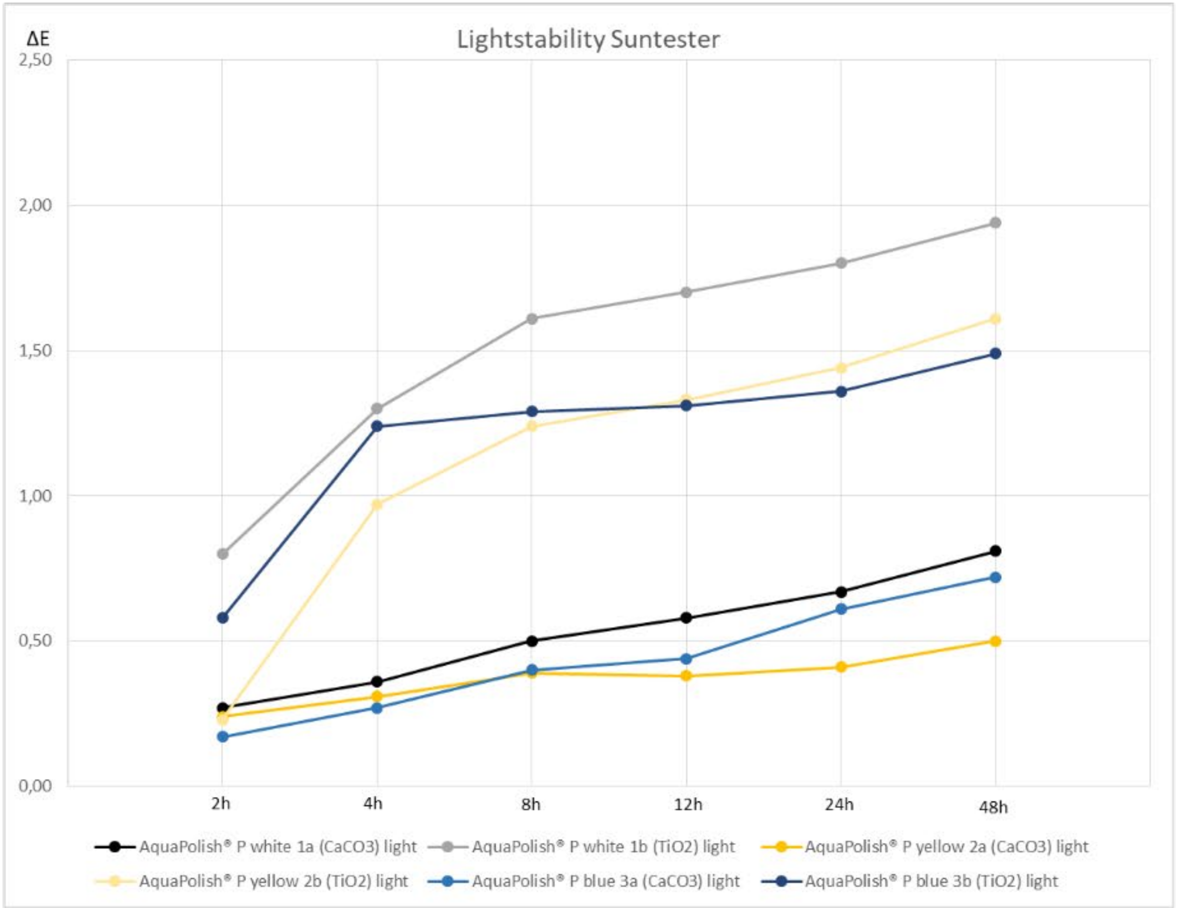
Some pigments and APIs may be sensitive to a higher pH environment, impacting color and potentially API stability

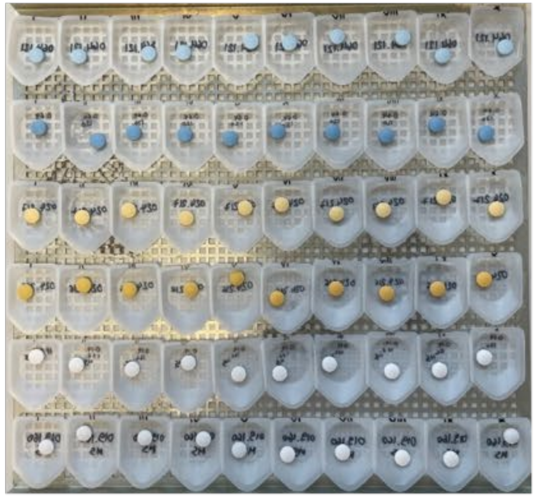
Mineral-free version

A Mineral free option is now available for both Opadry TF and Nutrafinish Label Friendly

Challenges – stability of coloring agent

Stability of TiO_2-free formulations





Suntester	Real Sun Exposure
2h	15h
4h	30h
8h	60h
12h	90h
24h	180h
48h	360h

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Challenges – stability of coloring agent

Resistance to day light - *Example:*

Dye: Riboflavin reference, less than 1%

→ Avoid low concentrations of coloring agents.

→ Use lakes or pigments

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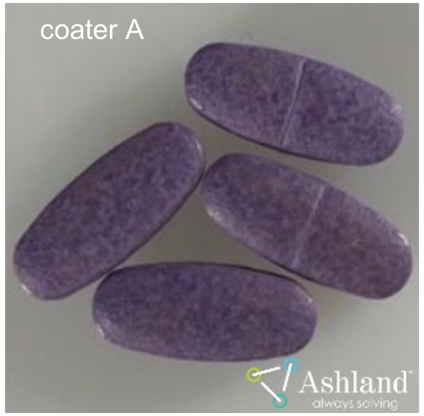
Scaling up

Scale-up related challenges

- in contrast to regular TiO_2 based film coating systems, the final film coating appearance of a TiO_2 free formulation can be impacted by the equipment and the equipment scale
  - lab scale vs. production scale: some TiO_2 free film coatings perform very well at lab scale, but fail at production scale
  - equipment suppliers: differences in the coater design (coating pan, spray gun positioning, air flow limitations, etc.) can impact the final film coating appearance

multivitamin cores
purple TF coating
lab scale
3kg batch size

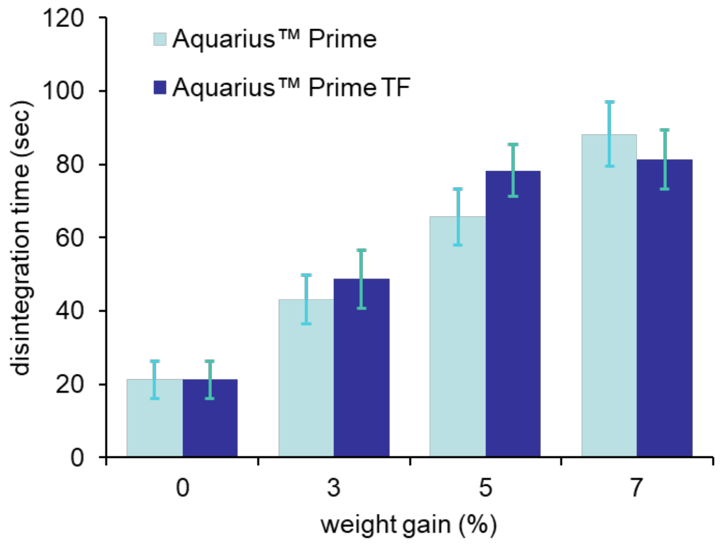
same coating & tablet cores
scale-up
50 kg batch size

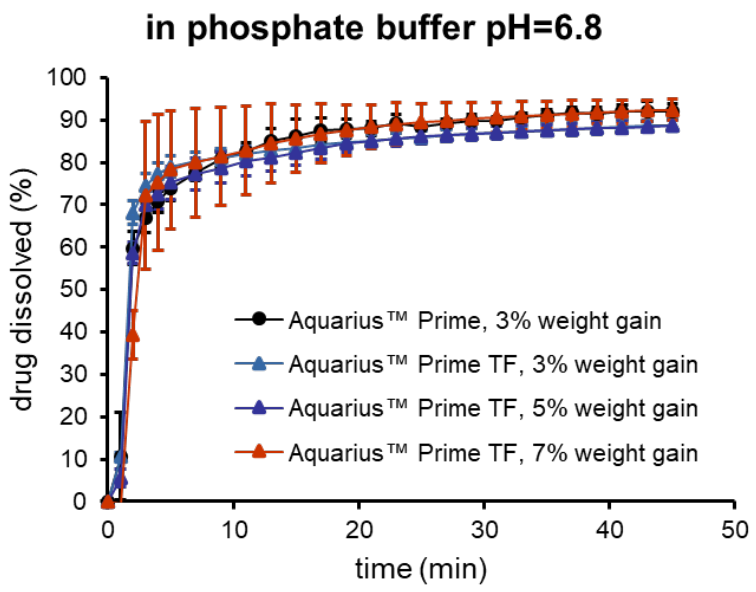


Disintegration/Dissolution

disintegration/dissolution characteristics of coated tablets

- film coatings can slightly increase tablet disintegration times → higher coating weight gain results in longer disintegration times
- aesthetic TF coatings show a similar disintegration behavior compared to titanium dioxide containing aesthetic coatings
- aesthetic TF coatings show a similar dissolution behavior compared to titanium dioxide containing aesthetic coatings
- tablet weight gain up to 7% (w/w) does not change the dissolution behavior significantly



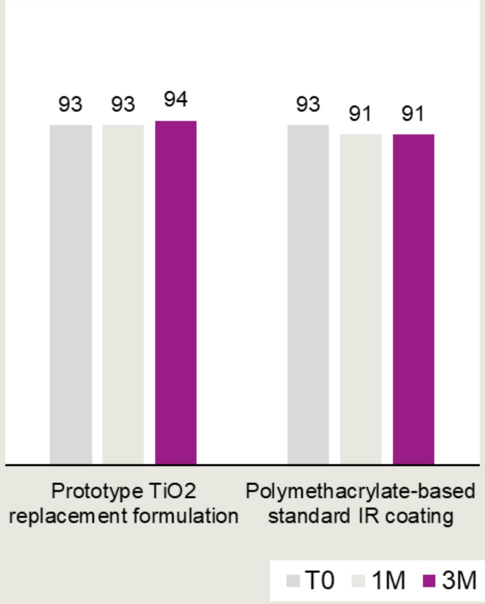


300 mg tablets (10 mm round biconvex) with 5% API loading (Theophylline monohydrate

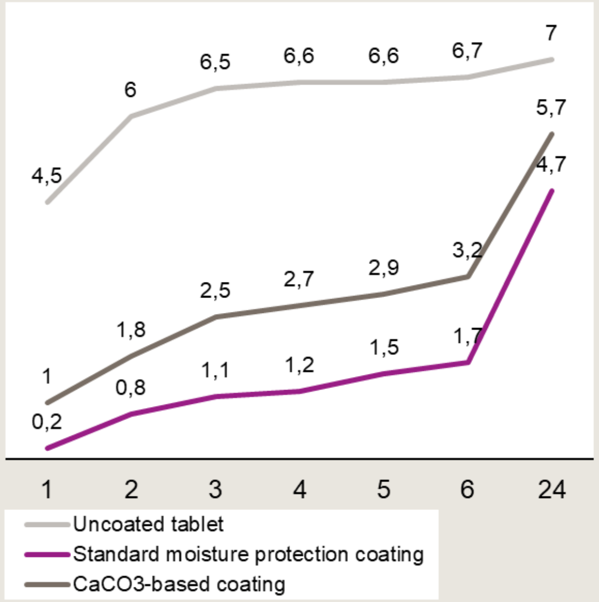
Influence of Calcium carbonate on functional coatings

Replacement of TiO_2 can modify film characteristics
Moisture protection is reduced

L-value on T0 and up to 3 months stability [40°C/75% RH]



Moisture uptake (%)
on silica tablets at 40°C/75% RH



- Target L-value for white coatings ≥ 85 is achieved also with polymethacrylate polymers
- Moisture uptake is slightly increased for $CaCO_3$ based coating, which brings additional challenge for functional coatings
- Impact on film characteristics must be taken into consideration when some functionality is expected.

Higher amount of opacifiers and combinations thereof tends to increase film permeability

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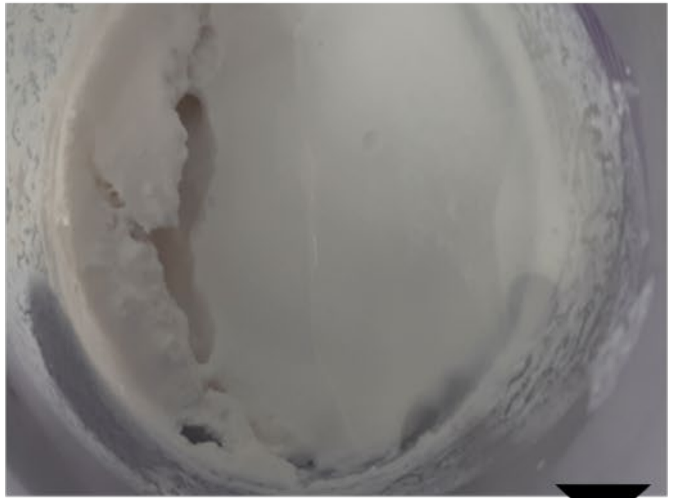
Compatibility of the excipients is key for enteric coatings

Ionic interactions are often observed due to enteric polymer characteristics

Challenges for enteric coatings

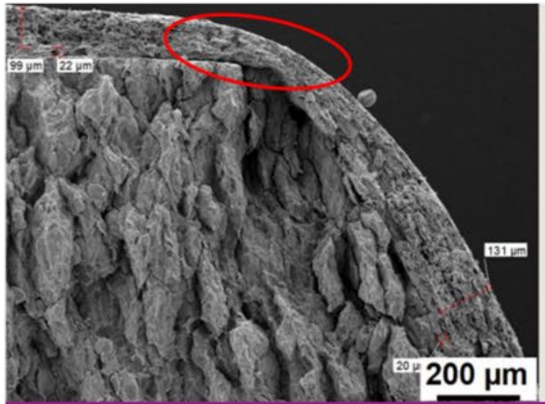


Alkaline excipients can interact with polymethacrylate polymers, leading to coagulation of the suspension.

Other ingredients can significantly reduce film flexibility.

$CaCO_3$ neutralizes polymethacrylate polymers, thus being inefficient for enteric application

- Interaction with alkaline material such as $CaCO_3$, ZnO, MgO and others due to ionic characteristics limits replacement options
- Permeability differences may also impact the replacement in sustained release coatings



Increased permeability due to more hydrophilic excipients is even more pronounced in the edges of the tablets, thus process parameters play a major role to avoid non-homogeneous coatings

For functional coatings, double layer still seems to be the most promising strategy

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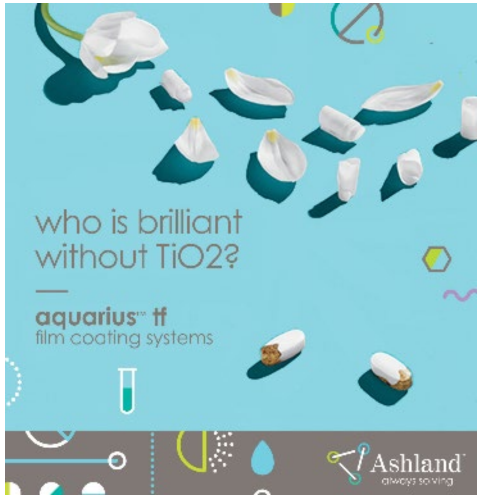
Conclusions

There are challenges, but …

Eudragit® ReadyMix

OPADRY® TF
TiO2 Free Formulated Film Coatings

SEPPIC
Sepifilm™ White TF
Sepifilm™ Naturally Colored PW



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