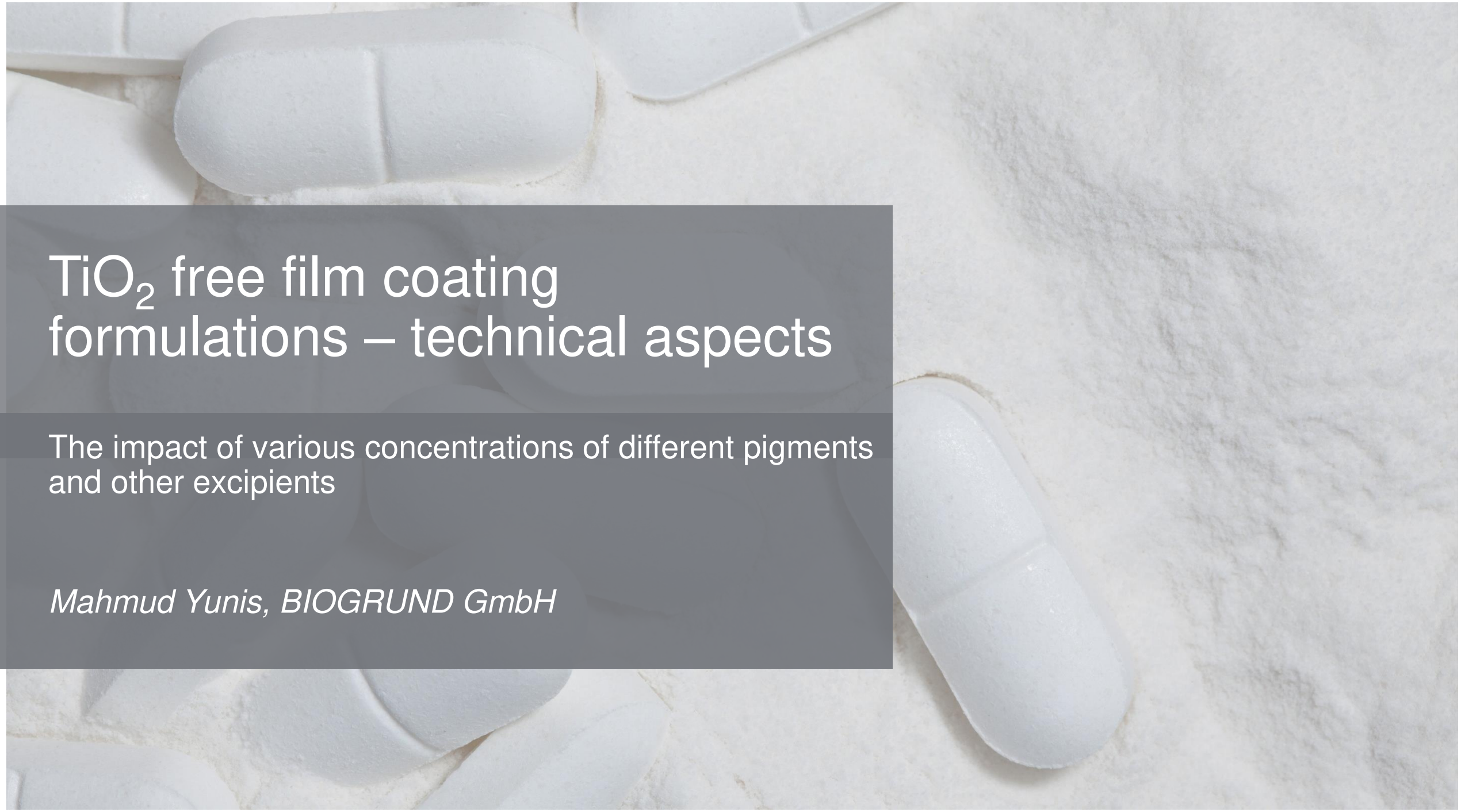


TiO_2 free film coating formulations – technical aspects

The impact of various concentrations of different pigments and other excipients

Mahmud Yunis, BIOGRUND GmbH

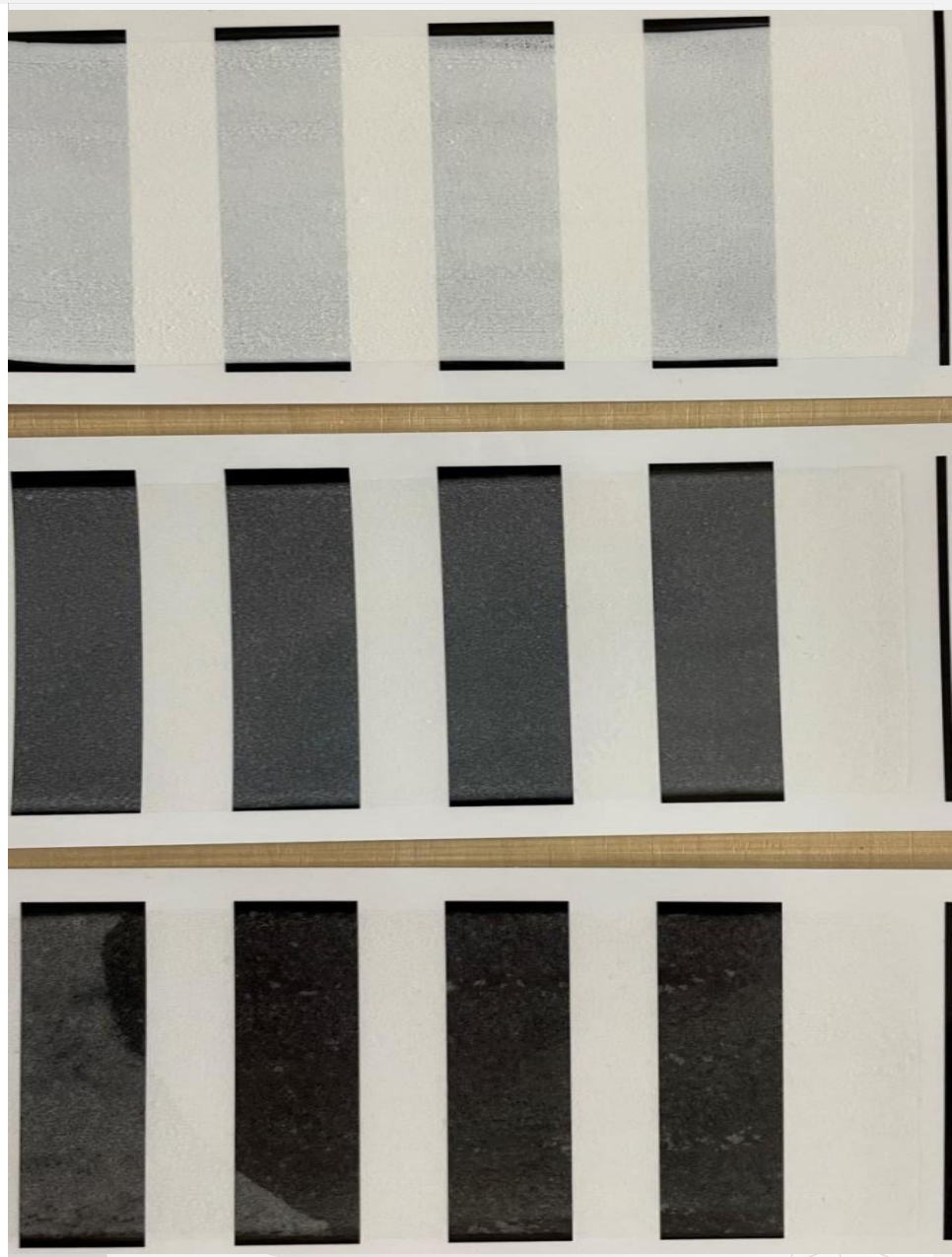
Titanium dioxide a critical excipient ?

- **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'



EU bans Titanium Dioxide (E171)

The regulation 2022/63 relating to the ban of titanium dioxide (TiO_2) has been published in the EU Official Journal. Until 7th August 2022, foods that contain E171 will be allowed on the market. After that date, E171 will be fully banned as food additive. However, foods that are already on the market may remain on the market until they reach their expiry date.

TiO_2 will remain on the list of approved additives for the time being to allow its use in pharmaceutical products. This will be reviewed within three years of the entry into force of this Regulation (February 7, 2025). During this time, the EU Commission encourages the pharmaceutical industry to accelerate the development of alternatives to replace TiO_2.

Challenges of TiO_2 free film coatings

... film coating users & manufacturers have to face several challenges by developing TiO_2 free film coating formulations

- Alternative raw materials require a higher content in a formulation compared to TiO_2 – there are only limited possibilities due to necessary amounts of functional excipients!
- Ensuring of comparable film coating functionality and film coating properties like TiO_2 containing formulations
- Key points: Brightness & opacity (L-Value), max 4% weight gain
- Ensuring a similar preparation and application of TiO_2 free film coatings

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TiO_2 containing standard

Standard formulation containing TiO_2 for comparison

Formula at 3 % WG	I
Opacity	++
Brightness	++
Film strength	114,5 g
Film surface/Appearance	-
Viscosity 15 % solid content (S.C.)	457 mPa*s

AP 014.32 MS

Excipient
Polymer
Plasticizer
Titanium Dioxide
Filler

- Formulation shows high opacity and brightness at 3% weight gain (wg), tablet edges are completely covered
- Formulation has a good film strength and can be sprayed at 15% S.C., though results show a rough film surface

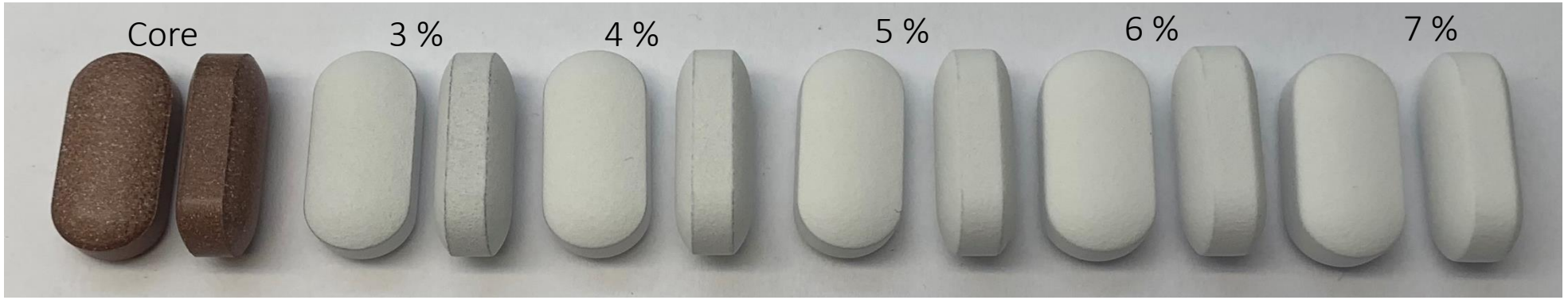
First series of tests

TiO_2-free formulations in comparison

Formula at 7 % WG	I
Opacity	+
Brightness	o
Film strength	19 g
Film surface/Appearance	o
Viscosity 15 % S.C.	1238 mPa*s

AP 00001 MS

Excipient
Polymer
Plasticizer
2 Pigments
Filler



- Formulation containing two different pigments/no calcium carbonate
  - From group: oxides/ sulphates/ carbonates/ phosphates/ silicates/ rice starch
- Formulation shows good opacity and moderate whiteness, at 7% wg tablet edges covered
- Formulation shows very low film strength

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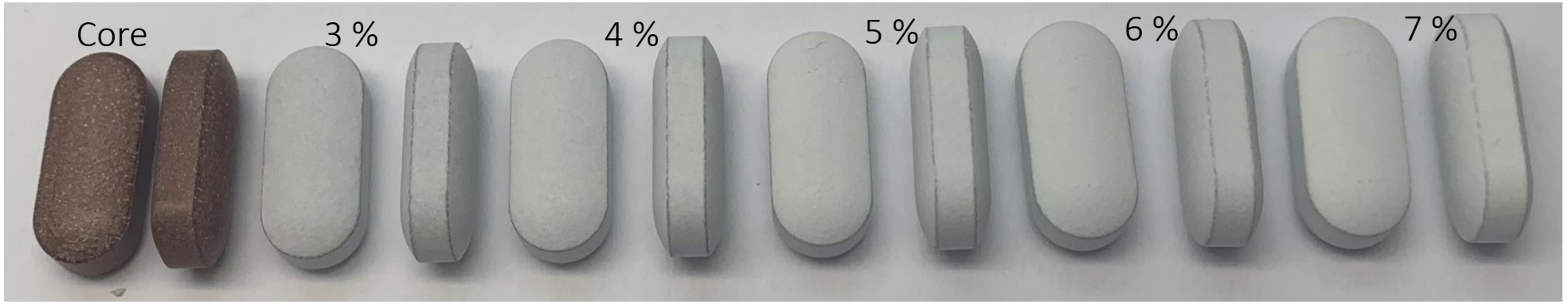
First series of tests

TiO_2-free formulations in comparison

Formula at 7 % WG	I
Opacity	-
Brightness	o
Film strength	127 g
Film surface/Appearance	+
Viscosity 15 % S.C.	666 mPa*s

AP 00002

Excipient
Polymer
Plasticizer
Calcium carbonate



- Formulation containing only polymer, plasticizer and calcium carbonate
- Formulation shows bad opacity and moderate whiteness, at 7% wg tablet edges are still not covered

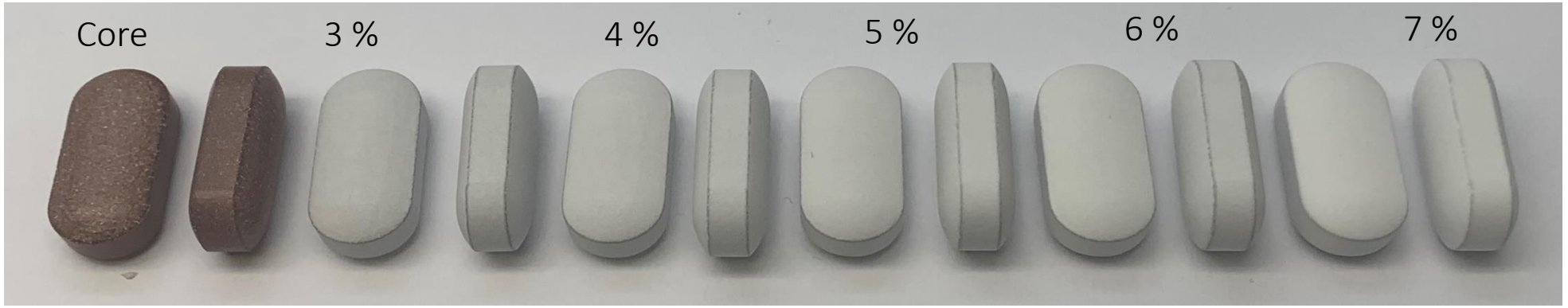
First series of tests

TiO_2-free formulations in comparison

Formula at 7 % WG	I
Opacity	-
Brightness	o
Film strength	Not measurable
Film surface/Appearance	+
Viscosity 15 % S.C.	194 mPa*s

AP 00003

Excipient
Polymer
Plasticizer
Calcium carbonate + additional pigments



- Formulation containing a mixture of calcium carbonate and additional pigments to enhance opacity
- Formulation shows bad opacity and moderate whiteness, at 7% wg tablet edges are still not covered

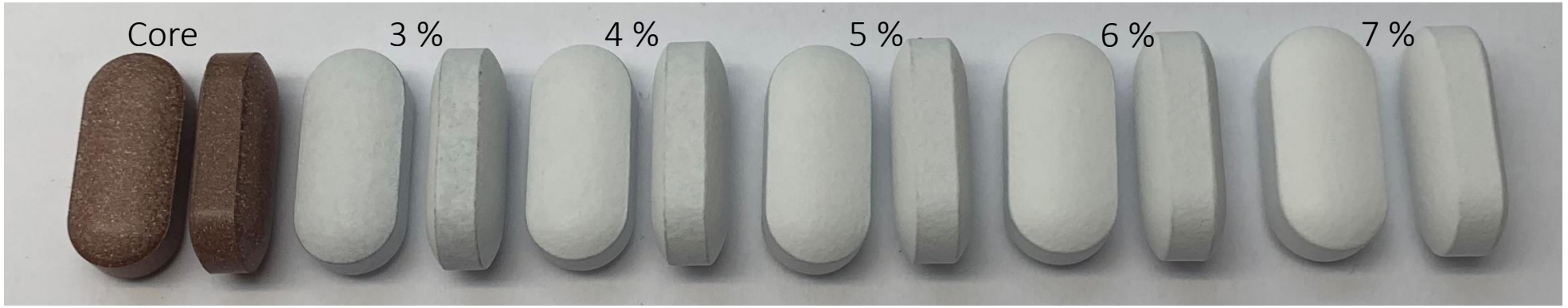
First series of tests

TiO_2-free formulations in comparison

Formula at 7 % WG	I
Opacity	+
Brightness	+
Film strength	88 g
Film surface/Appearance	+
Viscosity 15 % S.C.	1506 mPa*s

AP 00004

Excipient
Polymer
Plasticizer
Calcium carbonate
Glidant



- Formulation containing calcium carbonate and a glidant to improve tablet edge opacity
- Formulation shows good opacity and whiteness, at 6% wg tablet edges covered, viscosity is very high

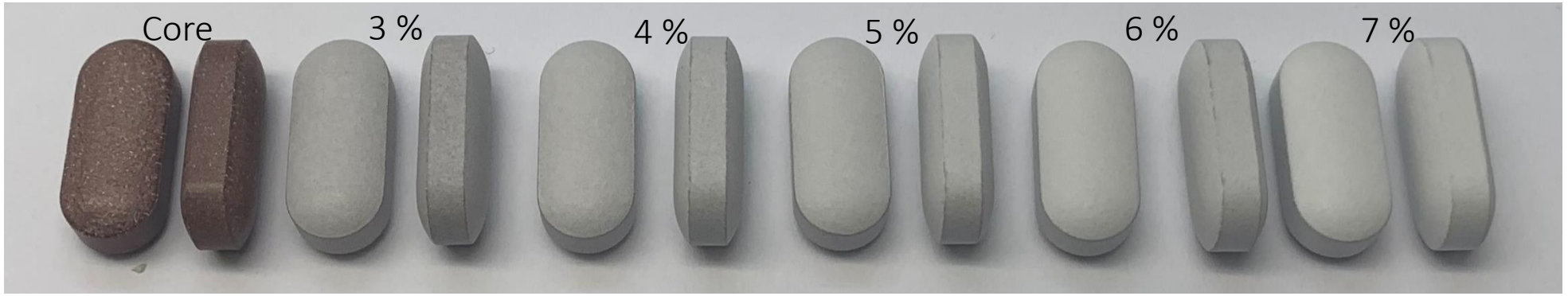
First series of tests

TiO_2-free formulations in comparison

Formula at 7 % WG	I
Opacity	-
Brightness	-
Film strength	158 g
Film surface/Appearance	o
Viscosity 15 % S.C.	331 mPa*s

AP 00005

Excipient
Polymer
Plasticizer
Calcium carbonate
2 different glidants



- Formulation containing two different glidants, supposed to intensify opacity and brightness of calcium carbonate
- Formulation shows mediocre opacity and bad whiteness, at 7% wg tablet edges are still not covered

First series of tests

TiO_2-free formulations in comparison

Formula at 7 % WG	I
Opacity	-
Brightness	-
Film strength	Not measured
Film surface/Appearance	o
Viscosity 15 % S.C.	Not measured

AP 019.XXX MS

Excipient
Polymer
Plasticizer
Calcium carbonate
Stabilizers

- Formulation containing only stabilizers, supposed to intensify opacity and brightness of calcium carbonate
- Formulation shows bad opacity and whiteness, at 7% wg tablet edges are still not covered and tablets are grey

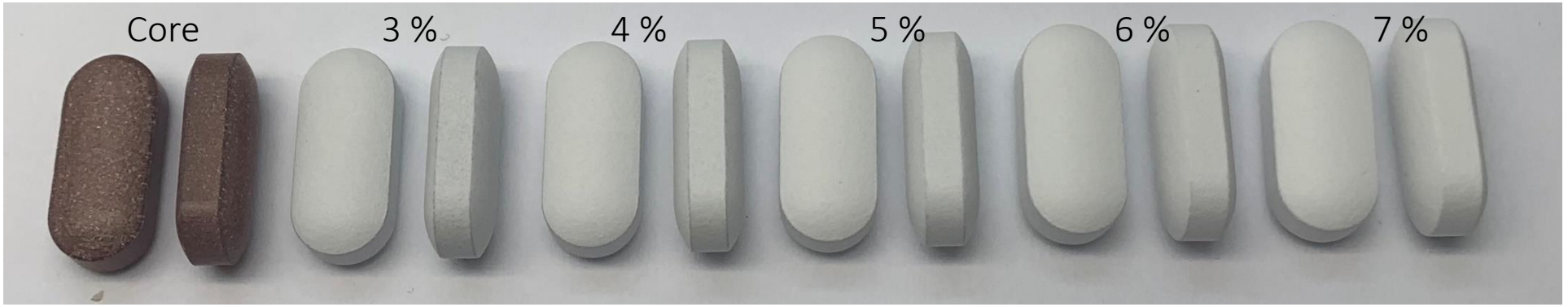
First series of tests

TiO_2-free formulations in comparison

Formula at 4 % WG	I
Opacity	+
Brightness	+
Film strength	117 g
Film surface/Appearance	+
Viscosity 17 % S.C.	409 mPa*s

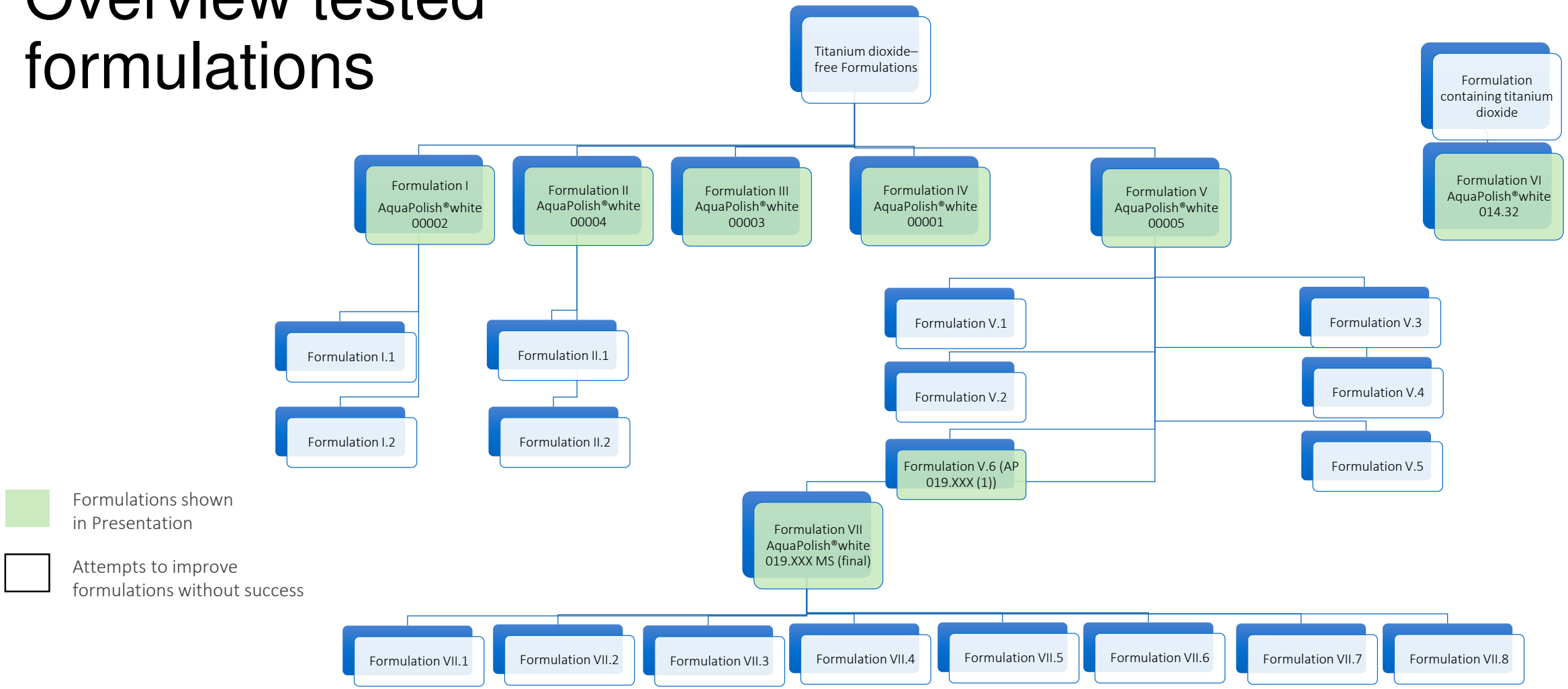
AP 019.XXX MS final

Excipient
Polymer
Plasticizer
Calcium carbonate
Stabilizers



- Formulation containing optimised amount of stabilizers
- Formulation shows good opacity and whiteness, at 4% wg tablet edges are covered and opacity can keep up with TiO_2 containing films

Overview tested formulations

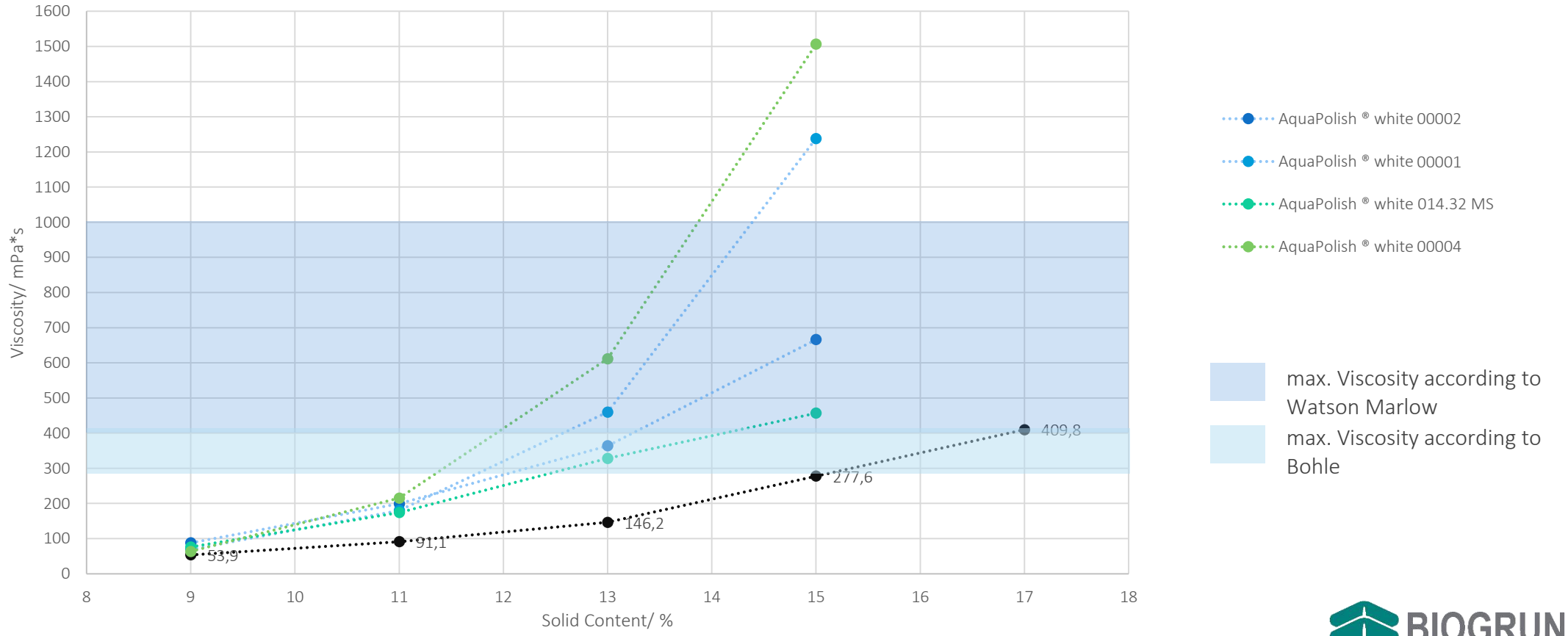


- Several attempts to further improve AP 019.XXX MS or other formulations (25 alternatives and nearly 200 combinations) showed no success

Comparison of viscosity

TiO_2-free formulations

- Formulation containing several pigments has the highest viscosity, can only be sprayed at 13% S.C.
- Compared to TiO_2 containing coating, AquaPolish® white 019.XXX MS shows lower viscosity, can be sprayed at 17% S.C or higher.
  → faster spraying process, lower cost of spraying



Comparison of results

TiO_2-free formulations

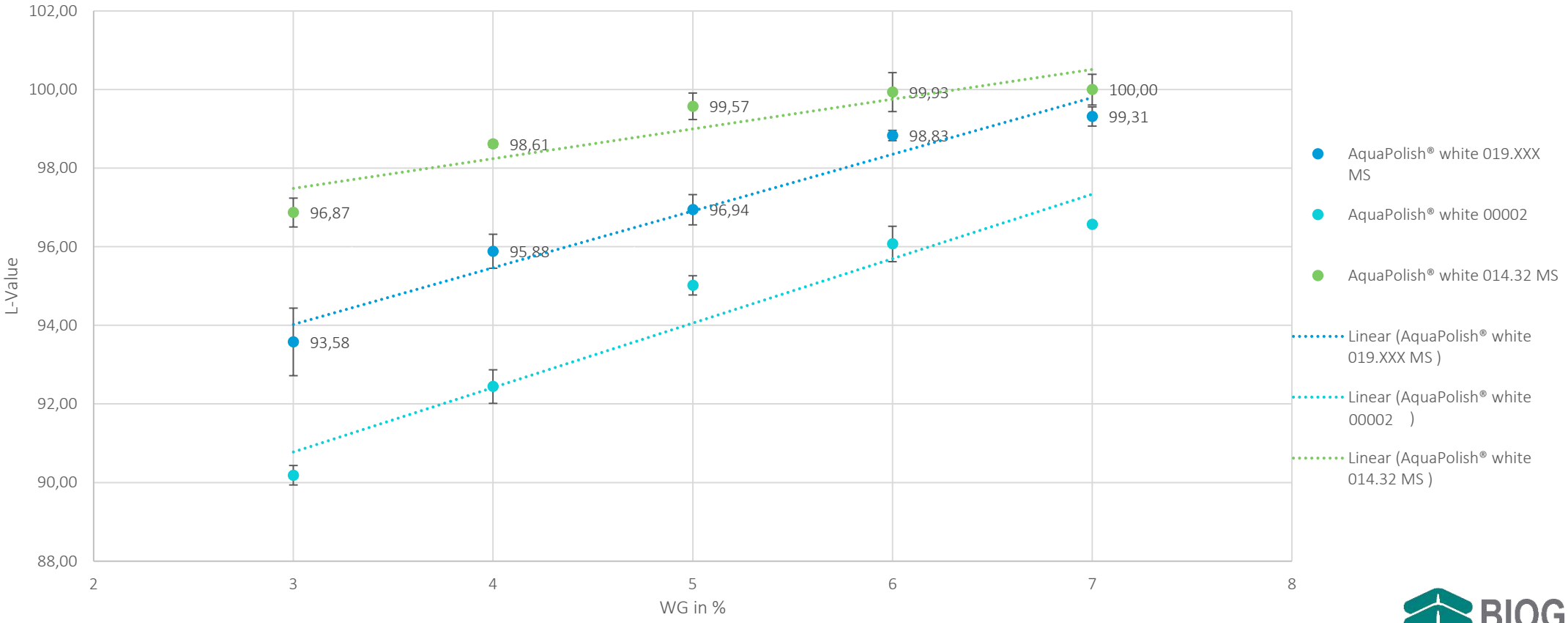
- 1. AquaPolish® 014.32 MS
- 2. AquaPolish® 019.XXX MS
- 3. AquaPolish® 00002

- 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

Comparison of L-Value

TiO_2-free formulations

- The lightness value, L defines black at 0 and white at 100.
- The gradient of the L-Value resembles the difference between the three coatings that can be seen by eye in the previous slide



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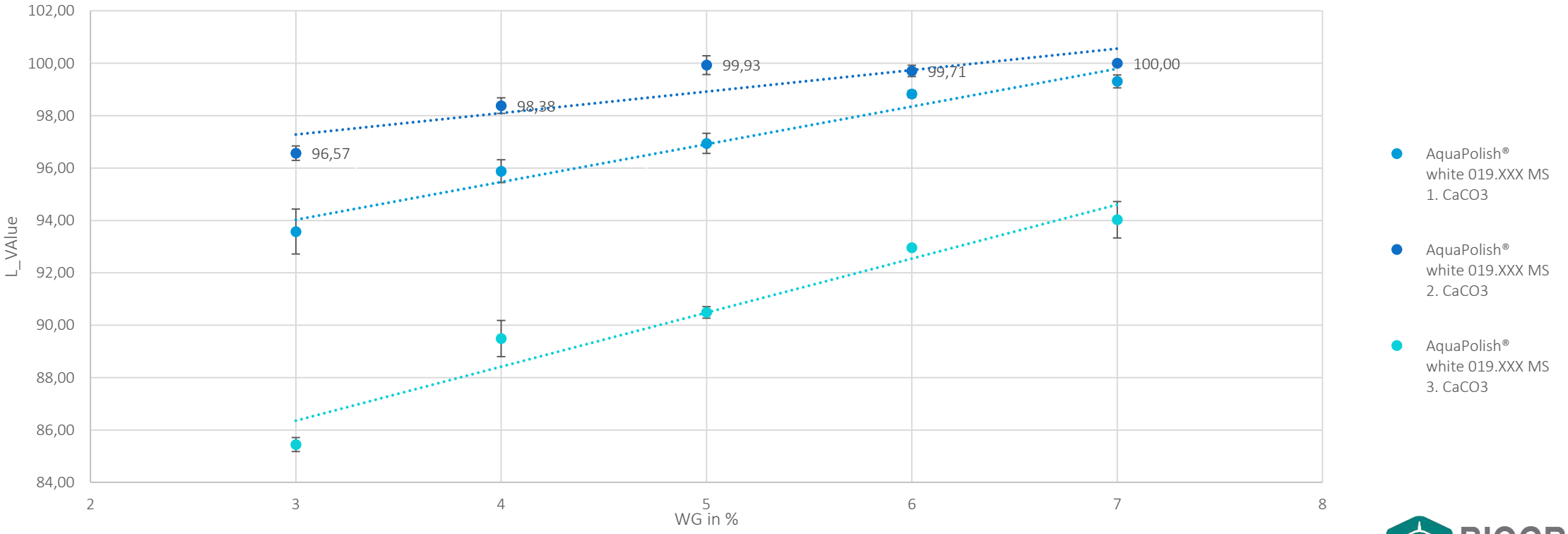
Comparison of L-Value – three different pigment manufacturers

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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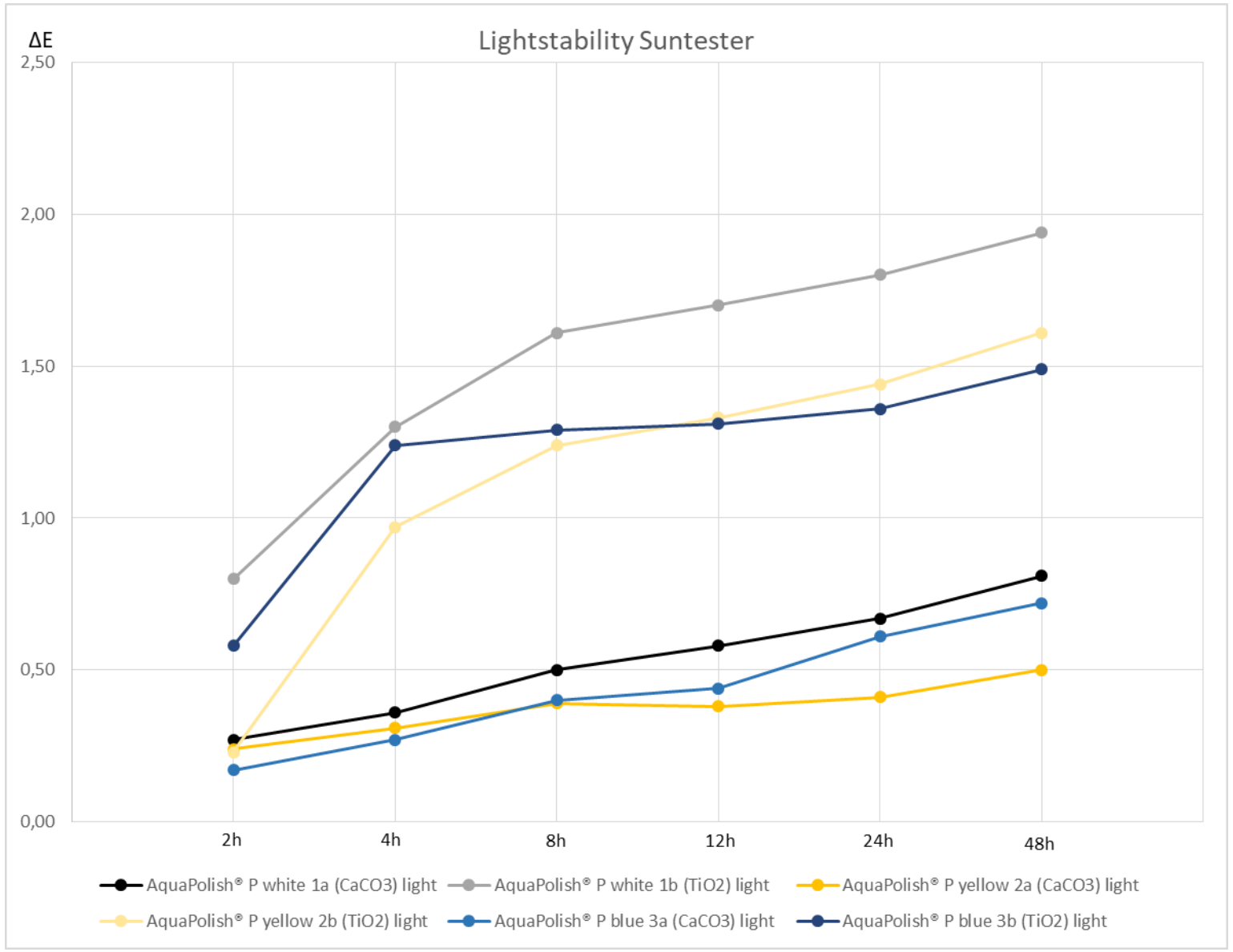
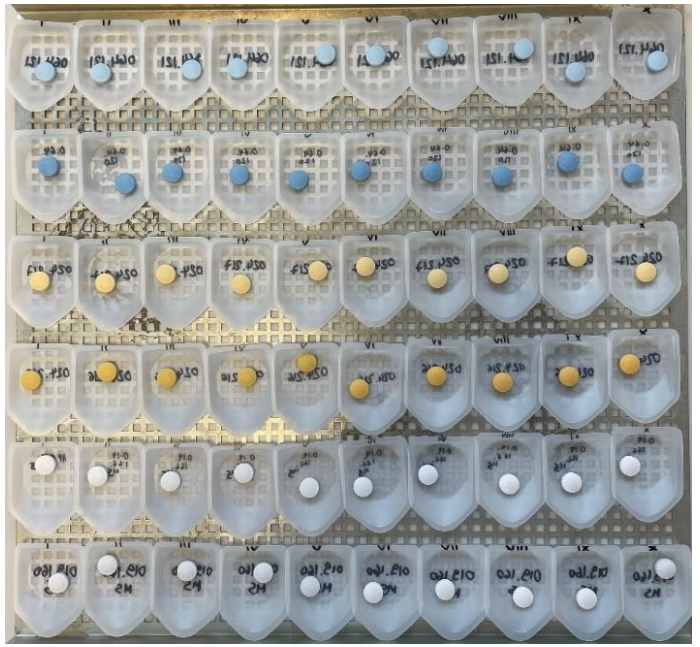
Stability of TiO_2-free formulations





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

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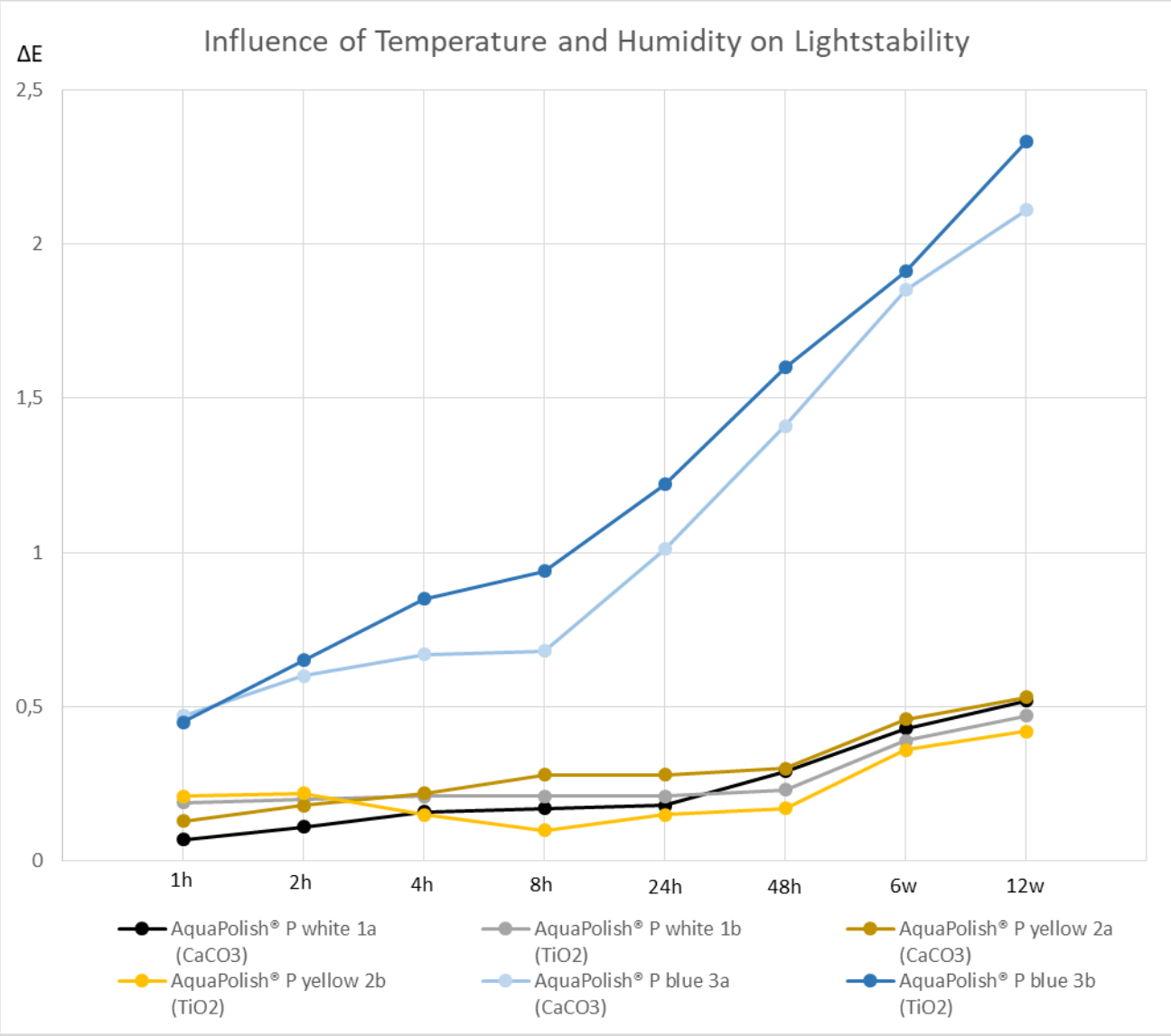
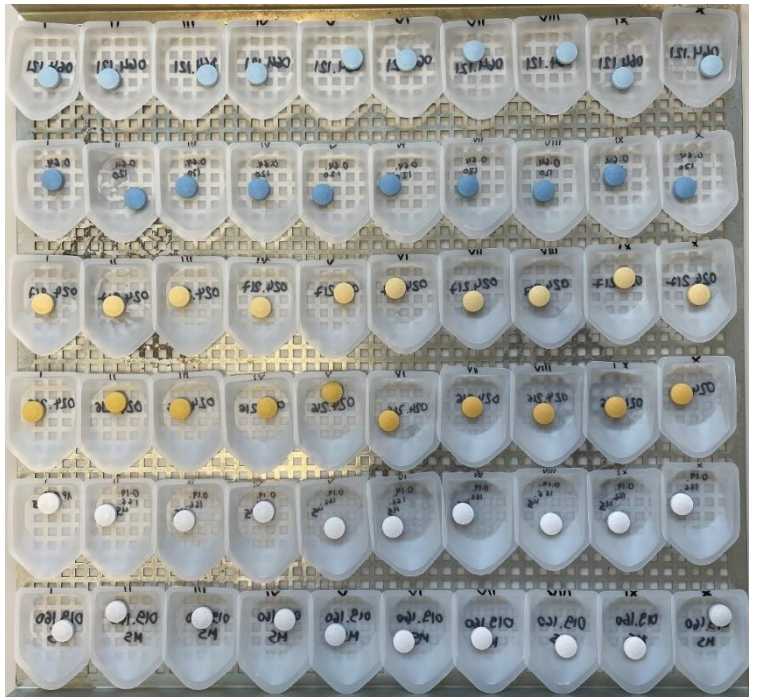
Stability of TiO2-free formulations





Duration	3 months
Temperature	40°C
rel. Humidity	75%

Conclusion

- White TiO_2 free formulations are available
- Comparable opacity & brightness can be achieved
- Study shows that 1:1 replacement is not possible
- Process Parameters can be improved with TiO_2 free formulation
- Comparable disintegration times
- pH of dispersion is slightly higher

- ➢ Calcium carbonate is **at the moment** the best suitable pigment for TiO_2 –free coatings
- ➢ Combining calcium carbonate and stabilizers clearly improves the opacity and brightness
- ➢ With AquaPolish® white 019.XXX MS a weight gain of almost 3 - 4% is sufficient
- ➢ Due to low viscosity AquaPolish® white 019.XXX MS can be coated at 17% S.C. or higher → decrease of process time and costs

Due to the combination of calcium carbonate and the right amount of stabilizers, a very good opacity can be achieved already at 3 - 4% weight gain. Thus, the film quality is comparable to TiO_2, the surface improves, and the lower viscosity improves the coating process and leads to lower costs.

Coloured TiO_2-free formulations

Conclusion

- White and coloured TiO_2 free formulations are available
- AP 019.XXX MS is not the only suitable formulation
- Different tablet cores can be coated

- ➢ BIOGRUND has a range of different TiO_2 free formulations
- ➢ Though having higher viscosity there are other formulations which ensure good opacity and whiteness
- ➢ Choosing from different BIOGRUND products the best formulation for respective cores should be selected

Due to the range of BIOGRUND ready-to-use TiO_2-free coating solutions, different tablet cores and coating processes can be managed successfully