Calcium carbonate as an alternative to titanium dioxide in coating: the importance of particle engineering

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Purpose

Based on a safety assessment of titanium dioxide (E171) by the European Food Safety Authority (EFSA)[1] regarding concerns about potential genotoxic effects, the EU Commission has withdrawn the authorization to use titanium dioxide in foods and dietary supplements.

The ban of titanium dioxide became effective in August 2022 based on the Commission Regulation (EU) 2022/63 and its removal from pharmaceutical products in the EU is now being considered.[2]

Objectives

Development of a calcium carbonate which addresses the need for both good opacity and process efficiency as a TiO_2 alternative in tablet coatings. This poster highlights how particle-engineering supports an optimal performance of calcium carbonate in coating application.

Methods

Scanning electron microscopy

Particle properties of the calcium carbonate were measured by scanning electronic microscopy (SEM): Tescan VEGA3 XMU, W cathode, low vacuum, high vacuum, accelerating voltage 0.2 kV to 30 kV, YAG BSE detector, SE detectors.

Powder x-ray diffraction

Powder x-ray diffraction (PXRD, STOE GmbH) was used to identify the crystalline structure; parameters: 40 kV, 40 mA.

Color card preparation

Color cards were prepared using a film cast unit from Moeller, CIK3-125-M. For the preparation of the coating solutions, a 20% PVA (polyvinyl alcohol)-based solution was mixed with different amount of $CaCO_3$ (Parteck® TA excipient, MilliporeSigma), 3,300 rpm, 2 min (Hauschild Engineering, SpeedMixer DAC 150). PVA: Parteck® COAT polymer, MilliporeSigma.

Viscosity measurement

The viscosity was measured with Thermo-Fisher Haake Mars Rheo 60 Measuring Geometry (P25/Ti Gap: 0.1 mm CR; $\dot{\gamma}$ 100.0 1/s; t 60,00 s; T 20.00 °C).

Tablet preparation

Composition of core tablet formulation: 98.5% mannitol containing core tablets with 1.5% lubricant produced with 11.0 mm round on SC punches. The white tablet cores were coated with a coating suspension with 10% w/w iron oxide black in an aqueous medium with 5% w/w weight gain to create black tablet cores.

Color measurements

In this study the CIE-Lab-based method was used to measure the tablet colors. The 3D color space is defined by the axes L*, a* and b* with each representing a quantitative measurement of L* (lightness), a* (redness-greenness) and b* (blueness-yellowness). The L* value of 100 refers to the ideal absolute white color, whilst the L* value of 0 refers to the ideal absolute black.

Results

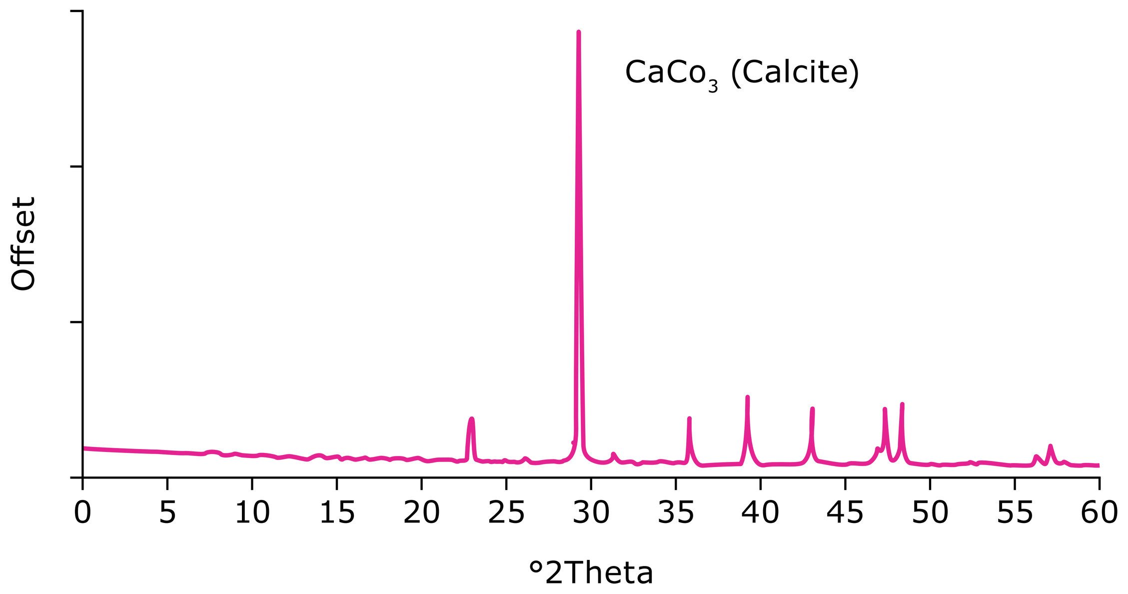

Figure 1.
Specific pattern of crystalline Parteck® TA (calcium carbonate) in diffractogram measured by powder x-ray diffraction (PXRD, STOE GmbH); parameters: 40 kV, 40 mA.

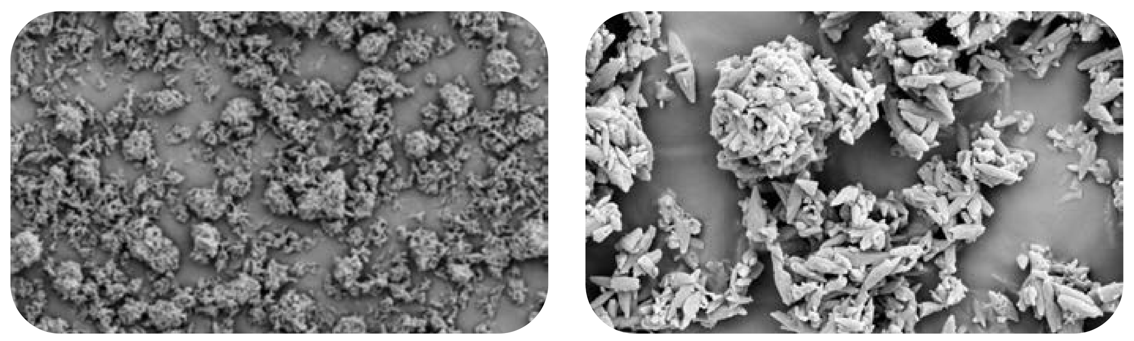

Figure 2.
Ground range images of Parteck® TA in 2 resolutions taken by scanning electron microscopy (SEM).

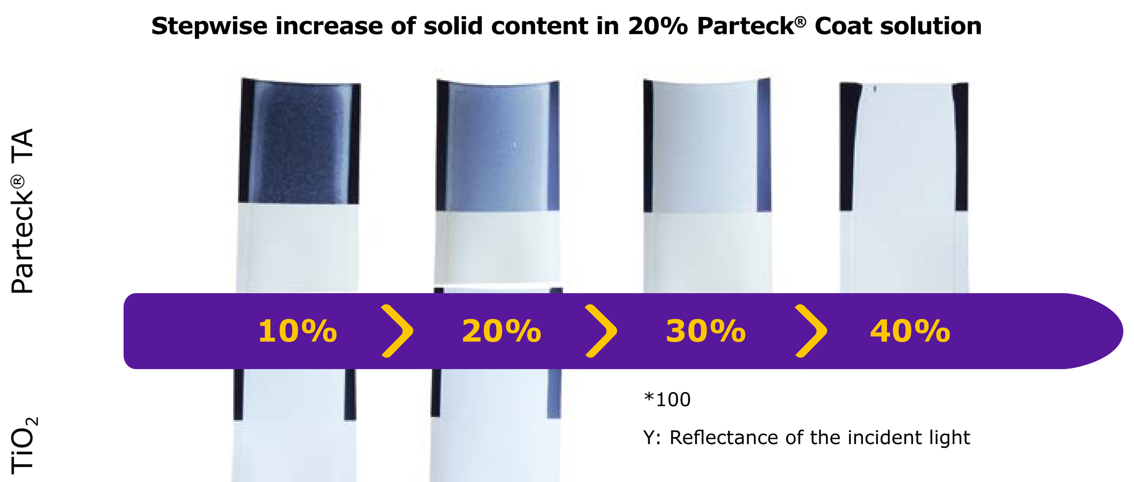

Figure 3.
Visual comparison of films with TiO_2 and Parteck® TA via color cards.

The CIE-Lab or CIE L* a* b*:

Quantitative measurement and relationship of colors.

Colorimeric values:

L axis: lightness
a axis: red-green values
b axis: yellow-blue values

- Identification of any color
- Quantification of color differences

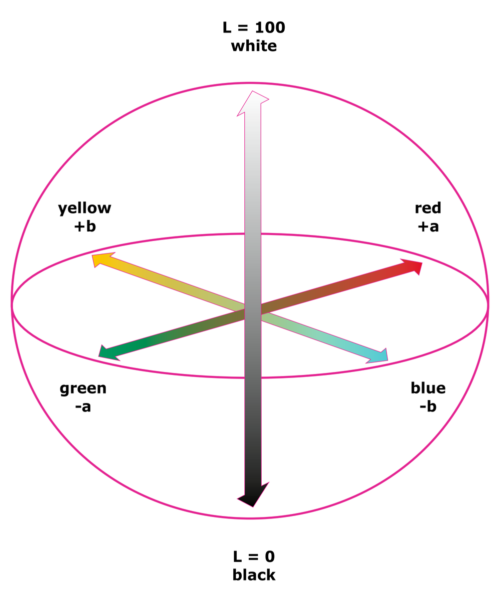

Figure 4.
The CIE-Lab 3D color space as devised by the International Commission on Illumination.

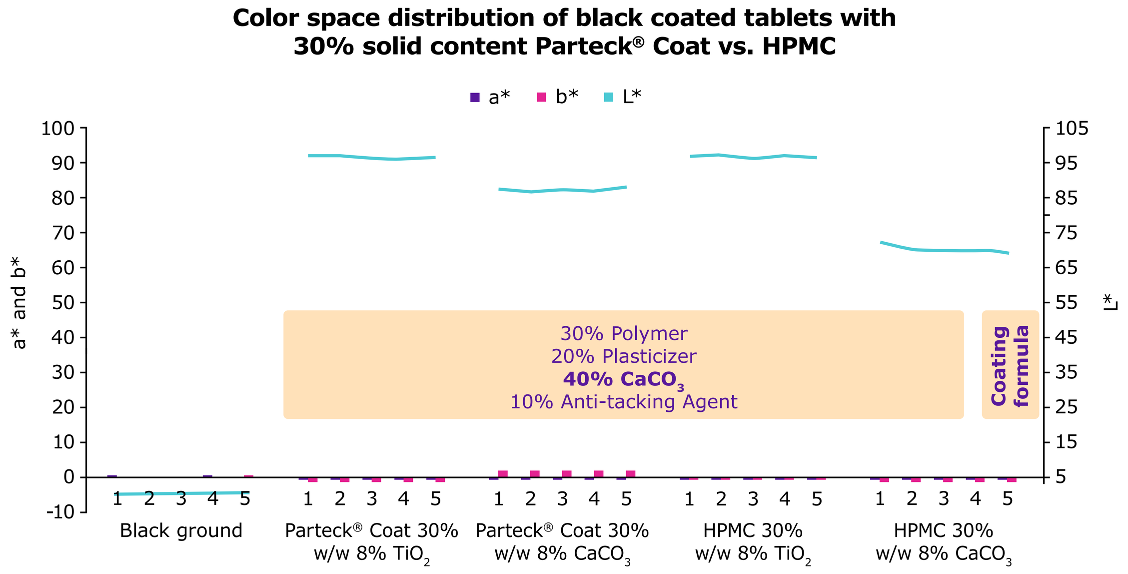

Figure 5.
Comparison of color measurement of various tablet coatings containing either PVA or HPMC.

Despite a higher solid content of $CaCO_3$ in the solution, which is necessary for comparable coating results in some cases, the particle engineered $CaCO_3$ has no influence on viscosity in comparison to basic PVA coating solutions with TiO_2 (Tab. 1). According to the results for the coated core tablets, a weight gain of 5–8% can lead to a good opacity and a good covering of the initial black tablet cores (Fig. 5 and Tab. 2).

Sample	Ingredients	Dyn. Viscosity (mPa·s)
Basic	6% Parteck® COAT Solution	10
1	Parteck® COAT + 4.5% Parteck® TA	13
2	Parteck® COAT + 8% Parteck® TA	19
3	Parteck® COAT + 8.0% TiO_2	39
Basic	6% HPMC Solution	41
4	HPMC + 4.5% Parteck® TA	78
5	HPMC + 8.0% Parteck® TA	91
6	HPMC + 8.0% TiO_2	114

Formulation of the coatina solutions 1–6: polymer (6%), triethyl citrate (3–4%), talc (1.5–2.0%), pigment (4.5–8.0%)

Table 1.
Viscosity of coating solutions with Parteck® TA vs. TiO_2.

Iron oxide black film-coated tablet	30% w/w solid content, 8% w/w weight gain ^		25% w/w solid content, 8% w/w weight gain ^	
	Titanium dioxide (FC-007-22-TiO_2)	Calcium carbonate (FC-007-22)	Titanium dioxide (FC-008-22-TiO_2)	Calcium carbonate (FC-008-22)
black colored coated round-shaped tablets, plain on both tablets sides	White to off-white colored coated round shaped tablets, plain on both tablets sides			

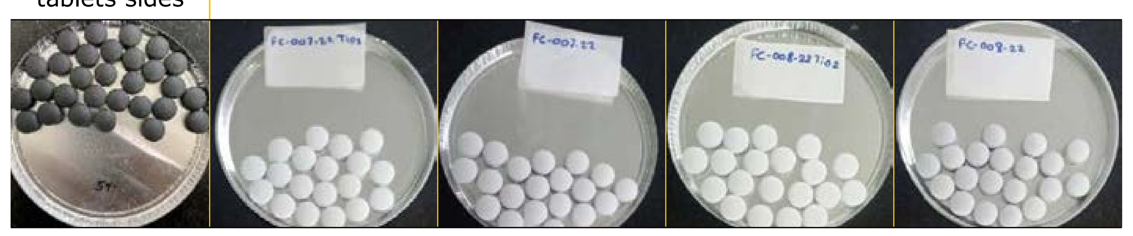

Table 2.
Coating trials with Parteck® TA vs. TiO_2 using black tablet cores.

References

1. European Food Safety Authority (EFSA), Safety assessment of titanium dioxide (E171) as a food additive, adopted 25 March 2021. EFSA Journal Volume 19 (May 2021).
2. Commission Regulation (EU) 2022/63 of 14 Jan 2022. Official Journal of the European Union L 11/1 (18 January 2022).

Conclusions

It could be demonstrated that a defined particle size distribution as well as a unique crystalline structure of the calcium carbonate enable a uniform finishing and good opacity. For strong pre-colored core tablets, a higher amount of calcium carbonate is required to achieve a level of covering comparable to titanium dioxide containing film coatings (Tab. 2). The low viscosity of the spraying liquid at higher solid contents helps to maintain a good process efficacy (Tab. 1). When combined with the PVA-based polymer, enhanced opacity can be achieved compared to standard HPMC formulations (Fig. 5). Use of screening methods via film casting can enable formulators to rapidly assess the performance of film coating formulations (Fig. 3) The proposed color measurement technique represents a suitable tool to quantify opacity and whiteness and can be utilized to optimize the final finishing in the formulation development.

Sample	Parteck® TA	C1	C2	C3	C4
Particle size/d50 (µm)	3	2	1	19	22
Particle size/d90 (µm)	8	5	5	39	44
BET spec. surface (m²/g)	3.8	12.0	10.8	0.3	0.3

Table 3.
Particle size distributions of Parteck® TA and several competitors C1–C4.

The benchmark overview of calcium carbonate grades shows that the particle engineered $CaCO_3$ provides a specific pattern of crystallinity in the diffractogram which corresponds to the morphology of calcite with rhombohedral structure and frequently hexagonal crystals (Fig. 1 and 2). The unique particle size distribution (PSD range) enables good opacity and surface characteristics (Tab. 3).

Overview	Parameter	Weight before coating [mg]	Weight before coating [mg]	Friability [%]	Hardness [N]	Disintegration time [sec]
Core	98% mannitol Core 0,5% iron oxide 1,5% magnesium stearate	500	/	0.29	266	325
Parteck® TA	30% Parteck® TA 3% weight gain	500	514	0.01	353	393
	30% Parteck® TA 5% weight gain	500	527	0.01	304	483
	40% Parteck® TA 5% weight gain	500	527	0.01	334	493
	40% Parteck® TA 8% weight gain	500	543	0.01	326	536
	Exemplary maximum loaded 40% Parteck® TA ~20% weight gain	500	611	0.0	326	643
TiO_2	40% TiO_2 5% weight gain	500	527	0.01	314	429

Table 4.
Tablets with PVA coating and Parteck® TA vs. TiO_2 (5% WG) Overall, the galenical values are in a similar range.

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The Life Science business of Merck operates as MilliporeSigma in the U.S. and Canada.

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