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White Paper

Calcium carbonate as a replacement for titanium dioxide in coating: the importance of particle engineering

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Uniform colored and white coatings applied to tablets create a homogeneous appearance across batches, improving aesthetics and patient compliance. Titanium dioxide is used extensively in solid dosage forms for this purpose, serving as an opacifier and colorant. Due to its high refractive index, it provides highest opacity and coverage for a coating.

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European Food Safety Authority (EFSA)[1] regarding concerns about potential genotoxic effects, the EU Commission has withdrawn the authorization to use titanium dioxide in foods and dietary supplements.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] A possible ban would have a major impact as it is estimated that 91,000 human medicinal products contain titanium dioxide.[3] Given these regulatory trends, there is a need to identify sustainable replacements for titanium dioxide.

With the current approval status as the only other white drug colorant in the EU, calcium carbonate is seen as the most likely alternative. Parteck® TA excipient – a calcium carbonate with a defined morphology and particle size distribution – has been developed for use in tablet film coatings and addresses the need for both good opacity and process efficiency.

This white paper highlights how particle engineering supports an optimal performance of calcium carbonate in coating applications, comparing Parteck® TA excipient to the industry benchmark titanium dioxide.

Physical Properties and Characterization

Selection of a suitable grade of calcium carbonate for coating formulations requires detailed understanding of the role particle morphology and particle design play in the development process.

The opacity of white pigments is largely due to their ability to scatter incident light. Scattering depends on several factors including the optical properties of the particles and their particle size, shape, surface structure, spatial orientation, and particle arrangement.[4]

In this study, Parteck® TA calcium carbonate was characterized by scanning electron microscopy (SEM) and powder x-ray diffraction (PXRD). The particle-engineered product provides a unique particle morphology as demonstrated in the SEM images (Figure 1).

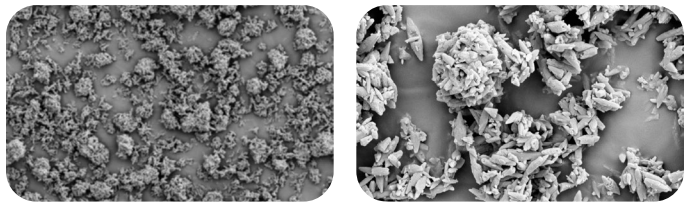

Figure 1.
Ground range SEM images of Parteck® TA excipient.

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Its specific pattern in the diffractogram corresponds to the morphology of calcite with rhombohedral structure and frequent hexagonal crystals as confirmed by PXRD measurements (Figure 2).

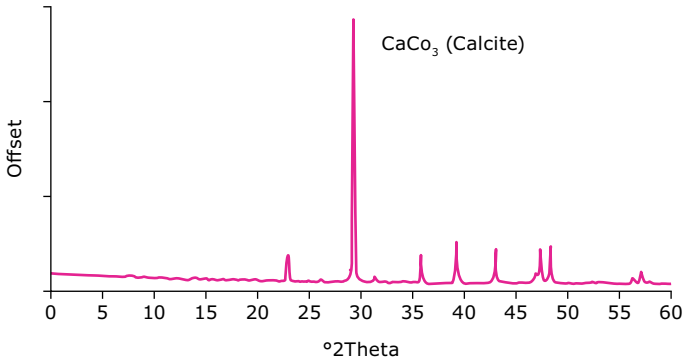

Figure 2.

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

Good coverage of tablet cores can be achieved by an optimized range of the particle size distribution (PSD, Figure 3 and Table 1); a reduction of the particle size to a certain extent can increase the light scattering properties and thus the opacity of the particles.[4] As an additional benefit, a defined PSD can ensure a consistent performance and minimize batch-to-batch variation.

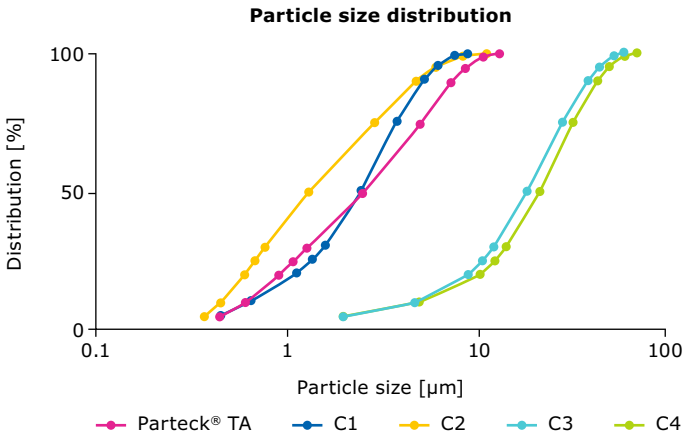

Figure 3.

Particle size distribution of Parteck® TA excipient compared to other marketed calcium carbonate (C1–C4) measured by laser diffraction with a Malvern Mastersizer 2000.

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

C1–C4: Calcium carbonate products from other suppliers.
Typical technical data for general characterization.
Specification of Parteck® TA available at SigmaAldrich.com

Table 1.

Particle sizes and BET specific surface areas of Parteck® TA excipient vs. other market samples (C1–C4). Particle size measured using laser diffraction; particle surface measured according to BET (Brunauer, Emmett and Teller) using nitrogen adsorption method.

Pre-screening with drawdown cards

To streamline the film coating development process and formulation design, dedicated screening methods can be used. Film casting on defined color cards allows rapid assessment of opacity at small scale without the necessity of coating trials. The opacity equates to the hiding power of a pigment, whereas the opacity degree of a film is defined by the ratio of the reflectance of the incident light on a black and a white background. In the case of a complete coverage of the black color card, the opacity is 100%.

Figure 4 shows results of a pre-screening step, conducted with films drawn on black and white cards. In comparison to titanium dioxide containing films, a similar coverage could be achieved with Parteck® TA excipient by using higher concentrations.

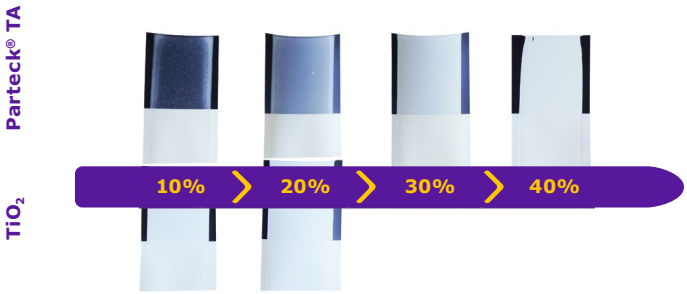

Figure 4.

Visual comparison of films with titanium dioxide and Parteck® TA excipient on drawdown cards.

Basis formulation: Parteck® COAT solution (20%)
Thickness of the film: 0.08–0.15 mm
Card film applicator: Moeller, CI-K3-125-M

Application in tablet film coatings

For the simulation of colored drug substances, core tablets were manufactured with a content of 0.5% red iron oxide. This approach mimics a challenging scenario presented by strong colored, heterogeneously distributed drug substance within the tablet core. The coating processes were performed in a rotating drum coater type LDCS (Vector Freund Corporation). For the comparative study, it was the purpose to investigate the coverage of the film coatings, the distribution on the tablet surface and galenical properties of the coated tablets.

Tablet cores:

Standard formulation: 98% mannitol, 1.5% magnesium stearate, 0.5% red iron oxide

Red iron oxide: Used to demonstrate the opacity performance

Convex tablets: 500 mg weight, 11 mm diameter; tabletting performed with tablet press Fette 1200i (Fette Compacting GmbH)

Coating suspension:

10% talcum, 20% triethyl citrate; the amount of HPMC and Parteck® COAT (PVA) was adapted to the individual formulations

Coverage of the film coatings

Enhanced coverage of the core tablets can be achieved by an increased tablet weight gain (Figure 5). A weight gain of 5–8% was typically sufficient to cover most of the strongly colored drug substance. A loading limit of up to 20% tablet weight gain was evaluated for information purposes.

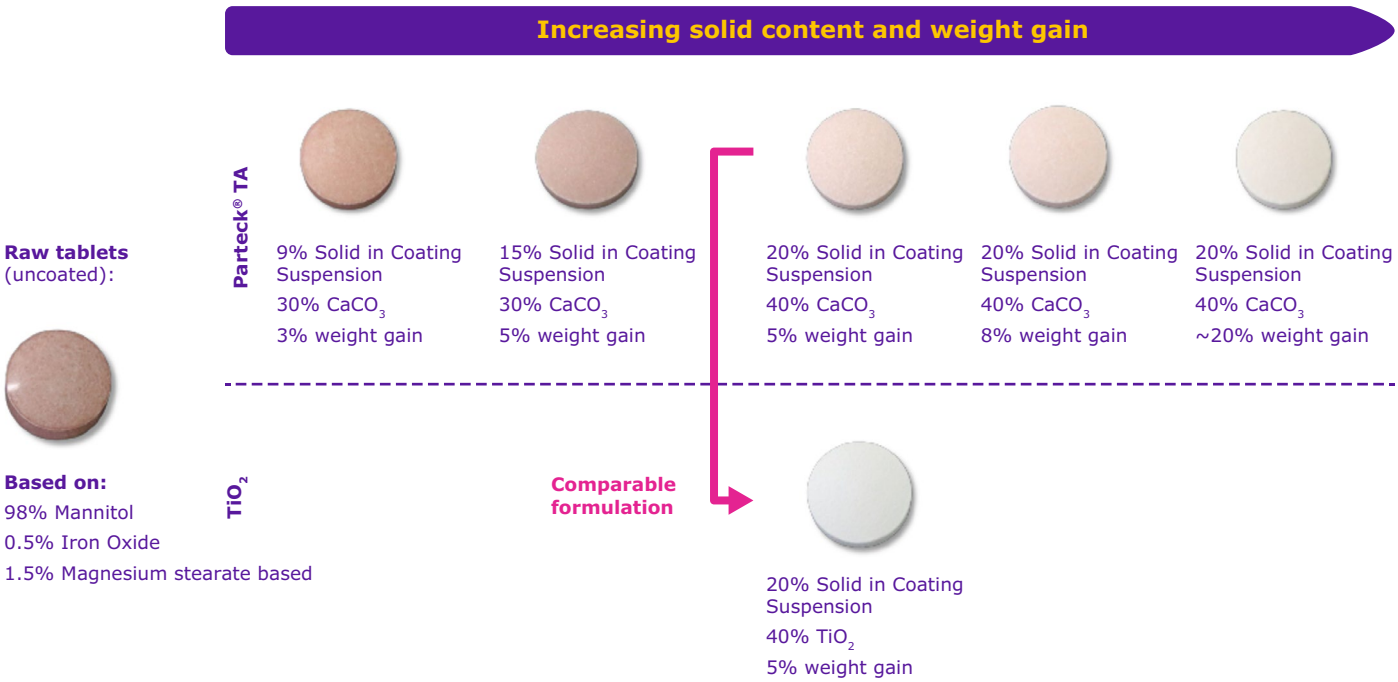

Figure 5.

Visual appearance of titanium dioxide and calcium carbonate containing tablets with increasing solid content and weight gain.

Distribution on tablet surface

SEM photos of the surface and the cut of the tablet show a homogeneous distribution of the calcium carbonate particles in the coating (Figure 6) and over the entire coating area.

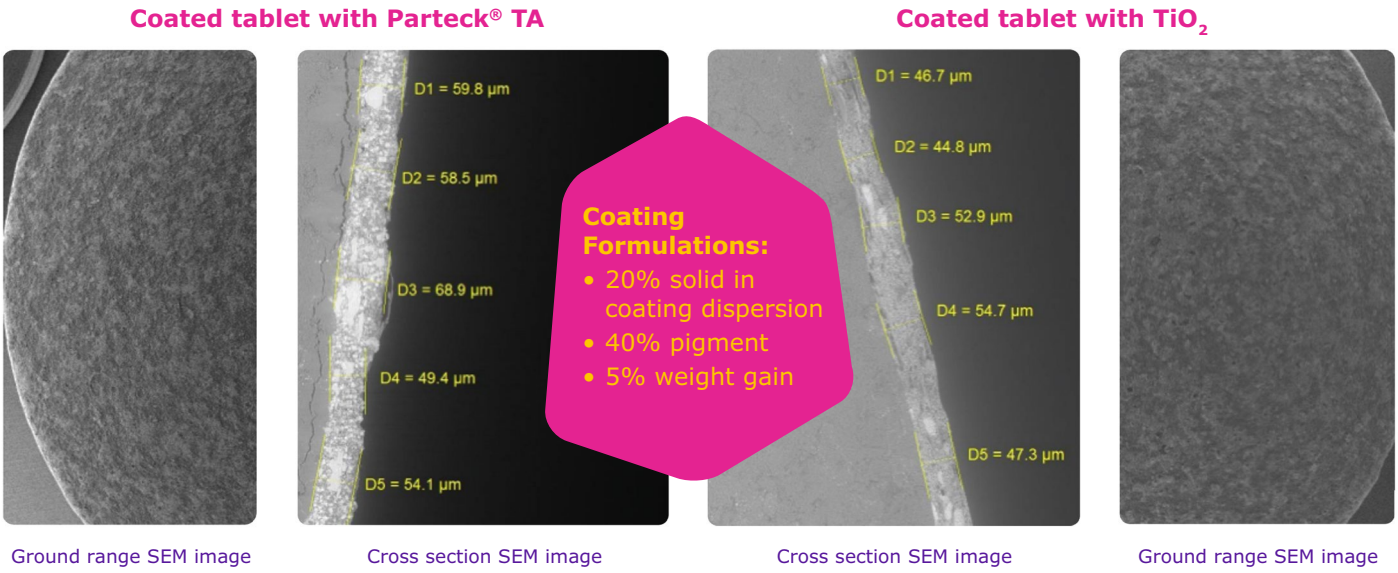

Figure 6.

Ground range and cross section SEM images of tablets coated with Parteck® TA excipient and titanium dioxide.

Galenical properties

According to the study results the galenical properties of tablets with Parteck® TA calcium carbonate (5% weight gain) were similar to the tablets with titanium dioxide (5% weight gain). No impact on friability or tablet hardness was observed (Table 2).

Overview	Parameter	Weight before coating [mg]	Weight after coating [mg]	Friability [%]	Hardness [N]	Disintegration time [s]
Core	98% mannitol 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 2.

Galenical parameters of tablets with Parteck® TA calcium carbonate and titanium dioxide; coating: PVA-based Parteck® COAT excipient.

Color Measurements

The CIELAB system is a mathematical model for the purpose of numerically describing all colors visible to the human eye. It was devised by the International Commission on Illumination (CIE: Commission Internationale d'Eclairage) and has become the universally accepted colorimetric reference system for quantifying and communicating color.

In this study the CIELab-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 lightness (L*), 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 (Figure 7).

Color measurements of tablets coated with Parteck® TA calcium carbonate and titanium dioxide allow a comparison of the two pigments regarding lightness L* and the chromaticity indices a* and b*. For the study, a Konica Minolta Spectrophotometer CM-700d was used for the measurement.

The impact of the tablet weight gain on these parameters is shown in Figure 8. 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 red and yellow colorings observed in the initial tablet cores.

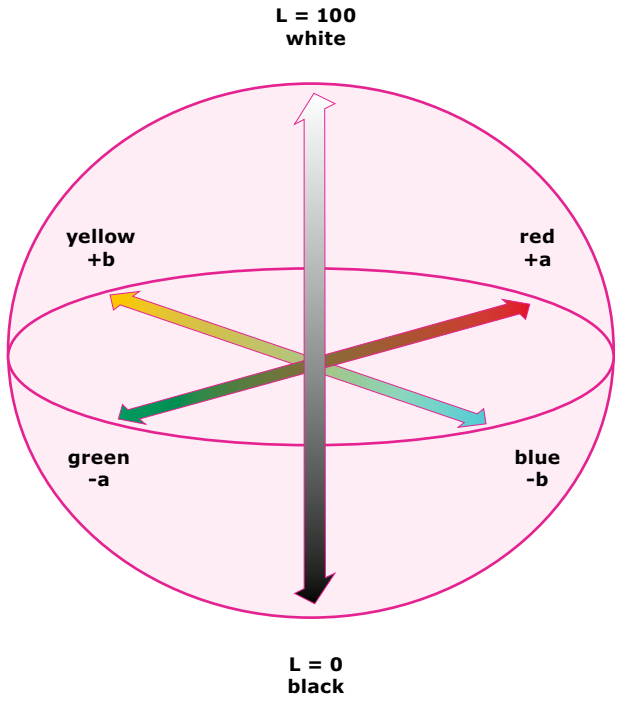

Figure 7.

The CIELab 3D space: The opponent color model.

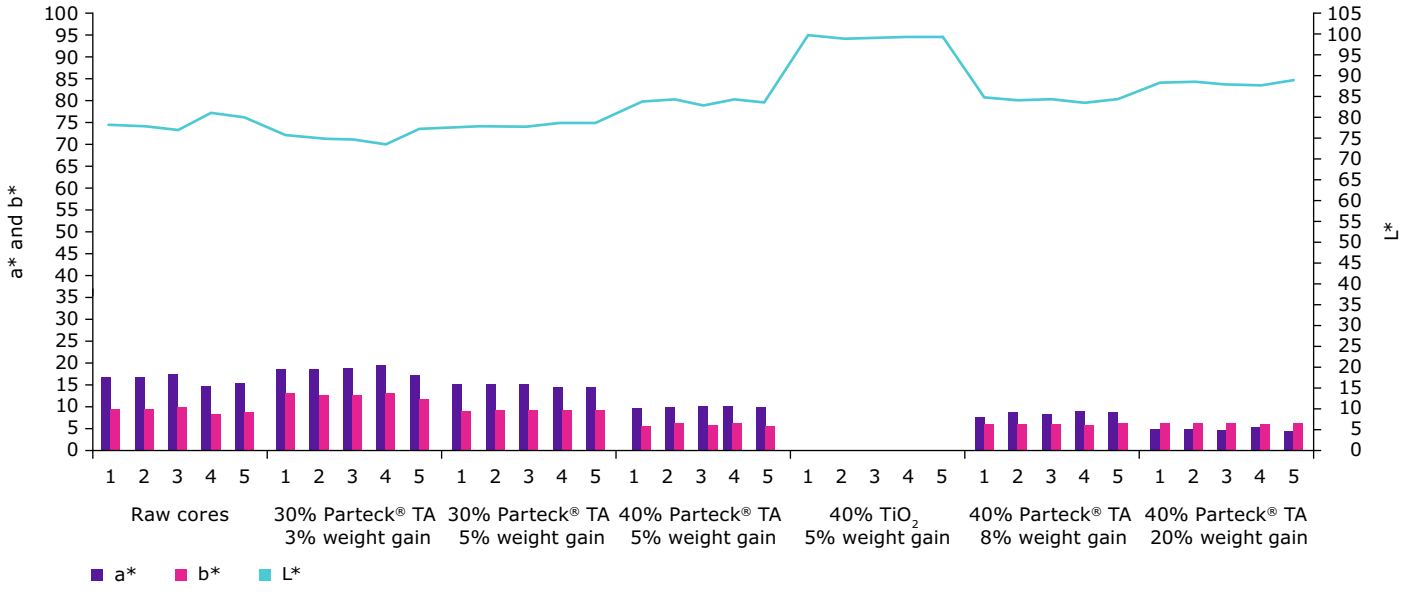

Figure 8.

CIElab values of coated tablets in dependence of increasing weight gains of Parteck® TA excipient vs. titanium dioxide.

Film coating formulation: based on Parteck® COAT excipient.

Color measurements of coated tablets with Parteck® TA excipient in comparison with other available calcium carbonate products were also conducted.

In comparison to the marketed products denoted earlier as C1–C4, the measured L* values of Parteck® TA excipient are in the top range and demonstrate good opacity (Figure 9).

Film coating formulation:

- **Parteck® COAT** solution (20%)
- pigment (40%)
- weight gain (8%)

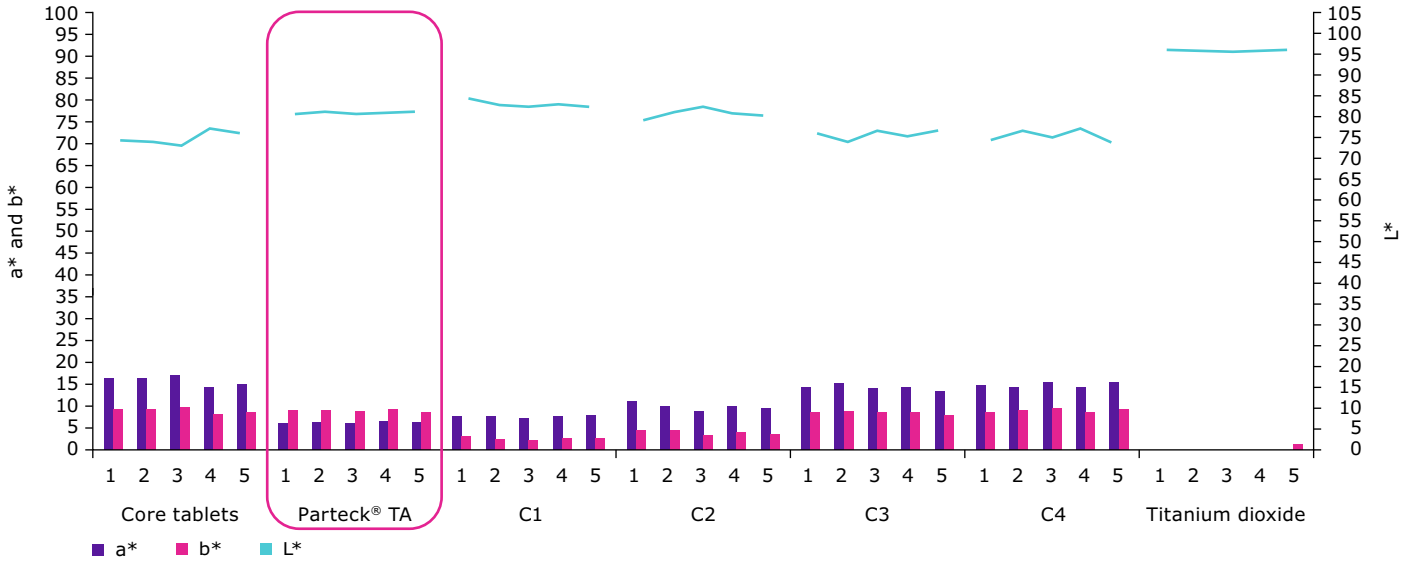

Figure 9.

CIElab values of coated tablets with Parteck® TA excipient vs. other market samples (C1–C4).

The compatibility of Parteck® TA excipient with the film-forming polymers hydroxypropyl methylcellulose (HPMC) and polyvinyl alcohol (PVA) was investigated with increasing weight gains and solid contents.

Figure 10 shows that Parteck® TA calcium carbonate is compatible with both HPMC and PVA based film coatings. An enhanced opacity, represented by the L* values, can be achieved when used in combination with the PVA based Parteck® COAT excipient.

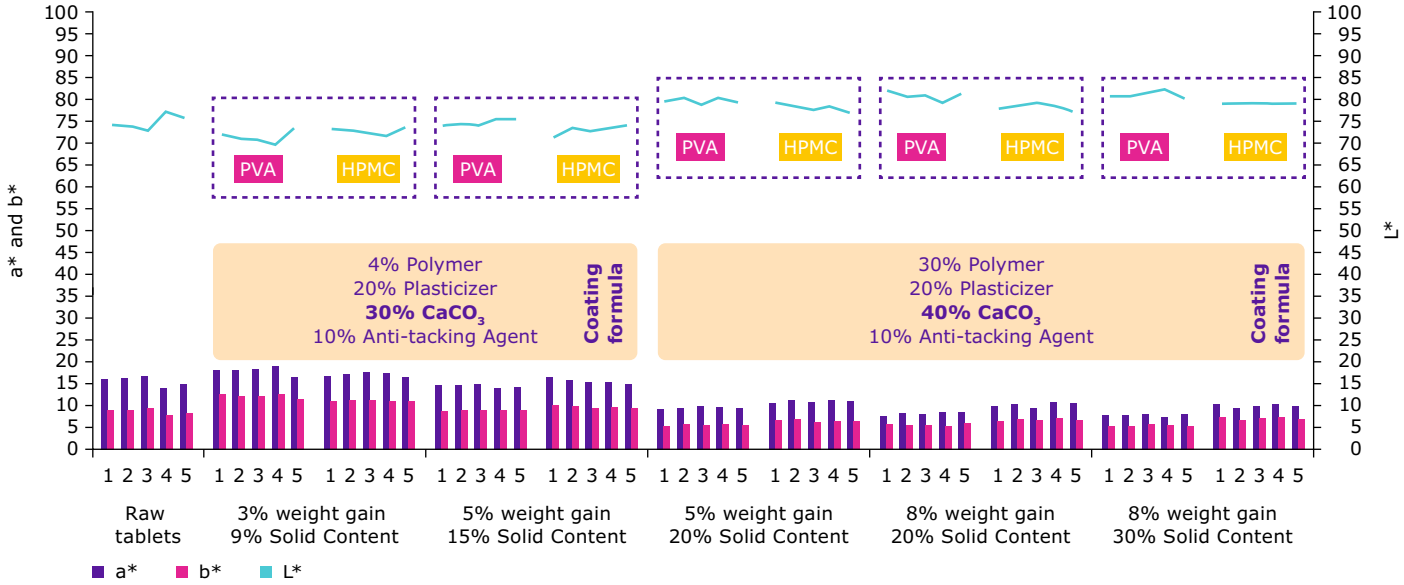

Figure 10.

CIElab values of Parteck® TA containing tablets; comparison of coatings with HPMC vs. coatings with Parteck® COAT in dependence of increasing weight gains and solid contents.

Effect on viscosity of spraying liquids

The dynamic viscosity and the viscoelastic behavior of the spraying liquid is an important parameter for the performance of a coating process. In general, the viscosity of the coating solution should be low enough to allow for an easy application and uniform distribution of the coating material onto the tablets, but high enough to ensure that the coating adheres well to the surface of the tablets and prevents sticking in the coating pan. A common viscosity range for tablet coatings is between 10 and 200 mPas. Maintaining a low viscosity at high solid contents can enhance process efficiency and process robustness.

Based on the results for the dynamic viscosity (Table 3), a lower influence was found for calcium carbonate in comparison to titanium dioxide. Higher pigment concentrations in the spraying liquid can be used and maintain efficient process times while achieving an opacity which is comparable to titanium dioxide.

In comparison to HPMC, an even lower influence on the viscosity increase was observed for the PVA based Parteck® COAT polymer enabling a broader process range.

Sample	Ingredients	Dyn. Visc. [mPas]
Basic	6% Parteck® COAT Solution	10
1	Parteck® COAT + 4.5% Parteck® TA	13
2	Parteck® COAT + 8.0% 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

Table 3.

Viscosity of coating solutions with Parteck® COAT and HPMC and different concentrations of Parteck® TA excipient.

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

Formulation example for a PVA-based film coating

The best way to prepare solutions for coating with Parteck® TA calcium carbonate and Parteck® COAT excipient is by gently introducing the polymer into the cold medium while stirring.

Once all particles are dispersed in the liquid, heat is applied to accelerate the dissolving process of Parteck® COAT excipient. Here the particle-engineered Parteck® COAT enables a greatly reduced dissolving time and required temperatures compared to PVA in scale form or other coating polymers such as HPMC.

After a clear solution is obtained, heating is stopped, and the solution is cooled down to room temperature. When room temperature is reached, plasticizer is added while stirring until it has dissolved.

The anti-tacking agent and Parteck® TA can then be added while stirring the medium. Stirring is continued until the coating solution looks uniform. It is recommended to keep the coating moving during the rest of the process.

The coating formulation and parameters are outlined in Tables 4 and 5.

Coating Formulation	Function	Art. No.
7.5% Parteck® COAT	Film coating agent, polymer	141517
5.0% Triethylcitrate	Plasticizer	817059
2.5% Parteck® LUB MST	Anti-tacking agent	100663
10.0% Parteck® TA	Colorant	124069

Table 4.

Formulation example with Parteck® TA excipient and PVA based Parteck® COAT polymer.

Coating parameters (lab scale)	Value
Pan load [kg]	1–2
Pan size [L]	2.5
Inlet air flow [m^3/h]	45
Gun to bed distance [mm]	10–15
Inlet air temperature [°C]	70–80
Outlet air temperature [°C]	35–45
Spraying rate [g/min]	5–10
Pan Speed [rpm]	10–20
Pattern air pressure [bar]	0.3–0.7
Atomizing air pressure [bar]	0.1–0.3
Drying temperature [°C]	40–50

Table 5.

Optimal process parameters for a lab scale coating process.

Disintegration time IPC [n=6]	Hardness IPC	Weight IPC Raw cores: 500 mg
609 sec	296 N	541 mg

Table 6.

Characteristics of tablets coated with Parteck® COAT and Parteck® TA.

IPC: Integrated process control

Conclusion

Toxicological concerns about titanium dioxide (E171) and the possible ban in some jurisdictions have led to an increased interest in suitable alternative drug colorants for use in solid dosage forms.

Results of the study described in this white paper show that Parteck® TA calcium carbonate is a viable alternative to titanium dioxide for use in film coatings of immediate release tablet formulations. Due to its unique morphology and designed particle size distribution, the nature-identical pigment enables a uniform finishing and good opacity. It well performs with both HPMC and PVA film coating, and the low viscosity of the spraying liquid at increased weight gains helps to maintain good process efficiency. When combined with the PVA-based Parteck® COAT excipient, enhanced opacity can be achieved compared to standard HPMC-containing formulations.

Use of screening via film casting methods can enable formulators to rapidly assess the performance of film coating formulations. 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.

In addition to a broad portfolio of coating ingredients, extensive application services are offered under MilliporeSigma's SAFC® portfolio to support formulators with the design of film coatings and product developments without titanium dioxide when anticipating potential future regulatory trends.

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