British Journal of Pharmacy

https://doi.org/10.5920/bjpharm.1349

British Journal of Pharmacy

www.bjpharm.hud.ac.uk

Proceedings of the 14th APS International PharmSci 2023

Comparison of Titanium Dioxide-containing and Titanium Dioxide-free Film Coating Systems

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ARTICLE INFO

Received: 30/05/2023
Accepted: 16/07/2023
Published: 30/12/2023

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KEYWORDS: Titanium dioxide; tablet coating, alternative pigments

SUMMARY

Titanium dioxide (TiO_2) is an important white pigment and opacifier that has been used in the pharmaceutical industry for over 50 years. It has been included ubiquitously in coloured coating systems and therefore many medicines. Its use in oral solid dosage forms, however, is now under scrutiny due to data linking TiO_2 particle inhalation with DNA damage. This also caused the European Union to ban its use as a food additive. Consequently, material suppliers have launched several TiO_2-free (TF) pharmaceutical coatings. In this study, two TF coatings based on different pigments were compared with a traditional TiO_2-containing coating assessing covering and colour quality. The TF coatings both showed a comparable quality in these parameters to the TiO_2-containing coating. The differences in colour and the degree of whiteness were also quantitatively measured and compared using CIELAB measurements derived from optical lens readings. The colour analysing tool used limited this data.

INTRODUCTION

In 2021, the European Food Safety Authority (EFSA) concluded that E171, the most common form of TiO_2, could no longer be considered safe as an additive in food (Blundell *et al*, 2022). This was due to new data which linked inhalation of E171 particles to DNA damage in rats (Younes *et al*, 2021). Consequently, the European Commission (EC) triggered a reassessment of TiO_2 use in medicines, to be completed by the European Medicines Agency (EMA) in 2025 (Blundell *et al*, 2022).

Initial findings by the EMA showed that over 60% of oral solid dose medicines used across Europe contain TiO_2 and that replacing it could cause significant drug shortages and discontinuations (Blundell *et al*, 2022). This would lead to major implications for patients. The challenge with finding TiO_2 alternatives is its range of functions in coatings. TiO_2 is not only a white pigment (Radtke *et al*, 2021), it also functions as an opacifier which enhances colour, helps prevent degradation of photosensitive API and aids tablet and capsule content blinding in clinical trials (Blundell *et al*, 2022).

The possibility of significant legislative changes in relation to the use of TiO_2 triggered the development and release of TF coatings by several major manufactures, such as Colorcon, Seppic and Biogrund. These aqueous coating systems are all based on hydroxypropyl methylcellulose but each use alternative pigments including carbonates, phosphates and cellulose derivatives.

To understand the impact of replacing TiO_2 in coating systems concerning its opacifying and colour qualities, a study was designed to compare the whiteness and cosmetic appearance of a TiO_2-containing coating with two TF alternatives.

MATERIALS AND METHODS

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The 7.95 mm, 250 mg, round biconvex placebo cores used for coating were prepared from a black tabletting premix supplied by BioGrund (BonuTab®, BioGrund, Germany). The three white coatings; Opadry® II, Opadry® TF (calcium carbonate) and Opadry® TF (rice starch), provided by Colorcon, United Kingdom were prepared according to the suppliers' reconstitution instructions. The Opadry® II, TF (rice starch) and TF (calcium carbonate) were applied at a 3%, 2-3% and 3-5% target weight gain respectively, using a Caleva Mini Coater/Drier 2 with top-spray nozzle. The CIELAB colour system values of the coated tablets were measured using a DataColor ColorReader. Six volunteers also assessed the cosmetic appearance and whiteness of the tablets in a blinded test.

RESULTS AND DISCUSSION

The average lightness or L* CIELAB values of the three coatings were all within L* = 3 of each other. This suggests the TF coating pigments had comparable efficacy to TiO_2. In contrast with the findings of other studies (Radtke *et al*, 2021, Palugan *et al*, 2022), TiO_2-based Opadry® II coated tablets had a lower average L* than those coated with Opadry® TF calcium carbonate (Table 1). The Opadry® TF rice starch coated tablets had the lowest average L*.

Table 1. *Average L* values for each set of coated tablets.*

Coating	Opadry II TiO_2	Opadry TF $CaCO_3$	Opadry TF Rice starch
Average L* ± SD	92.26 ±0.59	93.03 ±0.18	90.09 ±0.21

The blinded visual comparison test results (Table 2) showed the opposite, which may be attributable to the differences in the amounts of coating applied and the poorer cosmetic appearance of the Opadry® TF $CaCO_3$ coated tablets (Figure 1).

Ranking	Opadry II TiO_2	Opadry TF $CaCO_3$	Opadry TF Rice starch
Whitest	2	0	**4**
Middle	**4**	1	1
Least white	0	**5**	1

Table 2. *Blinded visual comparison test results, figures in bold represent the perceived whiteness ranking by volunteers (n=6).*

Fig. 1. *Image of tablets coated with (left to right): Opadry® II, Opadry® TF calcium carbonate and Opadry® TF rice starch.*

ACKNOWLEDGEMENTS

William A. James (Newcastle University) conducted this work as part of their 12-month Industrial Placement with Pharmaron UK Ltd.

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