

Iron Oxides in Titanium Dioxide-Free Coatings Protect Photolabile Active Pharmaceutical Ingredients in Oral Solid Dosage Forms

Authors: Ryan Kawakita, Diana Sperger, Ben Chal, Michael McCormick, Daniel To, David Ferrizzi, Ali Rajabi-Siahboomi

Colorcon, Inc. Harleysville, PA 19438, USA | AAPS Poster Reprint 2024

Introduction

Titanium Dioxide (TiO₂, E171)

In medicines, TiO₂ is often included in tablet coatings and capsule shells for the following effects ^{1,2}:

- Act as a pigment and opacifier
- Provide protection from UV-radiation
- Enable consistent product appearance

E171 Ban in European Union (EU)

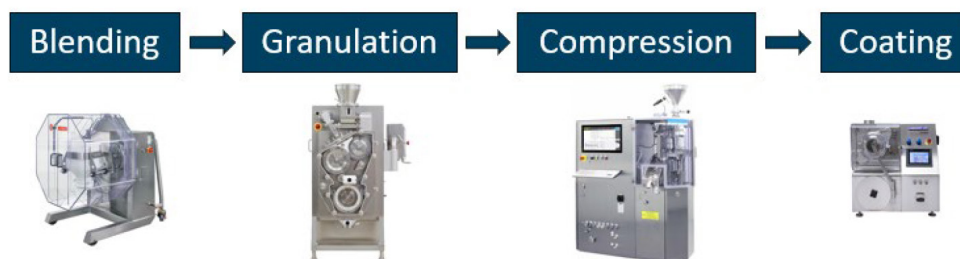
In 2022, the EU Commission banned TiO₂ in foods due to lack of evidence oral digestion of TiO₂ is safe. By February 2025, the EU will make a decision on whether to ban the use of TiO₂ in medicines, but highly suggested industry begin searching for alternatives.

Objectives

Evaluate the levels of iron oxide (FeO) necessary to protect photolabile active pharmaceutical ingredients (APIs) in tablets coated with titanium dioxide-free (TF) coatings.

Methods

Figure 1. Schematic of preparing and coating tablets.



- Photolabile API was blended with standard pharmaceutical excipients and compressed into 500 mg tablets.
- Tablets were coated to 4% weight gain (WG) using an O'Hara Labcoat benchtop coater with PVA-based TF coatings provided by Colorcon, and with TiO₂ reference coatings.
- Slack-variable mixture model DOE was set up in Fusion and JMP with the maximum total iron oxide concentration fixed at 1.5%.
- Coated tablets were tested in an Ametek Atlas Suntest CPS+ photochamber following ICH Q1B guidelines.
- Photodegradation was quantified by UPLC using a commercial stability indicating method

Table 1. Slack-variable mixture model design.

Run	Red FeO	Yellow FeO	Black FeO	CaCO ₃
1	0	0.50	0	34.50
2	0.62	0.62	0.25	33.51
3	1	0	0.50	33.50
4	0	1	0	34.00
5	0.50	1	0	33.50
6	0.22	0.22	0.34	34.22
7	0.50	0.50	0.50	33.50
8	0	0	0.25	34.75
9	0	1	0.50	33.50
10	1	0	0.50	33.50
11	0	1	0.50	33.50
12	0.44	0.44	0.19	33.93
13	1	0	0	34.00
14	0.72	0.22	0.34	33.72
15	0.22	0.72	0.34	33.72
16	1	0.50	0	33.50
17	0	0	0.50	34.50
18	0	0	0.50	34.50
19	0	0	0.00	35.00
20	0.44	0.44	0.19	33.93
21	0.50	0	0	34.50

Results

DOE Analysis and Response Surface Plots

Table 2. Statistically significant (p < 0.05) model coefficients.

Coded Name	Coefficient Value	Coefficient Standard Error	Coefficient Statistic	P-Value
Constant	0.200	---	---	---
Red FeO	-0.033	0.007	-4.9913	0.0002
Yellow FeO	-0.030	0.007	-4.5013	0.0005
(Red FeO) ²	0.027	0.009	2.8912	0.0118
(Yellow FeO) ²	0.038	0.009	4.1521	0.0010
(Black FeO) ²	-0.022	0.009	-2.3565	0.0335
Red*Yellow	0.041	0.007	5.5973	0.0001

Figure 2. Control groups. There is photodegradant present in tablet cores from API manufacturing and tablet compression.

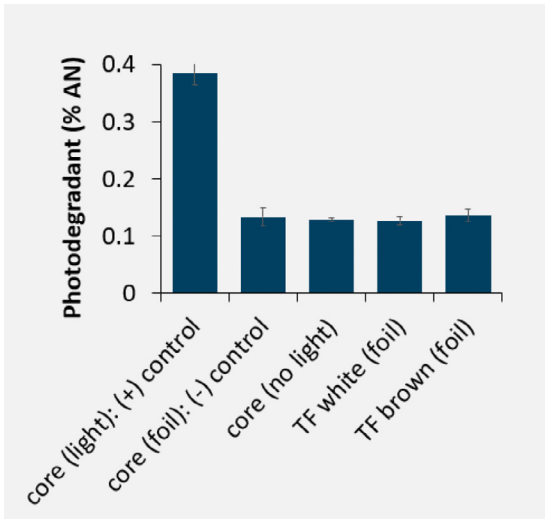


Figure 3. TF coatings with only Red FeO up to 8% w/w with corresponding tablet images.

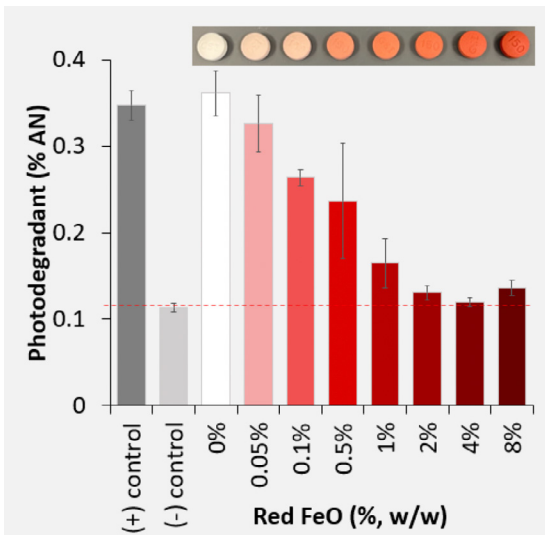


Table 3. Photodegradant ranked from lowest to highest levels formed.



















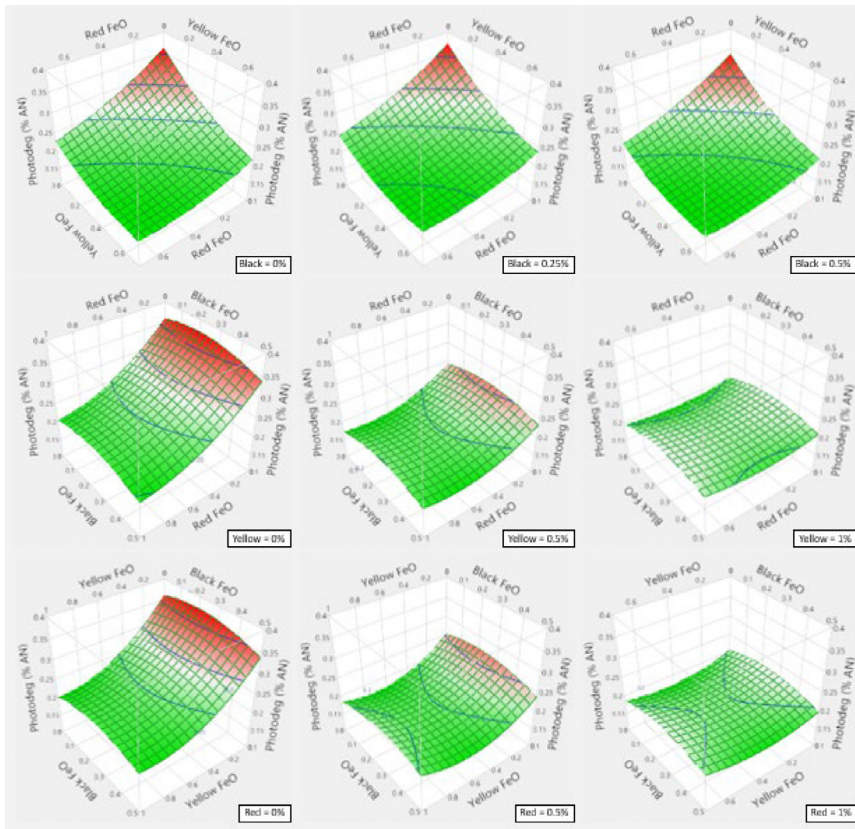
	%AN	Red	Yel	Blk
	0.172	1	0.50	0
	0.180	0.62	0.62	0.25
	0.184	0.50	0.50	0.50
	0.184	1	0	0.50
	0.190	0.50	1	0
	0.190	0.72	0.22	0.34
	0.197	0	1	0
	0.203	0	1	0.50
	0.208	0.44	0.44	0.19
	0.208	1	0	0
	0.222	0.22	0.72	0.34
	0.242	0.22	0.22	0.34
	0.243	0	0.50	0
	0.252	0.50	0	0
	0.280	TiO₂ standard		
	0.337	0	0	0.50
	0.355	0	0	0
	0.387	0	0	0.25

Figure 4. Response surface plots of formed photodegradant (% AN) with respect to FeO concentration. Each plot displays the relationship between two iron oxides with the third iron oxide black, yellow or red at a fixed concentration shown at the right bottom corner.



Absorbance and Transmittance Spectra of Coating Suspensions

Figure 5. Transmittance and absorbance from 200 to 800 nm of TiO² and TF coatings containing only one type of iron oxide.

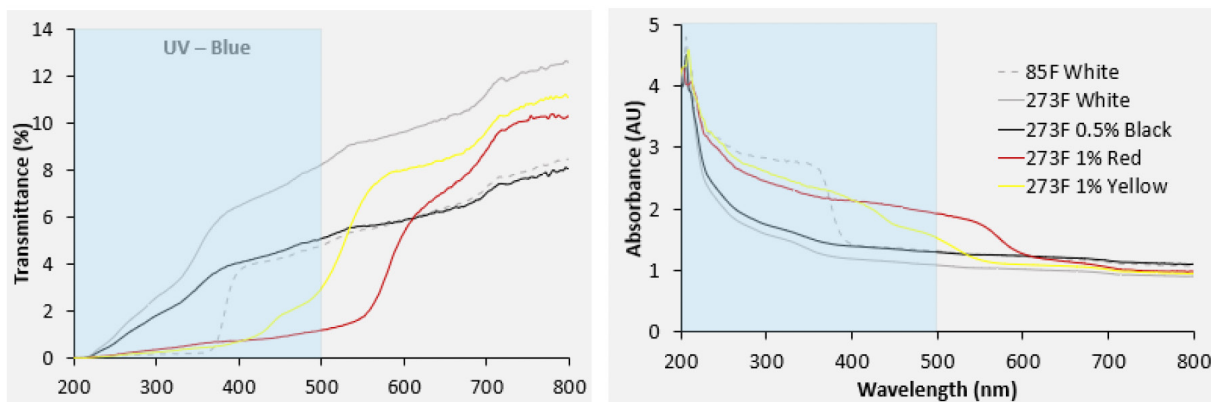
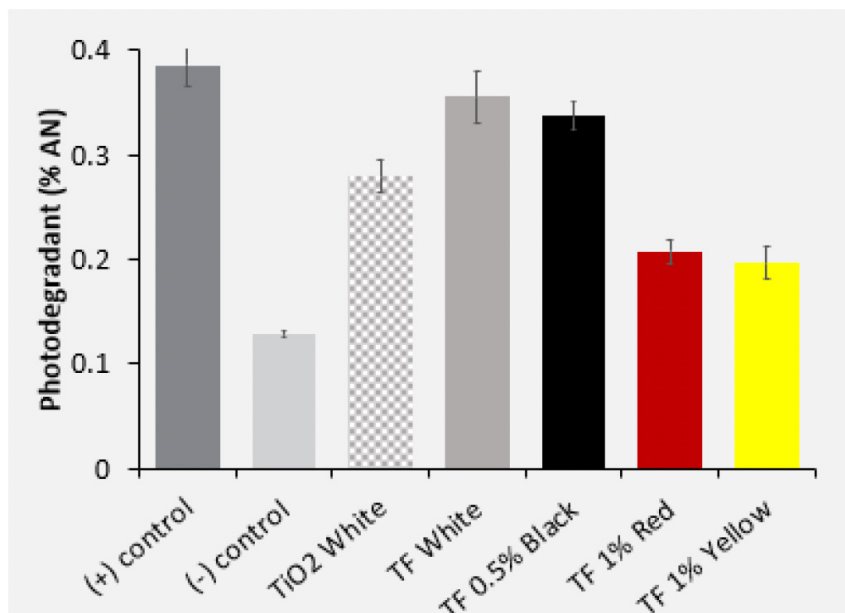


Figure 6. Photodegradant measured in TiO₂- and TF-coated tablets with one type of iron oxide whose transmittance and absorbance spectra are shown in Figure 5.



Conclusions

- TF coatings containing $\geq 1\%$ red or yellow FeO offered high levels of photoprotection, while black iron oxide had no effect. The TiO₂ standard had similar photodegradation to TF coatings with only 0.5% red or yellow.
- It is known that most photosensitive APIs degrade in UV-Blue light; when red or yellow iron oxide is present in this PVA-based TF coating, there is low transmittance in the UV-Blue wavelength range.
- Follow up experiments include studying the photoprotective impact of FeO in different polymer-based TF coatings and verifying the DOE results with other photolabile APIs.

References

1. Blundell R, Butterworth P, Charlier A, et al. The Role of Titanium Dioxide (E171) and the Requirements for Replacement Materials in Oral Solid Dosage Forms: An IQ Consortium Working Group Review. *Journal of Pharmaceutical Sciences* 2022;111(11):2943-2954. <https://doi.org/https://doi.org/10.1016/j.xphs.2022.08.011>.
2. Hancock B, Harris D, Kaye J, et al. Titanium Dioxide (E171 Grade) and the Search for Replacement Opacifiers and Colorants: Supplier Readiness Survey, Case Studies and Regulatory Perspective. *Journal of Pharmaceutical Sciences* 2024;113(5):1285-1298. <https://doi.org/https://doi.org/10.1016/j.xphs.2023.12.006>.

The information contained herein, to the best of Colorcon, Inc.'s knowledge is true and accurate. Any recommendations or suggestions of Colorcon, Inc. with regard to the products provided by Colorcon, Inc. are made without warranty, either implied or expressed, because of the variations in methods, conditions and equipment which may be used in commercially processing the products, and no such warranties are made for the suitability of the products for any applications that you may have disclosed. Colorcon, Inc. shall not be liable for loss of profit or for incidental, special or consequential loss or damages.

Colorcon, Inc. makes no warranty, either expressed or implied, that the use of the products provided by Colorcon, Inc., will not infringe any trademark, trade, copyright, patent or other rights held by any third person or entity when used in the customer's application.

For more information, contact your Colorcon representative or call:

North America	Europe/Middle East/Africa	Latin America	India	China
+1-215-699-7733	+44-(0)-1322-293000	+54-1-5556-7700	+91-832-6727373	86-21-61982300

You can also visit our website at www.colorcon.com