European Journal of Pharmaceutical Sciences 196 (2024) 106750

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Effects of omitting titanium dioxide from the film coating of a pharmaceutical tablet – An industrial case study of attempting to comply with EU regulation 2022/63

Dorián László Galata [a], Melinda Sinka Lázárné [b], Dorottya Kiss-Kovács [b], Gergő Fülöp [b], Barnabás Dávid [b], Botond Bogáti [b], Máté Ficzere [a], Orsolya Péterfi [a], Brigitta Nagy [a], György Marosi [a], Zsombor Kristóf Nagy [a,*]

[a] Department of Organic Chemistry and Technology, Faculty of Chemical Technology and Biotechnology, Budapest University of Technology and Economics, Műegyetem rkp. 3, Budapest H-1111, Hungary
[b] Gedeon Richter Plc., Formulation R&D, Gyömrői u. 19-21, Budapest H-1103, Hungary

ARTICLE INFO

Keywords:
Film coating
Titanium dioxide
Drug stability
Dissolution testing
HPLC
Photosensitive

ABSTRACT

Recently, concerns have been raised about the safety of titanium dioxide (TiO_2), a commonly used component of pharmaceutical film coatings. The European Union has recently prohibited the application of this material in the food industry, and it is anticipated that the same will happen in the pharmaceutical industry. For this reason, pharmaceutical manufacturers have to consider the possible impact of removing TiO_2 from the film coating of tablets. In this paper, we present a case study of a commercially produced tablet where the film coating containing TiO_2 was replaced with a coating using calcium carbonate ($CaCO_3$) or with a transparent coating. The performance of the coatings was compared by measuring the moisture absorption rate and the dissolution profile of the tablets. In these regards, there were negligible differences between the coating types. The tablets contained a highly photosensitive drug, the ability of the coatings to protect the drug was evaluated through environmental stability and photostability measurements. The HPLC results showed that the inclusion of TiO_2 does not provide additional benefits, when humidity and thermal stress is applied, however its role was vital in protecting the drug from external light. There were several decomposition products which appeared in large quantities when TiO_2 was missing from the coating. These results imply that photosensitivity is an issue, replacing TiO_2 will be challenging, though its absence can be tolerated when the drug does not need to be protected from light.

1. Introduction

In the recent past, the European Union (EU) has made a decision with serious consequences in the form of Regulation 2022/63, issued on 14th January 2022. In this, it was declared that titanium dioxide (TiO_2, E171) will be banned as an additive in the food industry from 7th August 2022 due to suspected genotoxicity. Many people now anticipate that soon it will be banned in the pharmaceutical industry as well (Schoneker, 2023). This would be an event of extraordinary impact, as TiO_2 is included in more than 90,000 drug products registered in the EU (Schoneker, 2023), reformulating these would require extraordinary efforts (Blundell et al., 2022). TiO_2 has great utility in the film coating of pharmaceutical products for multiple reasons. Firstly, it is responsible for the pleasant appearance of the tablet by providing opacity and brightness to the coating. However, its role goes beyond aesthetic functions. TiO_2 has a high refractive index which causes it to efficiently reflect light, thus it can prevent photons from reaching the tablet core and possibly damaging the molecules of the active pharmaceutical ingredient (API) (Crespo-Monteiro et al., 2022). Furthermore, it has a wide bandgap which gives this compound the ability to absorb ultraviolet light, preventing harmful interactions between these high-energy photons and the API (Haider et al., 2019). The combination of these attributes makes TiO_2 an attractive choice in most film tablets. It was successfully utilized for many years until 2021, when the European Food Safety Authority declared that they no longer consider TiO_2 (either anatase or rutile) to be safe (Younes et al., 2021).

Apart from the tremendous cost of altering the registration of every single formulation containing TiO_2, manufacturers must also consider

* Corresponding author.
E-mail address: zsknagy@oct.bme.hu (Z.K. Nagy).

https://doi.org/10.1016/j.ejps.2024.106750
Received 27 November 2023; Received in revised form 4 March 2024; Accepted 12 March 2024
Available online 13 March 2024

Table 1
Parameters of the film coating.

Coating liquid concentration	13 % w/w
Coating liquid mass flow rate	6.5 g/min
Drum rotation speed	20 rpm
Inlet air temperature	60 °C
Atomizing air pressure	2 bar
Inlet air flow rate	50 m^3/h
Air out flow rate	55 m^3/h

Table 2
Crushing strength and tablet weight of the 5 tested formulations. The displayed values are the average and standard deviation of 10 tablets.

Formulation	TiO_2	$CaCO_3$ 3 %	$CaCO_3$ 5 %	core	clear
Crushing strength (N)	127.4 ± 4.3	131.5 ± 4.0	143.4 ± 5.7	117.3 ± 5.5	131.0 ± 5.2
Tablet weight (mg)	309.23 ± 0.78	309.92 ± 1.42	315.92 ± 2.20	300.52 ± 1.20	309.10 ± 1.19

the possibility that in some instances, the removal of this opacifier will deteriorate the safety of the product due to photosensitivity issues (SeethaLekshmi et al., 2021). Although a large variety of options is available in the photostabilizating of drugs (Janga et al., 2018), such as using vesicles (Manconi et al., 2003), microcapsules (Ragno et al., 2003) or solid dispersions (Li et al., 2015), the reformulation of all impacted products is not feasible. The most practical solutions are replacing the coating with a TiO_2-free alternative or relying on the packaging (Janga et al., 2018) to protect the API from photodegradation. Recently, Palugan et al. (2022) tested numerous alternative opacifiers, and they found that in the case of dissolution and visual appearance of the tablets, they can yield results equivalent to TiO_2. Radtke et al. (2021) studied the performance of alternatives of TiO_2 and found that generally they are inferior in most aspects. Only ZnO was able to yield sufficient protection from external light, while in the case of appearance, none of the alternatives provided acceptable results. Considering the seriousness of the topic, it would be beneficial if more data were available about the capabilities of alternative coating solutions.

So far, the effects of omitting TiO_2 have only been studied on model formulations, therefore it would be interesting to know how an actual commercially produced formulation would be impacted by the loss of this opacifier. Our aim is to analyze the effects of replacing the coating that includes TiO_2 with commercially available alternatives that manufacturers can realistically access. For this reason, we did not utilize ZnO. Although ZnO is a promising opacifier, it is known to have an anti-inflammatory effect (Agarwal and Shanmugam, 2020), therefore it is an active ingredient by itself. The utilization of such a compound as an excipient can be problematic, probably partly because of this, there are no commercially available coatings using ZnO. The goal of our work is to compare the performance of a commercially available product coated using TiO_2 as opacifier with the uncoated tablet cores and with a coating using $CaCO_3$ and with a clear coating. The different coatings are tested by studying their moisture absorption, dissolution rate, environmental stability, photostability and the color of the tablets. This way we can learn about the impacts of omitting TiO_2 from pharmaceutical products.

2. Materials and methods

2.1. Film coating of tablets

This study was performed on a commercial film coated pharmaceutical tablet formulation, which composition is confidential. The formulation was selected for the study, because the API is known to have high photosensitivity. The tablets contain microcrystalline cellulose, lactose monohydrate, crospovidone, magnesium hydroxide and magnesium stearate as excipients. The tablet cores had a mass of 300 mg and a diameter of 9 mm. The friability of the tablet cores was measured by placing approximately 6.5 g of tablet cores in the drum of a Pharmatest PTF 10E friability tester (Pharma Test Apparatebau, Hainburg, Germany), then they were rotated 100 times. This test was repeated 3 times. The friability was found to be 0.14 % ± 0.02 %.

The tablet cores were coated using 3 different products, which exact type is confidential. All 3 use poly(vinyl-alcohol) (PVA) as polymer, the first contains TiO_2 as opacifier in a concentration of 25 w/w%. The second utilized $CaCO_3$ as an alternative opacifier in 25 w/w%, while the third was a clear coating. In order to study how TiO_2 performs compared to the alternatives, 4 different formulations were prepared, where one of the formulations is tested with two different coating levels, resulting in a total of 5 tested formulations. As a reference, the uncoated tablet cores were also examined (henceforth referred to as 'core'). PVA-based coatings were chosen exclusively because we intended to simulate a scenario where the manufacturer needs to omit TiO_2 from the coating, in this case other parameters of the technology need to remain as similar as possible. For this reason, changing the coating to a hydroxypropylmethylcellulose (HPMC)-based product would be considered a more drastic alteration of the technology. The coating containing TiO_2 was applied for a weight gain of 3 % ('TiO_2'). The coating with $CaCO_3$ was applied with 3 and 5 % weight gain to determine whether a thicker coating might offset the anticipated weaker performance of $CaCO_3$ in protection from light, these formulations will be called '$CaCO_3$ 3 %' and '$CaCO_3$ 5 %', respectively. The clear coating was applied with 3 % weight gain ('clear'). The weight gains of 3 % and 5 % are equivalent to 6.1 mg/cm^2 and 10.1 mg/cm^2 of coating weight per unit of tablet surface area, respectively.

Film coating was performed on batches of 800 g tablets in a Glatt GB2 L50-10026 pan coating machine (Pratteln, Switzerland). Table 1 contains the parameters used during the process. After film coating, the tablets were stored for 10 days in plastic bags inside a container that protected them from light at 25 °C and 30 % relative humidity before the measurements described below were carried out.

The hardness of the tablet cores and the film coated formulations was measured using a Dr. Schleuniger THP-4 M crushing strength tester (Dr. Schleuniger Productronic, Thun, Switzerland). 10 tablets were measured from each formulation. The weights of the tablet cores and coated tablets were measured using an analytical scale. The results are shown in Table 2.

2.2. Moisture absorption measurement

The rate at which tablets acquire and lose moisture was studied using a climate chamber (Binder DIN 12880, Binder, Tuttlingen, Germany). The combined weight of 20 tablets was measured to monitor percentage weight changes, 3 parallel experiments were performed with each formulation. Firstly, the device was set to 40 °C and 33 % relative humidity (RH). Tablets were stored under these conditions for 48 h to reach an initial state of low moisture content. Afterwards, the conditions were changed to 40 °C and 75 % RH. These conditions were maintained for 48 h during which the mass of the tablets was measured at several time points. Lastly, the climate chamber was set to 40 °C and 33 % RH for a duration of 32 h, the mass of the tablets was again measured several times.

2.3. Dissolution testing

The dissolution profile of the tablets was recorded using a Hanson SR8-Plus appliance (Chatsworth, CA, USA). The tablets were placed in 900 mL vessels filled with pH 6.6 citric acid solution. The dissolution measurement was performed in the USP II setting (paddle method) under non-sink conditions, the rotational speed of the paddles was 50 rpm. Samples were taken from the dissolution medium at 5, 10, 15, 20 and 30 min. A sample volume of 5 mL was taken at each time point, the

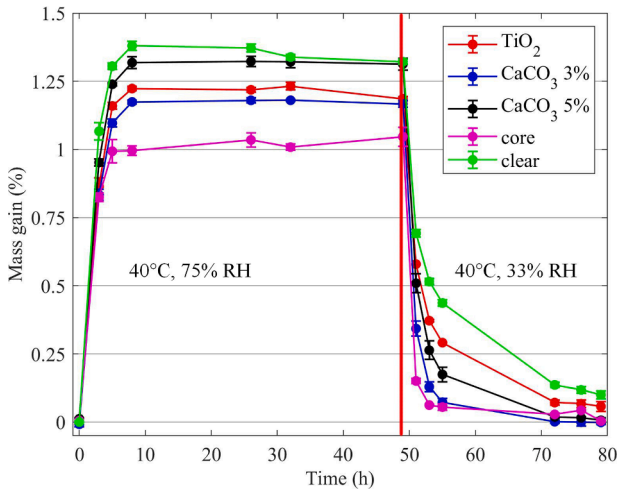

Fig. 1. Moisture uptake and loss of tablets stored at 40 °C, 75 % and 33 % RH, respectively. The red line represents the change from 75 % to 33 % RH. Error bars represent the standard deviation of 3 parallel measurements.

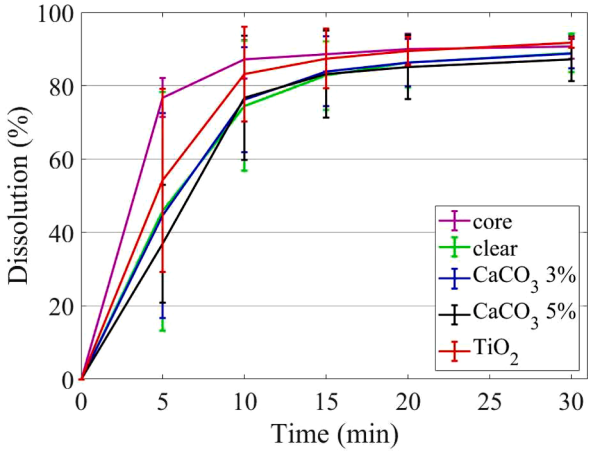

Fig. 2. Dissolution profile of the API from the tablets. Error bars represent the standard deviation of 6 measurements.

Table 3
Disintegration time of the 5 tested formulations. The displayed values are the average and standard deviation of 6 tablets.

Formulation	TiO_2	$CaCO_3$ 3 %	$CaCO_3$ 5 %	core	clear
Disintegration time (s)	111.7 ± 17.9	128.2 ± 18.4	150.3 ± 14.7	32.1 ± 1.8	116.5 ± 17.6

Table 4
f_2 values of formulations compared to the TiO_2 formulation.

Formulation	core	clear	$CaCO_3$ 3 %	$CaCO_3$ 5 %
f_2 compared to TiO_2	43.85	60.50	61.25	52.33

medium was not replaced in order to not dilute the system. The concentration of the API was measured with the HPLC method registered for this API. 6 tablets were measured from each of the 5 different formulations.

2.4. Stability studies

The tablet samples were subjected to stress caused by temperature and RH and by external light. Afterwards, the registered HPLC purity measurement was performed using an RP-HPLC method Agilent 1200 series (Santa Clara, CA, USA) apparatus with an USP classification L1 column with gradient elution and a flow rate of 1 mL/min and an injected volume of 10 µl. Detection of the compounds was performed using an UV spectrometer. The presented concentration values are calculated relative to the amount of drug in the tablets, therefore they represent what percentage of the drug was transformed into that decomposition product. A two-sample *t*-test (p-value threshold equal to 0.05) was used to compare the concentration values of the decomposition products of the TiO_2 formulation to all other formulations.

2.4.1. Environmental stability

The tablets were stored in a climate chamber (Weiss Technik, Vienna, Austria) at 40 °C and 75 % RH for 1 month and 3 months, afterwards the HPLC purity measurement was performed on them.

2.4.2. Photostability

The tablets were exposed to photostress according to ICH Q1B guideline in a Vötsch VP 500 L (Vötsch Industrietechnik, Balingen, Germany) type photostability chamber for two weeks at 25 °C and 60 % RH, with an irradiation of 1.2 million lux hours, the performance of the lighting system was 200 Wh/m^2. The tablets were then investigated with the HPLC purity method.

2.5. Disintegration testing

The disintegration time of the formulations was measured using an Erweka ZT4 disintegration tester (Erweka, Langen, Germany). The disintegration test was performed in distilled water, the temperature was kept at 37 ± 1 °C. 6 tablets were tested from each formulation.

2.6. Digital imaging of the tablets

Images of the tablets were recorded using a Canon 650D (Canon, Tokyo, Japan) DSLR (digital single-lens reflex) camera and Canon EFS 18–55 macro lens (Canon, Tokyo, Japan). The images had a resolution of 5184 × 3456 pixels. Illumination was provided by a ring light consisting of white light emitting diodes.

2.7. Statistical analysis of the results

The calculations described in this chapter were performed using MATLAB 9.8 software (Mathworks, Natick, MA, USA).

The dissolution profiles of the formulations were compared using the f_2 similarity factor (Eq. (1)).

$$f_2 = 50 log_{10}\left\{\left[1 + \frac{1}{n}\sum_{i=1}^{n} w_t (R_t - T_t)^2\right]^{0.5} * 100\right\} \quad (1)$$

In this equation, R_t is the dissolution value of the reference product and T_t is the dissolution value of the tested product at time point t, respectively, w_t is an optional weighing factor and n is the number of time points in the dissolution curve. For the calculation, only the points before 85 % dissolution is achieved and one point afterwards is considered in order to exclude the last parts of the curve where the dissolution is already complete.

The disintegration time, color value and HPLC results were compared using two-sample *t*-tests with 5 % significance level.

The digital images (Chapter 2.6) of the tablets were analyzed by subtracting the background, then the images were converted to the CIELAB L*a*b color space. The average values of pixels belonging to the tablets were obtained from each image.

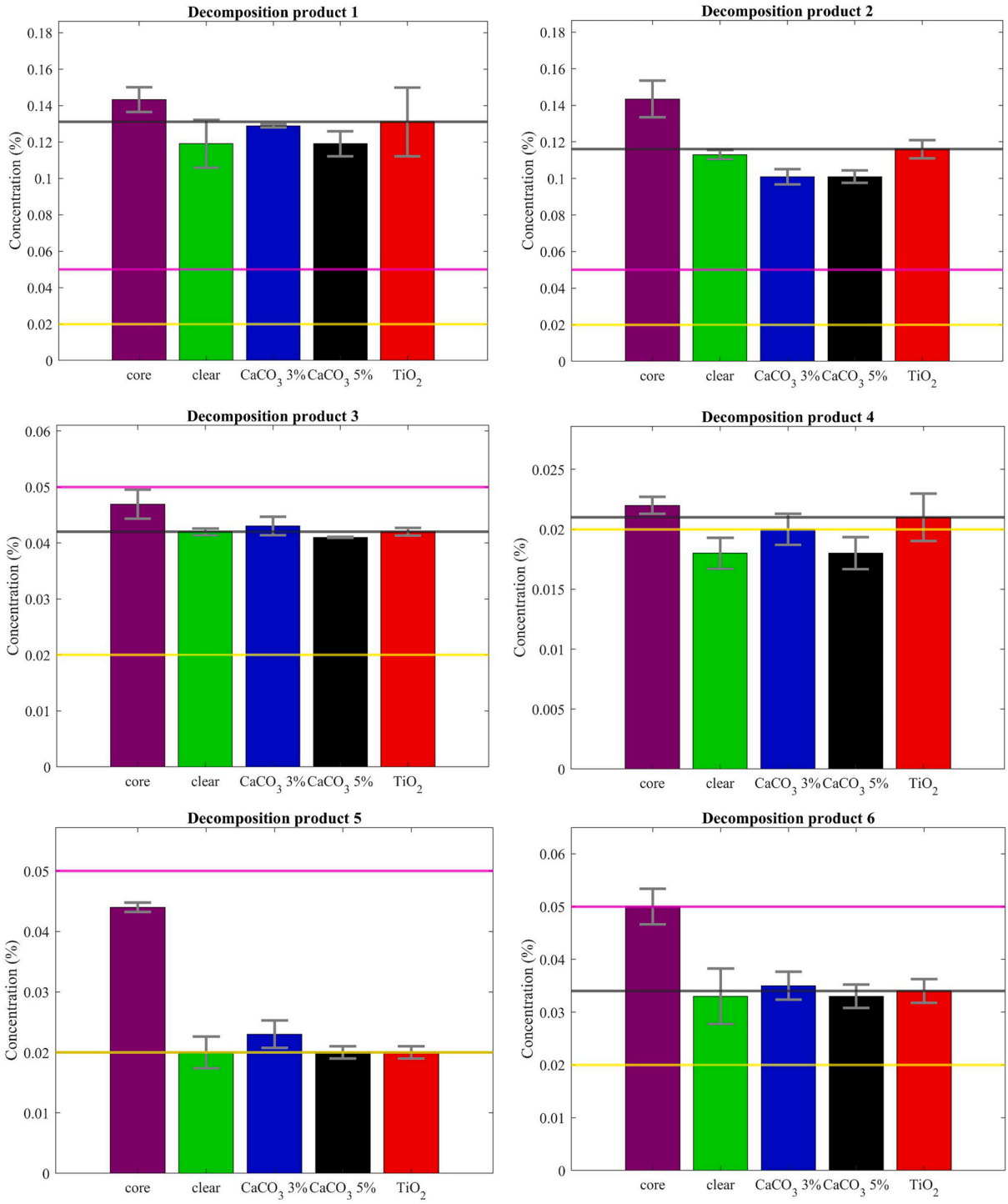

Fig. 3. Concentration of decomposition products relative to total API content after storage at 40 °C and 75 % RH for 1 month. The yellow line represents the detection limit, the magenta line is the quantification limit, the black line is the concentration in the TiO_2 tablets where comparison is applicable. The results were obtained by analyzing samples of 20 tablets. Error bars represent the standard deviation of 2 measurements. Asterisk above the bar represents a statistically significant difference compared to the TiO_2 sample.

3. Results and discussion

3.1. Moisture absorption

The weight change of the tablets stored at 75 %, then 33 % RH is shown in Fig. 1. It can be observed that basically all coated tablets exhibit a similar behavior. The tablet cores lose moisture faster when the RH becomes lower. The coating containing TiO_2 has a similar performance to the other coatings.

Therefore, it can be stated that in the case of this formulation, the omission of TiO_2 does not alter the moisture absorption of the tablets in an impactful way, as long as the tablets have sufficiently thick coating, the type of coating is not an important factor.

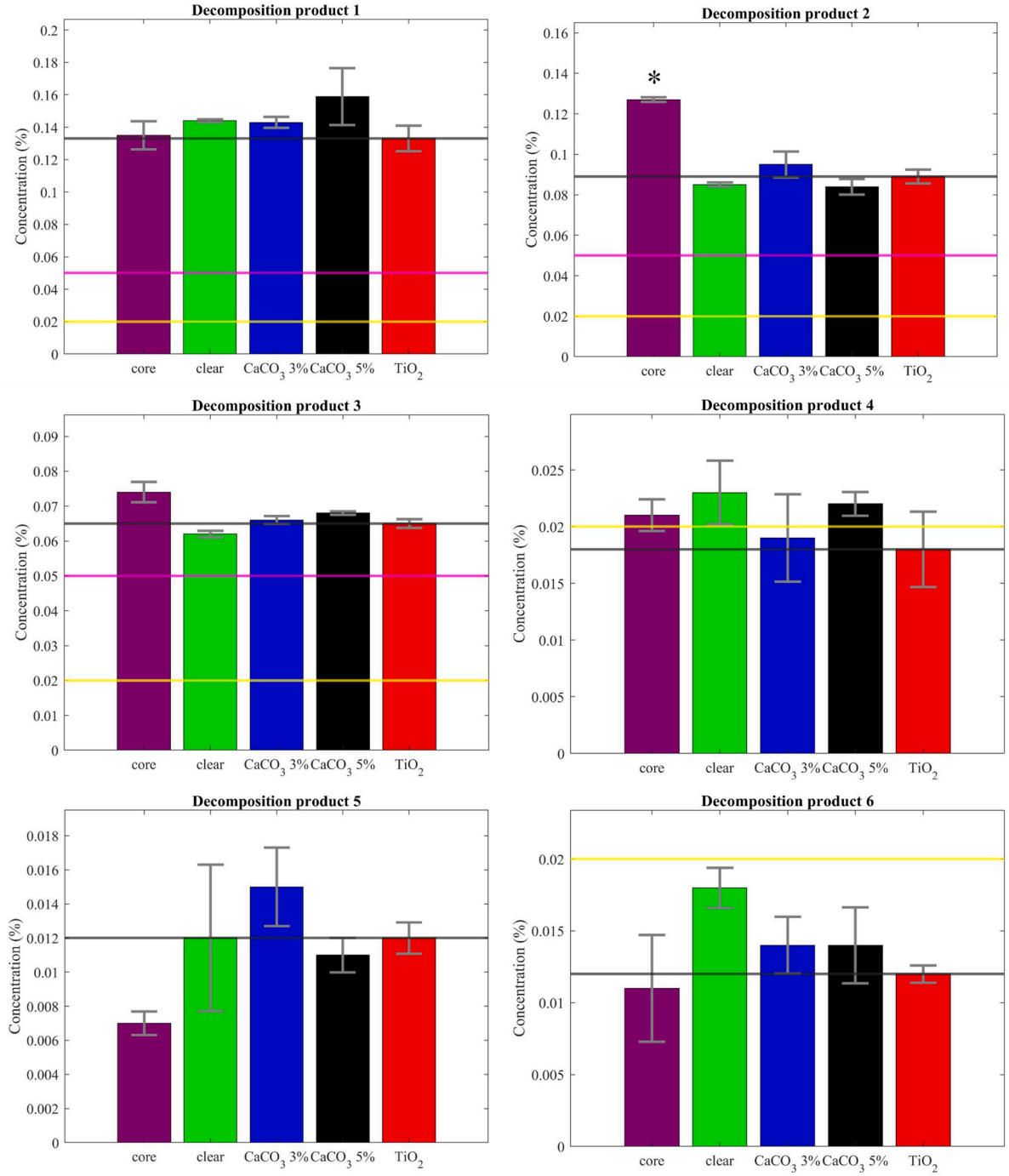

Fig. 4. Concentration of decomposition products relative to total API content after storage at 40 °C and 75 % RH for 3 months. The yellow line represents the detection limit, the magenta line is the quantification limit, the black line is the concentration in the TiO_2 tablets where comparison is applicable. The results were obtained by analyzing samples of 20 tablets. Error bars represent the standard deviation of 2 measurements. Asterisk above the bar represents a statistically significant difference compared to the TiO_2 sample.

3.2. Dissolution testing

Fig. 2 displays the dissolution profile of the API from the tablets. The performance here is very similar to the moisture absorption, tablets with any kind of coating have a slower dissolution rate than the tablet cores. This is most evident at the 5 min time point, afterwards the dissolution is almost complete. Apart from this, it can be observed that the coated tablets have a larger standard deviation than the tablet cores. At 5 min, the $CaCO_3$ 5 % tablets have the lowest dissolution percentage, presumably due to the thicker coating of these tablets or because these tablets spent more time exposed to the conditions inside the coating machine (most notably the humidity) and consequently their structure has changed resulting in a slower disintegration. The disintegration times of the 5 formulations are shown in Table 3. The difference between the two $CaCO_3$ formulations is statistically significant (two-sample *t*-test results in $p = 0.0046$), this shows that the thicker coating contributes to a slower disintegration.

The f_2 similarity parameter was calculated in order to compare the dissolution profiles to the TiO_2 tablets. Table 4 shows the obtained values. The results indicate that the dissolution profile of all coated

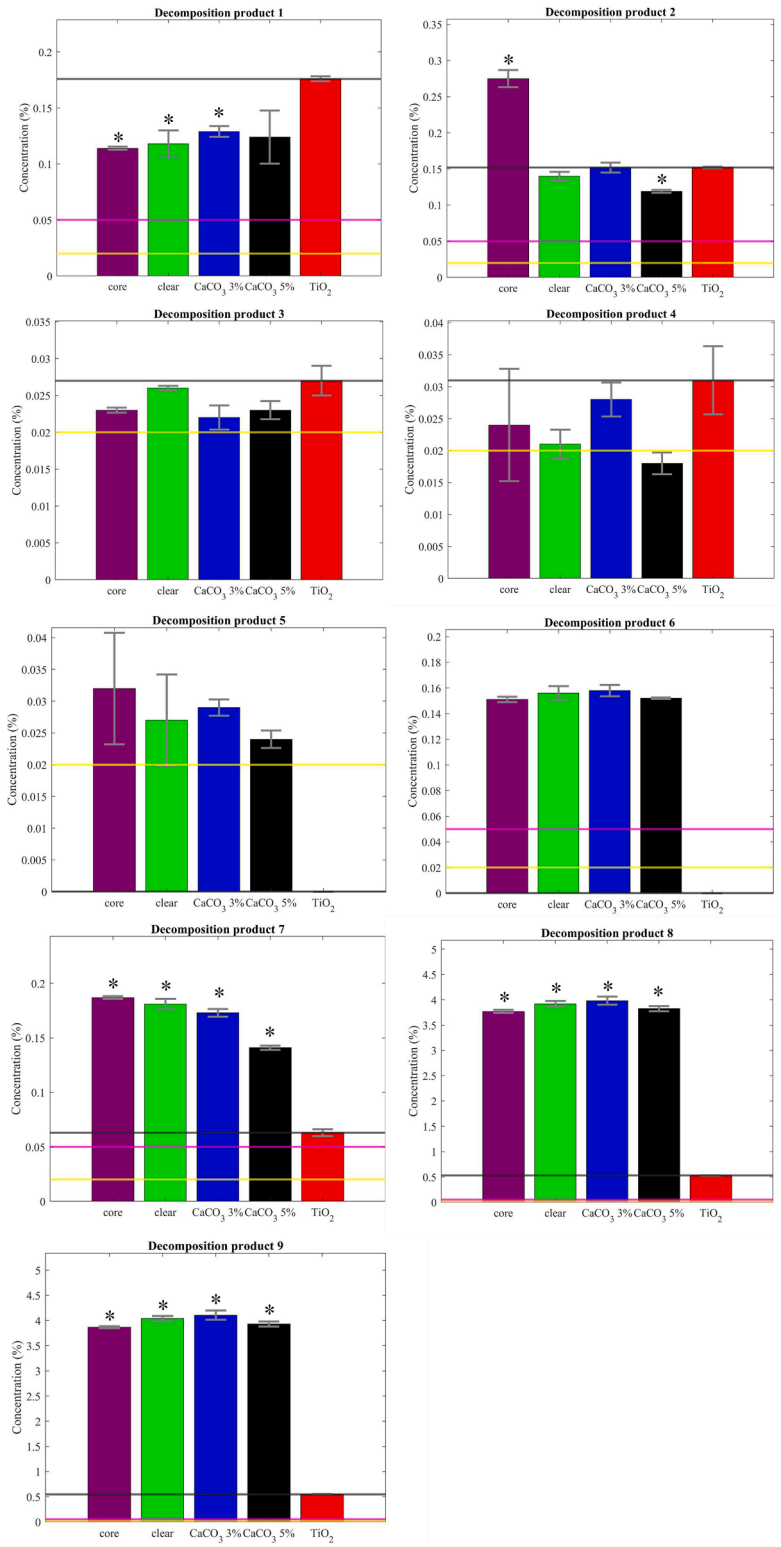

Fig. 5. Concentration of decomposition products relative to total API content after exposed to light according to ICH Q1B for 2 weeks. The yellow line represents the detection limit, the magenta line is the quantification limit, the black line is the concentration in the TiO_2 tablets where comparison is applicable. The results were obtained by analyzing samples of 20 tablets. Error bars represent the standard deviation of 2 measurements. Asterisk above the bar represents a statistically significant difference compared to the TiO_2 sample.

formulations can be considered similar to the TiO_2 tablets, only the cores had an f_2 value below 50. Among the coated tablets, the $CaCO_3$ 5 % formulation has the smallest f_2 value, this agrees with the observation that this formulations has a slightly slower dissolution at 5 min, therefore there is a larger difference between the curves.

3.3. *Environmental stability*

The environmental stability in this context means the resistance against humidity and thermal stress causing degradation. The concentration of decomposition products after storage at 40 °C, 75 % RH for 1

Table 5
Average color values of the 5 tested formulations. The displayed values are the average and standard deviation of 10 tablets.

Formulation	TiO_2	$CaCO_3$ 3 %	$CaCO_3$ 5 %	core	clear
L*	39.72 ± 0.73	40.15 ± 1.15	40.11 ± 1.00	39.16 ± 0.68	39.41 ± 0.86
a*	-3.36 ± 0.07	-3.66 ± 0.12	-3.59 ± 0.06	-3.57 ± 0.17	-3.60 ± 0.09
b*	-7.95 ± 0.07	-7.49 ± 0.08	-7.57 ± 0.16	-7.61 ± 0.08	-7.47 ± 0.08

month can be observed in Fig. 3. Out of the 6 decomposition products, the concentration of 4 (products 3–6) is below the quantification limit (QL) of the HPLC method (0.05 %). For this reason, quantitative comparison is only applicable in the case of products 1 and 2. The concentration of the other products is usually between the detection limit (DL) of 0.02 % and the QL. Compared to the concentration values measured in the TiO_2 tablets, two-sample *t*-tests have shown that none of the other formulations have a significantly different concentration of products 1 and 2.

The concentration of the decomposition products after 3 months is shown in Fig. 4. In this case, products 1–3 have concentration values above the QL, while products 4–6 are near or below the DL. When comparing the concentration of products 1–3 to the TiO_2 sample, it was found that only the concentration of product 2 in the tablet cores is significantly higher, in all other cases, the differences were not found to be significant.

The inclusion of TiO_2 does not influence the resistance of the tablets to environmental stress, therefore including the opacifier is not essential in this regard. The concentration of all decomposition products stayed below their respective acceptance limits. Figs. S1–S6 compare the concentration of the degradation products after 1 and 3 months.

3.4. Photostability

The results of the photostability study are shown in Fig. 5. In the case of the first 4 decomposition products, TiO_2 does not reduce the concentration relative to the other coatings. However, it provides a very strong protection against the formation of decomposition products 5–9. Products 5–6 could not be found in the tablets coated with TiO_2 and the concentration of product 7 is more than halved because of TiO_2. The most important decomposition products are 8 and 9, which appear in a concentration higher than 3.5 %; the application of TiO_2 reduces their concentration to slightly above 0.5 %. In the case of products 7–9, two-sample *t*-tests have shown that the concentrations in all other formulations are significantly higher compared to the TiO_2 tablets. Increasing the layer thickness of the $CaCO_3$-containing coating did not increase the protective capacity considerably. Products 1, 3 and 4 have the highest concentration in the tablets with TiO_2, presumably these products are not the result of decay by exposure to light. However only the concentration of product 1 is above the QL, thus the comparison of the actual values is applicable only in this case. This product might also be photosensitive, this could explain why its concentration is higher in the TiO_2 tablets, as the protection from light hindered its decomposition.

It was confirmed that photostability is the most important issue with the alternatives of TiO_2, therefore providing a solution to this problem could drastically improve the outlooks in a scenario where TiO_2 must be omitted from pharmaceutical products. This is in accordance with the findings of other researchers, who also concluded that the photostability aspect of TiO_2 is the hardest to substitute. Relying on the packaging to protect the tablets from external light could alleviate the problems caused by removing TiO_2 from the film coating of tablets.

3.5. Color analysis

The color of the tablets was analyzed based on images recorded with a digital camera. The color is characterized using the L*a*b color space. In this representation of color, the L* component describes the brightness, the a* is the place of the color between red and green, while the b* value is the chromaticity coordinate between blue and yellow. Table 5 summarizes the average color value and standard deviation of 10 tablets from each formulation.

The results show that the brightness value of the TiO_2 tablets is similar to the other formulations, two-sample *t*-tests show that the difference is not significant between the TiO_2 and the other formulations. In the case of the a* value, the TiO_2 tablets have the highest values, and although the difference between TiO_2 and the other tablets is small, it was found to be significant in two-sample *t*-tests. This shows that the TiO_2 tablets have a color slightly less green and closer to red. The b* values of TiO_2 tablets are lower than all other formulations, the difference is also significant here based on two-sample *t*-tests. The higher b* values of the formulations without TiO_2 mean that these tablets have a more yellow color. Consequently, the removal of TiO_2 from the coating has also an impact on the color of the tablets.

4. Conclusions

In this work, the film coating of a commercially available tablet was replaced in order to attempt to comply with EU regulation 2022/63. As TiO_2-free alternatives, a coating using $CaCO_3$ was applied in two different amounts, furthermore a clear coating and uncoated tablet cores were also tested. The alternative coatings performed well in the case of moisture absorption, in vitro dissolution and environmental stress. The color of tablets coated with TiO_2 was found to be less yellow than the other formulations. Furthermore, in the case of photostability, the alternatives did not yield satisfactory results. Therefore, removing TiO_2 from a formulation like this will not result in a safer product due to stability issues. Consequently, even though the formulation complies with the ban of TiO_2, it will conflict with other quality regulations. This situation can be solved in two different ways. The first scenario is where pharmaceutical manufacturers conduct intensive research to find viable alternatives to TiO_2, deteriorating the competitiveness of this sector in Europe. The second solution is considering that most pharmaceutical formulations contain less than 100 μg of TiO_2, therefore the consumer's exposition to this compound is negligible compared to food products, thus banning TiO_2 from pharmaceutical products might not be necessary.

CRediT authorship contribution statement

Dorián László Galata: Writing – original draft, Visualization, Investigation, Data curation. **Melinda Sinka Lázárné:** Resources, Methodology. **Dorottya Kiss-Kovács:** Resources, Project administration, Methodology, Conceptualization. **Gergő Fülöp:** Project administration, Methodology, Conceptualization. **Barnabás Dávid:** Methodology. **Botond Bogáti:** Methodology. **Máté Ficzere:** Investigation, Data curation. **Orsolya Péterfi:** Investigation, Data curation. **Brigitta Nagy:** Writing – review & editing, Validation, Conceptualization. **György Marosi:** Writing – review & editing, Supervision. **Zsombor Kristóf Nagy:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

Acknowledgments

This work was supported by OTKA grants K-143039 and PD-142970. Project no. TKP-9-8/PALY-2021 has been implemented with the support provided by the Ministry of Culture and Innovation of Hungary from the National Research, Development and Innovation Fund, financed under the TKP2021-EGA funding scheme. This work was supported by the ÚNKP-23-3-I-BME-23 and ÚNKP-23-3-I-BME-102 New National Excellence Program of the Ministry for Innovation and Technology from the source of the National Research, Development and Innovation Fund. This paper was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Science. The project supported by the Doctoral Excellence Fellowship Programme (DCEP) is funded by the National Research Development and Innovation Fund of the Ministry of Culture and Innovation and the Budapest University of Technology and Economics, under a grant agreement with the National Research, Development and Innovation Office.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejps.2024.106750.

References

Agarwal, H., Shanmugam, V., 2020. A review on anti-inflammatory activity of green synthesized zinc oxide nanoparticle: mechanism-based approach. Bioorg. Chem. 94, 103423.

Blundell, R., Butterworth, P., Charlier, A., Daurio, D., Degenhardt, M., Harris, D., Hancock, B., Johnston, M., Kasina, R., Kaye, J., Kelly, R., Lienbacher, P., Meehan, L., Melnick, J., Ojakovo, P., Schoell, J., Schimmelle, B., Tobyn, M., Wagner-Hattler, L., Wakeman, J., Wiedey, R., 2022. The role of titanium dioxide (E171) and the requirements for replacement materials in oral solid dosage forms: an IQ consortium working group review. J. Pharm. Sci. 111, 2934–2954.

Crespo-Monteiro, N., Hamandi, M., Usuga Higuita, M.A., Guillard, C., Dappozze, F., Jamon, D., Vocanson, F., Jourlin, Y., 2022. Influence of the micro-nanostructuring of titanium dioxide films on the photocatalytic degradation of formic acid under UV illumination. Nanomaterials 12, 1008.

Haider, A.J., Jameel, Z.N., Al-Hussaini, I.H., 2019. Review on: titanium dioxide applications. Energy Procedia 157, 17–29.

Janga, K.Y., King, T., Ji, N., Sarabu, S., Shadambikar, G., Sawant, S., Xu, P., Repka, M.A., Murthy, S.N., 2018. Photostability issues in pharmaceutical dosage forms and photostabilization. AAPS PharmSciTech 19, 48–59.

Li, J., Lee, I.W., Shin, G.H., Chen, X., Park, H.J., 2015. Curcumin-Eudragit® E PO solid dispersion: a simple and potent method to solve the problems of curcumin. Eur. J. Pharm. Biopharm. 94, 322–332.

Manconi, M., Valenti, D., Sinico, C., Lai, F., Loy, G., Fadda, A.M., 2003. Niosomes as carriers for tretinoin: II. Influence of vesicular incorporation on tretinoin photostability. Int. J. Pharm. 260, 261–272.

Palugan, L., Spoldi, M., Rizzuto, F., Guerra, N., Uboldi, M., Cerea, M., Moutaharrik, S., Melocchi, A., Gazzaniga, A., Zema, L., 2022. What's next in the use of opacifiers for cosmetic coatings of solid dosage forms? Insights on current titanium dioxide alternatives. Int. J. Pharm. 616, 121550.

Radtke, J., Wiedey, R., Kleinebudde, P., 2021. Alternatives to titanium dioxide in tablet coating. Pharm. Dev. Technol. 26, 989–999.

Ragno, G., Cione, E., Garofalo, A., Genchi, G., Ioele, G., Risoli, A., Spagnoletta, A., 2003. Design and monitoring of photostability systems for amlodipine dosage forms. Int. J. Pharm. 265, 125–132.

Schoneker, D.R., 2023. Why would the EU want to ban titanium dioxide in pharmaceutical products? What would be the potential impact on patients? J. Excip. Food Chem. 13, 94–98.

SeethaLekshmi, S., Thakur, T.S., Varughese, S., 2021. Photoinstability in active pharmaceutical ingredients: crystal engineering as a mitigating measure. J. Photochem. Photobiol. C Photochem. Rev. 49, 100455.

Younes, M., Aquilina, G., Castle, L., Engel, K.H., Fowler, P., Frutos Fernandez, M.J., Fürst, P., Gundert-Remy, U., Gürtler, R., 2021. Safety assessment of titanium dioxide (E171) as a food additive. EFSA J. 19, e06585.