DOI: 10.12923/cipms-2026-0007 Curr. Issues Pharm. Med. Sci., Vol. 39, No. 1, Pages 41-46

Current Issues in Pharmacy and Medical Sciences
Formerly ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA

journal homepage: https://czasopisma.umlub.pl/curipms

# Impact of $TiO_2$-free film coating composition on the dissolution of poorly soluble and poorly permeable drugs

Piotr Adam Chodak[1*], Renata Pawlak-Morka[1], Roberto Manganaro[1], Patrycja Stylska[1], Ewa Szymańska-Dębska[1]

[1] Research and Development Department, Gedeon Richter Polska Sp. z o.o., Grodzisk Mazowiecki, Poland

**ARTICLE INFO**

Received 30 September 2025
Accepted 20 February 2026

***Keywords:***
titanium dioxide,
dissolution profile,
pharmaceutical formulation,
drug dissolution.

**ABSTRACT**

The growing interest in developing coatings for pharmaceutical products that are free of titanium dioxide ($TiO_2$) stems from concerns about potential health risks and resulting regulatory changes. Finding alternatives to $TiO_2$ is essential to meeting the requirements of the new guidelines. For generic drugs, maintaining compliance with the dissolution profiles of the reference drug is also important. This study evaluated the impact of different $TiO_2$-free coating formulations on the dissolution profiles and eligibility for a biological equivalence exemption of a BCS Class IV drug product in two strengths. Specifically, the study aimed to determine whether these coatings could replicate the dissolution profile of the reference product for the high-strength and meet the criteria for exemption from the bioequivalence requirement for the low strength. Tablet cores containing two BCS Class IV active ingredients were manufactured and coated with four different $TiO_2$-free coatings in two strengths. We evaluated the tablets' physical parameters and dissolution profiles. Similarity of the dissolution profiles was statistically evaluated in relation to the reference medicinal product and between different strengths. Different $TiO_2$-free coatings altered the dissolution profile of a BCS Class IV drug product depending on the testing environment. This variability suggests that some coatings may hinder dissolution, while others may facilitate it under certain conditions. These results underscore the importance of thoroughly testing different $TiO_2$-free coatings during the development of BCS Class IV drugs. The choice of coating should be tailored to the specific drug formulation and its intended use.

## INTRODUCTION

Titanium dioxide ($TiO_2$, E171) has long been used as a common excipient in pharmaceutical formulations, primarily for its whitening, opacifying, and stability-enhancing properties. However, recent regulatory developments, particularly within the European Union (EU), have been prompted by concerns regarding the potential toxicity of $TiO_2$ nanoparticles. Authorities have questioned the continued use of $TiO_2$ as a food additive following reports of adverse effects associated with its ingestion [1,2], ultimately leading to its ban in the EU food industry in 2022 [3]. Additional concerns have since been raised regarding the presence of $TiO_2$ in pharmaceutical products by regulatory authorities. Consequently, efforts to identify suitable $TiO_2$-free alternatives have intensified, in anticipation of a potential similar ban for medicinal products.

* **Corresponding author**
e-mail: chodak.pio@gmail.com

In the context of generic drug development, it is essential to ensure that new formulations are comparable to reference medicinal products (RMPs) that contain $TiO_2$ and were developed and approved under previous regulatory standards. Achieving such equivalence presents significant challenges, particularly for Biopharmaceutics Classification System (BCS) Class IV drugs, which are characterized by low solubility and low permeability. Modifying the coating composition without compromising drug performance is therefore critical to maintaining therapeutic efficacy and ensuring regulatory compliance.

Many alternatives have been investigated to replace $TiO_2$ in coating formulations. Depending on the sensitivity of the active pharmaceutical ingredient (API), different substances may be used as alternatives. Formulations can incorporate carbonates (*e.g.*, magnesium and calcium), phosphates (*e.g.*, calcium), cellulose derivatives, oxides (*e.g.*, zinc oxide), polyols (particularly isomalt), talc, and other excipients.

In most cases, however, a single alternative is insufficient to replicate all the functional properties of $TiO_2$, and therefore combinations of these materials are required.

Some evaluations suggest that the use of alternative materials can result in a comparable appearance, provided that minor color variations are considered acceptable [4]. In another study, it was concluded that $TiO_2$-free white coatings were less effective than $TiO_2$-containing coatings when applied to colored core tablets, requiring weight gains of up to 7% to achieve acceptable coverage [5]. In addition to its opacifying properties, $TiO_2$ also functions as a barrier against ultraviolet (UV) radiation, which plays a crucial role in protecting tablets and capsules containing light-sensitive APIs. This protective function is not easily reproduced; however, zinc oxide (ZnO) appears to be a suitable alternative in this context [5].

## AIM

During the development of a generic film-coated tablet product in two dose-proportional strengths containing two BCS Class IV active substances, $TiO_2$-free coating alternatives were considered. The hygroscopic nature of both APIs presented an additional challenge, which was addressed by preparing the coating solutions in a 1:1 water-ethanol solvent mixture. The reference medicinal product (RMP), approved under previous regulatory requirements, contained titanium dioxide in its film coating.

The objective of this study was to achieve dissolution profiles comparable to those of the RMP in three media (pH 1.2, 4.5, and 6.8), with statistical evaluation performed in accordance with regulatory authority requirements [6]. Furthermore, to enable the possibility of a biowaiver for the additional strength based on proportional composition and similar dissolution characteristics, the dissolution profile of the higher strength was required to be comparable to that of the lower strength [6].

## MATERIALS

### Reference medicinal product (RMP)

The qualitative composition of the RMP tablet cores and film coating was determined based on publicly available documentation. The reported qualitative composition of the RMP tablet cores included two BCS Class IV APIs, microcrystalline cellulose (MCC), low-substituted hydroxypropyl cellulose (L-HPC), crospovidone (type A), colloidal anhydrous silica, talc, and magnesium stearate.

The film coating composition consisted of hypromellose, titanium dioxide ($TiO_2$), macrogol 4000, talc, iron oxide red, and iron oxide black (for both low- and high-strength tablets).

### Generic drug product

The generic tablet cores, formulated in dose-proportional compositions, contained two BCS Class IV APIs, microcrystalline cellulose (MCC), low-substituted hydroxypropyl cellulose (L-HPC), crospovidone (type A), colloidal anhydrous silica, talc, and magnesium stearate.

The following $TiO_2$-free coating systems were evaluated:

- Pink coat 1: hypromellose, calcium carbonate, isomalt, medium-chain triglycerides, hydroxypropyl cellulose, iron oxide red, iron oxide black
- Pink coat 2: hypromellose, lactose monohydrate, calcium carbonate, triacetin, iron oxide red
- White coat 1: hypromellose, calcium carbonate, macrogol
- White coat 2: hypromellose, calcium carbonate, lactose monohydrate, triacetin

## METHODS

### Preparation of tablet cores by dry granulation

The active substances, microcrystalline cellulose (MCC), low-substituted hydroxypropyl cellulose (L-HPC), colloidal anhydrous silica, a portion of crospovidone, and magnesium stearate were blended. Dry granulation was performed using an Alexanderwerk BT 120 Pharma roller compactor. The resulting compact was milled and calibrated using an Alexanderwerk RFG 150 DA granulator.

The external phase, consisting of the remaining excipients, was then added and blended with the granulate. The final blend was compressed into tablets using a Riva Piccola rotary tablet press.

Following evaluation of the physical parameters of the tablet cores, the tablets were coated with the appropriate formulations using a Glatt GMPC II coater. The coating suspension was prepared in a 1:1 (v/v) mixture of ethanol (96%) and purified water. For preparation of the coating suspension, the total quantities of ethanol and water were added to a suitable container and stirred to create a vortex, while avoiding air entrapment. The coating powder was then gradually added to the vortex region to prevent flotation on the liquid surface, and stirring was continued until complete dispersion was achieved.

High-strength tablets were coated with Pink Coat 1 and Pink Coat 2 formulations, whereas low-strength tablets were coated with White Coat 1 and White Coat 2 formulations.

### Tablet physical parameters

Tablet hardness and thickness were measured using an ERWEKA MultiCheck 3 tester (n = 10 per batch).

### Friability test

Friability was evaluated using a TDR 100 ERWEKA friability tester. A sample of tablets weighing at least 6.5 g was accurately weighed after removing any loose dust. The tablets were then placed in the drum and subjected to 100 rotations. Upon completion of the test, the tablets were removed, dedusted if necessary, and reweighed to determine the percentage weight loss.

### Disintegration time

The disintegration time of the film-coated tablets was determined using a Pharma Test PTZ AUTO disintegration tester. The test was performed on six tablets from each batch. One dosage unit was placed in each of the six basket tubes, and a disc was added to each tube. Purified water maintained at 37 ± 2°C was used as the disintegration medium.

According to the current edition of the European Pharmacopoeia (Ph. Eur.), film-coated tablets are required to disintegrate within 30 minutes [7].

### Dissolution profiles

Dissolution testing was performed using USP Apparatus 2 (paddle method) at a rotation speed of 50 rpm. The study was conducted in three dissolution media: pH 6.8 phosphate buffer, pH 4.5 acetate buffer, and pH 1.2 (0.1 M HCl). Samples were collected at predetermined time points of 10, 15, 20, 30, 45, and 60 minutes in each medium.

For the reference medicinal product (RMP) and formulations F1 and F2, dissolution testing was performed with six vessels (n = 6), with one tablet placed in each vessel. For formulations F3 and F4 (low-strength formulations), dissolution testing was conducted in accordance with the biowaiver approach based on dose proportionality.

For each test, 900 mL of the appropriate dissolution medium was used, and the temperature was maintained at 37 ± 0.5°C. At each sampling time point, aliquots were withdrawn, filtered through 10 μm filters, and analyzed using a UV-Vis spectrophotometer to determine the percentage of drug released relative to the labeled amount.

Simultaneous quantification of both APIs was performed using an analytical method that ensured specificity and accounted for potential spectral overlap. The analytical procedure was validated in accordance with Good Manufacturing Practice (GMP) and European Medicines Agency (EMA) requirements.

A statistical comparative analysis of the dissolution profiles was performed using a model-independent method based on the similarity factor $f_2$, as recommended by the European Medicines Agency (EMA) in *The Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**6). An $f_2$ value ≥ 50 was considered indicative of similarity between dissolution profiles.

In cases where the predefined conditions for application of the conventional $f_2$ method, as outlined by the EMA, were not met, a comparative analysis between the reference and test products was conducted using a model-independent bootstrap approach for $f_2$. This method is recommended in the document *Clinical Pharmacology and Pharmacokinetics: Questions and Answers* (EMA, 2022, Q&A 3.11). For the bootstrap approach, similarity was concluded if the lower bound of the 90% confidence interval for $f_2$ was ≥ 50.

Statistical analyses were performed using Statistica® software, version 13.3 (StatSoft DPC ver. 2.6.0).

## RESULTS

### Formulation study

To ensure that the coating composition was the only independent variable, tablet cores FC1–FC4 were manufactured separately using identical qualitative and quantitative compositions. Process parameters were maintained consistently within each strength. After evaluation of the tablet core properties, each batch was coated with a distinct coating formulation.

This approach resulted in the production of batches F1–F4. Batches F1 and F2 were coated with pink formulations to identify the coating system most comparable to that of the reference product. Batches F3 and F4 were coated with white formulations and were subsequently evaluated for biowaiver eligibility.

A summary of the coating formulations applied to batches F1–F4 is provided in Table 1.

***Table 1.*** Coating used for tablet batches F1–F4

| Coatings | Core batch | | | |
|---|---|---|---|---|
| | F1 | F2 | F3 | F4 |
| Pink coat 1 | + | - | - | - |
| Pink coat 2 | - | + | - | - |
| White coat 1 | - | - | + | - |
| White coat 2 | - | - | - | + |

### Evaluation of tablet cores

The physical characteristics of the tablet cores in batches FC1–FC4 were evaluated to ensure intra-batch consistency and to confirm that core properties would not influence the final study outcomes. The assessed parameters included tablet thickness and hardness for each oblong tablet.

For each batch, the mean, minimum, and maximum values, as well as the relative standard deviation (RSD), were calculated to evaluate uniformity and identify potential variability within the batches. In addition, tablet core friability was determined.

The results for the physical parameters of batches FC1–FC4 are presented in Table 2.

***Table 2.*** Physical properties of tablet cores (batches FC1–FC4)

| Parameter | | Batch | | | |
|---|---|---|---|---|---|
| | | FC1 | FC2 | FC3 | FC4 |
| Thickness [mm] | Mean | 5.36 | 5.41 | 3.48 | 3.56 |
| | Min | 5.33 | 5.36 | 3.46 | 3.53 |
| | Max | 5.4 | 5.45 | 3.50 | 3.61 |
| | RSD [%] | 0.39 | 0.52 | 0.35 | 0.65 |
| Hardness [N] | Mean | 112.30 | 119.90 | 105.80 | 91.70 |
| | Min | 99.00 | 91.00 | 100.00 | 79.00 |
| | Max | 128.00 | 137.00 | 114.00 | 99.00 |
| | RSD [%] | 7.26 | 12.11 | 4.25 | 8.23 |
| Friability [%] | | <0.05 | <0.05 | <0.05 | <0.05 |

### Evaluation of film-coated tablets

To assess the impact of different film coatings on tablet physical quality, the coated batches F1–F4 were evaluated following the coating process. The measured parameters included thickness, hardness, and disintegration of the film-coated tablets.

For each parameter, the mean, minimum, maximum, and relative standard deviation (RSD) were calculated. This evaluation aimed to determine the influence of each coating formulation on the physical properties of the tablets and to verify intra-batch consistency. The results provide insight into the effects of the coating on the final product's uniformity and robustness.

The results for the physical parameters of batches F1–F4 are presented in Table 3.

***Table 3.*** Physical properties of film-coated tablets (batches F1–F4).

| Parameter | | Batch | | | |
|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 |
| Thickness [mm] | Mean | 5.61 | 5.56 | 3.71 | 3.66 |
| | Min | 5.57 | 5.53 | 3.66 | 3.56 |
| | Max | 5.66 | 5.66 | 3.73 | 3.75 |
| | RSD [%] | 0.52 | 0.66 | 0.58 | 1.75 |
| Hardness [N] | Mean | 146.50 | 157.80 | 107.10 | 111.20 |
| | Min | 124.00 | 141.00 | 90.00 | 99.00 |
| | Max | 169.00 | 181.00 | 120.00 | 120.00 |
| | RSD [%] | 11.87 | 7.86 | 8.39 | 5.78 |
| Disintegration time [mm:ss] | Mean | 15:12 | 11:29 | 08:04 | 07:32 |
| | Min | 10:32 | 10:26 | 07:20 | 06:54 |
| | Max | 18:18 | 12:32 | 08:50 | 08:08 |
| | RSD [%] | 22.1 | 7.7 | 7.9 | 6.6 |

## DISCUSSION

Different amounts of coating material per tablet were required for the pink formulations to achieve the desired color uniformity and overall appearance. Batch F1 required a 7% weight increase, and batch F2 required a 5% increase. The higher coating level in batch F1 led to an extended disintegration time, likely due to the increased film thickness. It was also influenced by variability observed in the individual tablets. Nevertheless, this difference did not affect drug release rates, as F1 exhibited faster dissolution despite the higher weight gain. A corresponding increase in hardness relative to the tablet cores was observed, which is consistent with the known effects of the film-coating process on tablet mechanical properties [9]. Although F1 had a greater coating amount than F2, the F2 formulation had slightly higher tablet hardness. This suggests that the mechanical properties of the coatings vary depending on their specific formulation. White formulations did not influence tablet hardness, and the differences between F3 and F4 were not significant.

To assess the similarity of the dissolution profiles, the profiles were evaluated for batches F1–F4 (after coating) and the RMP. The dissolution results for both APIs for batches F1–F4 are shown in Tables 4 and 5. A graphical comparison is shown in Figures 1-3.

Statistical comparisons were conducted to evaluate the similarity between the formulations. According to the guidelines, F1 and F2 were compared with the RMP with the intent of later comparing the lower strengths to the most promising high-strength formulation. Based on the results, F1 was shown to be similar to the RMP, achieving higher dissolution values at subsequent time points despite higher weight gain. These results support the claim that the amount of coating is not a rate-controlling factor for drug release. The underlying mechanisms require further investigation for full explanation.

One possible explanation for F1's faster dissolution is the addition of hydroxypropyl cellulose (HPC) to its HPMC-based matrix. HPC has been reported to exhibit faster water uptake than HPMC [10], which could lead to earlier wetting of the tablet core and initiate faster dissolution of the active

***Table 4.*** API 1 dissolution profiles in three media (pH 6.8, 4.5 and 1.2) for RMP and batches F1–F4

| pH conditions | Time [min]↓ | RMP | F1 | F2 | F3 | F4 |
|---|---|---|---|---|---|---|
| | | API 1 – amount of drug released [%] | | | | |
| pH 6.8 | 10 | 45 | 44 | 35 | 45 | 53 |
| | 15 | 65 | 69 | 54 | 69 | 74 |
| | 20 | 79 | 84 | 71 | 84 | 86 |
| | 30 | 91 | 94 | 83 | 92 | 93 |
| | 45 | 96 | 97 | 90 | 95 | 96 |
| | 60 | 98 | 97 | 93 | 96 | 98 |
| pH 4.5 | 10 | 51 | 42 | 39 | 35 | 50 |
| | 15 | 73 | 65 | 61 | 57 | 70 |
| | 20 | 85 | 82 | 78 | 73 | 82 |
| | 30 | 95 | 94 | 91 | 84 | 89 |
| | 45 | 98 | 96 | 94 | 88 | 92 |
| | 60 | 99 | 97 | 94 | 89 | 93 |
| pH 1.2 | 10 | 6 | 5 | 0 | 0 | 6 |
| | 15 | 15 | 12 | 0 | 0 | 12 |
| | 20 | 20 | 17 | 1 | 1 | 16 |
| | 30 | 26 | 23 | 7 | 3 | 22 |
| | 45 | 33 | 29 | 14 | 5 | 25 |
| | 60 | 35 | 32 | 24 | 7 | 27 |

***Table 5.*** API 2 dissolution profiles in three media (pH 6.8, 4.5 and 1.2) for RMP and batches F1–F4

| pH conditions | Time [min]↓ | RMP | F1 | F2 | F3 | F4 |
|---|---|---|---|---|---|---|
| | | API 2 – amount of drug released [%] | | | | |
| pH 6.8 | 10 | 46 | 44 | 35 | 45 | 54 |
| | 15 | 67 | 69 | 54 | 70 | 74 |
| | 20 | 80 | 84 | 71 | 84 | 87 |
| | 30 | 92 | 94 | 84 | 93 | 94 |
| | 45 | 98 | 97 | 90 | 95 | 97 |
| | 60 | 99 | 97 | 93 | 97 | 98 |
| pH 4.5 | 10 | 54 | 43 | 52 | 37 | 52 |
| | 15 | 76 | 67 | 72 | 61 | 72 |
| | 20 | 88 | 84 | 84 | 76 | 84 |
| | 30 | 98 | 96 | 91 | 88 | 91 |
| | 45 | 101 | 97 | 94 | 91 | 94 |
| | 60 | 101 | 98 | 95 | 92 | 95 |
| pH 1.2 | 10 | 5 | 5 | 0 | 0 | 6 |
| | 15 | 14 | 11 | 0 | 0 | 12 |
| | 20 | 19 | 16 | 1 | 2 | 16 |
| | 30 | 25 | 22 | 7 | 3 | 22 |
| | 45 | 32 | 28 | 15 | 7 | 26 |
| | 60 | 34 | 31 | 24 | 12 | 29 |

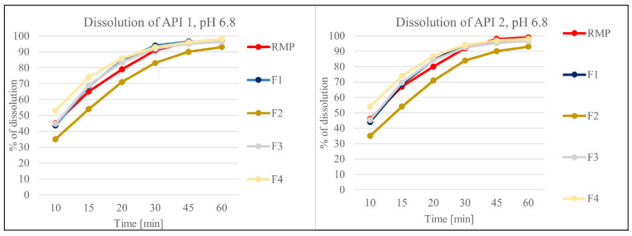


***Figure 1.*** Dissolution profiles of API 1 and API 2 in RMP and formulations F1–F4 in pH 6.8

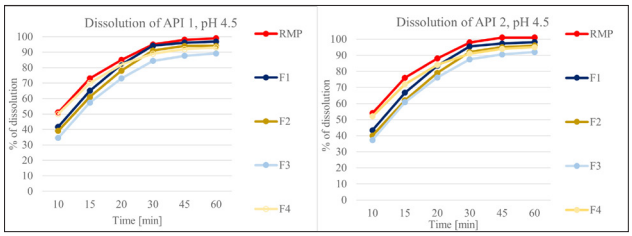


***Figure 2.*** Figure 2. Dissolution profiles of API 1 and API 2 in RMP and formulations F1–F4 in pH 4.5

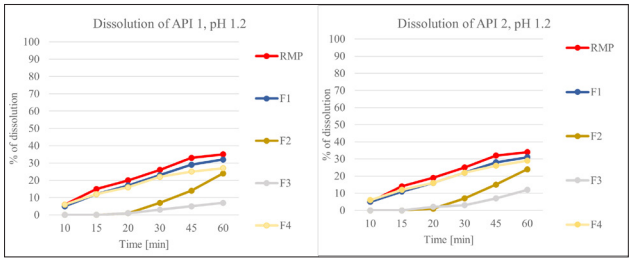


***Figure 3.*** Dissolution profiles of API 1 and API 2 in RMP and formulations F1–F4 in pH 1.2

substances. Isomalt, a polyol present in F1, could also act synergistically by forming pores in the polymer matrix and by increasing osmotic pressure, thus facilitating faster water uptake and leading to a similar effect [11].

Eligibility for a biowaiver for lower-strength formulations was assessed only for F1, which was used as a reference for the comparisons made between F1 and F3/F4. The methods section provides the approach for assessing dissolution profile similarity, including the guidelines for calculating $f_2$ factors and performing statistical evaluations using the bootstrap method. The evaluation is summarized in Tables 6 and 7.

The dissolution profile analysis revealed that formulation F2 did not meet the similarity requirements with the RMP. Formulation F2 exhibited $f_2$ factors below 50 for both APIs across all tested media. In contrast, formulation F1 demonstrated similarity to the RMP. Lower RSD values allowed for direct $f_2$ calculation without requiring the bootstrap method.

The lower-strength formulation F3 significantly underperformed at pH 1.2, with minimal drug release observed, suggesting a strong interaction between the coating components and the acidic medium. Since F3 and F4 have the same base of hydroxypropyl methylcellulose (HPMC) and calcium carbonate, the difference in performance could be attributed to the presence of macrogol in F3 compared to a combination of lactose monohydrate and triacetin in F4. The mechanisms of such action require further investigation, especially since macrogol is considered soluble in aqueous media independent of pH; therefore, hindering dissolution must be more complex. It has been reported that macrogol can influence the matrix by slowing the hydration process under acidic conditions [12]. Another possible explanation relates to the ratio of macrogol to HPMC. While the exact quantitative composition of the coating is a trade secret, studies suggest that the macrogol-to-polymer concentration ratio influences the dissolution rate. More macrogol generally leads to faster dissolution [13]. It is possible that the amount of macrogol in F3 was insufficient to facilitate proper dissolution. In contrast, the lactose-triacetin system in F4 may provide a more effective mechanism for media penetration and subsequent drug release.

F4 showed acceptable similarity to F1 at pH 4.5 and 1.2. However, at pH 6.8, despite yielding F2 factors of 59 and 60, high RSD values necessitated the use of the bootstrap method, which resulted in a value of 48. These results suggest that variability within batch F4 was likely a limiting factor in meeting the criteria for biowaiver eligibility. Consequently, eliminating this variability by improving the coating process to achieve a more uniform coating could lead to statistical similarity.

The results for both the pink and white coatings imply that the composition of the film coat formulation significantly affects the dissolution profile. These findings expand upon prior research that often highlights the goal of nonfunctional coatings as serving aesthetic, compliance, and brand recognition purposes [14,15] without addressing the impact of coatings on drug release rates under various conditions. Further studies should investigate the potential influence of specific excipients used in coating compositions to determine how they interact with different dissolution media and affect drug release behavior.

***Table 6.*** Statistical evaluation of similarity of dissolution profiles for API 1 and API 2 in three media (pH 6.8, 4.5 and 1.2) with RMP as a reference to F1 and F2

| RMP vs F1, F2 | | | | | |
|---|---|---|---|---|---|
| Reference | pH | API 1 | | API 2 | |
| | | F1 | F2 | F1 | F2 |
| RMP | pH 6.8 | SIMILAR f2= 70.0 | NOT SIMILAR f2= 50.8 LL (90% BCA)* = 39.6 | SIMILAR f2= 75.3 | NOT SIMILAR f2= 47.4 LL (90% BCA) = 37.0 |
| | pH 4.5 | SIMILAR f2= 56.7 | NOT SIMILAR f2= 47.9 LL (90% BCA) = 38.9 | SIMILAR f2= 54.1 | NOT SIMILAR f2= 45.4 LL (90% BCA) = 37.1 |
| | pH 1.2 | SIMILAR f2= 75.5 LL (90% BCA) = 66.6 | NOT SIMILAR f2= 44.4 LL (90% BCA) = 40.9 | SIMILAR f2= 75.3 LL (90% BCA) = 66.6 | NOT SIMILAR f2= 46.0 LL (90% BCA) = 42.4 |

* - lower limit of the 90% bootstrap confidence analysis interval

***Table 7.*** Statistical evaluation of similarity of dissolution profiles for API 1 and API 2 in three media (pH 6.8, 4.5 and 1.2) with F1 as a reference to F3 and F4

| F1 *vs* F3, F4 | | | | | |
|---|---|---|---|---|---|
| Reference | pH | API 1 | | API 2 | |
| | | F3 | F4 | F3 | F4 |
| F1 | pH 6.8 | SIMILAR f2= 94.6 | NOT SIMILAR f2= 60 LL (90% BCA) = 48 | SIMILAR f2= 92.8 | NOT SIMILAR f2=59 LL (90% BCA) = 48 |
| | pH 4.5 | NOT SIMILAR f2=54.7 LL (90% BCA) = 45.1 | SIMILAR f2= 62.7 | NOT SIMILAR f2= 59.3 LL (90% BCA) = 48.5 | SIMILAR f2=60.8 |
| | pH 1.2 | NOT SIMILAR f2= 37.0 LL (90% BCA) = 34.0 | SIMILAR f2= 77.9 LL (90% BCA) = 65.9 | NOT SIMILAR f2= 40.0 LL (90% BCA) = 37.0 | SIMILAR f2= 89.2 LL (90% BCA) = 83.3 |

* - lower limit of the 90% bootstrap confidence analysis interval

## Study limitations

This study provides insights into the impact of $TiO_2$-free coatings on the dissolution behavior of a BCS Class IV drug product. However, several limitations must be acknowledged. First, the investigation was restricted to a single drug product containing two APIs, limiting the versatility of the results in relation to other compounds within this

biopharmaceutical class. Additionally, only a few alternative coating formulations were evaluated; all of these formulations contained calcium carbonate instead of $TiO_2$, so the potential effects of other $TiO_2$ substitutes on drug release profiles were not explored. Third, all dissolution assessments were performed under *in vitro* conditions only, which may not fully predict *in vivo* behavior. Clinical studies are necessary to confirm the impact on bioequivalence.

## CONCLUSIONS

This study emphasizes the substantial influence of coating composition on the dissolution behavior and overall efficacy of coated tablets, especially for BCS Class IV medicinal products. $TiO_2$-free formulations present unique challenges in maintaining product consistency, achieving regulatory equivalence with the reference product, and meeting the criteria for a biological testing exemption for generic products.

The coating composition influences several critical quality attributes, including disintegration time, dissolution rate, and variability across different media. Replacing $TiO_2$ with calcium carbonate, as well as incorporating additional excipients within the coating formulation, can modify the product's performance characteristics. The presence or absence of specific components affects coating uniformity and the tablet's behavior under dissolution conditions, contributing to the observed differences in dissolution profiles and their statistical similarity.

Furthermore, the type of coating formulation impacts the physical properties, which affect dissolution variability. Differences in coating composition can make it difficult to achieve consistent drug release across pH media and can sometimes considerably hinder the dissolution of the active substance. Variability in dissolution results highlights the importance of carefully selecting and optimizing coating materials to balance functional attributes, such as opacity and stability on one side, with drug release kinetics on the other.

This case study demonstrates that $TiO_2$-free coatings are a viable alternative to standard $TiO_2$-containing coatings. However, their performance must be thoroughly evaluated during formulation development. These findings underscore the necessity of a tailored approach to designing generic medicinal product formulations that considers different coating compositions to ensure consistent drug release across relevant physiological pH conditions. This contributes valuable knowledge to the development of safer and more effective pharmaceutical products.

## ORCID iDs

Piotr Adam Chodak https://orcid.org/0009-0008-2323-261X
Renata Pawlak-Morka https://orcid.org/0000-0001-8828-6661
Roberto Manganaro https://orcid.org/0000-0002-6522-9362
Patrycja Stylska https://orcid.org/0009-0008-9473-2750
Ewa Szymańska-Dębska https://orcid.org/0009-0000-0554-4435

## REFERENCES

1. Bischoff NS, de Kok TM, Sijm DTH, van Breda SG, Briedé JJ, Castenmiller JJM, et al. Possible adverse effects of food additive E171 (titanium dioxide) related to particle specific human toxicity, including the immune system. *Int J Mol Sci.* 2021;22(1):207. https://doi.org/10.3390/ijms22010207
2. Bettini S, BoutetRobinet E, Cartier C, Coméra C, Gaultier E, Dupuy J, et al. Foodgrade $TiO_2$ impairs intestinal and systemic immune homeostasis, initiates preneoplastic lesions and promotes aberrant crypt development in the rat colon. *Sci Rep.* 2017;7:40373. https://doi.org/10.1038/srep40373
3. Commission Regulation (EU) 2022/63 of 14 January 2022 Amending Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council as regards the food additive titanium dioxide (E171). *Off J Eur Union*. Accessed May 13, 2025. https://eur-lex.europa.eu/eli/reg/2022/63/oj
4. Palugan L, Spoldi M, Rizzuto F, Guerra N, Uboldi M, Cerea M, et al. What's next in the use of opacifiers for cosmetic coatings of solid dosage forms? Insights on current titanium dioxide alternatives. *Int J Pharm.* 2022;616:121550. https://doi.org/10.1016/j.ijpharm.2022.121550
5. Radtke J, Wiedey R, Kleinebudde P. Alternatives to titanium dioxide in tablet coating. *Pharm Dev Technol.* 2021;26(9):989-999. https://doi.org/10.1080/10837450.2021.1968900
6. European Medicines Agency. *Guideline on the investigation of bioequivalence.* CPMP/EWP/QWP/1401/98 Rev. 1/Corr. Published 2010. Accessed May 13, 2025. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-bioequivalence-rev1_en.pdf
7. *European Pharmacopoei*a. 11th ed. European Directorate for the Quality of Medicines & Health Care; 2022.
8. European Medicines Agency. *Clinical pharmacology and pharmacokinetics - Questions and answers*. Updated 2022. Accessed May 13, 2025. https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/clinical-pharmacology-pharmacokinetics-questions-answers
9. Stern PW. Effects of film coatings on tablet hardness. *J Pharm Sci.* 1976;65(9):1291-1295. https://doi.org/10.1002/jps.2600650908
10. Patel NG, Banella S, Serajuddin ATM. Moisture sorption by polymeric excipients commonly used in amorphous solid dispersions and its effect on glass transition temperature: II. Cellulosic polymers. *J Pharm Sci.* 2022;111(11):3114-3129. https://doi.org/10.1016/j.xphs.2022.07.020
11. Jang EH, Park YS, Choi DH. Investigation of the effects of materials and dry granulation process on the mirabegron tablet by integrated QbD approach with multivariate analysis. *Powder Technol.* 2021;382:23-39. https://doi.org/10.1016/j.powtec.2020.12.044
12. Jannin V, Duysburgh C, Gonzalez V, Govaert M, Agisson M, Marzorati M, et al. *In vitro* evaluation of the gastrointestinal delivery of acid-sensitive pancrelipase in a next generation enteric capsule using an exocrine pancreatic insufficiency disease model. *Int J Pharm.* 2023;630:122441. https://doi.org/10.1016/j.ijpharm.2022.122441
13. Samuelov Y, Donbrow M, Friedman M. Sustained release of drugs from ethylcellulose-polyethylene glycol films and kinetics of drug release. *J Pharm Sci.* 1979;68(3):325-329. https://doi.org/10.1002/jps.2600680318
14. Suzzi D, Stefan R, Khinast JG. Local analysis of the tablet coating process: Impact of operation conditions on film quality. *Chem Eng Sci.* 2010;65:5699-5715. https://doi.org/10.1016/j.ces.2010.07.007
15. Xie C, You Y, Ma H, Zhang X, Li T, Liu Y, et al. Mechanism of inter-tablet coating variability: Investigation about the motion behavior of ellipsoidal tablets in a pan coater. *Powder Technol.* 2020. https://doi.org/10.1016/j.powtec.2020.10.088