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Impact of antioxidant addition on drug dissolution: implications for NDSRI mitigation biowaivers

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ABSTRACT

Nitrosamine impurities have garnered recent attention due to their presence in pharmaceuticals and their mutagenic risks. Recent studies have emphasized controlling impurities and suggest ways to mitigate the further formation of nitrosamines by the addition of antioxidants to tablets and capsules. Recent Food and Drug Administration (FDA) guidance supports this, however, practical experience with this new guidance update remains limited. This study investigates the impact of added antioxidants on dissolution of diclofenac potassium tablets. Six antioxidants were tested for their effect on in vitro dissolution. Two tablet formulation families of 50mg diclofenac potassium were fabricated with and without antioxidant. Tablets were subjected to quality testing, including in vitro dissolution in United States Pharmacopeia Simulated Intestinal Fluid (USP SIF) and in sodium bicarbonate buffer. Dissolution profiles were compared using the similarity factor f_2. All tablets using ascorbic acid, cysteine, or sodium bicarbonate did not impact dissolution in USF SIF and sodium bicarbonate buffer, per a liberal interpretation of f_2 calculation in the 1997 FDA dissolution guidance, except formulation B tablets with antioxidant sodium bicarbonate in sodium bicarbonate buffer. Meanwhile, due to coning, all tablets using caffeic acid, fumaric acid, or sodium ascorbate slowed dissolution in USF SIF and sodium bicarbonate buffer, except formulation B tablets with antioxidant sodium ascorbate. Overall, results point towards the feasibility of added antioxidant to not impact dissolution.

KEYWORDS

Nitrosamine

Antioxidants

Diclofenac potassium

Dissolution

Nitrosamine mitigation

ABBREVIATIONS

Nitrosamine Drug Substance Related Impurities, NDSRIs;

Active Pharmaceutical Ingredient, API;

Food and Drug Administration, FDA;

Immediate Release, IR;

Biopharmaceutics Classification System, BCS;

Nonsteroidal Anti-Inflammatory Drug, NSAID;

Microcrystalline Cellulose, MCC;

United States Pharmacopeia, USP;

United States Pharmacopeia Simulated Intestinal Fluid, USP SIF;

Polyvinylidene Difluoride, PVDF;

High Performance Liquid Chromatography, HPLC;

Names of chemical compounds studied in this article include: diclofenac potassium, ascorbic acid, cysteine, sodium bicarbonate, caffeic acid, fumaric acid, sodium ascorbate.

1. INTRODUCTION

Nitrosamine impurities, labeled as "cohort of concern" by the International Council for Harmonization (ICH), have garnered significant attention due to their potential to cause deoxyribonucleic acid (DNA) damage. The activated N-nitroso groups can directly alkylate DNA, leading to mutations (Food and Drug Administration, 2024).

Nitrosamine impurities are classified into two main types: small molecule nitrosamine impurities and nitrosamine drug substance related impurities (NDSRIs). The former generally does not share any structural similarities to the active pharmaceutical ingredient (API), whereas the latter is structurally related to the API by being derived from API and includes an API fragment in its structure (Food and Drug Administration, 2024). NDSRIs are generally formed in drug products by nitrosation of API by residual nitrosating agent in excipients or API raw material (Food and Drug Administration, 2023). The nitrite levels in an excipient and its proportion in the formulation may contribute to nitrosamine impurirty formation, including microcrystalline cellulose, lactose, croscarmellose sodium, and magnesium stearate, which are used here (Boetzal et al., 2023). Diclofenac potassium has a vulnerable amine, which can lead to formation of NDSRI, nitroso-diclofenac (Osorio et al., 2022).

Current literature suggests the formulation addition of an antioxidant as a nitrite scavenger to deactivate nitrosating agents and prevent formation of NDSRI (Shakleya et al., 2023; Nanda et al., 2021). Shakleya et al. showed the addition of an antioxidant (i.e. ascorbic acid, caffeic acid and ferulic acid) or the pH modifier sodium bicarbonate mitigated nitrosamine formation in wet granulated bumetanide tablets (Shakleya et al., 2023). Additional studies showing antioxidants' lack of modulation of drug permeability support this approach (Lu et al., 2024; Yu et al., 2024; Kulkarni et al., 2024).

The Food and Drug Administration (FDA) control of nitrosamine impurities in human drugs guidance, updated in 2024, indicates reformulation of immediate release (IR) oral solid dosage forms (or oral suspensions) containing a Biopharmaceutics Classification System (BCS) I, II or III drug in order to mitigate NDSRI formation was generally permissible, with possibility of a biowaiver. The guidance highlighted the use of ascorbic acid, α-tocopherol, propyl gallate, cysteine hydrochloride or a pH modifier in an amount no more than 10 mg per dose or maximum daily exposure (whichever is lower) (Food and Drug Administration, 2024).

The objective here was to assess the effect of antioxidants on the dissolution of IR tablets of diclofenac potassium. Two families of diclofenac potassium IR tablets were formulated: a rapid Formulation A and less rapid Formulation B. Formulation A mimics the composition of a marketed tablet of diclofenac potassium. For each Formulation A and Formulation B tablet families, one formulation contained no antioxidant. The other six formulations in each family contained a single antioxidant: ascorbic acid, cysteine, sodium bicarbonate, caffeic acid, fumaric acid, or sodium ascorbate. Sodium bicarbonate is considered an antioxidant here, although it functions to potentially reduce NDSRI formation by reducing acidity. Also, here, ascorbic acid, cysteine, and sodium bicarbonate are denoted as preferred antioxidants, since the FDA nitrosamine control guidance indicates their use at 10mg is expected to be non-problematic. Meanwhile, caffeic acid,

fumaric acid, and sodium ascorbate are denoted as other antioxidants, since the FDA guidance does not specifically indicate their use to be non-problematic.

For each Formulation A and B families, dissolution profiles of each of the six formulations with antioxidants in compendial (i.e., USP SIF) and sodium bicarbonate buffer were studied and compared to tablets without antioxidant to elucidate any change in dissolution with different types of antioxidant.

Diclofenac potassium was used as the model drug. It is a nonsteroidal anti-inflammatory drug (NSAID) belonging to BCS class II. It is the salt of a weak acid (pK_a=4.0) and is well absorbed after oral administration (National Center for Biotechnology Information, 2025a; Chuasuwan et al., 2009). Although diclofenac potassium has low solubility of 0.0012 mg/ml and 0.0036 mg/ml at pH 1.2 and pH 4.5, respectively, it is highly soluble at pH 6.8 (Chuasuwan et al., 2009). It has a solubility of 0.14 mg/ml at pH 5.8. Nevertheless, previous examination recommended potential biowaivers for IR drug products of diclofenac salt forms (Chuasuwan et al., 2009). The six antioxidants were selected since they are weak acids or sodium salts of weak acids.

Results show the feasibility of added antioxidant to not impact dissolution. When dissolution was impacted, dissolution dissimilarity appeared to be due to coning, as apex vessels substantially eliminated slower dissolution. An unlikely explanation of antioxidant effect was that antioxidant locally decreased pH to cause slower dissolution of the weakly acidic drug.

2. MATERIALS AND METHOD

2.1.Materials

Diclofenac potassium was purchased from Chem Shuttle (Burlingame, CA). Microcrystalline cellulose, croscarmellose sodium and dibasic calcium phosphate were purchased from JRS Pharma (Patterson, NY). Anhydrous lactose (Supertab21) was purchased from DFE Pharma (Paramus, NJ). Pregelatinized starch was purchased from Colorcon (Westpoint, PA). Magnesium stearate was purchased from Spectrum (New Brunswick, NJ). All antioxidants (i.e., ascorbic acid, cysteine, sodium bicarbonate, caffeic acid, fumaric acid, and sodium ascorbate), potassium phosphate, sodium hydroxide, sodium chloride, sodium bicarbonate and all organic solvents were purchased from SigmaAldrich (St. Louis, MO). Marketed tablets of diclofenac potassium 50mg (Advagen; Plainsboro, NJ) were commercially obtained.

2.2.Tablet formulation

Two families of diclofenac potassium IR tablets (50mg strength) were formulated: a rapid Formulation A family and less rapid Formulation B family. Table 1 lists compositions of Formulation A and Formulation B tablets. For each family, one formulation contained no antioxidant, and the other six formulations contained a single antioxidant: ascorbic acid, L-cysteine, sodium bicarbonate, caffeic acid, fumaric acid, or sodium ascorbate. Of note, sodium

bicarbonate is considered an antioxidant here, although functions to potentially reduce NDSRI formation by reducing acidity (i.e. via serving as a pH modifier).

Formulation A was composed of microcrystalline cellulose (MCC), anhydrous lactose, croscarmellose sodium, and magnesium stearate, along with a possible antioxidant. Formulation B was composed of microcrystalline cellulose, dibasic calcium phosphate, pregelatinized starch, and magnesium stearate, along with a possible antioxidant.

For each formulation, 49.5g of drug and excipients (except magnesium stearate) were added to a plastic 500cc bottle in the amounts and order listed in Table 1 and blended for 5 min at 101 RPM using a Turbula mixer. Magnesium stearate (0.5g) was added and blended for 5 min at 101 RPM. Total powder blend was 50 g (Kale et al, 2009; Obidiro et al., 2022;). Compared to tablets without antioxidant, tablets with antioxidant had less bulking agents.

2.3.Direct compression

Powder blend was weighed and punched into 250 mg tablets (i.e. 50mg drug per tablet) using a single station Natoli NP-RD10A hydraulic press with a 10mm diameter flat punch. Based on preliminary studies of tablet hardness and tablet disintegration, compaction force was 10,000N for Formulation A and 20,000N for Formulation B.

2.4.Tablet characterization

Each tablet was weighed. Any tablet with a weight that differed by more than 1.6% from target weight of 250 mg was rejected. Each tablet batch (i.e. each of the 14 tablet formulations) was subjected to tablet breaking force (n=3) and disintegration testing (n=6). Disintegration was performed per the United States Pharmacopeia (USP) with disks in 650 ml of water at 37^0C. (USP-NF 2025a)

2.5.Dissolution testing using compendial vessels

Dissolution testing was performed using a mechanically calibrated USP apparatus II into USP simulated intestinal fluid (SIF) (pH=6.8) and sodium bicarbonate buffer (pH=6.5) (USP-NF, 2025b; Sakamoto et al., 2021). The compendial method for diclofenac potassium tablets was followed and involved USP SIF without enzyme (900ml), using USP apparatus II at 50rpm at 37°C. Additionally, using these same conditions, dissolution was performed here into sodium bicarbonate buffer (500ml) using the floating lid method (Sakamoto et al., 2023). For both media, paddle rpm was increased from 50 rpm to 200 rpm at 90 min to reduce coning which was generally present. From each vessel, 2 ml samples were taken at 10, 20, 30, 45, 60, 90, and 120 min (and 180 min for sodium bicarbonate buffer) without replacement.

For compendial dissolution testing, 6L USP SIF without enzyme was made using 50mM potassium phosphate monobasic monohydrate and 462 ml of 0.2N NaOH. pH was adjusted to 6.8. 900ml of degassed SIF media was added to each 1L vessel. Tablets were added along the right-side wall of the dissolution vessel in order to measure dissolution of a single tablet (n=6).

For dissolution into sodium bicarbonate buffer, the floating lid method of Sakamoto et al. was followed. Freshly made 490ml solution containing 10mM sodium bicarbonate and 140mM sodium chloride was added to each dissolution vessel. 10 ml of 0.165N HCl was then added. CO_2 generated in-situ was trapped using a floating lid made of Styrofoam, with the aim to maintain the pH at 6.5. pH was monitored using a wireless pH meter (PASCO, Roseville, CA). For the first 120 min, pH tended to increase from pH 6.5 to about 7.0. At 120 min, the floating lid was removed, and pH tended to increase to 8.0. Tablets were added via the center of the vessel. Each vessel assessed dissolution of a single tablet (n=6).

2.6. Dissolution testing using apex vessels into USP SIF

As results show, coning occurred across all formulations, particularly for Formulation B. The two slowest profiles were Formulation B with either caffeic acid or fumaric acid into USP SIF, which showed marked coning and were markedly slower than Formulation B without antioxidant. To assess the impact of coning, identical dissolution studies were conducted as above but using apex vessels, for Formulation B with caffeic acid and Formulation B with fumaric acid into USP SIF, as well as Formulation B without antioxidant (n=6). Of note, apex vessels are used in some USP dissolution methods (e.g. carbamazepine extended-release capsules) (USP-NF 2025c), although not for diclofenac potassium tablets. Hence, here, apex vessels are denoted to be non-compendial.

2.7.Drug quantification

All dissolution samples were filtered using a 0.45 µm pore size polyvinylidene fluoride (PVDF) syringe filter and analyzed using high performance liquid chromatography (HPLC). Filtrate from bicarbonate buffer (but not from compendial media) was diluted 1:1 with mobile phase. Diclofenac potassium in sample was analyzed via reverse phase HPLC with UV detection (280nm) using a Waters E2695 Alliance HPLC System (Milford, MA). The mobile phase consisted of 35% water at pH 2.5 (adjusted with phosphoric acid) and 65% methanol. A ZORBAX SB-C18 column (4.6 x 150 mm 5-micron) was used. The flow rate was 1mL/min. Column temperature was 37 °C. Diclofenac potassium retention time was about 11 min.

2.8.f_2 analysis

For each Formulation A and B families, dissolution profile comparisons of tablets with antioxidant versus without antioxidant were performed using f_2:

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

where n is number of observations, t is the time point, R_t and T_t are the mean percent diclofenac potassium dissolved from reference (i.e. without antioxidant) and test formulation (i.e. with antioxidant) at time t, respectively (Moore et al., 1996; Polli et al., 1997). Profile of marketed product versus tablets without antioxidants was also compared.

f_2 values are well known to be dependent on selection of time points (Jamil et al., 2024). Hence, several differing ways to calculate f_2 were computed. For example, BCS M9, which concerns BCS-based biowaivers, suggests the fewest number of time points, typically leading to a most conservative approach to calculate f_2 (Food and Drug Administration, 2024). Meanwhile, the FDA 1997 IR dissolution guidance can be interpreted in two ways, denoted conservative and liberal (Jamil et al., 2024; Food and Drug Administration, 1997). Here, the liberal interpretation of the FDA 1997 guidance (i.e. promotion of regulatory relief) was applied in drawing conclusions. f_2 was also calculated using a range of differing timepoints (e.g. 10-45 min).

2.9.Assessment of antioxidant solubility

Antioxidant solubility was estimated using visual inspection (Janey, 2021). Given the relatively small amount of antioxidant in each tablet (i.e. 10mg), the main question was whether or not 10mg of each antioxidant exhibited a large solubility (i.e. 10mg solubility in about 100ml of USP SIF). For each antioxidant, 50mg of antioxidant was added to 100ml of USP SIF at room temperature. As results shown, all powder visually dissolved within 10 min. An additional 50mg was added (total 100mg antioxidant per 100ml) and visually inspected after 10min, as well as 24 hr. later.

3. RESULTS

3.1. Tablet characterization and overall dissolution observations

Table 2 lists tablet hardness disintegration time, and maximum weight difference from target for each specific tablet formulation. There was a total of 14 specific formulations, with seven for each Formulation A and B families. The seven formulations contained either one of six different antioxidants (at 4% w/w/ level) or no antioxidant.

In Table 2, all tablet formulations exhibited favorable content uniformity and rapid disintegration. Overall, in Table 2, tablet properties across Formulation A and B were not remarkedly different. For example, hardness ranged from 47.3-79.5 N for formulation A, while ranged from 33.2 - 60.1 N for Formulation B. Formulation A disintegration sometimes exceeded 6 min, while Formulation B tended to never be more than 5 min. For both formulation families, all tablets were within 1.6% of the target total tablet weight (i.e. 250 mg), and hence content uniformity of these 50mg diclofenac potassium tablets was acceptable.

Table 3 lists overall dissolution observations for each added antioxidant. During in vitro dissolution, coning was present in all vessels. As expected, coning was more prominent in all Formulation B tablets than Formulation A tablets. Formulation B included dicalcium phosphate dihydrate, while Formulation A included lactose. Relatedly, profiles from Formulation B were slower than Formulation A. All Formulation B tablets showed an increase in dissolution after 90 min, when stirring speed was increased from 50 rpm to 200 rpm, and coning dissipated.

Visually, coning of a fine powder persisted for a longer duration for Formulation B tablets containing caffeic acid or sodium ascorbate. Meanwhile, upon disintegration, Formulation B tablets with fumaric acid formed a cone as well as suspended clumps in the first 30 min. Overall,

all three of these other antioxidants appeared, visually, to hinder Formulation B dissolution via relatively greater coning, compared tablets with no antioxidant, and compared to tablets with preferred antioxidants.

3.2. *Dissolution profiles of tablets with preferred antioxidants*

Ascorbic acid, cysteine, and sodium bicarbonate are denoted here to be preferred antioxidants, since the FDA nitrosamine control guidance indicates their use at 10mg is expected to be non-problematic. The USP compendial method for diclofenac potassium tablets, which was followed in using USP SIF media, requires at least 75% of diclofenac potassium to be dissolved at 60 min. In Fig 1, in USP SIF, Formulation A tablets with preferred antioxidants were similar to Formulation A tablets without antioxidant (panel A). All profiles were above 75% by 30 min, including the marketed product. In Table 4, f_2 values were calculated using eight different data selection criteria, including a liberal interpretation of the FDA 1997 dissolution guidance. It has been previously described that differing guidance have different data selection criteria, including two distinct interpretations of the FDA 1997 dissolution guidance. Using the liberal interpretation of the FDA 1997 dissolution guidance, Formulation A tablets with preferred antioxidants were similar to Formulation A tablets without antioxidant. Using more conservative interpretation of the guidance or using the BCS M9 guidance criteria, tablets with ascorbic acid or cysteine were not similar to tablets without antioxidant (i.e. were each faster).

In Fig 1, in sodium bicarbonate buffer, Formulation A tablets with preferred antioxidants were also similar to Formulation A tablets without antioxidant (panel B). Again, all profiles were above 75% by 30 min, including the marketed product. In Table 4, all f_2 calculations, including the liberal interpretation of the FDA 1997 dissolution guidance, found profiles to be similar to the profile from tablet without antioxidant.

In Fig 2, in USP SIF, Formulation B tablets with preferred antioxidants were also similar to Formulation B tablets without antioxidant (panel A). All profiles of test tablets showed incomplete release from 20-90 min due to coning, which was dispersed upon increasing paddle speed at 90 min. In Table 5, all f_2 calculations of test tablets concluded that profiles with preferred antioxidants were similar tablets without antioxidant.

In Fig 2, in sodium bicarbonate buffer, Formulation B tablets with ascorbic acid or cysteine were similar to Formulation B tablets without antioxidant (panel B), from all f_2 calculations in Table 5. Meanwhile, Formulation B tablets with sodium bicarbonate were not similar (i.e. slower).

Overall, all tablets using the preferred antioxidants ascorbic acid L-cysteine or sodium bicarbonate did not impact dissolution in USF SIF and sodium bicarbonate buffer, per a liberal interpretation of f_2 calculation in the 1997 FDA dissolution guidance, except Formulation B tablets with antioxidant sodium bicarbonate in sodium bicarbonate buffer.

3.3. Dissolution profiles of tablets with other antioxidants

Caffeic acid, fumaric acid, and sodium ascorbate are denoted here as other antioxidants, since the FDA nitrosamine control guidance does not specifically indicate their use to be non-problematic.

Figure 3 and 4 plots dissolution profiles of tablets with other antioxidants. Overall, compared to profiles with preferred antioxidants (i.e. Fig 1 versus Fig 3 for Formulation A, and Fig 2 versus Fig 4 for Formulation B), caffeic acid and fumaric acid tended to slow dissolution, particularly between 20-90 min. Likewise, tablets with caffeic acid and fumaric acid appeared to cone more.

Figure 3 plots the dissolution profiles of Formulation A tablets, and Table 6 lists f_2 values. Figure 4 plots the dissolution profiles of Formulation B tablets, and Table 7 lists f_2 values. All profiles with antioxidants differed from profiles without antioxidant in USP SIF and sodium bicarbonate buffer, except Formulation B tablets with antioxidant sodium ascorbate (in each USP SIF and sodium bicarbonate buffer). Except for this one formulation, added antioxidant resulted in f_2 less than 50, including for data points based upon the liberal interpretation of the 1997 FDA guidance.

Interestingly, in Fig 3, all Formulation A tablets with an antioxidant were faster (at least initially) than without antioxidant. At about 30 min and later, tablets with caffeic acid in USP SIF and tablets with fumaric acid in sodium bicarbonate buffer were slower. In Fig 4, all Formulation B test tablets with an antioxidant (except with sodium ascorbate) were slower than without antioxidant, particularly caffeic acid and fumaric acid. Formulation B tablets with caffeic acid or fumaric acid exhibited marked coning.

3.4. *Using apex vessels increased dissolution rate*

Figure S1 (in supplementary information) compares dissolution profiles of Formulation B without antioxidant into USP SIF using apex and non-apex (i.e. compendial) vessels. Apex vessels reduced coning and increased dissolution profiles.

Figure 5 plots Formulation B dissolution profiles with caffeic acid or fumaric acid into USP SIF using apex vessels, along with Formulation B without antioxidant. For all three tablets, dissolution was faster in apex vessels, in part since there was reduced coning. Table 7 lists f_2 values, including when apex vessels were used. Formulation B with caffeic acid was similar to no antioxidant, although Formulation B with fumaric acid was still below f_2 value of 50.

4. DISCUSSION

The FDA nitrosamine control guidance allows potential biowaivers for BCS class I, II, and III drugs when preferred antioxidants are added in limited quantities to a formulation to mitigate nitrosamine formation (Food and Drug Administration, 2024). The described biowaiver approach requires comparative in vitro dissolution testing, although it does not specify f_2 evaluation.

Studies here aim to evaluate the impact of added antioxidants, including acidic antioxidants, on an ionizable BCS Class II drug. Diclofenac potassium is a BCS II drug, as it is a lowly soluble drug under acid conditions. Nevertheless, we have previously indicated that a biowaiver can be generally recommended for its IR drug products (Chuasuwan et al., 2009). Since several preferred antioxidants are acids, diclofenac potassium was selected as a model drug for study here. Each antioxidant here was a weak acid or the salt of a weak acid. For example, the water-soluble antioxidants ascorbic acid (pK_a=4.1) (Doseděl et al., 2021; National Center for

Biotechnology Information, 2025b) caffeic acid (pK_a=4.6) (National Center for Biotechnology Information, 2025c) and fumaric acid (pK_a=3.03) (National Center for Biotechnology Information, 2025d) can be expected to reduce the pH in the local environment during their dissolution from a tablet. Given the drug's solubility profile, a potential qualitative concern is that acidic antioxidants could reduce local pH and hence reduce diclofenac potassium dissolution.

However, results do not support that antioxidant effect occurred via antioxidant to locally decreased pH to slow drug dissolution. For example, ascorbic acid (pK_a =4.1) did not impact dissolution at all. Meanwhile, the slightly stronger weak acid, fumaric acid (pK_a =3.03), slowed dissolution the most, although yielded particle clumps during dissolution, including in apex vessels. Both sodium ascorbate and sodium bicarbonate each slowed dissolution on occasion, pointing away from a local pH to cause slower dissolution. Rather, coning was observed in all studies and was more prominent when dissolution slowed the most (i.e. Formulation B with caffeic acid and fumaric acid).

f_2 was employed to assess dissolution profile similarity of formulations with and without antioxidant. USP SIF (pH=6.8) was used as a medium since it is the USP compendial medium for diclofenac potassium tablets, and since we expected pH 6.8 to be a more sensitive medium than pH 1.2 or pH 4.5, where less than 10% of drug can dissolve (Chuasuwan et al., 2009). Additionally, dissolution was also conducted in sodium bicarbonate buffer (pH=6.5), which has been employed as a more physiological buffer, including with a lower buffering capacity than USP SIF (Silva et al., 2019).

4.1.Formulation A and B as model tablets

Two tablet formulation families of 50mg diclofenac potassium were fabricated via direct compression, with and without antioxidant in each family. Compositionally, Formulation A family and Formulation B family differed modestly, where Formulation A employed anhydrous lactose and croscarmellose sodium, while Formulation B used dibasic calcium phosphate and pregelatinized starch. Although all formulations exhibited coning during dissolution, Formulation B visually exhibited greater coning than Formulation A, as expected, given the insolubility of dibasic calcium phosphate and the solubility of lactose. At 90 min, paddle speed was increased from 50 rpm to 200 rpm, often resulting in a notable increase in dissolution, particularly for Formulation B. In the context of tablet Formulations A and B differing, the impact of added antioxidant was generally greater for Formulation B than A and typically slowed dissolution.

4.2.*Impact of antioxidant on Formulation A dissolution*

In Table 3, the three preferred antioxidants generally did not affect the dissolution of Formulation A tablets in either medium. Meanwhile, the three other antioxidants initially provided faster profiles than Formulation A tablets with no antioxidant. Then, most notably, at about 30 min and later, Formulation A tablets with caffeic acid in USP SIF and Formulation A

tablets with fumaric acid in sodium bicarbonate buffer were slower than without antioxidant. Overall results reflect caffeic acid and fumaric acid slowed dissolution from formulation A via an enhanced coning effect. Meanwhile, ascorbic acid did not, even though ascorbic acid is also weakly acidic with favorable solubility (Doseděl et al., 2021), like caffeic acid and fumaric acid. From solubility assessment here, each antioxidant exhibited a solubility of at least 100mg/100ml, such that 10mg of antioxidant was easily soluble in dissolution testing.

4.3.*Impact of antioxidant on Formulation B dissolution*

The three preferred antioxidants, ascorbic acid, cysteine and sodium bicarbonate, did not affect the dissolution of Formulation B tablets in USP SIF or sodium bicarbonate buffer, except tablets with sodium bicarbonate were much slower than tablets without antioxidant in sodium bicarbonate buffer. An explanation for this result is not evident.

Dissolution of Formulation B tablets with the other antioxidants caffeic acid and fumaric acid (but not sodium ascorbate) were slower than tablets without antioxidants in USP SIF and in sodium bicarbonate buffer. Results are similar to results from Formulation A, where all three of these other antioxidants slowed diclofenac potassium dissolution after 30 min. Overall, caffeic acid and fumaric acid showed greater coning in both Formulation A and B. Dissolution of Formulation B was also conducted in apex vessels, which markedly increased dissolution and reduced coning; only tablets with fumaric acid showed a differing dissolution profile. Observations point to coning in the compendial vessel as a main basis for slower – and hence different – dissolution profiles with antioxidant.

4.4.Coning and implications for potential addition of antioxidant

Prior research has shown that antioxidants in certain quantities do not modulate in vitro drug permeability of BCS Class III drugs and are not expected to modulate in vivo drug permeability (Yu et al., 2024; Lu et al., 2024; Kulkarni et al., 2024). The FDA control of nitrosamine impurities in human drugs guidance indicates the addition of certain antioxidants (i.e. ascorbic acid, α-tocopherol, propyl gallate, cysteine hydrochloride or a pH modifier) in low quantifies to BCS I, II or III drug products was generally permissible, with possibility of a biowaiver (Food and Drug Administration, 2024). A consideration is in vitro dissolution testing.

The compendial method in USP SIF (pH 6.8) was performed, along with dissolution in sodium bicarbonate buffer. In general, sodium bicarbonate buffer results were the same as profile comparisons using USF SIF. Dissolution in pH 1.2 and 4.5 was not performed due to diclofenac's low solubility at these lower pHs, rendering these conditions less sensitive to profile differences, compared to USP SIF pH 6.8.

Six antioxidants were studied. Interestingly, none of the preferred antioxidants impacted dissolution, based on a liberal interpretation of the 1997 FDA dissolution guidance, except sodium bicarbonate for Formulation B in sodium bicarbonate buffer. Although both formulation A and B families showed coning, Formulation B showed greater coning, including with the addition of sodium bicarbonate as an antioxidant in the tablet. Meanwhile, the three other antioxidants often slowed dissolution due to enhanced coning. Using apex vessels to reduce

coning showed faster dissolution profiles for Formulation B with caffeic acid and fumaric acid in USP SIF, which were the slowest performing formulations.

5. CONCLUSION

To mitigate nitrosamine formation, the addition of ascorbic acid, cysteine, and sodium bicarbonate, which the FDA indicates does not impact drug intestinal permeability, did not change diclofenac potassium dissolution. Added caffeic acid, fumaric acid, and sodium ascorbate each slowed dissolution under most situations, with fumaric acid slowing dissolution even with apex vessels, where coning was not eliminated.

Overall, results point towards the feasibility of added antioxidant to not impact dissolution. All tested antioxidants were weak acids or a sodium salt. When dissolution was impacted, dissolution dissimilarity appeared to be due to coning, as apex vessels substantially eliminated slower dissolution. An unlikely explanation of antioxidant effect was that antioxidant locally decreased pH to cause slower dissolution of the weakly acidic drug. For example, ascorbic acid did not impact dissolution at all.

CRediT Authorship Contribution Statement

Rutu Rajeevan Valapil: Conceptualization, Methodology, Investigation, Visualization, Writing - Original Draft.

James E. Polli: Conceptualization, Investigation, Resources, Supervision, Writing – Original Draft, Writing - Review & Editing.

Declaration of the Competing Interest

The authors declare no competing interests that could influence the work in this study.

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Data Availability

Data can be made available upon request.

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FIGURE CAPTIONS

Figure 1. Formulation A dissolution profiles with preferred antioxidants ascorbic acid, cysteine, and sodium bicarbonate. Panel A is dissolution into USP SIF. Panel B is dissolution into sodium bicarbonate buffer. Formulation A contained MCC, anhydrous lactose, croscarmellose sodium, and magnesium stearate, along with 50mg diclofenac potassium. Tablets with either ascorbic acid, cysteine, or sodium bicarbonate exhibited dissolution profiles that were similar to the tablet with no antioxidant. Also shown is the dissolution profile of a marketed generic tablet of diclofenac potassium.

Figure 2. Formulation B dissolution profiles with preferred antioxidants. Panel A is dissolution into USP SIF. Panel B is dissolution into sodium bicarbonate buffer. Formulation B contained MCC, dibasic calcium phosphate, pregelatinized starch, and magnesium stearate, along with 50mg diclofenac potassium. In USP SIF, tablets with either ascorbic acid, cysteine, or sodium bicarbonate exhibited dissolution profiles similar to the tablet with no antioxidant. In sodium bicarbonate buffer, tablet with sodium bicarbonate exhibited slow dissolution. Also shown is the dissolution profile of a marketed generic tablet.

Figure 3. Formulation A dissolution profiles with other antioxidants caffeic acid, fumaric acid, and sodium ascorbate. Panel A is dissolution into USP SIF. Panel B is dissolution into sodium bicarbonate buffer. In each USP SIF and sodium bicarbonate buffer, caffeic acid, fumaric acid, and sodium ascorbate each initially increased dissolution. At longer times, caffeic acid and fumeric acid slowed dissolution in USP SIF, and fumaric acid slowed dissolution in sodium bicarbonate buffer. Also shown is the dissolution profile of a marketed generic tablet.

Figure 4. Formulation B dissolution profiles with other antioxidants. Panel A is dissolution into USP SIF. Panel B is dissolution into sodium bicarbonate buffer. In USP SIF, caffeic acid and fumaric acid slowed dissolution. In sodium bicarbonate buffer, fumaric acid slowed dissolution. Also shown is the dissolution profile of a marketed generic tablet.

Figure 5. Formulation B dissolution profiles with other antioxidants caffeic acid and fumaric acid into USP SIF using apex vessels. Compared to their corresponding profiles using compendial (i.e. non-apex) vessels in Fig 4 panel A, dissolution was faster in apex vessels with reduced coning. However, fumaric acid still slowed dissolution.

TABLES

Table 1. Tablet compositions for Formulation families A and B. Formulation A employed lactose and croscarmellose sodium, while Formulation B employed dicalcium phosphate dihydrate and pregelatinized starch. Weight percentages of diclofenac potassium and excipients are listed. Total tablet weight was 250mg, with 50mg diclofenac potassium strength. Compared to tablets without antioxidant, tablets with antioxidant had less bulking agents. Antioxidants were ascorbic acid, cysteine, sodium bicarbonate, caffeic acid, fumaric acid, and sodium ascorbate.

Formulation A			Formulation B		
Component	Weight percent with antioxidant	Weight percent without antioxidant	Component	Weight percent with antioxidant	Weight percent without antioxidant
Microcrystalline cellulose	36.5	38.5	Microcrystalline cellulose	32.5	34.5
API	20	20	API	20	20
Antioxidant	4	0	Antioxidant	4	0
Lactose	36.5	38.5	Dibasic calcium phosphate dihydrate	32.5	34.5
Croscarmellose sodium	2	2	Pregelatinized starch	10	10
Magnesium stearate	1	1	Magnesium stearate	1	1
Total	100	100	Total	100	100

Table 2. Tablet properties of Formulation A and Formulation B diclofenac potassium tablets with differing antioxidants. Properties were hardness, disintegration time, and maximum tablet weight deviation from target tablet weight. Properties support that tablets exhibited accurate content uniformity and rapid tablet disintegration. None, AA, Cys, SB, CA, FA, and SA denote no antioxidant, ascorbic acid, cysteine, sodium bicarbonate, caffeic acid, fumaric acid, and sodium ascorbate, respectively.

Formulation name	**Formulation family**	**Hardness (N)**	**Disintegration time (minutes)**	**Maximum weight difference from target (%)**
A-none	A	57.9	4-6.5	<1.06
A-AA		62.6	3.3-4.5	<0.8
A-Cys		62.1	5.1-6.3	<1.2
A-SB		79.5	4.5-6.3	<1.6
A-CA		50.4	5.1-6.5	<1.2
A-FA		53.9	3.1-4.2	<1.6
A-SA		47.3	4.5-6.1	<1.6
B- none	B	55.3	1.1- 3.1	<1.2
B-AA		58.1	0.5-1.3	<1.2
B-Cys		60.1	4.3-5	<1.2
B-SB		54.1	2-3.3	<1.6
B-CA		33.2	2.1-3.0	<1.6
B-FA		51.1	1.0-1.52	<1.6
B-SA		42.0	2.0-3.4	<1.2

Table 3. Overall tablet dissolution observations for each added antioxidant. Of secondary note, caffeic acid, fumaric acid, and sodium ascorbate each initially increased dissolution of Formulation A in each USP SIF and sodium bicarbonate buffer. pK_a values from National Center for Biotechnology Information 2025.

Antioxidant	**Chemical nature**	**pK_a**	**Overall dissolution observations**
Ascorbic acid	Weak acid	4.1	Never modulated dissolution
Cysteine	Weak acid	8.3	Never modulated dissolution
Sodium bicarbonate	Salt of weak acid	6.3	Slowed Formulation B dissolution in sodium bicarbonate buffer
Caffeic acid	Weak acid	4.6	Slowed Formulation A dissolution
Fumaric acid	Weak acid	3.03	Slowed Formulation A and Formulation B dissolution, including Formulation B in apex vessels
Sodium ascorbate	Salt of weak acid	4.1[21]	Slowed Formulation A dissolution

Table 4. f_2 values for Formulation A with preferred antioxidants ascorbic acid, cysteine, and sodium bicarbonate. Profiles are compared to Formulation A without antioxidant. Dissolution comparisons were conducted in USP SIF (left side) and in sodium bicarbonate buffer (right side). Also listed are comparisons for a marketed generic tablet of diclofenac potassium. f_2 values were calculated using eight different data selection criteria, including a liberal interpretation of the FDA 1997 guidance.

Data selection criteria	**USP SIF**				**Sodium bicarbonate buffer**			
	Marketed	Ascorbic acid	Cysteine	Sodium bicarbonate	Marketed	Ascorbic acid	Cysteine	Sodium bicarbonate
FDA 97 liberal	37.5	51.2	50.5	58.5	30.7	50.2	59.4	51.1
FDA 97 conservative	34.4	49.7	48.4	56.4	27.7	50.7	60.8	50.2
BCS M9	31.5	47.5	45.5	54.7	34.0	53.5	60.8	49.7
10-30 min	34.4	47.4	45.5	54.6	27.7	53.5	60.8	49.6
10-45 min	37.5	49.7	48.4	56.4	30.7	50.7	60.8	50.2
10-60 min	39.8	51.3	50.5	58.5	33.2	50.2	59.5	51.1
10-90 min	41.7	52.5	52.3	60.5	35.1	51.4	61.4	52.2
10-120 min	43.3	54.2	53.8	61.6	36.8	53.0	63.0	53.2

Table 5. f_2 values for Formulation B with preferred antioxidants. Profiles are compared to Formulation B without antioxidant. Dissolution comparisons were conducted in USP SIF (left side) and in sodium bicarbonate buffer (right side). Also listed are comparisons for a marketed generic tablet of diclofenac potassium. f_2 values were calculated using eight different data selection criteria, including a liberal interpretation of the FDA 1997 guidance.

Data selection criteria	**USP SIF**				**Sodium bicarbonate buffer**			
	Marketed	Ascorbic acid	Cysteine	Sodium bicarbonate	Marketed	Ascorbic acid	Cysteine	Sodium bicarbonate
FDA 97 liberal	34.3	61.4	58.3	71.7	34.6	54.1	59.5	33.8
FDA 97 conservative	34.3	61.4	58.3	71.7	34.6	54.1	59.5	33.8
BCS M9	31.2	61.4	58.0	71.7	33.0	52.9	58.3	32.2
10-30 min	31.2	57.1	58.3	78.8	31.0	57.4	62.7	27.8
10-45 min	32.2	59.1	60.9	81.3	31.4	54.3	58.5	29.2
10-60 min	32.8	58.1	62.0	80.2	32.2	50.2	57.1	30.7
10-90 min	32.8	59.8	58.0	78.2	33.0	51.4	58.3	32.2
10-120 min	34.3	61.4	58.3	71.7	34.6	53.0	59.5	33.8

Table 6. f_2 values for Formulation A with other antioxidants caffeic acid, fumaric acid, and sodium ascorbate. Profiles are compared to Formulation A without antioxidant. Dissolution comparisons were conducted in USP SIF (left side) and in sodium bicarbonate buffer (right side). Also listed are comparisons for a marketed generic tablet of diclofenac potassium.

Data selection criteria	**USP SIF**				**Sodium bicarbonate buffer**			
	Marketed	Caffeic acid	Fumaric acid	Sodium ascorbate	Marketed	Caffeic acid	Fumaric acid	Sodium ascorbate
FDA 97 liberal	37.5	28.7	38.4	33.3	30.7	33.1	38.9	33.7
FDA 97 conservative	34.4	25.6	36.3	30.2	27.7	30.1	37.6	30.6
BCS M9	31.5	21.4	33.6	25.8	34.0	30.1	38.7	30.6
10-30 min	34.4	25.6	33.6	30.2	27.7	30.1	38.7	30.6
10-45 min	37.5	28.7	36.3	33.3	30.7	33.1	37.6	33.7
10-60 min	39.8	31.1	38.4	35.7	33.2	35.3	37.6	36.1
10-90 min	41.7	33.0	40.2	37.6	35.1	37.1	38.9	38.0
10-120 min	43.3	34.6	41.9	39.3	36.8	38.7	40.3	39.6

Table 7. f_2 values for Formulation B with other antioxidants. Profiles are compared to Formulation B without antioxidant. Dissolution comparisons were conducted in USP SIF (left side) and in sodium bicarbonate buffer (right side). f_2 values also shown for dissolution performed in USP SIF using apex vessels (center). Also listed are comparisons for a marketed generic tablet of diclofenac potassium

Data selection criteria	**USP SIF**				**USP SIF (apex vessel)**		**sodium bicarbonate buffer**			
	Marketed	Caffeic acid	Fumaric acid	Sodium ascorbate	Caffeic acid	Fumaric acid	Marketed	Caffeic acid	Fumaric acid	Sodium ascorbate
FDA 97 liberal	34.3	45.9	25.9	64.1	59.9	42.2	34.6	51.5	22.7	69.2
FDA 97 conservative	34.3	45.9	25.9	64.1	52.9	38.9	34.6	51.5	22.7	69.2
BCS M9	31.2	45.9	25.9	66.5	52.9	34.7	33.0	50.1	21.1	67.7
10-30 min	31.2	41.0	20.8	67.7	64.1	42.2	31.0	58.6	23.5	66.7
10-45 min	32.2	42.7	22.2	70.2	66.9	44.9	31.4	53.4	21.9	68.1
10-60 min	32.8	43.3	23.1	72.0	68.9	47.0	32.2	50.9	21.3	68.7
10-90 min	32.8	44.4	24.3	66.5	70.5	48.9	33.0	50.1	21.1	67.7
10-120 min	34.3	45.9	25.9	64.1	71.7	50.5	34.6	51.5	22.7	69.2

FIGURES

Figure 1.

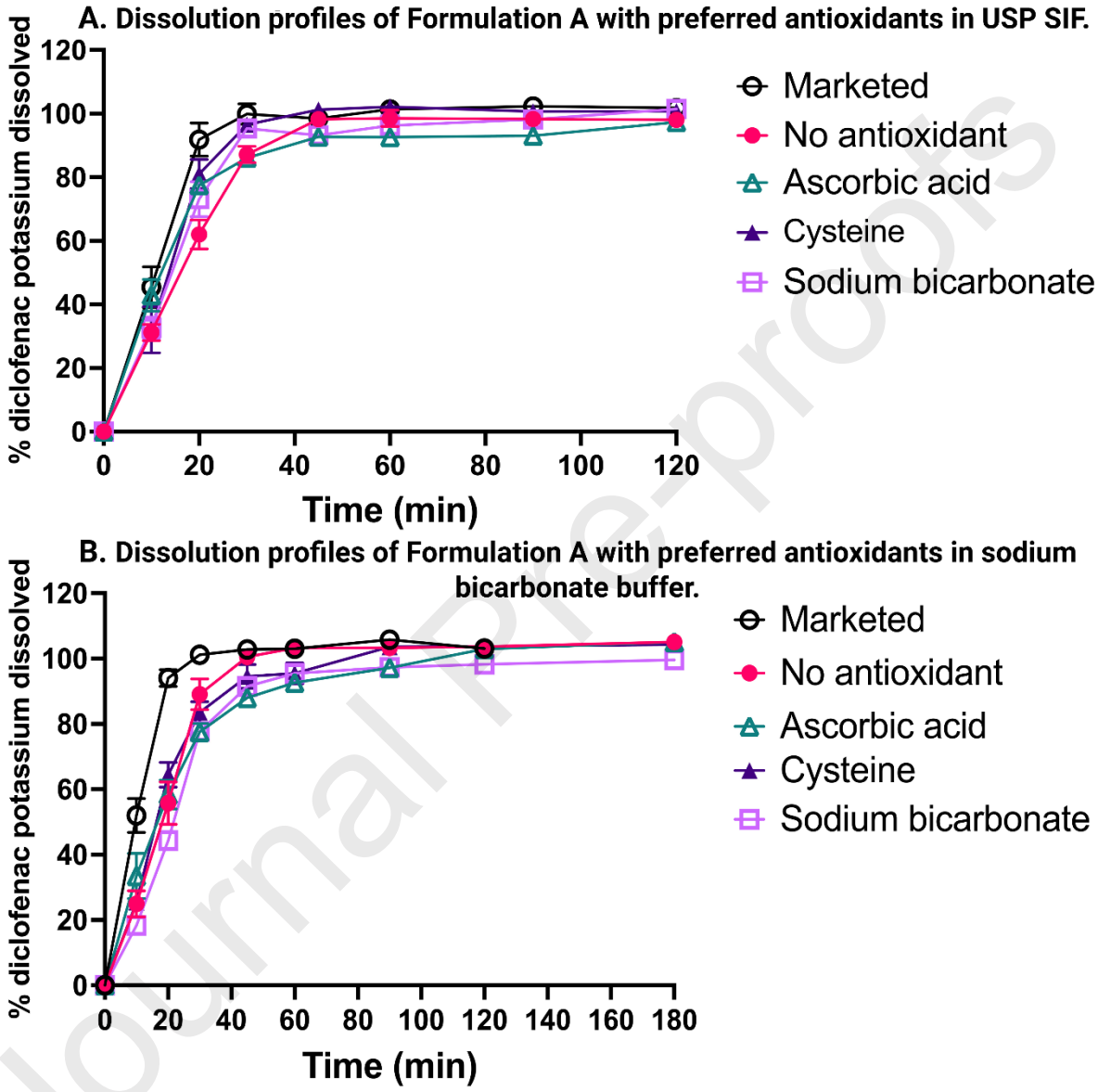
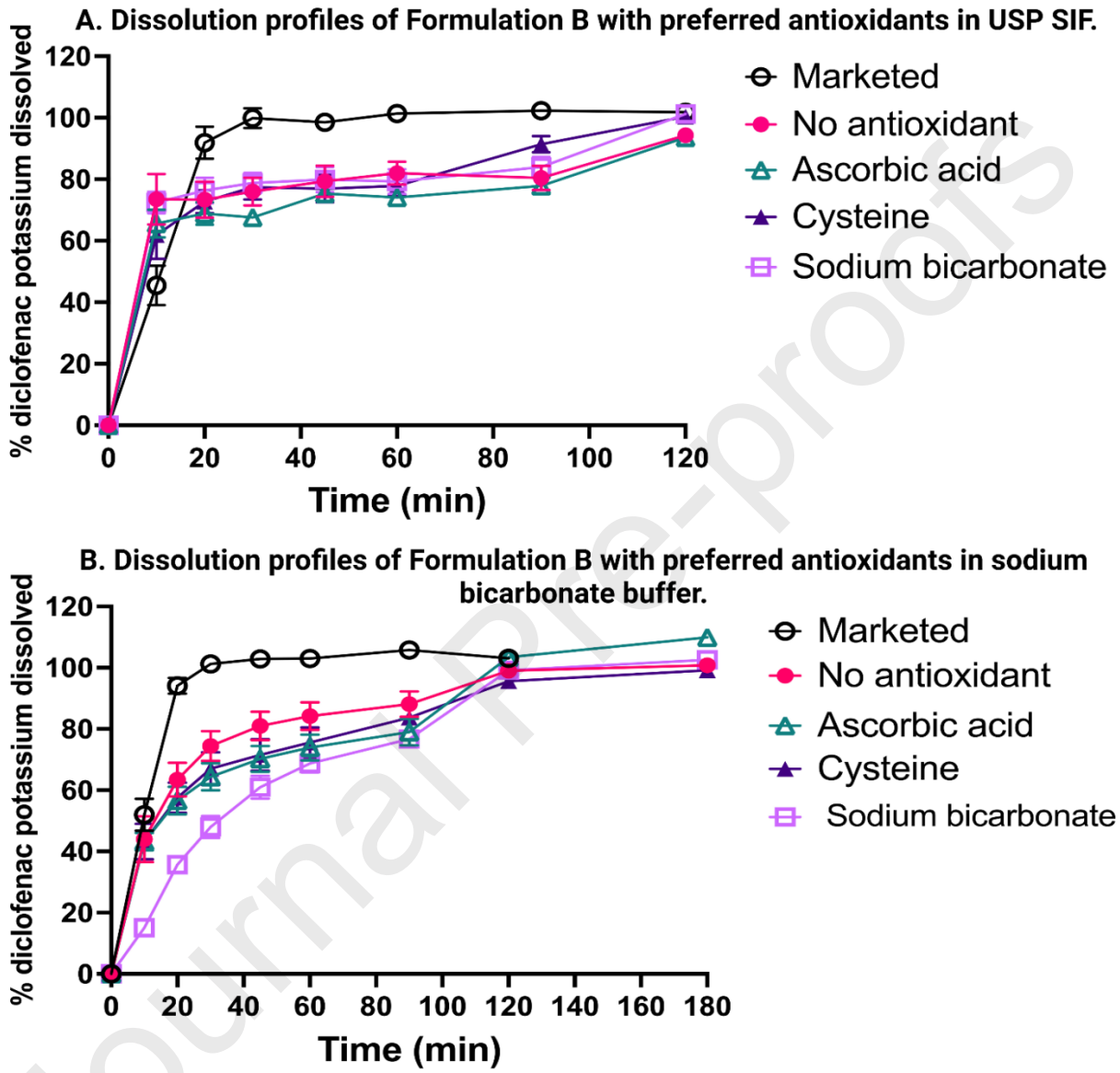


Figure 2.



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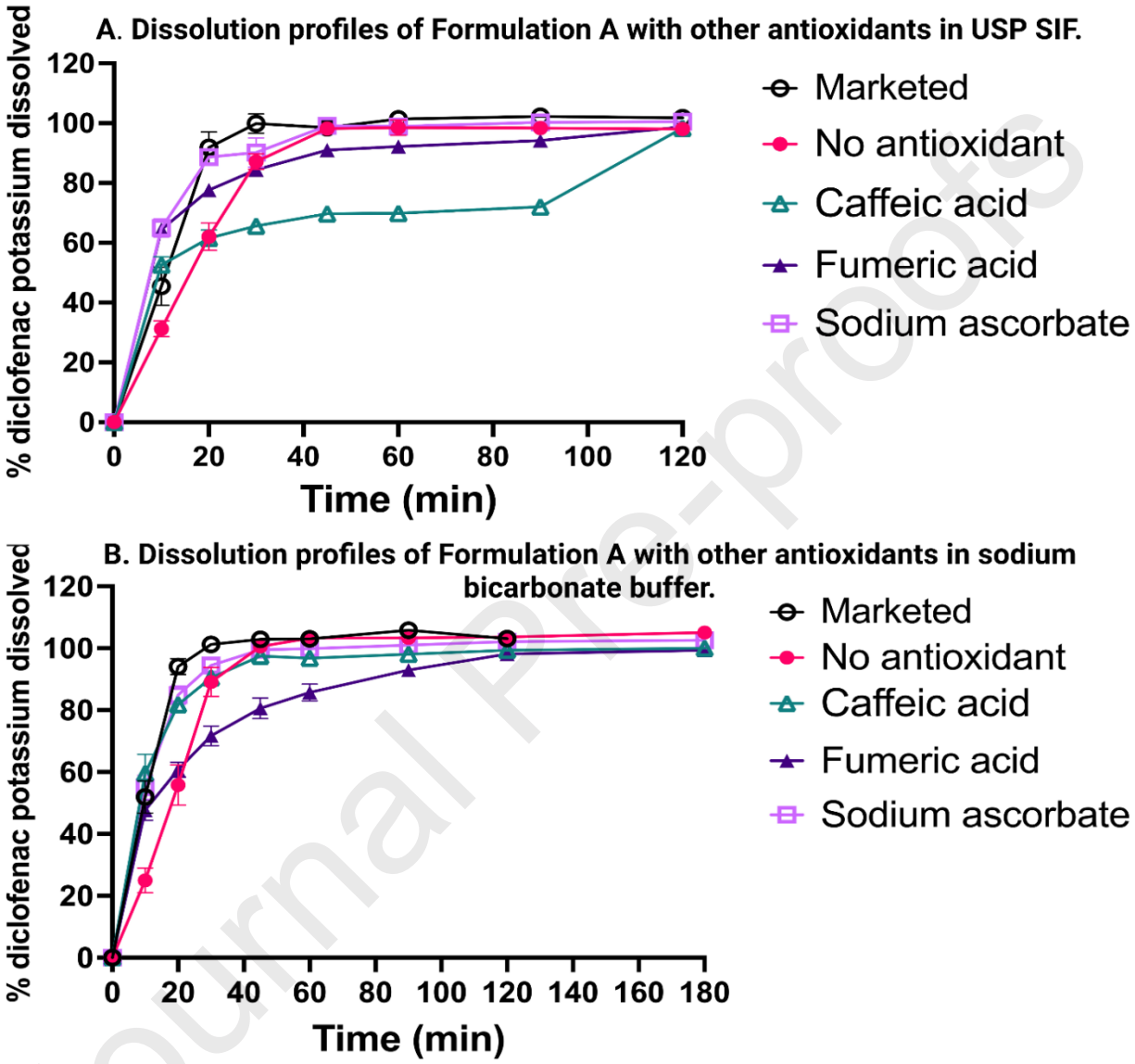

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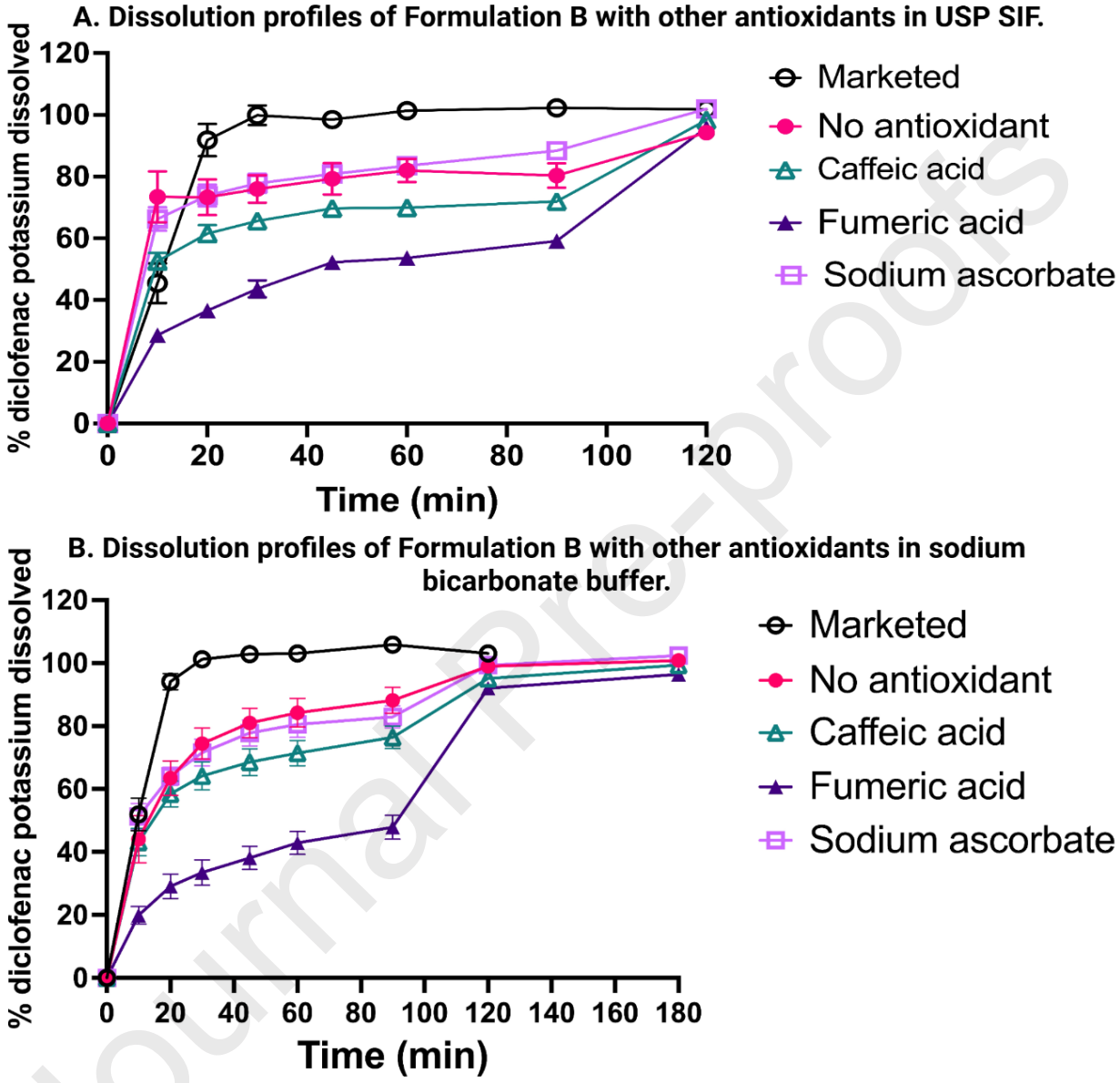

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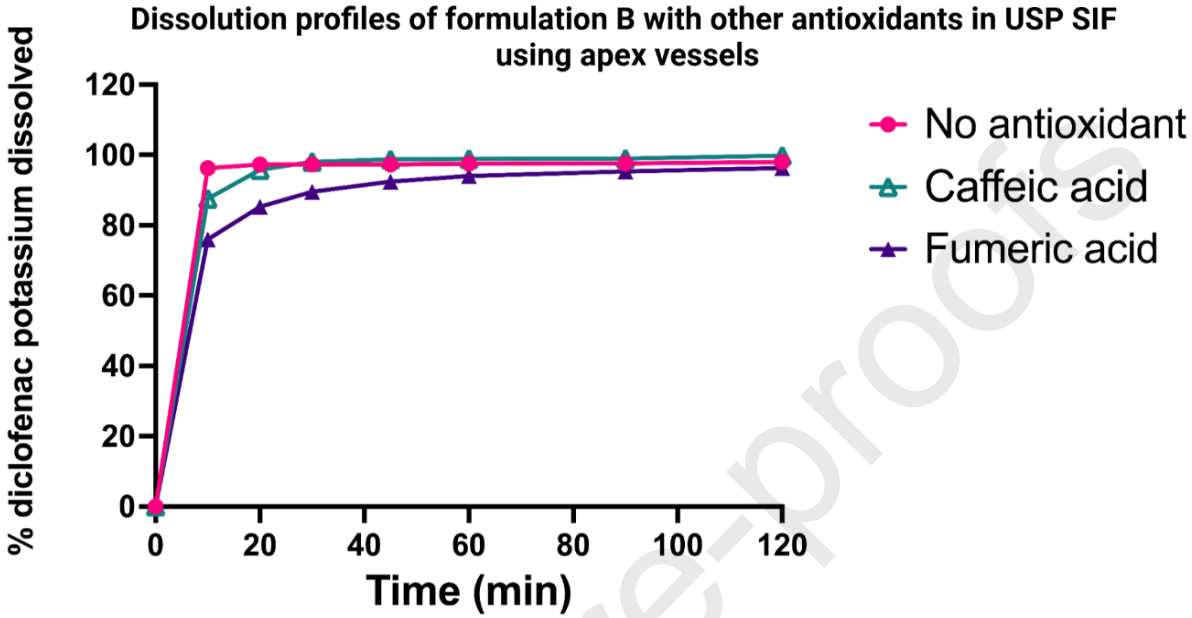

Declaration of the Competing Interest

The authors declare no competing interests that could influence the work in this study.