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Original article

Development and evaluation of febuxostat solid dispersion through screening method

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ABSTRACT

Febuxostat (Febux) is a BCS II drug and has a very low solubility. In order to overcome this shortcoming, the purpose of study is to increase the *in vitro* dissolution (%) and drug release (%) of Febux by using a screening method. The Febux-SD formulation was prepared by screening solubilizers, pH agents, and carriers using with a solvent evaporation method.

The novel Febux SD formulation was successfully developed. The dissolution (%) of Febux of optimal formulation (SD3) was higher than that of Feburic® tab in pH 1.2, distilled water (DW), and pH 6.8 buffer by 6.3-, 2.6-, and 1.1-fold, respectively, at 60 min. The *in vitro* drug release (%) and permeability (μg/cm^2) of SD3 formulation were improved compared to those of Feburic® tab in the pH shifting method and PBS (7.4), respectively. The SD3 formulation was well maintained the stability for 6 months, and that of physicochemical properties were altered. In conclusion, the Febux solubilization study with meglumine was first attempted and successfully performed. Through the improved dissolution (%) of Febux, high bioavailability of SD3 formulation is expected in animal and human studies.

1. Introduction

Since 40% of existing drugs have low solubility, many pharmaceutical companies are investing significant time, effort, and funds to solubilize poorly soluble drugs to increase oral bioavailability. Thus, the research is being conducted on the solubilization of poorly soluble drugs using various substances and methods. Drug solubilization methods include solid dispersion (Sohn and Choi, 2022; Sohn et al., 2021a; Sohn et al., 2021b; Zaki et al., 2023), complexation (Aung et al., 2022; Kamel et al., 2017; Volkova et al., 2021), self-micro and nano-emulsifying formulations (Al-Amodi et al., 2020; Habib et al., 2021; Rangaraj et al., 2019), micelles (Choi et al., 2020), and co-crystals (Jagia et al., 2022).

The model drug, febuxostat (Febux), which is commercial product as Uloric®, is a new bipurine-selective xanthine oxidase inhibitor. It is approved for treatment of hyperuricemia in gout patients (Davoodi et al., 2020; Jagia et al., 2022). Uloric® (40 and 80 mg) tablets consist of various excipients such as mannitol, lactose monohydrate, microcrystalline cellulose, hydroxypropyl cellulose, and sodium croscarmellose in RxList. Febux belongs to the BCS class II drugs with a pH-dependent solubility profile (weakly acidic drug) that exhibits improved solubility at a basic pH (Yin et al., 2018). The BCS class II drugs have low solubility and high intestinal permeability. These drugs can improve solubility, making them more readily bioavailable than other BCS classes (Tambe et al., 2022).

The most recent research trends of Febux were SD formulations (Amin et al., 2020; El Shenawy et al., 2019; Kaur et al., 2020; Moinuddin et al., 2020; Patel et al., 2021), as well as self-micro and nano-emulsifying formulations (Al-Amodi et al., 2020; Habib et al., 2021; Rangaraj et al., 2019), nanostructure lipid carriers (Varia et al., 2022), and co-crystal (Jagia et al., 2022). Among them, the SD manufacturing method was selected owing to the reason that our group has established a drug solubilization method with

Abbreviations: Febux, Febuxostat; SD, Solid dispersion; DW, Distilled water; BCS, Biopharmaceutics Classification System; DSC, Differential scanning calorimetry; PXRD, Powder X-ray diffraction; ATR-FT-IR, Attenuated total reflectance Fourier transform infrared spectroscopy.

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an SD manufacturing method, and has an approach and manufacturing technology accordingly. Moreover, the SD manufacturing method can ease obtaining a final product through solidification (Sohn and Choi, 2022). Also, the solvent evaporation method in SD techniques was applied since it can be prepared at a low cost and is time-efficient (requires only a stirrer and drying oven).

The most recent solubilization of the Febux formulation is as follows. Febux cocrystals were prepared using the following methods; Febux and co-formers were mixed with acetonitrile (50 μL). The samples were dried at 80 °C for 2 h in a drying oven (Jagia et al., 2022). Febux-SD formulations were prepared using different polymers (Kolliphor P® [188 and 237] and Eudragit RLPO). Then, SD manufacturing methods using hot melt (fusion), solvent evaporation, and spray drying techniques were compared (Patel et al., 2021). Febux-co-processed excipient formulations were prepared with crospovidone and microcrystalline blend (1:1) with solvent evaporation method (Kaur et al., 2020). The Febux-SD formulations were prepared using poloxamer (Kolliphor P® [188 and 237]). The samples were pasted using a mixture of 50% (v/v) ethyl alcohol (5 mL) to obtain a paste and then dried in an oven at 60 °C for 30 min (El Shenawy et al., 2019). The Febux-β-cyclodextrin-nanosponge formulations were also prepared using the following method: β-cyclodextrin dissolved in dimethylformamide and diphenyl carbonate was added to the reaction mixture at 100 °C for 4 h and then the white powder was dried at 40 °C in an oven overnight and was subsequently ground in a mortar. Febux was dissolved in dichloromethane, and then β-cyclodextrin-nanosponges were added, following which the solution was pulverized until the dichloromethane evaporated (Amin et al., 2020). As described above, Febux formulations have been developed by various methods.

The purpose of this study was to design the Febux-SD formulation with stable and enhanced dissolution (%) of Febux. It is believed that novelty can be secured if a weak base formulation that has not been performed in previous Febux studies is developed. It was hypothesized that the dissolution (%) of Febux would improve if a weakly-basic substance was used as a weakly-acidic drug (Febux). The Febux strategies are as follows: The solubilization potential was first determined by measuring the solubility of Febux in various polymer solutions (1%, w/v) and pH buffers. Second, formulations were developed by adding selected weakly basic substances and solubilizers. Third, an optimal formulation was developed using a carrier selection (Sohn and Choi, 2022). The prepared formulations were subjected to a pre-dissolution test, and an optimal formulation was selected according to the results. The final formulation was tested with dissolution, *in vitro* drug release, and permeability tests. Lastly, physicochemical properties and stability were analyzed.

2. Materials and methods

2.1. Materials

Febuxostat (Febux), meglumine, MgO, PVP/VA S-630, and Neusilin® (US2 and UFL2) were provided by Yuyu Pharma Inc. (Korea, Suwon-si). Sodium oleate (extra pure) was purchased from Junsei Chemical Co. Ltd. (Tokyo, Japan). Sodium hydroxide was purchased from Daejung Chemicals & Metals Co. LTD (Siheung, Korea). Kolliphor® (P188 and P407), PEG6000, Kollicoat® (IR), Kollidon® (K12, K17, K30, and K90), Kolliphor® (HS 15), Soluplus®, and TPGS were obtained from BASF (Ludwigshafen, Germany). Fumed silica Aerosil® (200 and 300) were provided by Evonik (Essen, Germany). Mannitol, lactose, microcrystalline cellulose, granular dicalcium phosphate anhydrate (DCP-A), and granular dicalcium phosphate dihydrate (DCP-D) were obtained from Whawon Pharm (Seoul, Korea). Sodium carbonate anhydrous, sodium bicarbonate, potassium hydroxide, sodium phosphate dibasic anhydrous, ethyl alcohol, and universal buffers were purchased from Samchun Pure Chemical Co., Ltd. (Pyeongtaek, Korea).

2.2. Solubility test

The reason for performing the Febux solubility test is to select choose which polymer and pH substance to use. Thus, the solubility of Febux was evaluated in 1% (w/v) polymeric solutions, DW, and universal buffers (pH 1.0, 4.0, 7.0, and 10.0)(Sohn and Choi, 2021b). However, the pH4 buffer and Soluplus® prepared for the above solubility measurements were excluded due to UV–vis interference. For this reason, a universal buffer (pH 4.0) was prepared by the pH 4.0 buffer preparation method of Korean Pharmacopoeia (edition 12).

Febux (10 mg) was put into the various solution and buffer solutions (10 mL) under the stirring at 400 rpm using a multi-channel stirrer (MS-33MH, JEIO TECH, Korea) for 24 h at 37 ± 1 °C (n = 3). The sampling times were at 1, 2, 4, and 24 h and then assayed.

2.3. Preparation of the Febux formulations

The B (base) formulations (1–24) were prepared with various basic substances (including meglumine, MgO, sodium oleate, sodium hydroxide, sodium carbonate anhydrous, sodium bicarbonate, potassium hydroxide, and sodium phosphate dibasic anhydrous) using the solvent evaporation method (**Table S1**). Briefly, Febux (40 mg), basic substances (different ratios of Febux: basic substances = 1:1, 1:2, and 1:3), and ethyl alcohol (5 mL) were stirred at 400 rpm for 30 min using a multi-channel stirrer at room temperature. The remaining solvent was dried overnight at 80 °C using an oven.

The F (polymer-base) formulations (1–12) were prepared based on the B2 formulation (meglumine), and various polymers (including P188®, P407®, PEG6000, Soluplus®, IR®, PVP/VA S-630, K12®, K17®, K30®, K90®, TPGS, and HS 15®), were prepared using the same method as described above B formulations (Table 1). It was selected as the most used polymer in pharmaceuticals and a non-ionic polymer with good solubility in water.

The SD formulations (1–9) were prepared based on the F2 formulation and various carriers (Aerosil® 200, Aerosil® 300, mannitol, Flowlac® 100, MCC, DCP-A, DCP-D, US2, and UFL2) using the same method as described above F formulations (Table 2). Carriers most commonly used in pharmaceuticals, such as mannitol, Flowlac® 100, MCC, and porous silica, direct excipients, were selected. The prepared B, F, and SD formulations were passed through a 20-mesh sieve (0.841 mm).

Additionally, experiments were performed to identify the major factors in the solubilization of SD3 formulations (Sohn and Choi, 2022). This is done by excluding the excipient of the SD3 formulation by one as follows. The SD3 (Febux, meglumine, P407®, and mannitol in a 1:2:1:1 ratio), SD3-1 (Febux, meglumine, P407®, and mannitol in a 1:0:1:1 ratio), SD3-2 (Febux, meglumine, P407®, and mannitol in a 1:2:0:1 ratio), and SD3-3 (Febux, meglumine, P407®, and mannitol in a 1:2:1:0 ratio) were prepared in the same manner as described above (Table 3).

2.4. UV–vis spectrophotometry

For all formulations, drug content (%), pre-dissolution (%), and dissolution (%) of Febux were measured using a UV–vis spectrophotometer (X-ma 1000; Human Co., Korea) at 315 nm (Amin et al., 2020; Patel and Thakkar, 2023). Undissolved Febux was separated by centrifugation (10,000 × *g*, 10 min) using a CF-10

Table 1
Composition of the febuxostat (Febux) F formulations (mg, per batch).

	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Febux	40	40	40	40	40	40	40	40	40	40	40	40
Meglumine	80	80	80	80	80	80	80	80	80	80	80	80
P188®	40	–	–	–	–	–	–	–	–	–	–	–
P407®	–	40	–	–	–	–	–	–	–	–	–	–
PEG6000	–	–	40	–	–	–	–	–	–	–	–	–
Soluplus®	–	–	–	40	–	–	–	–	–	–	–	–
IR®	–	–	–	–	40	–	–	–	–	–	–	–
PVP/VA S630	–	–	–	–	–	40	–	–	–	–	–	–
K12®	–	–	–	–	–	–	40	–	–	–	–	–
K17®	–	–	–	–	–	–	–	40	–	–	–	–
K30®	–	–	–	–	–	–	–	–	40	–	–	–
K90®	–	–	–	–	–	–	–	–	–	40	–	–
TPGS	–	–	–	–	–	–	–	–	–	–	40	–
HS 15®	–	–	–	–	–	–	–	–	–	–	–	40
Total	160	160	160	160	160	160	160	160	160	160	160	160

Table 2
Composition of the febuxostat (Febux) SD formulations (mg, per batch).

	SD1	SD2	SD3	SD4	SD5	SD6	SD7	SD8	SD9
Febux	40	40	40	40	40	40	40	40	40
Meglumine	80	80	80	80	80	80	80	80	80
P407®	40	40	40	40	40	40	40	40	40
Aerosil®200	40	–	–	–	–	–	–	–	–
Aerosil®300	–	40	–	–	–	–	–	–	–
Mannitol	–	–	40	–	–	–	–	–	–
Flowlac	–	–	–	40	–	–	–	–	–
MCC	–	–	–	–	40	–	–	–	–
DCP-A	–	–	–	–	–	40	–	–	–
DCP-D	–	–	–	–	–	–	40	–	–
US2	–	–	–	–	–	–	–	40	–
UFL2	–	–	–	–	–	–	–	–	40
Total	200	200	200	200	200	200	200	200	200

Table 3
Composition of the febuxostat (Febux) SD formulations (mg, per batch).

	SD3	SD3-1	SD3-2	SD3-3
Febux	40	40	40	40
Meglumine	80	–	80	80
P407®	40	40	–	40
Mannitol	40	40	40	–
Total	200	120	160	160

microcentrifuge. The supernatants were evaluated. All samples were measured in triplicate, and the measured absorbance was calculated by a calibration curve (coefficient of determination, R^2 = 0.9996). The calibration curve was calculated at 0.39–50 μg/mL concentrations, and the samples were analyzed using appropriate dilutions.

2.5. Pre-dissolution test

The convenient pre-dissolution test method was performed in DW for the selection of an optimal Febux formulation using a multichannel magnetic stirrer (Sohn and Choi, 2022). The Febux formulations (equivalent to 4 mg of Febux) were added to the beaker in DW (90 mL) and stirred at 400 rpm at 37 ± 1.0 °C. All samples were withdrawn (1 mL) at 5, 15, 30, 45, and 60 min.

2.6. Dissolution test

All samples (optimal formulation [SD3], physical mixture [PM3], pure Febux, Feburic® tab [commercial product; replaced Uloric tab®], equivalent to 40 mg of Febux) were performed using a dissolution tester (Distek 6300; New Brunswick, NJ, USA) in dissolution media (pH 1.2, DW, and pH 6.8 buffer [900 mL]) at 37 ± 0.5 °C and 100 rpm, in accordance with the United States Pharmacopoeia Apparatus II paddle method (n = 6). The sampling times were 5, 15, 30, 45, and 60 min.

2.7. In vitro release test

An *in vitro* drug release study was performed using the pH-shifting method. The reason for conducting this study is to predict the drug dissolution behavior *in vivo*. All samples (optimal formulation [SD3], physical mixture [PM3], pure Febux, Feburic® tab [commercial product; replaced Uloric tab®]) were pulverized in powder form using a mortar and pestle. An amount equivalent to 4 mg of Febux was taken and dispersed in 5 mL of a pH 1.2 release media for each sample. The subsequent method is the same as the previous study method (Sohn and Choi, 2021a).

2.8. In vitro permeability test

The *in vitro* permeability test was performed with various membranes in Franz diffusion cell system (Bandctech Co., Ltd., Korea). Febux (equivalent to 0.4 mg/mL) was added to the donor chamber, and then the samples were withdrawn at 1, 2, 4, 8, and 24 h. The protocol and membranes were identical to the previous ones (Sohn and Choi, 2023).

2.9. Physicochemical properties of the Febux-SD formulation

Pure Febux, mannitol, meglumine, P407®, PM3, and SD3 were thermally analyzed using a DSC 60A (Shimadzu, Japan). The samples (2–5 mg) were put into the aluminum pan and then sealed. The samples were heated from 5 °C to 350 °C at a scanning rate of 10 °C/min under a nitrogen purge at 40 mL/min.

The chemical interactions of pure Febux, mannitol, meglumine, P407®, PM3, and SD3 were confirmed using a FT-IR spectrometer (Nicolet6700, Thermo Scientific, USA). The range is from 4,000 to 500 cm^{-1} at a resolution of 2 cm^{-1}.

The crystallinities of pure Febux, mannitol, meglumine, P407®, PM3, and SD3 were analyzed using a high-resolution XRD (X'pert Pro MRD, PANalytical, The Netherlands). The samples were scanned in 0.02° steps from 5° to 70° (diffraction angle 2θ) at 40 kV with 150-mA Cu-Kα radiation.

2.10. Stability

Stability tests of the Febux formulations were performed using a pre-dissolution test for 1 and 6 months. Stability samples are placed in glass vials with caps in powder form and stored under laboratory environmental conditions (temperature 20–25 °C, relative humidity 50–60%). The Febux formulations (equivalent to 4 mg Febux) were put into the beaker in DW (90 mL) and stirred at 400 rpm at 37 ± 1.0 °C for 60 min.

2.11. Statistical analysis

Statistical analysis was performed using the Student's *t*-test on SigmaPlot (ver. 12.5). Data are presented as mean ± standard deviation (sd). In all analyses, $p < 0.005$ (***), $p < 0.01$ (**), and $p < 0.05$ (*) were considered statistically significant.

3. Results

3.1. Characterization of the Febux formulations

3.1.1. Solubility test

Febuxostat (Febux) is a BCS II drug with good permeability and poor solubility in water. However, permeability can further be increased with improved solubility. First, the solubility test was conducted to determine the most elemental direction of the Febux formulations in various 1% (w/v) polymeric solutions and pH buffers (**Fig. S1**). The solubility of Febux was 32.5 ± 15.5 μg/mL (P188®), 55.2 ± 3.7 μg/mL (P407®), 12.7 ± 1.9 μg/mL (PEG6000), 66.1 ± 2.8 μg/mL (IR®), 17.6 ± 1.7 μg/mL (PVP/VA S-630), 15.8 ± 1.5 μg/mL (K12®), 16.1 ± 1.0 μg/mL (K17®), 6.1 ± 0.4 μg/mL (K30®), 28.3 ± 1.6 μg/mL (K90®), 235.8 ± 9.9 μg/mL (TPGS), and 174.9 ± 8.3 μg/mL (HS 15®). The solubility test results showed that TPGS has the highest Febux solubility. In the pH buffers, the solubility of Febux were 0.2 ± 0.1 μg/mL (pH 1), 1.9 ± 0.1 μg/mL (pH 4.0), 911.4 ± 59.1 μg/mL (pH 7.0), 1004.8 ± 7.1 μg/mL (pH 10.0), and 31.3 ± 1.6 μg/mL (DW) for 24 h. In conclusion, a change in pH environment is a crucial factor for improving the solubility of Febux. When comparing the solubility of Febux in TPGS solution (1%, w/v) and other polymer solutions (1%, w/v), the *p*-value was less than 0.005 (*t*-tests) for 24 h. When comparing the solubility of Febux in pH buffer (pH 10) and other buffers and DW, the *p*-value was less than 0.005 (*t*-tests) for 24 h. Therefore, the B formulations were prepared using basic substances.

3.1.2. Pre-dissolution test

The solubility test showed that Febux is more sensitive to pH than the polymer. Formulations were prepared using various basic substances. The B formulations (1–24) were fabricated with various basic substances at different ratios (**Table S1**). The B formulations (B1-3) showing burst release showed a pre-dissolution (%) of over 90% at 60 min (Fig. 1). The pre-dissolution (%) of the B3 formulation was more than 95% at 60 min. In general, the pre-dissolution (%) of the B (1–3) formulations increased as the amount of meglumine increased. Therefore, meglumine was selected as the basic substance, and the Febux to meglumine ratio was determined for B2 (1:2) and B3 (1:3) formulations by comparing the initial and final pre-dissolution (%) of Febux. Although the pre-dissolution (%) of B2 (92.5 ± 1.4%) and B3 (95.1 ± 2.1%) formulations were similar at 60 min, the B2 formulation was selected due to its lower total weight in the formulation. When comparing the pre-dissolution (%) of Febux in the B2 formulation and other formulations, the *p*-value was less than 0.005 (*t*-tests) at 5 min, except for the B3 formulation. With solubility and pre-dissolution tests, meglumine, a basic substance, was chosen as the solubilizing agent of Febux.

The F formulations (1–12) were fabricated with various polymers (such as P188®, P407®, PEG6000, Soluplus®, IR®, PVP/VA S-630, K12®, K17®, K30®, K90®, TPGS, and HS 15®) based on the B2 formulation (meglumine) (**Table 1**). The pre-dissolution (%) of Febux in the F formulations were 91.3 ± 0.7% (F1), 97.0 ± 2.8% (F2), 86.1 ± 1.1% (F3), 87.7 ± 2.0% (F4), 92.6 ± 0.7% (F5), 86.6 ± 0.1% (F6), 85.5 ± 1.3% (F7), 86.8 ± 0.4% (F8), 90.1 ± 1.4% (F9), 86.4 ± 0.3% (F10), 91.4 ± 0.4% (F11) and 86.1 ± 1.4% (F12) at 60 min. Although the pre-dissolution (%) of Febux decreased due to the addition of most polymers, F formulations (F1, F5, F9, and F11) showed minor differences from the B2 formulation, and only the F2 formulation increased (Fig. 2**a**). Compared to the B2 formulation, the F2 formulation (P407®) improved the initial pre-dissolution (%) by approximately 4% and the final dissolution (%) by 5%. When comparing the pre-dissolution (%) of Febux in the F2 formulation and other formulations, the *p*-value was less than 0.005 (*t*-tests) at 60 min.

The SD formulations (1–9) were prepared based on the F2 formulation (meglumine-P407®) with various carriers such as Aerosil® 200, Aerosil® 300, mannitol, Flowlac® 100, MCC, DCP-A, DCP-D, US2, and UFL2 (Table 2). The pre-dissolution (%) of SD formulations were 93.2 ± 1.4% (SD1), 95.3 ± 2.1% (SD2), 99.6 ± 0.3% (SD3), 95.3 ± 1.6% (SD4), 93.9 ± 1.6% (SD5), 91.4 ± 1.7% (SD6), 87.1 ± 1.5% (SD7), 88.2 ± 1.4% (SD8), and 95.1 ± 1.3% (SD9) at 60 min (Fig. 2**b**). Compared with the F2 formulation, the SD3 formulation (mannitol added) improved by approximately 2% in the initial dissolution (%) and final dissolution (%). Compared to the F2 formulation, there was no significant improvement of the SD3 formulation numerically since it is challenging to increase further due to the high value of final dissolution (%) of Febux. When comparing the pre-dissolution (%) of Febux in SD3 formulation and other formulations, the *p*-value was less than 0.005 (*t*-tests) at 60 min. The SD3 formulation with the highest dissolution (%) of the Febux was selected as the final formulation.

3.2. Dissolution study

The dissolution of Febux in SD3 formulation was compared with that of PM3, pure Febux, and Feburic® tab (commercial product), as shown in Fig. 3. The dissolution methods for Febux were the paddle method (Ⅱ-method) and the dissolution medium (consist of 0.05 M phosphate buffer [pH 6.0]) in US FDA dissolution method. The dissolution of Febux was conducted in a commonly used media (pH 1.2, DW, and pH 6.8 buffer). Although Febux has been identified as a pH-dependent drug through a solubility test, the solubilization effect at low pH must be confirmed.

The dissolution (%) of samples in pH 1.2 media was low for pure Febux and Feburic® tab (within 5%), but the dissolution (%) of PM3 and SD3 was 8.5 ± 1.4% and 30.7 ± 6.5%, respectively, at 60 min (Fig. 3**a**). At 5 min, SD3 showed higher dissolution (%) of Febux by 58.1-, 13.2-, and 5.0-fold compared to pure Febux, Feburic tab®, and PM3 in pH 1.2 media, respectively. At 60 min, SD3 showed higher dissolution (%) of Febux by 12.6-, 6.3-, and 3.6-fold compared to pure Febux, Feburic® tab, and PM3, respectively, in pH 1.2 media. Although the dissolution (%) of Febux in pH 1.2 media

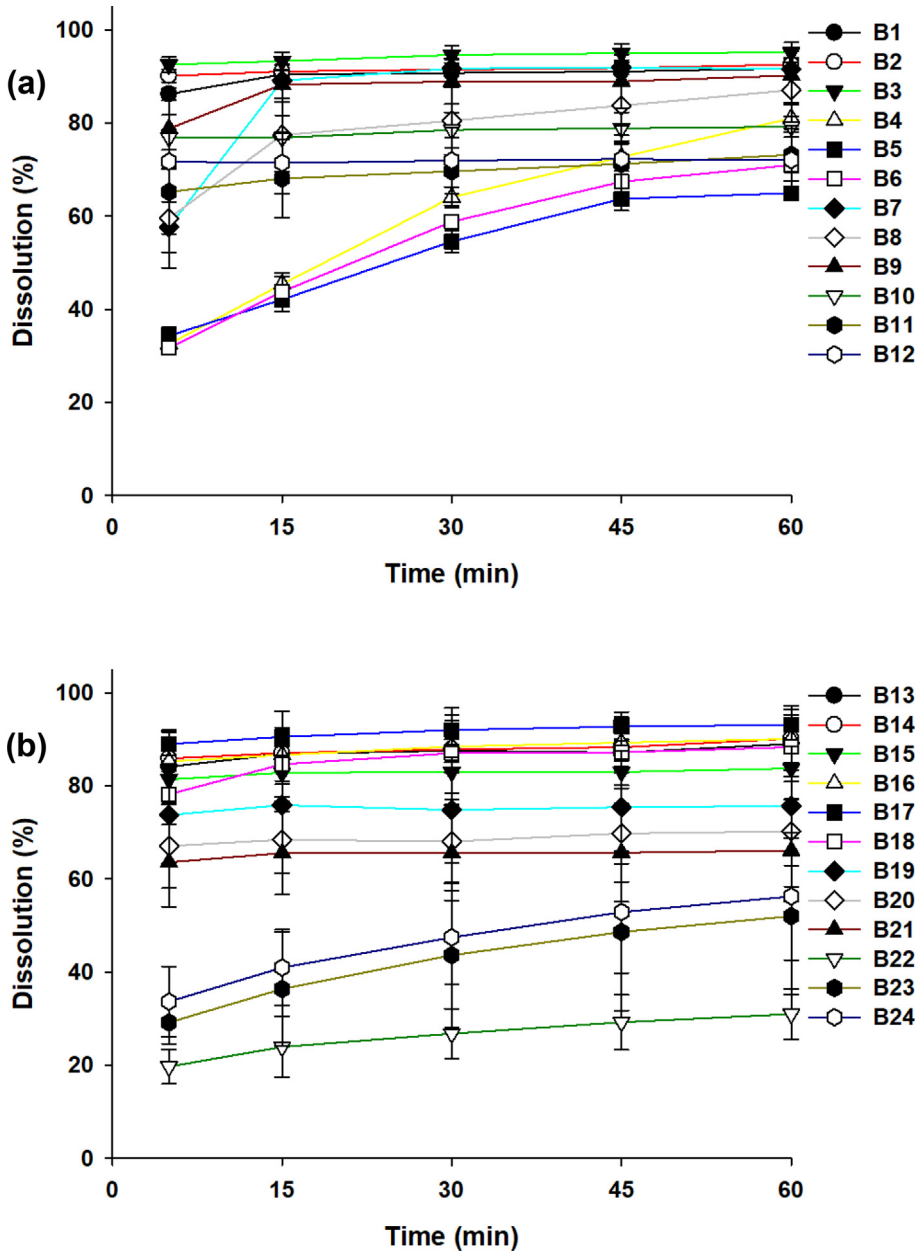

Fig. 1. Pre-dissolution study of the B formulations. Pre-dissolution (%) of B formulations (B1–24) in distilled water was tested at 37 ± 1 °C for 60 min. Data are expressed as mean ± standard deviation (sd, n = 3).

seemed low, SD3 showed a definite improvement in dissolution (%) of Febux compared to that of the Feburic® tab.

The dissolution (%) of samples in DW was low for pure Febux (within 5%) and Feburic® tab (38.9 ± 2.9%), while the dissolution (%) of Febux in PM3 and SD3 was 89.9 ± 4.5% and 100.4 ± 0.3%, respectively, at 60 min (Fig. 3**b**). The dissolution (%) of Febux in SD3 was improved compared to that in PM3, Feburic tab ®, and pure Febux. At 5 min, SD3 showed higher dissolution (%) of Febux by 104.3-, 3.9-, and 1.2-fold than pure Febux, Feburic® tab, and PM3, respectively, in DW. At 60 min, SD3 showed 29.7-, 2.6-, and 1.1-fold higher dissolution (%) of Febux than that of pure Febux, Feburic® tab, and PM3 in DW, respectively.

The dissolution (%) of samples in pH 6.8 buffer was pure Febux (77.9 ± 10.0%), Feburic® tab (88.9 ± 7.4%), PM3 (80.7 ± 1.3%), and SD3 (98.8 ± 1.2%) at 60 min (Fig. 3**c**). The dissolution (%) of Febux in SD3 was improved compared to that in PM3, Feburic tab ®, and pure Febux. At 5 min, SD3 showed higher dissolution (%) of Febux by 1.3-, 1.2-, and 1.2-fold compared to pure Febux, Feburic® tab, and PM3 in pH 6.8 media, respectively. At 60 min, SD3 showed 1.3-, 1.1-, and 1.2-fold higher dissolution (%) of Febux than pure Febux, Feburic® tab, and PM3 in pH 6.8 media, respectively. In pH 6.8 buffer, the dissolution (%) of Febux in PM3 and SD3 tended to be slightly lower than in DW. The analysis results of SD3 were significantly different (p less than 0.005, Student's t-test) from those of the pure Febux, Feburic® tab, and PM3 formulations in all media at 5 and 60 min.

These results showed that the dissolution (%) of Febux in the SD3 formulation was significantly improved compared to that of the Feburic® tab.

3.3. In vitro drug release study

The *in vitro* drug release profiles of pure Febux, Feburic® tab, PM3, and SD3 formulations were evaluated in pH-shifting media

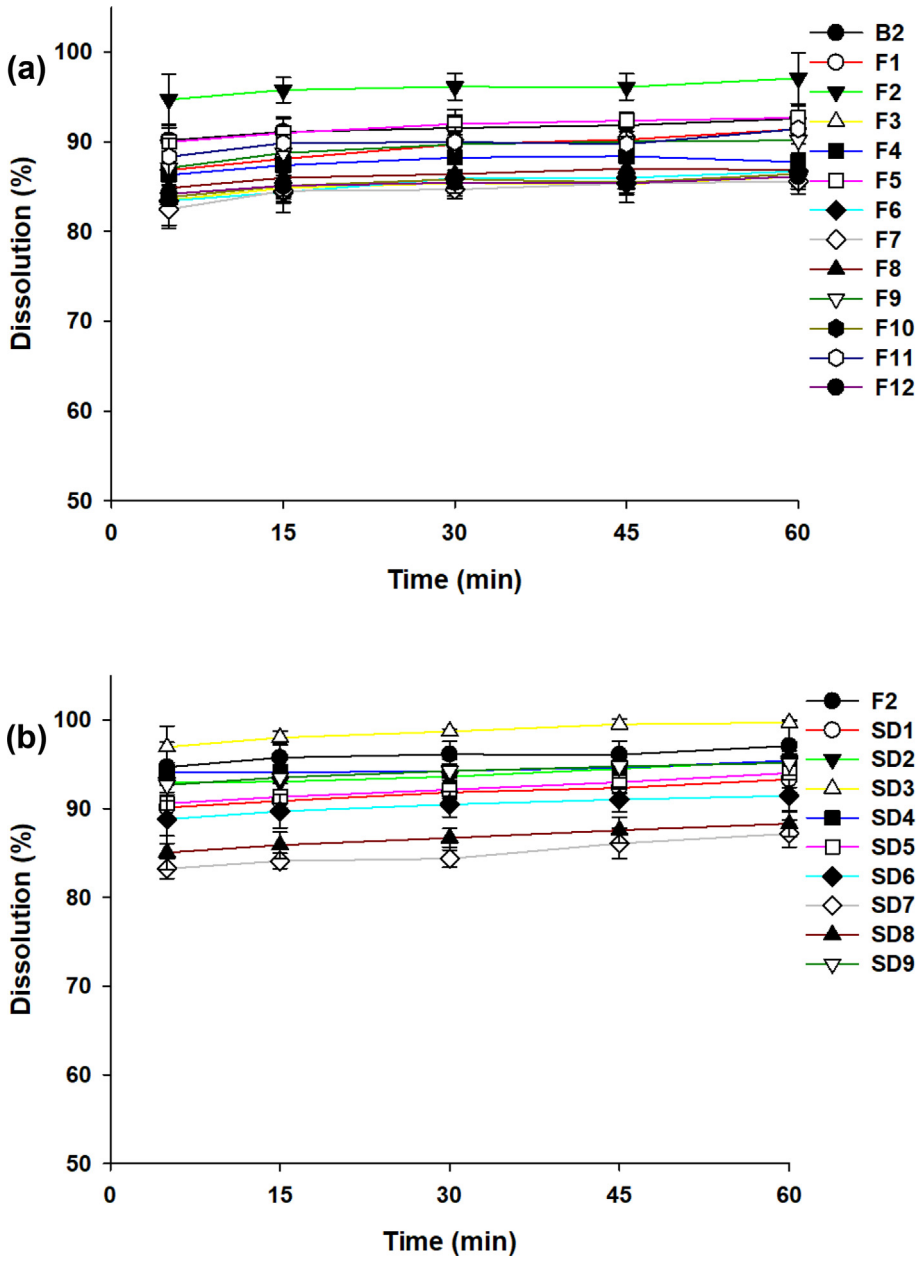

Fig. 2. Pre-dissolution study of the F and SD (solid dispersion) formulations. Pre-dissolution (%) of F formulations (F1-12) in distilled water was tested at 37 ± 1 °C for 60 min (a). Pre-dissolution (%) of SD formulations (SD1-9) in distilled water was tested at 37 ± 1 °C for 60 min (b).

such as SGF (pH 1.2) for 2 h and SIF (pH 6.8) for 48 h in Fig. 4. The *in vitro* Febux release of samples in SGF media showed low release (%) as below 10%. It was confirmed that the dissolution (%) of Febux in SD3 at pH 1.2 increased compared to that in other formulations. The *in vitro* Febux releases of samples in SIF media were 83.4 ± 7.2% (pure Febux), 79.6 ± 4.0% (Feburic® tab), 76.4 ± 4.9% (PM3), and 95.2 ± 7.2% (SD3) after 24 h. The *in vitro* Febux releases of samples in SGF media were 64.8 ± 3.0% (pure Febux), 57.9 ± 5.5% (Feburic® tab), 61.5 ± 5.8% (PM3), and 89.5 ± 4.6% (SD3) after 48 h. Overall, it showed a pattern of increasing drug release up to 24 h and then decreasing for 48 h. In most samples, drug release decreased by 15–20%, but SD3 decreased by 6%, and the decrease was also low. These results confirmed that SD3 has superior stability in *in vitro* drug release media compared to other formulations. As a result of comparing the *in vitro* drug release of Febux in SD3 formulation and Feburic® tab and PM3 formulations, the *p*-value was less than 0.005 (*t*-tests) at 24 h, except for pure Febux (p = 0.08). Through this *in vitro* release, the SD3 formulation is expected to have a higher dissolution (%) of Feburic® tab even *in vivo*.

3.4. In vitro permeability study

The samples as Feburic® tab, PM3, and SD3 formulations were evaluated with four types of membranes in Franz diffusion cell system. In PVDF (hydrophilic and hydrophobic) membranes, *in vitro* permeabilities in samples were 38.2 ± 2.4 μg/cm^2 and 16.5 ± 3.1 μg/cm^2 (Feburic® tab), 47.6 ± 1.3 μg/cm^2 and 15.2 ± 2.3 μg/cm^2 (PM3), and 54.3 ± 2.9 μg/cm^2 and 22.9 ± 1.2 μg/cm^2 (SD3) for 24 h in Fig. 5**(a, b).** According to these results, the SD3 formulation had 1.42-/1.38- and 1.14-/1.50- fold higher Febux permeability in PVDF (hydrophilic and hydrophobic, respectively) than Feburic® tab and PM3. In PCTE (hydrophilic and hydrophobic) membranes,

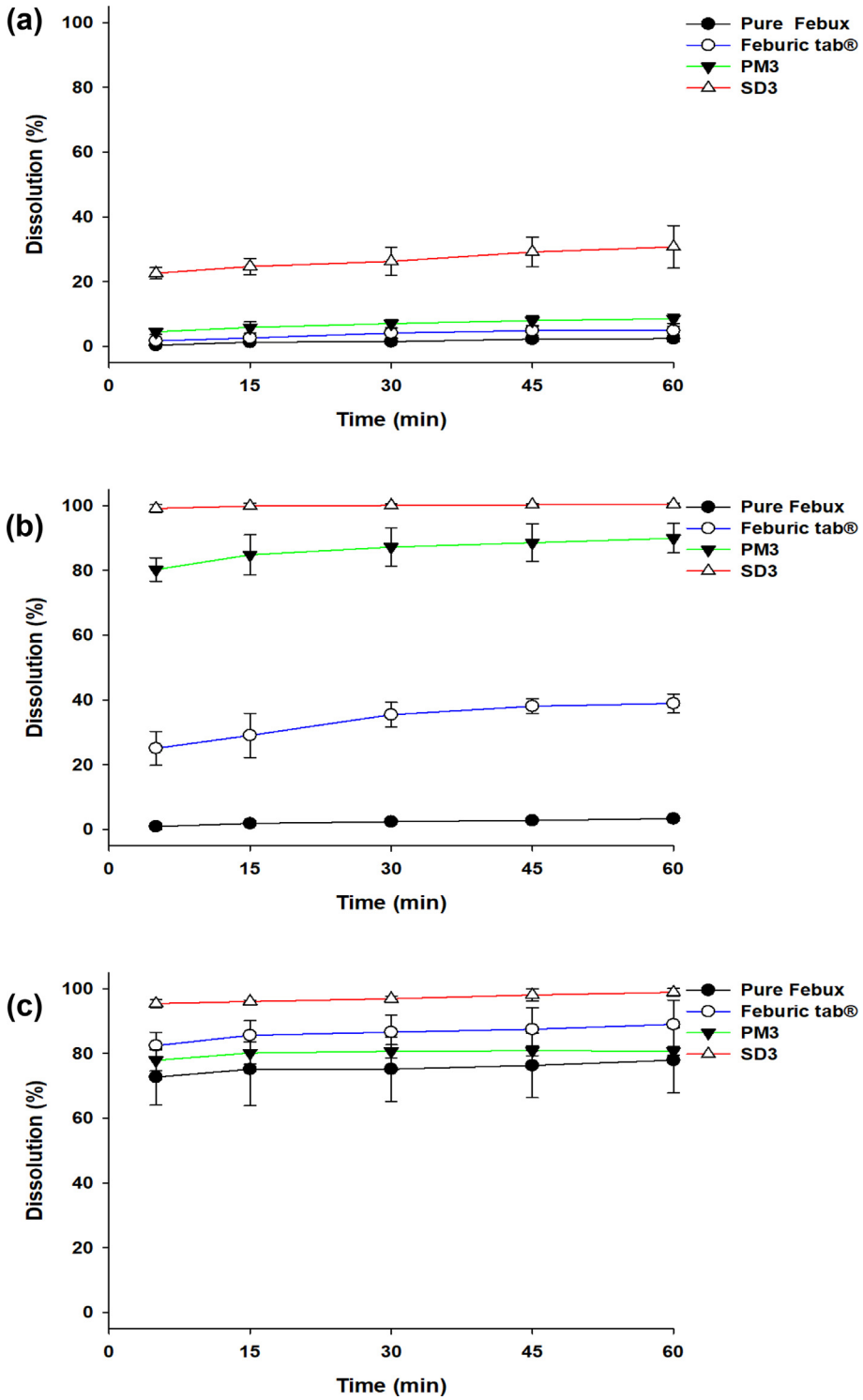

Fig. 3. Dissolution study of the optimal formulation. Dissolution (%) of pure Febux, Feburic® tab, physical mixture (PM3), and solid dispersion (SD3) was tested in pH 1.2 (a), distilled water (DW) (b), and pH 6.8 buffer (c) at 37 ± 1 °C for 60 min. Data are expressed as mean ± standard deviation (sd, n = 6).

in vitro permeabilities in samples were 38.5 ± 1.7 μg/cm^2 and 40.6 ± 3.1 μg/cm^2 (Feburic® tab), 42.1 ± 3.5 μg/cm^2 and 44.3 ± 0. 6 μg/cm^2 (PM3), and 54.2 ± 3.6 μg/cm^2 and 56.0 ± 3.8 μg/cm^2 (SD3) for 24 h in Fig. 5 **(c, d).** According to these results, the SD3 formulation had 1.40-/1.37- and 1.28-/1.26- fold higher Febux permeability in PCTE (hydrophilic and hydrophobic, respectively) than Feburic® tab and PM3. Moreover, except for PVDF-hydrophobic, each formulation showed similar results in various membranes. The SD3 formulation showed the highest permeability in various membrane filters, and the *p*-value was lower than 0.005 compared to other formulations.

3.5. Physicochemical properties

Pure Febux, excipients, PM3, and SD3 were analyzed using DSC to confirm the thermal change in SD3, which is the optimal formu-

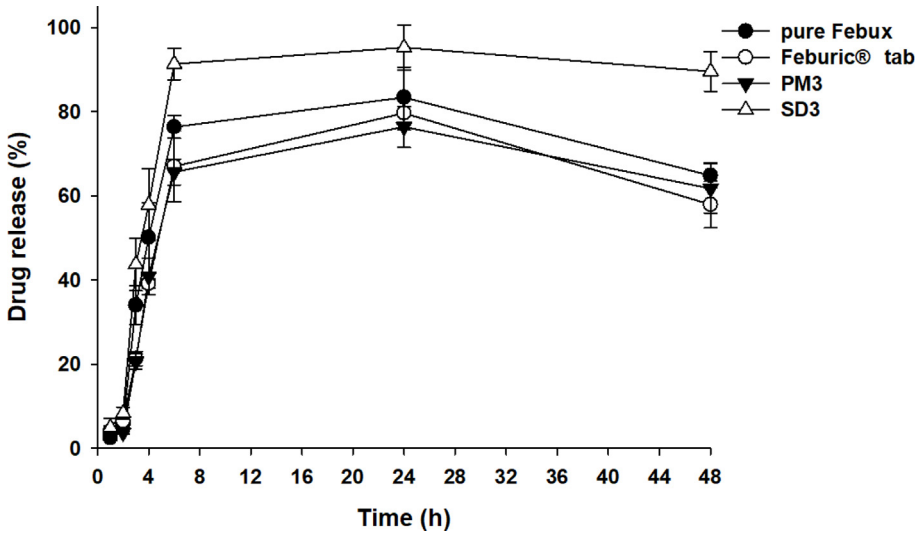

Fig. 4. *In vitro* drug release test. The *in vitro* drug release test of pure Febux, Feburic® tab, physical mixture (PM3), and solid dispersion (SD3) was evaluated in pH shifting method. Data are expressed as mean ± standard deviation (sd, n = 3).

lation. The samples of melting peaks were confirmed at 209.7 °C (pure Febux), 169.3 °C (mannitol), 131.6 °C (meglumine), and 57.7 °C (P407®). PM3 had melting peaks at 55.7 °C, 119.6 °C, and 154–163 °C (broad pattern), and SD3 had melting peaks at 54.3 °C, 118.6 °C, and 154–163 °C (broad pattern), shown in Fig. 6**a**. As shown in the above, the melting peaks of SD3 and PM3 were observed in the order of P407®, meglumine, and mannitol, whereas the melting peak of pure Febux was not observed. The results showed that it is difficult to distinguish the thermal changes in SD3.

The interaction between Febux and excipients in SD3 were performed using FT-IR (Fig. 6**b**).

The FT-IR spectra of Febux showed at 2229.3 (C≡N stretching), at 1674.5 cm^{-1} (C═O stretching), at 1604.7 cm^{-1} and 1511.5 cm^{-1} (C═C stretching), and at 1422.9 cm^{-1}(C—H stretching). The FT-IR spectra of meglumine showed at 1074.2 cm^{-1} (C—O),

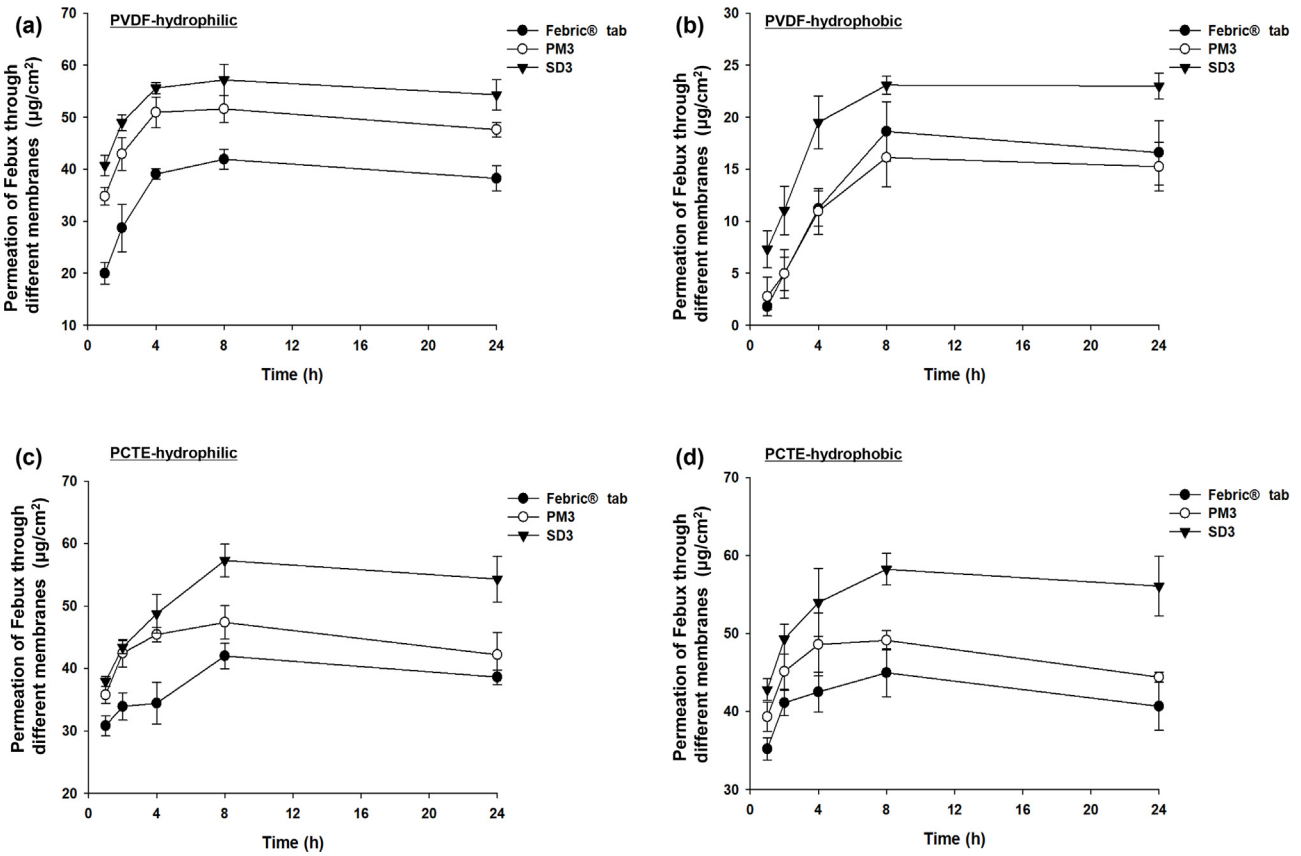

Fig. 5. *In vitro* permeability test. The *in vitro* permeability test of Feburic® tab, physical mixture (PM3), and solid dispersion (SD3) was evaluated with PBS (pH 7.4) in Franz diffusion cell system. Data are expressed as mean ± standard deviation (sd, n = 3).

1239.6 cm^{-1} (C—N) and at 2868.7 cm^{-1} and 2918.4 cm^{-1} (aliphatic C–H). The broad peaks at 3237.9 cm^{-1} and 3316.0 cm^{-1} were attributed to NH and OH stretching modes, respectively. The FT-IR spectra of P407® showed at 1466.8 cm^{-1} (C—H bending). A difference between PM3 and SD3 was that C=O stretching band shifted from 1676.1 cm^{-1} (PM3) to 1628.3 cm^{-1} (SD3). This result indicates that Febux and the excipient have hydrogen bonds. Thus, the dissolution (%) of Febux in SD3 may have improved because of the chemical interactions between Febux and meglumine.

The PXRD patterns of pure Febux, excipients, PM3, and SD3 are shown in Fig. 6**c**. The peaks of pure Febux were identified at 6.5, 6.6, 12.7, 16.2, 19.8, 21.7, 23.7, 24.4, 25.7, and 25.8. The peaks of mannitol were identified at 10.3, 14.5, 18.6, 20.3, 20.9, 21.0, 23.3, 28.1, 29.3, 31.6, 32.4, 33.4, 35.9, and 38.6. The peaks of meglumine were identified at 8.9, 9.6, 12.3, 17.1, 17.9, 19.4, 21.9, 24.0, and 26.9. The peaks of P407® were identified at 18.9 and 23.1. The peaks of PM3 were identified at 8.9, 12.3, 17.2, 17.9, 21.8, and 23.3. The peaks of SD3 were identified at 8.9, 12.2, 17.9, 18.7, 21.7, and 23.3. The XRD patterns of PM3 and SD3 were similar and mostly coincided with meglumine peaks. The peak intensity of Febux was considered weak and could not be observed for PM3 and SD3.

3.6. Stability study

The pre-dissolution (%) of Febux in F and SD formulations was similar to that on the initial day (within 3%), except for SD1 and SD2 (over 5%). Most formulations maintained stability for 1 month (**Fig. S1**).

Composition of Febux-SD formulations after excluding each variable to identify the main factors in Fig. 7. Initially, the pre-dissolutions (%) of formulations were 99.6 ± 0.3% (SD3), 24.3 ± 2.2% (SD3-1), 93.8 ± 3.1% (SD3-2), and 97.0 ± 2.8% (SD3-3) at 60 min. The pre-dissolutions (%) of formulations after 1 month were 98.7% ± 1.2% (SD3), 22.4 ± 3.9% (SD3-1), 92.3 ± 1.1% (SD3-2), and 93.5 ± 1.6% (SD3-3) at 60 min. The pre-dissolutions (%) of formulations after 3 months were 99.4% ± 2.2% (SD3), 22.6 ± 3.9% (SD3-1), 92.1 ± 0.9% (SD3-2), and 88.1 ± 7.4% (SD3-3) at 60 min. The pre-dissolutions (%) of formulations after 6 months were 99.6% ± 3.1% (SD3), 21.7 ± 2.2% (SD3-1), 91.6 ± 0.5% (SD3-2), and 87.1 ± 3.4% (SD3-3) at 60 min. In most formulations, stability was maintained but tended to decrease by approximately 10% in SD3-3.

Also, the crystallinity of Febux in SD3 was stable for 6 months, as shown in Fig. 6**c**. In previous studies, the Febux-SD formulations did not undergo stability tests (Amin et al., 2020; El Shenawy et al., 2019; Jagia et al., 2022; Kaur et al., 2020; Moinuddin et al., 2020; Patel et al., 2021).

Additionally, solubility tests of pure Febux, Feburic® tab, PM3, and SD3 were performed.

The solubilities of the samples were 14.7 ± 3.1 μg/mL and 37.1 ± 1.6 μg/mL (pure Febux), 34.8 ± 3.9 μg/mL and 153.5 ± 6.4 μg/mL (Feburic® tab), 250.0 ± 23.8 μg/mL and 871.1 ± 14.3 μg/mL (PM3), 298.9 ± 28.7 μg/mL, and 949.0 ± 13.7 μg/mL (SD3) for 1 h and 24 h, respectively, indicating that the solubilities of SD3 were 25.5-fold (pure Febux), 6.2-fold (Feburic® tab), and 1.1-fold (PM3) higher than that of the other samples after 24 h. It was confirmed that SD3 is superior to the other formulations regarding pre-dissolution (%), dissolution (%), and solubility.

4. Discussion

Through the solubility test, it was confirmed that Febux is pH-dependent (**Fig. S1**). Based on these results, the development of Febux formulations using a basic substance that has yet to be studied was selected as a strategy. The B (base) formulations (1–24) were developed with eight basic substances. Meglumine was selected through screening of several types of basic substance (Fig. 1). Comparing the pre-dissolution (%) of Febux in B2 formulation and other formulations, the *p*-value was less than 0.005 (*t*-tests) at 5 min, except for the B3 formulation. The basic substance was determined, and several types of polymers were added to develop the F formulation (Table 1). The pre-dissolution (%) results of F formulations showed similar or lower pre-dissolution (%) results to that of B2 formulation, showing unexpected results (Fig. 2**a**). Among the F formulations, only the F2 formulation to which P407® was added increased pre-dissolution (%) of Febux. In a recent study on the solubilization of felodipine, solubilization was successful using a P407®. In Ex vivo permeation study comparing pure felodipine and felodipine SD-loaded rapidly dissolving oral films, the felodipine SD-loaded rapidly dissolving oral films showed about 5 times higher permeability in the porcine buccal mucosa (Sana et al., 2023). Although the drugs were different, the solubilizing effect of P407®, a solubilizing agent, was found. Depending on the properties of the polymer, the viscosity of the formulations may increase to decrease dispersibility. Accordingly, it is considered that the pre-dissolution (%) of Febux has decreased (Sohn et al., 2020a; Sohn et al., 2021b). **In** Fig. 2**b**, according to the pre-dissolution (%) results, the SD3 (mannitol) increased the pre-dissolution (%) of Febux by 2% compared to the F2 formulation. It is expected that there will be changes due to its higher physicochemical interactions than Aerosil® and Neusilin®, which have good dispersibility.

The dissolution of Febux in the SD3 formulation was compared with that of PM3, pure Febux, and Feburic® tab (commercial product), as shown in Fig. 3. In pH 1.2 media, the SD3 formulation showed higher dissolution (%) of Febux by 12.6-, 6.3-, and 3.6-fold compared to pure Febux, Feburic® tab, and PM3, respectively at 60 min. Although the low solubility at low pH due to the characteristics of Febux was not clearly overcome, the improvement of the dissolution (%) of Febux in the SD3 formulation was confirmed. In DW, The SD3 formulation showed 29.7-, 2.6-, and 1.1-fold higher dissolution (%) of Febux than that of pure Febux, Feburic® tab, and PM3 in DW, respectively at 60 min. The SD3 formulation showed superior dissolution (%) of Febux increase compared to that of the Feburic® tab. Because the pH-shifting role of meglumine in DW is clear, it appears that the dissolution (%) of Febux is greatly improved. In pH 6.8 buffer, SD3 formulation showed 1.2-, 1.2-, and 1.2-fold higher dissolution (%) of Febux than pure Febux, Feburic® tab, and PM3, respectively at 60 min. The dissolution (%) of Febux in PM3 and SD3 tended to be slightly lower than that in DW. This may be because meglumine could not increase the pH to the same extent as DW in pH 6.8 buffer. The initial and final dissolutions (%) of Febux in the SD3 formulation were similar, because the Febux in the SD3 formulation showed rapid wetting and dispersion (Sohn et al., 2020b). In previous studies, the dissolution (%) of Febux in fast-dissolving tablets (Febux-co-containing blend crospovidone and microcrystalline [1:1]) was approximately 87% in the pH 6.8 buffer (900 mL) for 10 min and after 30 min decreased to 79%. It is considered to be due to the recrystallization of Febux in pH 6.8 buffer (Kaur et al., 2020). Also, the dissolution (%) of the Febux-SD formulation (Febux: Kolliphor P® 188 = 1:1) was approximately 90% in a pH 7.4 buffer (900 mL) containing 0.35% w/v Tween 20® for 60 min. However, the Febux-SD formulation showed a low Febux dissolution (%) of approximately 50% at 5 min (El Shenawy et al., 2019). The release of Febux-β-cyclodextrin-nanosponges tablets showed a sustained release pattern in pH 6.8 buffer (900 mL) for 10 min (Amin et al., 2020). Furthermore, the dissolution (%) of Febux co-crystals (Febux:isonicotiamide = 2:1) was approximately 14.6% (13 μg/mL) in pH 6.8 buffer (500 mL) for 60 min (Jagia et al., 2022). The dissolution tests in the above

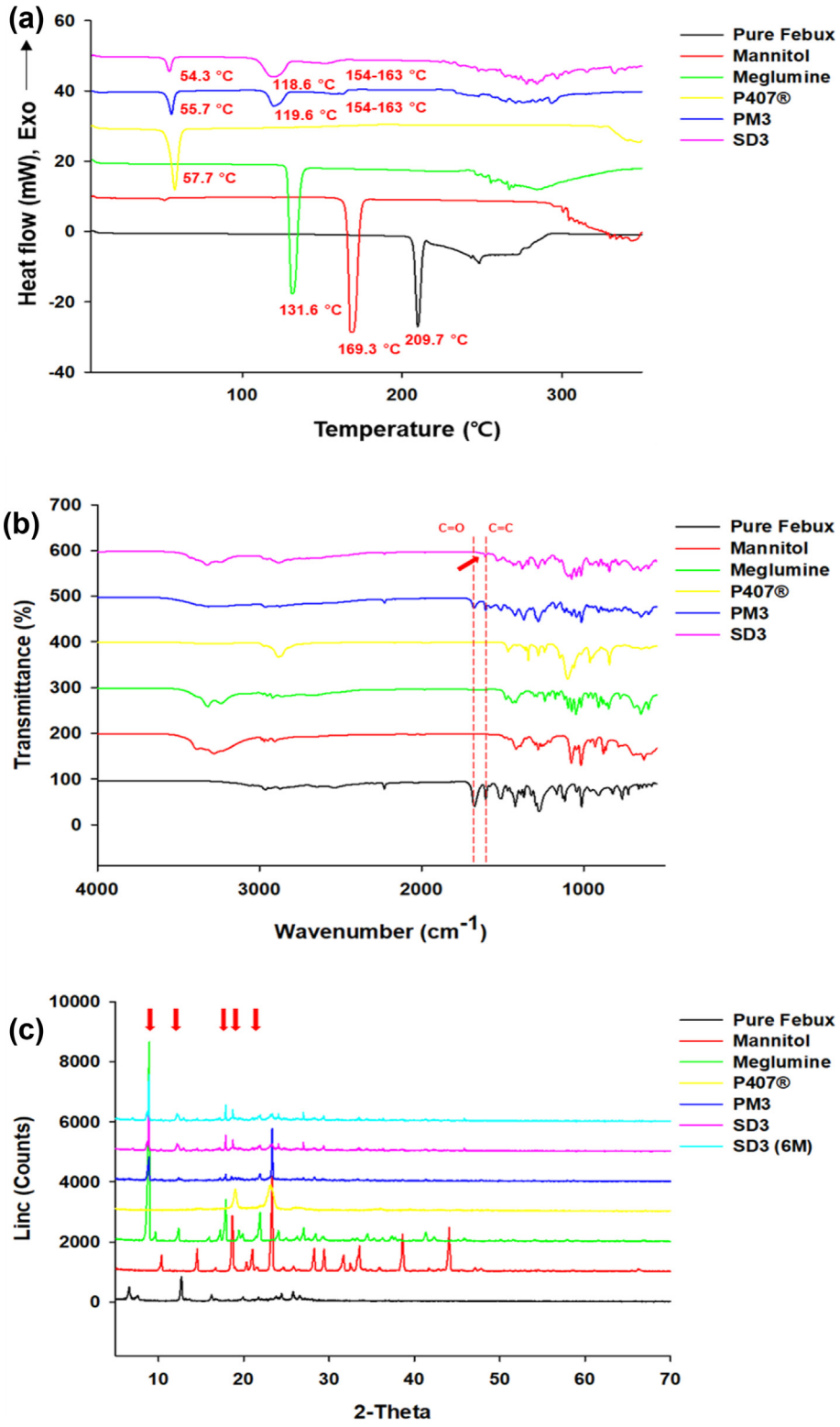

Fig. 6. Physicochemical properties. DSC images of pure Febux, Feburic® tab, physical mixture (PM3), and solid dispersion (SD3) (a). FT-IR spectra of pure Febux, Feburic® tab, physical mixture (PM3), and solid dispersion (SD3) (b). PXRD images of pure Febux, Feburic® tab, physical mixture (PM3), and solid dispersion (SD3) (c).

studies were performed in pH 6.8 buffer or higher and showed a significantly lower dissolution (%) of Febux than that of our SD3 formulation. These results showed that the dissolution (%) of Febux in the SD3 formulation was significantly improved compared to that of the Feburic® tab.

In Fig. 4, the *in vitro* Febux release of samples in SGF media showed low release (%) as below 10%. It was confirmed that the dissolution (%) of Febux in SD3 at pH 1.2 increased compared to that in other formulations. However, the low release (%) of Febux in SD3 was considered to be due to the weak shear force compared

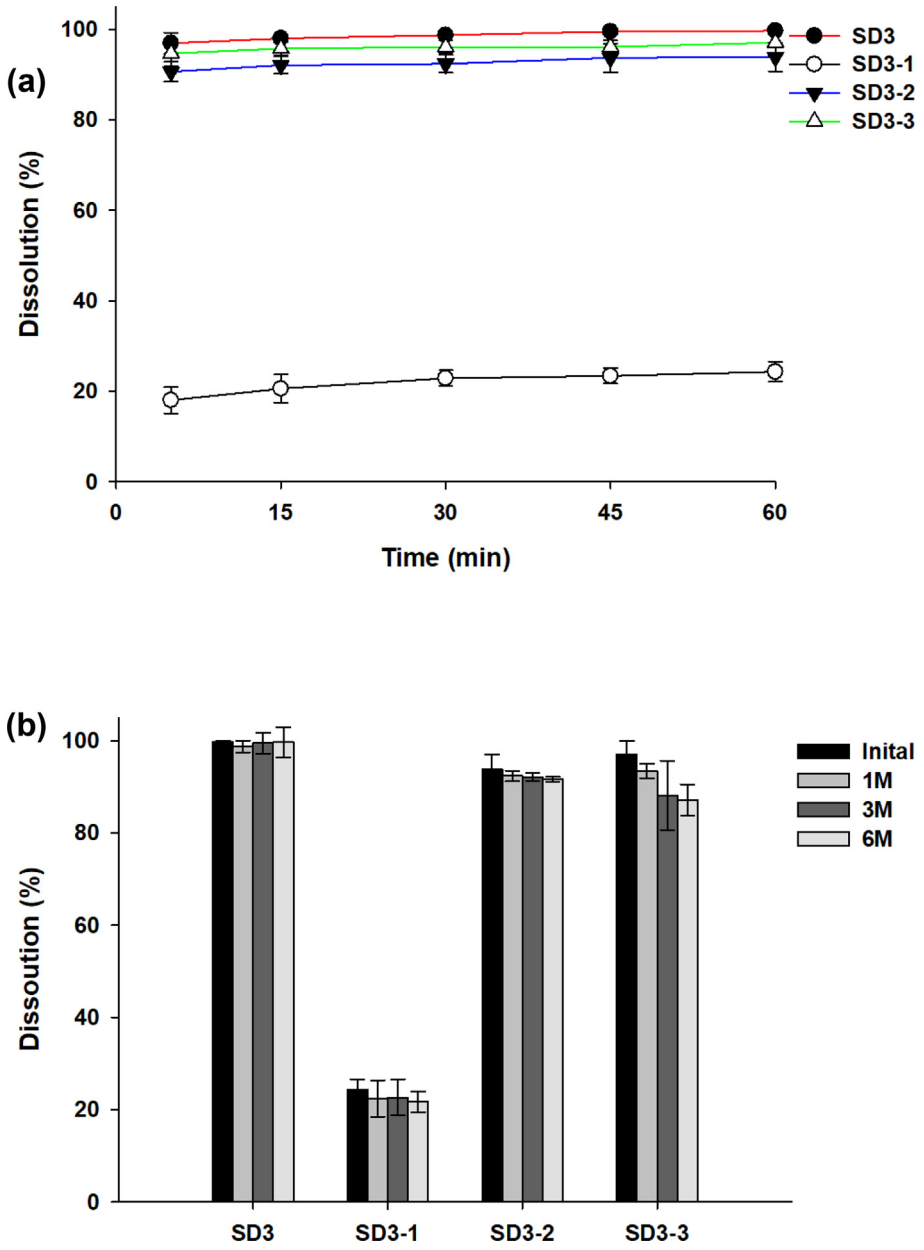

Fig. 7. Stability test. Composition of Febux-solid dispersion (SD) formulations by excluding each variable to identify main factors. SD3 (Febux, meglumine, P407® and mannitol in a 1:2:1:1), SD3-1 (Febux, meglumine, P407® and mannitol in a 1:0:1:1), SD3-2 (Febux, meglumine, P407® and mannitol in a 1:2:0:1) and SD3-3 (Febux, meglumine, P407® and mannitol in a 1:2:1:0)(a). Moreover, stability test was performed for 6 months. The pre-dissolution (%) of Febux in SD3 formulations was performed in DW at 37 ± 1 ℃ at 60 min (b). Graph represents the mean ± standard deviation (n = 3).

with that of the dissolution test. Overall, it showed a pattern of increasing drug release up to 24 h and then decreasing for 48 h in SIF media. This is likely due to due to the recrystallization of the drug in the release media. Through this *in vitro* release, the SD3 formulation is expected to have a higher dissolution (%) of the Feburic® tab even in *in vivo*.

In Fig. 5, the SD3 formulation had 1.40-/1.37- and 1.28-/1.26-fold higher Febux permeability in PCTE (hydrophilic and hydrophobic, respectively) than Feburic® tab and PM3.

Although it is not an artificial barrier, SD3 showed superior results in four types of membranes. Through this, intestinal permeability is also expected to be improved.

However, the limitation of this study is that it is challenging to prove changes in the Febux of SD3 formulation in the body because there is no animal experiment. Therefore, in this paper, it can be confirmed through previous research papers. In the first previous study, Febux-self-nano-emulsifying formulations (Capmul MCM: Labrasol: Transcutol HP = 15:56.92:28.07 (% w/w) as liquid, solid, and pellet formulations showed fast dissolution patterns similar to the SD3 formulation. Also, oral bioavailability improved by 1.4- to 2.1-fold for the above three formulations compared to pure Febux suspension in Sprague Dawley rats (Rangaraj et al., 2019). In the second previous study, Febux-loaded β cyclodextrin based nanosponge tablets with a controlled release system were developed. The compositions of formulations were Febux: nanosponge = 1:1 (composition of nanosponges were β cyclodextrin: Diphenyl carbonate = 1:2, 1:4, 1:6, 1:8, and 1:10). The dissolution (%) and *in vitro* release pattern was lower than that of SD3 and Goutifade tablet® (commercial products). Still, oral bioavailability was twice as high as that of Goutifade tablet® in Sprague Dawley

rats (Amin et al., 2020). In the third previous study, the dissolutions (%) of Febux solid dispersions (Febux:PVP K30®:P188® = 1:3:3 and Febux:PVP K30®:P407® = 1:3:3) were below 50% and 95% in DW and pH 6.8 buffer, respectively. Compared to the SD3, it showed significantly lower dissolution results (100.4 ± 0.3% and 98.8 ± 1.2% in DW and pH 6.8 buffer, respectively.) The AUC_{0-24h} (μh/mL) Febux solid dispersions showed 1.5-fold (P188® formulation) and 1.4-fold (P407® formulation) higher than pure Febux in Sprague–Dawley (SD) rats (Tang et al., 2018).

The our SD3 formulation is expected to have high oral bioavailability compared to the above papers by considering the high dissolution (%) and *in vitro* release pattern. Basically, when drug solubilization increases the total weight in the formulation. However, the SD3 formulation is considered to have no problem with dosage compliance even when compared to the existing 260 mg reference drug with a total weight of 200 mg.

In Fig. 6, the melting peaks of SD3 and PM3 were observed in the order of P407®, meglumine, and mannitol, whereas the melting peak of pure Febux was not observed in DSC data. Therefore, it was difficult to distinguish the thermal changes in SD3. A difference between PM3 and SD3 was that C═O stretching band shifted from 1676.1 cm^{-1} (PM3) to 1628.3 cm^{-1} (SD3). This result indicated that Febux and the excipient have hydrogen bonds. Thus, the dissolution (%) of Febux in SD3 may have improved because of the chemical interactions between Febux and meglumine. The XRD patterns of PM3 and SD3 were similar and mostly coincided with meglumine peaks. The peak intensity of Febux was considered weak and could not be observed for PM3 and SD3.

The composition of Febux-solid dispersion (SD) formulations was excluded one by one to identify the main factors in Fig. 7. To confirm this, it was confirmed while excluding the excipient of the SD3 formulation by one. The SD3 (Febux, meglumine, P407®, and mannitol in a 1:2:1:1 ratio), SD3-1 (Febux, meglumine, P407®, and mannitol in a 1:0:1:1 ratio), SD3-2 (Febux, meglumine, P407®, and mannitol in a 1:2:0:1 ratio), and SD3-3 (Febux, meglumine, P407®, and mannitol in a 1:2:1:0 ratio) were prepared in the same manner as described above (Table 3). In most formulations, stability was maintained but tended to decrease by approximately 10% in SD3-3 for 6 months. The results suggest that mannitol is effective in maintaining stability. Moreover, meglumine had the highest solubilizing effect on Febux, and the effect of P407® or mannitol was insignificant. In previous studies, tadalafil-SD formulation was performed to find the main factors. PVP/VA S-630 was important to improve the pre-dissolution (%) of tadalafil in tadalafil-SD formulation (consist of chitosan, Aerosil®200 and PVP/VA S-630) (Sohn and Choi, 2021b). Additionally, the naftopidil-SD formulation was confirmed as the key factor. Fumaric acid was essential to increase the pre-dissolution (%) of naftopidil in naftopidil-SD formulation (consisting of fumaric acid, chitosan, and US2®) (Sohn et al., 2021a). Also, the crystallinity of Febux in SD3 was stable for 6 months, as shown in Fig. 6**c**. In previous studies, the Febux-SD formulations did not undergo stability tests (Amin et al., 2020; El Shenawy et al., 2019; Jagia et al., 2022; Kaur et al., 2020; Moinuddin et al., 2020; Patel et al., 2021).

5. Conclusion

In this study, the solubilization of Febux, a BCS II drug, was successfully developed with meglumine with the SD technique. The SD3 formulation consisted of Febux, meglumine, P407®, and mannitol in a 1:2:1:1 wt ratio. The dissolution (%) of Febux in SD3 formulation significantly enhanced the dissolution (%) of Febux compared to the Feburic® tab in all media. Moreover, in *in vitro* release, the SD3 formulation showed a faster release pattern than the Feburic® tab in the pH shifting method. In the *in vitro* permeability test, the SD3 formulation showed a higher value than to Feburic® tab in four membrane types.

Furthermore, in SD3 formulation, hydrogen bonding between Febux and meglumine was confirmed. It is thought that the dissolution (%) and *in vitro* release of Febux in SD3 was improved owing to the change in this chemical interaction. The order of meglumine > P407® > mannitol in the SD3 formulation was important for improving the pre-dissolution (%) of Febux. The SD3 formulation was maintained for 6 months. This research developed a formulation by applying meglumine to Febux for the first time. The SD3 formulation improved dissolution (%), drug release (%), and stability compared to commercial products (Feburic® tab). Moreover, it is a formulation that does not increase total weight compared to the commercial products (Feburic® tab). Therefore, it seems that there is no problem with patient compliance. Based on these results, the SD3 formulation is able to increase the oral bioavailability of Febux in animal or human studies.

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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.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2023.101724.

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