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Development of taste-masked enteric granules containing diclofenac sodium utilizing Eudragit® E PO as a taste-masking agent

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ABSTRACT

This study aimed to develop a taste-masking method for Eudragit® L 100-based enteric microparticles containing diclofenac sodium (DS) using Eudragit® E PO and to determine the optimal polymer ratio for effective taste-masking. The taste-masked enteric granules (TEGs) were fabricated via rotary evaporation with dichloromethane as the solvent, with enteric microparticle-to-Eudragit® E PO weight ratios of 1:0.1, 1:0.25, 1:0.5, and 1:1. Reducing the polymer ratio to 0.1 caused enteric microparticles to disperse independently from the polymer, while higher ratios embedded them in the polymeric carrier. To evaluate the taste-masking efficiency of TEGs, drug release in 10-mL simulated salivary fluid (SSF) was tested. The results revealed that increasing the polymer ratio enhanced the inhibition of drug release in SSF, indicating improved taste masking. However, in the in vitro drug dissolution in a two-stage biorelevant medium, TEGs with high polymer ratios of 1 and 0.5 released only 69.80±1.47% and 78.87±1.21% of DS after 3 h in the buffer stage dissolution, while TEGs with lower polymer ratios of 0.25 and 0.1 exhibited higher drug release percentages of 92.61±1.23% and 97.14±0.58%, respectively. From this study, the optimal enteric particle-to-Eudragit® E PO ratio was 1:0.25, effectively masking the bitter taste of DS while minimally affecting drug release in a gastrointestinal-mimicking environment.

Keywords: taste-masking; Eudragit® E PO; rotary evaporation; granules; diclofenac sodium

1. INTRODUCTION

Taste masking plays a crucial role in the formulation design of pharmaceuticals, especially those intended for oral administration, due to the fact that numerous active pharmaceutical ingredients (APIs) have unpalatable tastes. To mask the bitter taste, three major approaches were utilized to prevent the APIs from interacting with taste buds. These strategies comprised the utilization of flavoring agents, chemical modifications, and employing physical barriers. Utilizing flavoring agents is a common and widely used method. Sweeteners, flavoring agents, and

additional pharmaceutical excipients are employed to disguise the bitter taste of drug substances (Lenik et al., 2016). Nevertheless, this technique is constrained in its ability to mask the taste of highly potent drugs and may not entirely eliminate strong taste and odor. Chemical modification for taste masking involves transforming the drug structure into a prodrug. Alternatively, drug substances may be formulated as complex compounds, such as inclusion complexes with cyclodextrins (Adamkiewicz and Szeleszczuk, 2023). Taste masking of drugs occurs due to decreased dissolution of drugs in saliva, resulting in a reduced amount of drug stimulating taste receptors. The final method employed for taste masking utilizes a physical barrier by coating a drug with polymers to prevent its dissolution in the oral cavity (Felton, 2018). These polymers have limited or no solubility in saliva, thus preventing direct contact of the drug with taste receptors on the tongue. Various techniques for polymer coating include extrusion-spheronization, hot-melt extrusion, granulation, coacervation, emulsion solvent diffusion, and spray drying (Petrovick et al., 2016; Maniruzzaman et al., 2012; Nishiyama et al., 2016; Comunian et al., 2013; Gao et al., 2006; Yi et al., 2014).

Polymers utilized in taste masking may include water-soluble polymers, water-insoluble polymers, or polymers with solubility dependent on pH. Polymers with pH-dependent solubility are widely favored for taste masking applications. These polymers contain functional groups that ionize differently across varying pH levels, resulting in distinct solubility profiles in different solutions. This characteristic renders them effective in preventing drug dissolution in the oral cavity (pH = 6.97–7.40), while ensuring adequate dissolution in acidic gastric conditions. Commonly utilized polymers include Eudragit® E, a cationic copolymer featuring dimethyl aminoethyl methacrylate, butyl methacrylate, and methyl methacrylate (Nollenberger and Albers, 2013). Eudragit® E, which incorporates tertiary amine functional groups, rapidly ionizes under acidic conditions, allowing for dissolution in gastric fluids while maintaining insolubility in the oral cavity. Consequently, the thickness of the coating layer does not affect drug release kinetics in the stomach (Joshi and Petereit, 2013). Eudragit® E is marketed in different formulations, including granules (Eudragit® E 100) and powder (Eudragit® E PO), both of which are colorless to yellow-tinged and have a characteristic amine-like odor. Additionally, Eudragit® E 12.5 is an organic solution of Eudragit® E 100, containing 12.5% w/w dry substance in a mixture of 60% w/w isopropyl alcohol and 40% w/w acetone. This solution appears as a light yellow, low-viscosity liquid that is clear to slightly cloudy, with a distinctive solvent odor. Eudragit® E demonstrates solubility in acetone and alcohols, as well as in solutions with pH levels lower than 5 (Rowe et al., 2012).

Several studies have documented the utilization of Eudragit® E PO in taste masking of drug particles through various techniques. Spray-drying is a widely employed method. This technique involves dispersing or dissolving the drug and polymer in a dispersion medium, typically including additional additives to prevent particle aggregation and achieve a more uniform coating on the drug particles. Yan et al. (2010) successfully prepared taste-masked microparticles of donepezil hydrochloride via spray-drying and found that the optimal drug-to-polymer ratio for taste masking using Eudragit® E PO was 1:2. Georgieva et al. (2020) also reported the same optimal ratio of 1:2 for taste masking, achieving a drug loading of approximately 24% in their study. In contrast, Bora et al. (2008) reported a similar optimal drug-to-polymer ratio with higher drug loading when using an organic solvent, dichloromethane, as the dispersion medium for Eudragit® E PO without the addition of other additives.

Fluid bed coating is another technique utilized for taste-masking drug particles. In this approach, a dispersion of Eudragit® E PO is sprayed onto drug particles suspended in air. Drašković et al. (2017) prepared Eudragit® E PO in an aqueous medium containing sodium lauryl sulfate, stearic acid, and talc, which acted as a wetting agent, plasticizer, and glidant, respectively. This method successfully masked the bitter taste of the drug, with the drug content of the coated microparticles reported to be approximately 70%. Fluid bed coating has also been utilized in the preparation of enteric taste-masked pellets, as demonstrated in the study by Alotaibi et al. (2019). This study employed fluid bed coating to create enteric taste-masked pellets containing diclofenac sodium (DS). The drug was initially layered onto sugar spheres before being enteric-coated with Eudragit® L 100 using a layering technique. Subsequently, the enteric-coated pellets were taste-masked by coating them with Eudragit® E 100, also via a layering method. This approach effectively produced enteric taste-masked pellets that could prevent drug release in both the oral cavity and the stomach. However, this method requires the use of several additional additives, such as inert cores, anti-adherents, and plasticizers like talc and PEG 6000.

The potential applications of taste-masked microparticles and pellets extend to drug administration for patients with dysphagia, including pediatric and geriatric populations, due to their small size and ease of swallowing (Liu et al., 2014). Similar to pellets, taste-masked granules are also suitable for drug administration in these populations because of their manageable size and ease of ingestion. Furthermore, taste-masked granules can be formulated into oral dispersible dosage forms, such as orally disintegrating tablets (ODTs), due to their suitable flow properties. Taste-masking granules have been developed in various studies, employing techniques such as melt granulation (Forster and Lebo, 2021), coating by fluid bed granulation (Nishiyama et al., 2016), dispersion (Sangnim and Huanbutta, 2019) and granulation by high shear mixer (Albertini et al., 2004).

In this study, taste-masked enteric granules (TEGs) were developed to encapsulate Eudragit® L 100-based enteric microparticles loaded with DS, fabricated as described in our prior work (Burapapadh et al., 2024). DS, a potent non-steroidal anti-inflammatory drug (NSAID), was chosen as the model drug in this study due to its intense bitterness and potential to cause local stomach irritation as a side effect. The primary objective of formulating the TEGs was to mask the drug's bitter taste while preserving the enteric properties of the enteric microparticles, thus improving both acceptability and therapeutic efficacy. Figure 1 presents a schematic representation of the composition of TEGs. Taste-masking was achieved through the dispersion of enteric microparticles in Eudragit® E PO to hinder the dissolution of Eudragit® L 100 in the oral cavity. Various amounts of Eudragit® E PO, as the taste-masking polymer, were utilized in the preparation of TEGs through solvent

evaporation employing a rotary evaporator. A thorough investigation was carried out to ascertain the optimal polymer ratio. The morphology of TEGs was investigated through SEM, and the physicochemical properties of the TEGs were analyzed by FT-IR, DSC, and PXRD analysis. Furthermore, simplified drug release and biphasic dissolution tests were performed to assess the taste-masking efficiency and drug release characteristics of the TEGs in a simulated gastrointestinal environment, respectively.

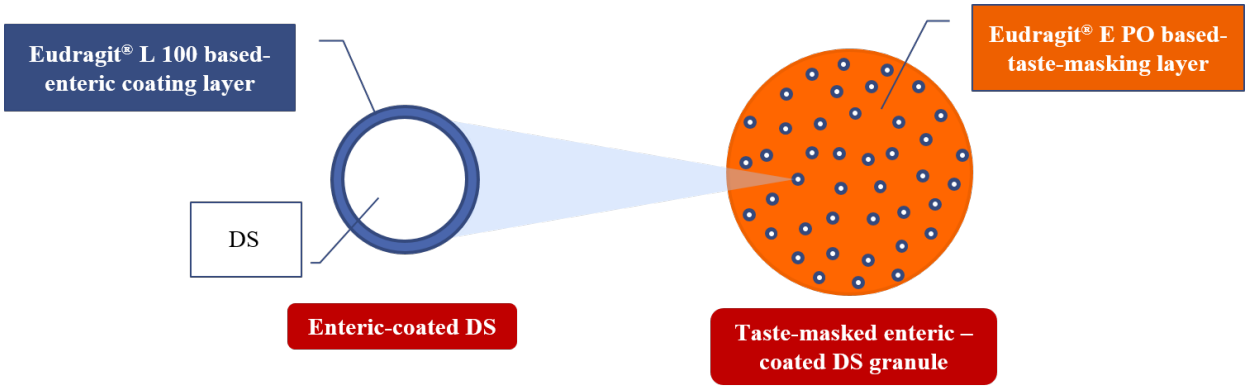

Figure 1. Schematic representation of composition of TEGs

2. MATERIALS AND METHODS

2.1 Materials

Diclofenac sodium (Batch no. DFS/19050129) was obtained from Aarti Drugs Limited, India. Eudragit® E PO (Batch no. G180631579) and Eudragit® L100 (Batch no. 190303201), which were sourced from Evonik Nutrition & Care GmbH, Germany, were generously donated by Jebsen & Jessen Ingredients (Thailand). HPLC-grade methanol was purchased from Fischer Scientific, Korea, and ultrapure water was employed as the mobile phase. Reference standard dichloromethane (Lot no. G1257711) for the residual solvent analysis was from Dr. Ehrenstorfer GmbH, Germany. All chemicals, unless otherwise stated, were of analytical grade and were utilized without additional purification.

2.2 Preparation of TEGs

The DS loaded enteric microparticles were previously produced via spray drying, using Eudragit® L 100 as the enteric polymer and phosphate buffer pH 7.0 as the aqueous-based feed dispersion medium, in accordance with the procedure detailed in our earlier study (Burapapadh et al., 2024). In summary, Eudragit® L 100 was dissolved in the solution and stirred gently for 6 hours for complete dissolution. DS underwent sieving through an 80-mesh sieve and was then dispersed in the polymer solutions for 60 minutes to ensure uniform distribution. The drug-to-polymer weight ratio was maintained at 1:1, with the feed dispersions containing a total solids content of 2% w/v. The continuously stirred feed dispersions were subsequently subjected to spray-drying using the mini spray dryer B-290 (Buchi, Switzerland).

The taste-masking of the drug-loaded enteric microparticles was achieved using the solvent evaporation method. Initially, Eudragit® E PO was dissolved in dichloromethane at a concentration of 10% w/v. Following this, the drug-loaded enteric microparticles, sieved through mesh no. 80, were subsequently added to the solution with enteric microparticle-to-Eudragit® E PO weight ratios of 1:0.1, 1:0.25, 1:0.5, and 1:1. The 100-mL dispersion was then subjected to drying using a rotary evaporator (Rotavapor® R-100, Buchi, Switzerland) maintained at 45°C under a pressure of 540 mbar until most of the solvent was removed. Subsequently, the pressure was reduced to 230 mbar for 2 h before releasing the vacuum. After the residual solid was removed from the round-bottom flask, the product underwent gentle milling with a pestle and mortar, followed by sieving through a No. 40-mesh to obtain the TEGs. Subsequently, the TEGs were stored in a desiccator prior to further analyses.

2.3 Morphology and physicochemical property evaluation of TEGs

2.3.1 Morphology

The morphology of the TEGs was assessed using an SEM. The TEGs were attached to stubs using double-sided adhesive tape and then coated with a thin layer of gold for optimal visualization before analysis via a Mira3 instrument from Tescan, Czech Republic. Magnifications of 1,000× and 10,000× were applied during the examination.

2.3.2 FTIR analysis

Each TEG sample was mixed with KBr powder and then compressed into a disk before being placed into the sample holder. The FTIR spectra were analyzed using an FTIR spectrophotometer (Nicolet Avatar 360, USA) within the 4000 to 400 cm^{-1} range at a resolution of 4 cm^{-1}. The spectral characteristics of the samples were obtained through software (OMNIC FT-IR Software, version 7.2a, Thermo Electron Corporation, USA).

2.3.3 Thermal analysis

The differential scanning calorimeter (DSC 8000, PerkinElmer, USA) was utilized to examine the thermal characteristics of the TEGs. The temperature spectrum extended between 25°C and 320°C, while undergoing heating at a rate of 10°C per minute. The analysis took place in an atmosphere of nitrogen flowing at a rate of 20 mL/min.

2.3.4 Powder X-ray diffraction (PXRD) analysis

The characterization of the crystallinity of the TEGs was conducted employing a powder X-ray diffractometer (PXRD) (Model Miniflex II, Rigaku, Japan), operating at 40 kV and 40 mA. Measurements were undertaken within the angular range of 5–45° 2θ, utilizing Cu Kα radiation with a wavelength of 1.5406 Å.

2.3.5 Drug content

The determination of DS loading in TEGs involved dissolving accurately weighed TEGs samples, approximately 50 mg, in 10 mL of methanol. The drug concentrations were analyzed using high-performance liquid chromatography (HPLC) equipped with an Inertsil-ODS3 column (4.6 × 250 mm. I.D., 5 µm) from GL Sciences, Japan. The HPLC system operated at a flow rate of 1.0 mL/min with a mobile phase consisting of methanol (80%) and 0.1% acetic acid (20%) adjusted to pH 4.0. The oven temperature was maintained at 35°C, and detection was performed using a diode array detector (DAD) set at 280 nm, with an injection volume of 10 µL. Calibration was achieved using DS standards ranging from 1 to 32 µg/mL dissolved in methanol. The drug content was measured and represented as loading capacity and loading efficiency, calculated using Equation (1) and Equation (2) respectively. Each sample was analyzed in triplicate.

$$Loading\ capacity\ (\%) = \frac{Total\ amount\ of\ DS\ (\mathrm{mg}) \times 100}{Amount\ of\ granules\ (\mathrm{mg})} \quad (1)$$

$$Loading\ efficiency\ (\%) = \frac{Total\ amount\ of\ DS\ (\mathrm{mg}) \times 100}{Total\ initial\ amount\ of\ DS\ added\ (\mathrm{mg})} \quad (2)$$

2.3.6 Simplified dissolution test

Drug release in small-volume simulated salivary fluid (SSF) was utilized as a modified in vitro technique to assess taste masking, following the method described by Shirai et al. (1996). SSF with a pH of 6.8 was prepared as described by Marques et al. (2011) consisting of 8 g sodium chloride, 0.19 g potassium phosphate monobasic, and 2.38 g sodium phosphate dibasic dissolved in 1 L of deionized water. An accurate amount of TEGs, equivalent to 25 mg of DS, was introduced into 10 mL syringes filled with 10 mL of SSF. The syringes were then agitated by rotation ten times within 30 s and 3 min. Following agitation, the dispersions were filtered through a 0.22–µm nylon syringe filter (Millipore, Bedford, MA, UK), and the quantity of dissolved DS was analyzed using the previously described method. Each sample underwent triplicate analysis.

2.3.7 In vitro drug release studies

A biorelevant drug release investigation was conducted in two stages, adhering to the protocol outlined by Alotaibi et al. (2019). This involved an initial 2-h acid phase carried out in 750 mL of 0.1 N HCl (pH 1.2), followed by a transition to a pH 6.8 basic stage with the addition of 250 mL of 0.2 M tribasic sodium phosphate for an additional 3 h. The precise quantity of TEGs equivalent to 25 mg of DS was transferred to the acidic medium within the USP apparatus II dissolution tester (Dissolution system 2100B, Distek, USA), operating at a paddle speed of 50 rpm and a controlled temperature of 37±0.5°C. Aliquots of 5 mL were withdrawn at specific time points and filtered through a 0.22-µm nylon syringe filter before being replaced with an equal volume of fresh dissolution media. Sampling intervals occurred at 120 min during the acid stage and at subsequent time points of 125, 130, 140, 150, 165, 180, 210, 240, and 300 min during the basic stage. The determination of DS quantity was performed using the previously outlined HPLC conditions.

In order to compare the dissolution profiles, the values of *f1* (difference factor) and *f2* (similarity factor) were calculated using Equations (3) and (4), respectively. To determine similarity and bioequivalence between two dissolution profiles, the *f1* value should be within the range of 0 to 15, and the *f2* value should be within the range of 50 to 100 (Polli et al., 1997).

$$f1 = \{[\textstyle\sum_{t=1}^{n}|R_t - T_t|] \,/\, [\sum_{t=1}^{n} R_t]\} \times 100 \quad (3)$$

$$f2 = 50 \cdot \log\{[1 + \tfrac{1}{n}\textstyle\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \times 100 \quad (4)$$

where n is the number of sampling times, R_t and T_t are the mean percentages dissolved at each time point of the reference and test sample, and t is the time point.

2.4 Residual solvent analysis

The residual amount of dichloromethane was evaluated using TEGs with a polymer ratio of 0.25 as a representative. The evaluation followed the protocol outlined by Gad et al. (2015), with specific modifications. A headspace-gas chromatography (HS-GC) system (7890A, Agilent Technologies, USA) with a DB-5 column (30m × 0.250 mm, 0.25 µm), helium flow maintained at 1 mL/min, and a flame ionization detector (FID) was utilized. The TEGs were sieved through a 40-mesh sieve, followed by precise weighing of approximately 100 mg before being transferred into a 20-mL glass vial sealed with a septum closure and aluminum crimp. Subsequently, the vial was incubated at 120°C for 5 min. Following incubation, 2 mL of the headspace was injected into the GC column. Initially, the GC temperature was set at 40°C for 4 min for equilibration, followed by a ramp to 55°C at a rate of 2°C/min, and finally to 235°C at a rate of 30°C/min. The concentration of each solvent in the test solution, expressed in parts per million (ppm), was determined using Equation (5).

$$Content\ (\mathrm{ppm}) = \frac{Pi}{Pst - Pi} \times \frac{Vi\ (\mathrm{mL})}{Wt\ (\mathrm{g})} \times Activity \times Density\ (\mathrm{g/mL}) \times 20 \quad (5)$$

where P_i is the peak area of test residual solvent, P_{st} is the peak area of standard residual solvent, W_t is the test weight, V_i is the residual solvent volume in standard, density is the density of residual solvent, and activity is the activity percent of solvent.

2.5 Data analysis

The experiments were conducted at least in triplicate. Data was presented as mean ± standard deviation and were statistically analyzed using one-way analysis of variance (one-way ANOVA) and t-test in Microsoft Excel, with significance established at a 0.05. ANOVA was employed to determine differences among the groups, and t-tests were used to ascertain differences between two groups if the ANOVA p-value was significant.

3. RESULTS AND DISCUSSION

3.1. Preparation of TEGs

The Eudragit® E PO was completely dissolved in dichloromethane before dispersing the enteric microparticles in the polymer solution. The dispersion was then subjected to regular rotation during solvent evaporation using a rotary evaporator under elevated temperature and reduced pressure. This method facilitated the dispersion of the enteric microparticles throughout the mixture before concentrating and drying. As a result, the enteric microparticles were uniformly and compactly dispersed within the Eudragit® E PO matrix. Upon drying, the products formed brittle off-white lumps. Following the grinding and sieving processes, granules with consistent size and desirable flow characteristics were obtained, indicating their potential suitability for incorporation into different pharmaceutical dosage forms such as tablets and capsules.

3.2. Morphology of TEGs

The examination under the SEM revealed the characteristic morphology of TEGs, which appeared as spherical microparticles embedded in Eudragit® E PO granules, serving as the carrier material (Figure 2). Notably, observations indicated the presence of fragments of drug particles, suggesting their leakage from TEGs that had undergone milling and sieving processes. However, when the quantity of Eudragit® E PO was reduced, as indicated by a polymer ratio of 0.1, the particles exhibited a rough surface morphology with a wide size distribution, along with irregularly shaped particles dispersed independently. This phenomenon was attributed to the insufficient quantity of Eudragit® E PO to adequately coat and function as a carrier for the enteric particles. Consequently, some Eudragit® E PO residual adhered to the surface of the enteric particles, while others dispersed widely. Thus, the utilization of Eudragit® E PO in lower ratios may not effectively encapsulate the enteric particles. In contrast, increasing the polymer ratio can result in the encapsulation of multiple enteric microparticles simultaneously. TEGs with a polymer ratio of 0.25 were approximately 50 µm in size. When the polymer ratios were increased to 0.5 and 1, there was a significant increase in granule size. This is likely attributable to the higher polymer content, which forms more robust granules that resist fragmentation. Consequently, this phenomenon could influence the dissolution of the drug from the granules. Larger granules, due to their reduced surface area, may hinder the dissolution process, potentially impacting both taste-masking effectiveness and drug release in biorelevant media.

From this study, the optimal weight ratio of enteric microparticles-to-Eudragit® E PO for TEGs preparation was determined to be within the range of 1:0.25 to 1:1. However, it is noteworthy to observe that the TEGs may experience cracking, resulting in partial leakage of DS from the carrier, which could potentially affect the drug dissolution protection in acidic conditions. The inadequate coating of Eudragit® E PO on the enteric particles may also impact the protection of the drug upon release in the oral cavity.

3.3. FT-IR analysis

Figure 3 displays the FT-IR spectra of Eudragit® E PO, DS, and TEGs. DS exhibited distinct peaks associated with the N–H stretching of the secondary amine functional group at a wavenumber of 3382 cm^{-1}, asymmetric O=C–O– at 1571 cm^{-1}, metallic salt (Na+) at 1452 cm^{-1}, and stretching of aromatic (C–Cl) at 743 cm^{-1}. Eudragit® E PO exhibited a weak hydroxyl (O–H) stretching signal at 3437.43 cm^{-1}, a prominent aromatic C–H stretching band at 2946 cm^{-1}, an alkene C=C stretching peak at 1449 cm^{-1}, and a strong peak corresponding to C–C stretching at 1149 cm^{-1}. The sharp peak at 1744 cm^{-1} indicated the presence of carbonyl groups in the polymer. Additionally, the characteristic functional group peak for dimethyl amino groups is observed between 2765 and 2817 cm^{-1}.

TEGs prepared from different weight ratios of enteric particles to Eudragit® E PO exhibited a consistent pattern, closely resembling the spectra of Eudragit® E PO. The absorption peaks associated with the functional groups of Eudragit® E PO at 2946, 1744, 1449, and 1149 cm^{-1} were observed in all TEGs spectra, with intensity increasing as the polymer ratio increased. Nevertheless, absorption peaks resembling those of DS were also detected at 1571 and 743 cm^{-1}, indicating the presence of DS on the surface of the TEGs.

3.4. Thermal analysis

The DSC thermograms of Eudragit® E PO DS, and TEGs are shown in Figure 4. Eudragit® E PO displayed amorphous properties, as evidenced by the absence of any discernible peak indicating energy absorption. Conversely, the melting point of DS was identified at 279°C, exhibiting a sharp and well-defined peak, characteristic of its high energy absorption capacity as a crystalline solid (Giron, 1998). The thermographs of TEGs with varying weight ratios of enteric particles-to-Eudragit® E PO revealed the absence of a heat absorption peak at 279°C in all formulations. This observation suggested a potential shift in the molecular arrangement of DS from crystalline to amorphous, or it could be attributed to the polymer encapsulating the majority of the active ingredient, thereby not manifesting significant alterations in thermal characteristics (EL-Badry et al., 2010). Furthermore, the thermogram analysis of TEGs displayed endothermic absorption occurring between 50 to 100°C, suggesting moisture loss, and another peak observed at 200–225°C, indicative of polymer degradation, as reported by Lin and Yu (1999).

3.5 PXRD analysis

The diffraction pattern of DS displayed distinct peaks typical of crystalline solids, with notable peaks observed at 2θ = 6.62, 8.5, 10.24, 11.22, 15.18, 19.90, 21.04, 23.46, 25.92, 27.08, and 27.90° (Figure 5). Conversely, Eudragit® E PO exhibited a clear halo pattern characteristic of amorphous solids. The drug crystallinity in all formulations was confirmed by PXRD method, as also shown in Figure 5. Despite the findings from scanning electron micrograph in Figure 2, which showed partial drug leakage from the enteric particles embedded in TEGs, no TEG prepared across different enteric microparticles-to-Eudragit® E PO ratios exhibited the typical characteristics of crystalline solid drug particles, even though the enteric particles displayed a crystallinity PXRD pattern (data not shown). This phenomenon may be

attributed to DS existing in an amorphous solid state after the preparation of TEGs. The rapid precipitation of the drug during the dissolution process prevents molecular arrangement into crystalline structures (Liu et al., 2023). Consequently, DS within the TEGs is both encapsulated within the enteric microparticles and dispersed externally in an amorphous solid state. Moreover, the ratio of enteric particles to Eudragit® E PO used in preparation appeared to have no discernible influence on the structural arrangement of the drug.

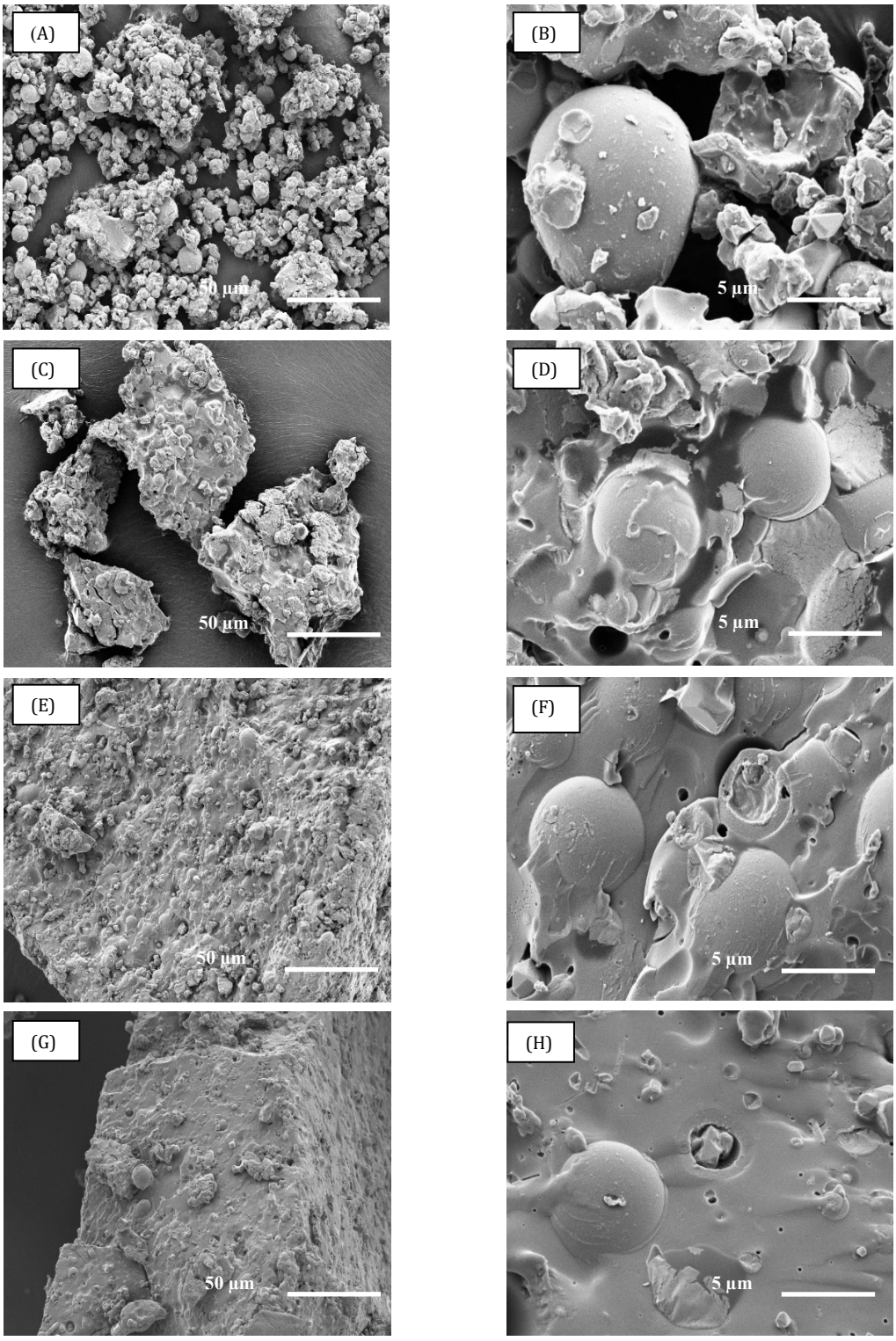

Figure 2. Morphology of TEGs prepared using enteric microparticles-to-Eudragit® E PO in the weight ratios of 1:0.1 (A and B), 1:0.25 (C and D), 1:0.5 (E and F), and 1:1 (G and H) at magnifications of 1,000× and 10,000×

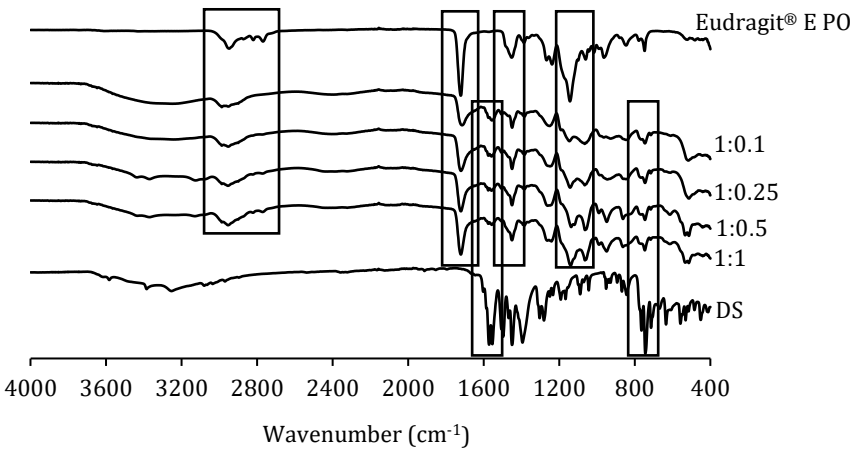

Figure 3. FT-IR spectra of Eudragit® E PO, DS, and TEGs derived from formulations with varying ratios of enteric microparticles-to-Eudragit® E PO; namely, 1:0.1, 1:0.25, 1:0.5, and 1:1

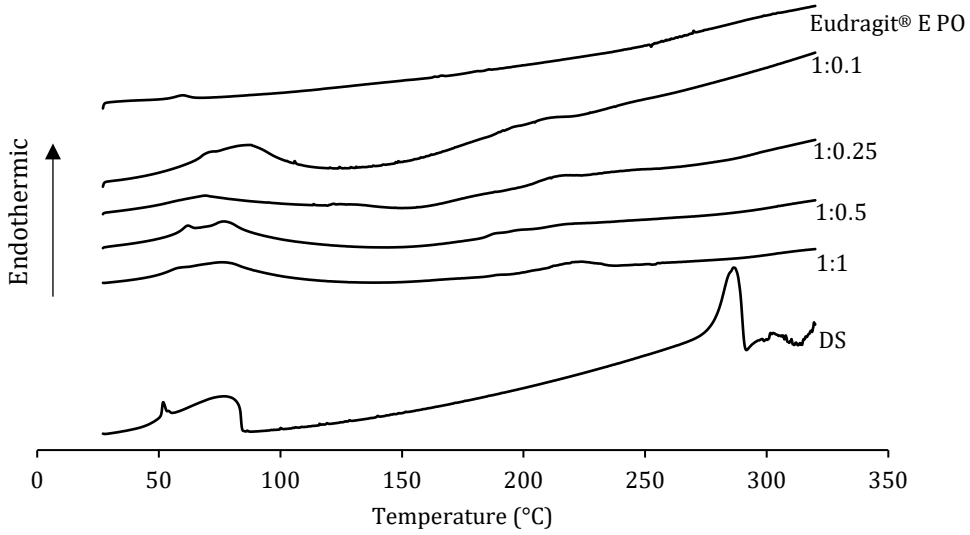

Figure 4. DSC thermograms of Eudragit® E PO, DS, and TEGs derived from formulations with varying ratios of enteric microparticles-to-Eudragit® E PO; namely, 1:0.1, 1:0.25, 1:0.5, and 1:1

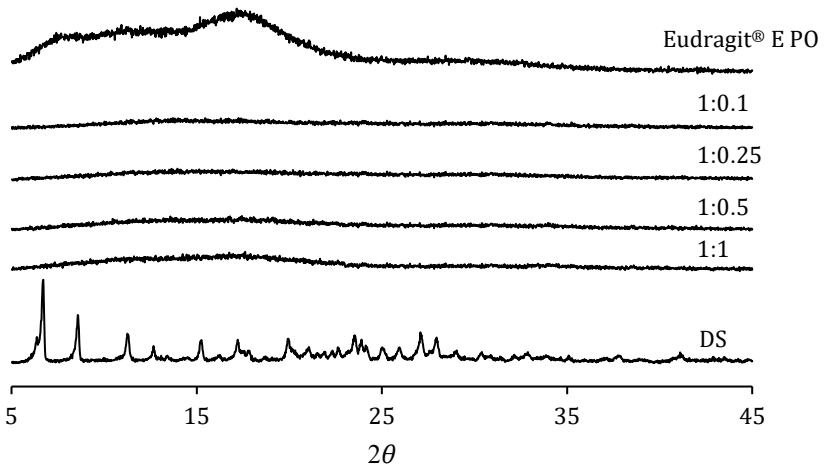

Figure 5. PXRD patterns of Eudragit® E PO, DS, and TEGs derived from formulations with varying ratios of enteric microparticles-to-Eudragit® E PO; namely, 1:0.1, 1:0.25, 1:0.5, and 1:1

3.6 Drug contents

The loading capacity and loading efficiency of DS in TEGs are shown in Table 1. The loading capacity approximately ranged from 17% to 30%. An increase in the polymer ratio in TEGs resulted in a significant decrease ($p<0.05$) in loading capacity due to the relatively lower proportion of the drug compared to that of lower polymer ratios. While all TEGs exhibited a high drug loading efficiency, exceeding 90%, employing lower polymer ratios led to a significant decrease in loading efficiency. These occurrences may be attributed to inadequate amounts of Eudragit® E PO, resulting in incomplete coating of the enteric particles. Consequently, some DS may remain exposed and susceptible to loss during subsequent processing steps, or it may adhere to the inner walls of the round-bottom flask, resulting in drug loss.

Table 1. Loading capacity and loading efficiency of TEGs

Enteric microparticle-to-Eudragit® E PO ratio	Loading capacity (%)	Loading efficiency (%)
1:0.1	29.85 ± 0.38^{a}	93.69 ± 1.19^{a}
1:0.25	25.91 ± 0.47^{b}	92.40 ± 1.68^{a}
1:0.5	23.15 ± 0.26^{c}	99.08 ± 1.13^{b}
1:1	17.17 ± 0.27^{d}	98.01 ± 1.55^{b}

Note: $^{a\text{-}d}$ Values in each column that have different letters are significantly different ($p<0.05$)

3.7 Simplified dissolution test

According to a study conducted by Schiffman et al., (2000), the bitterness threshold of DS in volunteers was determined to be 1.008 ± 0.220 mM (320.54 µg/mL ± 69.96). Figure 6 illustrates the dissolution of DS from the TEGs in pH 6.8 SSF over a duration of 30 s and 3 min. DS encapsulated within the enteric microparticles exhibited a dissolution of up to 285.02 ± 32.46 µg/mL in 3 min, while the uncoated drug dissolved up to 1,259.99 ± 238.12 µg/mL within 30 s (data not shown). A decrease in the Eudragit® E PO ratio in the formulation of TEGs resulted in the increased dissolution of DS. This was attributed to the completeness of coating of Eudragit® EPO, which is a pH-responsive polymer that did not dissolve in the pH of the SSF, thus affecting the taste-masking effectiveness (Yoshida et al., 2014). However, reducing the Eudragit® E PO ratio to 1:0.1 resulted in greater DS dissolution compared to the uncoated enteric particles. This occurrence could be explained by the condition encountered during rotary evaporation, wherein the enteric particles become more delicate due to insufficient Eudragit® E PO serving as a carrier, as evidenced by the SEM morphology analysis. Consequently, the drug may leak, leading to increased dissolution in the SSF. Based on these findings, it could be concluded that the optimal ratio of enteric particles-to-Eudragit® E PO for the preparation of TEGs was within the range of 1:0.25–1:1.

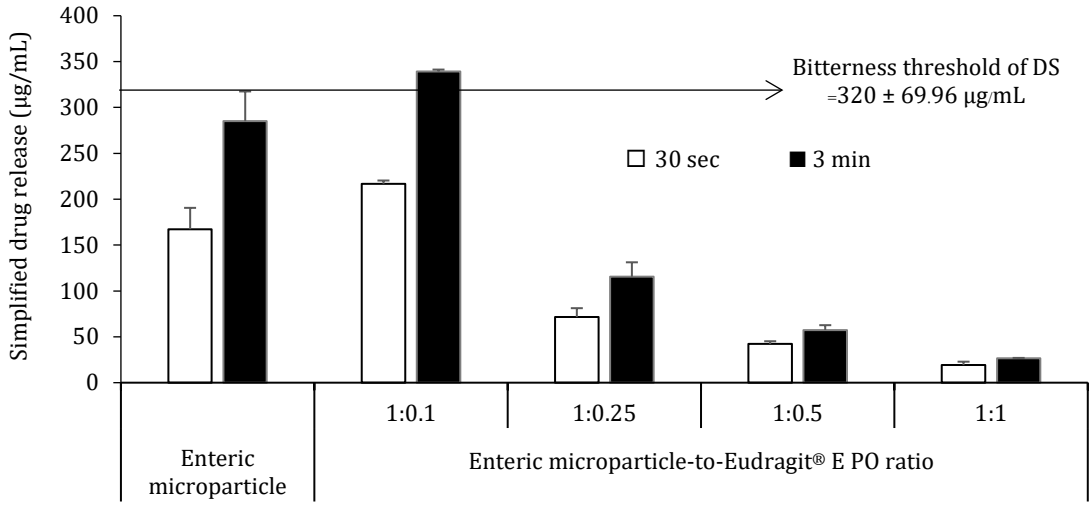

Figure 6. Simplified drug release of DS from TEGs in pH 6.8 SSF at (□) 30 sec and (■) 3 min

3.8 In vitro drug release studies

Figure 7 illustrates the dissolution of DS from enteric particles and TEGs under biorelevant conditions, comprising acidic conditions from 0 to 120 min followed by an alkaline conditions from 120 to 300 min. Notably, under acidic conditions, DS remained undissolved in the enteric microparticles but exhibited dissolution from the TEGs in the range of 2.12% to 3.32%. Interestingly, the variation in the ratio of Eudragit® E PO did not yield differences in drug dissolution under acidic conditions. This occurrence could be attributed to the preparation of TEGs using the solvent evaporation method, which resulted in partial attrition of the enteric particles, as evidenced by the morphological analysis. However, the drug dissolution remained below 10% in acidic conditions, in accordance with the specifications outlined in the United States Pharmacopeia and National Formulary (USP NF), 2024, for delayed-

release dosage forms (The United States Pharmacopeial Convention Committee of Revision, 2024a).

After the pH transition from acidic stage (pH 1.2) to basic stage (pH 6.8), DS demonstrated faster dissolution from the TEGs compared to the enteric particles. The difference factor (*f1*) and similarity factor (*f2*) between each TEGs formulation and enteric particles were utilized to compare their dissolution profiles (Table 2). The results indicated significant differences in the dissolution profiles of TEGs and enteric particles, as evidenced by *f1* values exceeding 15 and *f2* values below 50. This was attributed to the amorphous solid state of DS within the TEGs, as determined by the PXRD analysis, which exhibited superior dissolution properties compared to the crystalline form found in the enteric particles.

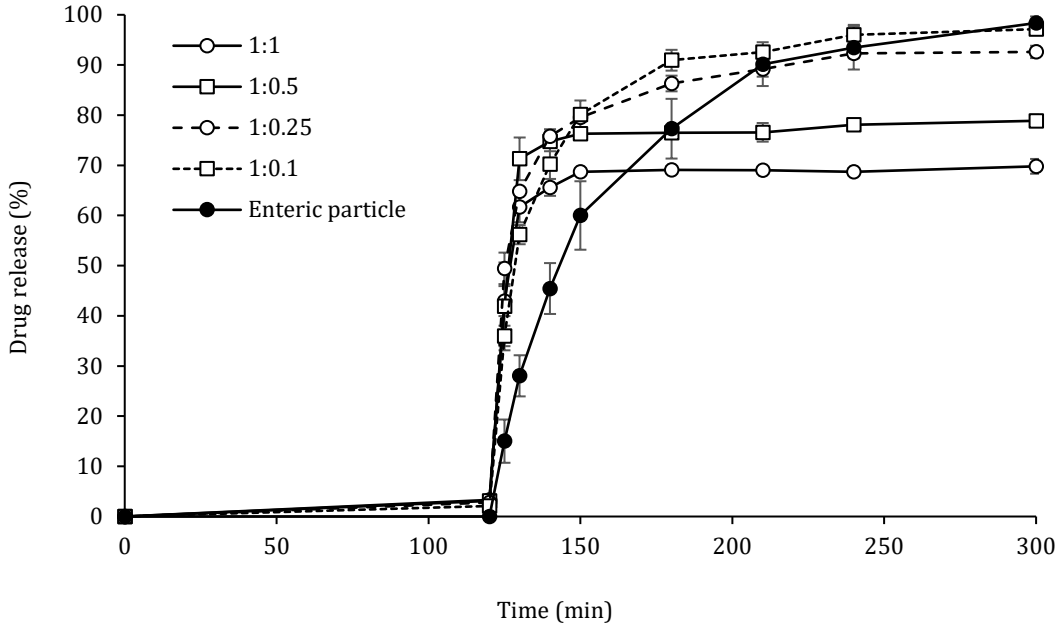

Figure 7. Drug release of DS from enteric microparticles and TEGs in biphasic medium

Table 2. Difference factor (*f1*) and similarity factor (*f2*) between each TEG's formulation and enteric particles

Enteric microparticle-to-Eudragit® E PO ratio	Difference factor (*f1*)	Similarity factor (*f2*)
1:0.1	18.66	40.21
1:0.25	22.24	35.02
1:0.5	29.12	33.58
1:1	33.98	34.02

However, only the TEGs prepared with drug-to-polymer ratios of 1:0.1 and 1:0.25 met the acceptance criteria for drug dissolution in the buffer stage, as specified in the United States Pharmacopeia and National Formulary (USP NF), 2023, for delayed-release dosage forms. According to these standards, not less than 75% (Q) + 5% of the drug should dissolve within 45 min (The United States Pharmacopeial Convention Committee of Revision, 2024a). This phenomenon could be related to the precipitation observed when the pH of the medium changed from 1.2 to 6.8. The pH alteration resulted in the appearance of white particles within the solution, which is attributed to the precipitation of Eudragit® E PO due to its poor solubility under neutral conditions. This precipitation might occur alongside the formation of interpolyelectrolyte complexes between the countercharged polymer, Eudragit® E PO and Eudragit® L 100, which was utilized in enteric coating, resulting in the hindrance of DS dissolution (Moustafine et al., 2013). Consequently, the dissolved drug amount from the TEGs, formulated with a 1:1 and 1:0.5 ratio of enteric microparticles to Eudragit® E PO, was lower than the overall drug content in the formulation and did not meet the USP criteria for dissolution. However, decreasing the Eudragit® E PO ratio to 1:0.25 and 1:0.1 yielded dissolved DS amounts resembling those of the enteric particles. Remarkably, employing both ratios did not significantly alter the DS dissolution (*f1* = 7.13, *f2* = 60.95). This could be due to insufficient Eudragit® E PO amounts to form complex compounds capable of entrapping DS, as the binding ratio of a unit molecule of Eudragit® E PO with Eudragit® L 100 was determined to be 2:1 at neutral pH (Moustafine et al., 2013). Consequently, the dissolution of DS was not inhibited by employing the enteric particles-to-Eudragit® E PO ratios of 1:0.1 and 1:0.25 in the formulation of TEGs.

3.9 Residual solvent analysis

Dichloromethane, categorized as a class 2 solvent in accordance with the <467> Residual Solvent section of the US Pharmacopeia (The United States Pharmacopeial

Convention Committee of Revision, 2024b), was subjected to stringent criteria regarding its acceptable concentration within pharmaceutical formulations. According to USP guidelines, the residual content of dichloromethane must not surpass 600 ppm, and the permitted daily exposure (PDE) should remain below 6.0 mg. In this study, the residual amount of dichloromethane found in the TEGs was determined to be 18.35 ± 12.34 ppm. Upon extrapolating this concentration to the daily intake when taking the TEGs equivalent to a dosage of DS 150 mg (50 mg per dose, three times a day), the calculated intake was found to be 0.01 mg per day. This calculated intake level falls significantly below the threshold specified by the USP, indicating that the prepared TEGs contained a residual solvent quantity well within the pharmacopeial standards.

4. CONCLUSION

The TEGs were successfully developed using the solvent evaporation technique. They demonstrated significant drug loading capacity and efficiently masked the bitterness of the drug. Despite the need for organic solvents in the manufacturing process, residual solvent levels in the final product were below pharmacopeial standards since they were effectively removed. The enteric microparticles were dispersed within Eudragit® E PO, which acted as the taste-masking carrier. The effectiveness of bitterness masking of the TEGs was notably influenced by the proportion of the polymer matrix employed. When the polymer ratio was insufficiently low, it was found to be ineffective in adequately masking the bitterness of DS. Conversely, the high polymer ratio improved the taste-masking efficacy but also presented obstacles by diminishing the loading capacity of the TEGs. Moreover, an elevated ratio of polymer enhanced the probability of interpolyelectrolyte complex formation between Eudragit® E PO and Eudragit® L 100, which led to the partial entrapment of DS within the TEGs, thereby impeding its complete dissolution from the dosage form. TEGs formulated with ratios of enteric microparticles-to-Eudragit® E PO at 1:0.1 and 1:0.25 demonstrated satisfactory drug release in accordance with the criteria outlined for delayed-release dosage forms in the USP. However, TEGs with Eudragit® E PO at a ratio of 0.1 proved ineffective in masking the taste. Consequently, TEGs with a ratio of enteric microparticles-to-Eudragit® E PO of 1:0.25, which maintained both acceptable drug release and taste-masking properties, were identified as the most suitable formulation.

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