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Development of Enteric Diclofenac Sodium Microparticles Through a Spray-Drying Process Facilitated by Different Aqueous Dispersion Systems

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Abstract

The objective of this study was to prepare enteric diclofenac sodium microparticles using an aqueous dispersion system via spray-drying. Two aqueous-based solvent systems, phosphate buffer at pH 7.0 and ammonium hydrogen carbonate solution, were employed as the feed dispersion media in the spray-drying process based on the solubility characteristics of Eudragit® L100. At a drug-to-polymer ratio of 1:1, the optimal solids concentration in the feed dispersion was determined to be 2% w/v, as it enabled an approximately 5-30 µm smooth-surfaced spherical microparticle with a high production yield. Diclofenac sodium was efficiently encapsulated within the microparticles, existing as solid dispersion in a partially amorphous form. Notably, the spray-drying conditions utilized in this study obviated the need for further heating for microparticles prepared using ammonium hydrogen carbonate solution, as the residual ammonium could be completely eliminated during the spray-drying process. The two-stage biorelevant drug release profile of enteric microparticles demonstrated their ability to inhibit drug dissolution under acidic conditions while facilitating drug release under basic conditions. The phosphate buffer-based microparticles exhibited greater protection efficiency under acidic conditions compared to ammonium hydrogen carbonate-based systems, despite residual alkaline salt being present in the microparticles. These results validate the potential of the developed microparticles for use as an enteric drug delivery system.

Keywords**:** *Enteric coating; microparticles; spray-drying, Eudragit® L100; diclofenac sodium*

1. Introduction

Spray-drying technique involves converting a substance from a liquid state to a dried particulate form by dispersing the feed liquid into a hot drying gas medium (usually air). This process comprises atomizing the liquid feed, drying it within the gas, forming dry particles, and finally separating and collecting the dry product from the drying gas (Sosnik, & Seremeta, 2015). The spray-drying technique has found applications in various industries, such as cosmetics, food, and pharmaceuticals. In the pharmaceutical sector, the spray-drying technique has been utilized to improve the stability of active pharmaceutical ingredients and to develop particulate systems tailored to meet specific drug delivery requirements such as site-specific delivery, microorganism delivery, and enteric-controlled release systems (Perkušić et al., 2022; Gullifa et al., 2023; Tang et al., 2023; Akanny et al., 2020; Dalmoro et al., 2010).

Enteric microparticles were primarily prepared using pH-responsive polymers due to variations in the pH levels of gastrointestinal fluid across different

anatomical locations. The polymer, acting as a carrier, must prevent drug release in acidic conditions in gastric fluid but should release the drug in intestinal or colonic environments. These polymers mostly contain polyacid functional groups, such as cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), hydroxyl propyl methyl cellulose acetate succinate (HPMCAS), and methacrylic acid copolymers (Rowe et al., 2012). Among these polymers, methacrylic acid methylmethacrylate copolymers, namely Eudragit® L and Eudragit® S, have been widely utilized in numerous studies. (Puccetti et al., 2018; Xu et al., 2018; Nguyen et al., 2017).

Eudragit® L is an anionic copolymer derived from the copolymerization of methacrylic acid and methyl methacrylate, with an approximate 1:1 ratio of free carboxyl groups to ester groups. It is soluble in pH environments above 6.0. However, the solvent for diluting Eudragit® L was suggested to be acetone or ethanol (Rowe et al., 2012). Typically, the manufacturing methods for enteric microparticles utilizing Eudragit® L as a carrier require significant quantities of organic solvents (Al-Ghananeem et al., 2010; Nadal et al., 2016; Leclair et al., 2018), which are flammable and pose a risk of explosion. Furthermore, these solvents present environmental hazards and may leave behind residual solvent within the product (Saß, & Lee, 2014).

The utilization of aqueous-based solvent systems as feed liquids in spray-drying for the preparation of enteric microparticles has garnered interest in this study due to the advantages of safety, environmental friendliness, and cost-effectiveness. The utilization of an alkaline solution in the preparation of the polymer aqueous solution for spray-drying has been previously reported. Eudragit® S100 dissolved in a sodium hydroxide solution was employed in the preparation of sodium pantoprazole-loaded enteric microparticles via spray-drying (Raffin et al., 2006). Using this approach, any remaining hydroxide ions present on the microparticles' surface may undergo ionization when exposed to the acidic conditions of gastric fluid. Consequently, this can cause an increase in the pH levels surrounding the microparticles, which might contribute to the partial dissolution of the polymer matrix and subsequent loss of enteric function. The utilization of a phosphate buffer to facilitate the dissolution of the polymer was carried out by Akanny et al., (2020). Eudragit® S100 was dispersed in a phosphate-buffered solution with a pH of 7.4, and subsequently, the pH was adjusted to 7.6 using sodium hydroxide solution to create the soluble salt form of the polymer. In the context of the research aimed at microorganism delivery, a substantial quantity of sugar was incorporated into the formulations as a protective agent to enhance bacterial viability. As a result, the enteric properties of the microparticles may be compromised if the sugar dissolves and is released into the gastric fluid. Ammonium salt was also employed to enhance polymer solubility in the aqueous phase before being utilized as the feed solution in the spray-drying process (Alhnan et al., 2011). This approach offered the advantage of no residual presence, as the ammonium salt can be eliminated by incubating the microparticles at elevated temperatures (70–130°C) for several hours. However, aside from being time-consuming, prolonged heating of the microparticles may affect their stability, as some polymers may degrade under the incubating condition.

Diclofenac sodium (DS) was employed as a model drug in this study. It is a well-known non-steroidal anti-inflammatory drug (NSAID) prescribed for the treatment of aches and pains, as well as joint, muscle, and bone problems, including osteoarthritis and rheumatoid arthritis (Altman et al., 2015). The drug's mechanism of action involves inhibiting prostaglandin synthesis by suppressing the enzyme cyclooxygenase (COX), which includes both COX-1 and COX-2. Consequently, this inhibition may lead to adverse effects such as gastric irritation, nausea, and vomiting. To minimize the local irritation effect of DS, the marketed drug dosage form was formulated as enteric-coated tablets, which control drug release specifically within the small intestine (Gan, 2010). However, a limitation of enteric-coated tablets is their inability to be crushed, as this action would destroy the controlled release mechanism of the tablet. Consequently, this characteristic makes them inappropriate for patients with swallowing difficulties. The formulation of DS as enteric microparticles presents an opportunity for enhanced flexibility in drug delivery (Rukari et al., 2023). Microparticles can be incorporated into various oral formulations, including powders, capsules, or orodispersible tablets (ODTs), thereby potentially improving patient adherence and treatment efficacy.

2. Objectives

The objective of this study was to fabricate enteric DS microparticles using an aqueous dispersion system via spray-drying and to investigate the impact of different feed dispersions on the physicochemical

properties and dissolution behavior of the microparticles.

3. Materials and methods

3.1 Materials

Diclofenac sodium (Batch no. DFS/19050129) was supplied from Aarti Drugs Limited, India. Eudragit® L100 (Batch no. 190303201, Evonik Nutrition & Care GmbH, Germany) was kindly donated by Jebsen & Jessen Ingredients (Thailand) Ltd. All other chemicals were of analytical grade and used without further purification.

3.2 Preparation of enteric DS microparticles

The drug-loaded enteric microparticles were prepared via the spray-drying method, employing Eudragit® L100 as the enteric-coating polymer. Two aqueous-based solvent systems, phosphate buffer (PB) at pH 7.0 and 0.5% and 1.0% w/v ammonium hydrogen carbonate (AHC, NH_4HCO_3) solution, were utilized as media for the feed dispersion. The preparation of phosphate buffer pH 7.0 was conducted following the guidelines outlined in the United States Pharmacopeia (USP) regarding buffer solutions (The United States Pharmacopeial Convention Committee of Revision, 2021a). Briefly, 0.2 M solution of monobasic potassium phosphate (KH_2PO_4) was prepared by dissolving 27.22 g of KH_2PO_4 in purified water and adjusting the volume to 1,000 mL. Subsequently, a 50 mL aliquot of the solution was separated and combined with 29.1 mL of 0.2 M NaOH solution before adjustment of the total volume to 200 mL. Eudragit® L100 was dissolved in each solution and gently stirred for 6 hours, using a magnetic stirrer, to ensure the complete dissolution. DS underwent a sieving process through an 80-mesh sieve and was subsequently dispersed in the polymer solutions for 60 minutes to ensure uniform dispersion. The drug-to-polymer ratio was fixed at 1:1, as pre-determined in the preliminary study (data not shown). The feed dispersions, based on phosphate buffer and with total solids content of 1%, 2%, and 4% w/v, were designated as PB1, PB2, and PB3, respectively. The solids content of the AHC-based feed dispersion was fixed at 2% w/v, while the AHC concentration was varied to 0.5% and 1.0% w/v in the formulations AHC1 and AHC2. The composition of the dispersions is illustrated in Table 1.

The continuously stirred feed dispersions were subsequently subjected to spray-drying using the Mini spray dryer B-290 (Buchi, Switzerland). The operational parameters were set as follows: the inlet air temperature was 165°C, the feed flow rate was 10 mL/min, aspiration rate was 90%, and the gas pressure was maintained at 30 mmHg. The collected enteric DS microparticles were weighed to determine the production yield and subsequently stored in a desiccator for further analysis.

3.3 Morphological examination

The enteric DS microparticles were affixed onto SEM stubs using double-sided adhesive tape, and subsequently coated with a thin layer of gold prior to analysis via scanning electron microscopy (SEM) (Mira3, Tescan, Czech Republic). Magnification of 2000× was employed in the investigation.

3.4 FT-IR analysis

The FT-IR spectra of the enteric DS microparticles were analyzed using a FTIR spectrophotometer (Nicolet Avatar 360, USA) in the range of 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1}. The spectral characteristics of the samples were acquired using the software package (OMNIC FT-IR Software, version 7.2a, Thermo Electron Corporation, USA).

3.5 Thermal properties

The thermal properties of the enteric DS microparticles were investigated by a differential scanning calorimeter (DSC 8500, PerkinElmer, USA) employing a temperature program ranging from 25°C to 320°C, with a heating rate set at 10°C/min. The analysis was carried out under a nitrogen purge flow rate of 20 mL/min.

Table 1 Composition of the feed dispersions used in spray-drying.

Ingredient (%w/v)	PB1	PB2	PB3	AHC1	AHC2
DS	0.5	1	2	1	1
Eudragit® L100	0.5	1	2	1	1
Phosphate buffer pH 7.0	qs to 100	qs to 100	qs to 100	-	-
0.5% w/v AHC solution	-	-	-	qs to 100	-
1.0% w/v AHC solution	-	-	-	-	qs to 100

3.6 PXRD analysis

The crystallinity of the enteric DS microparticles was characterized using a powder X-ray diffractometer (PXRD) (Model Miniflex II, Rigaku, Japan) operating at 40 kV and 40 mA. Measurements were conducted across the range of 5– 45º 2θ, employing Cu K_α radiation with a wavelength of 1.5406 Å.

3.7 Drug content

To determine the concentration of DS within the microparticles, a standard curve with the correlation coefficient $R^2 = 0.9999$ was established by preparing standard solutions of DS in methanol at concentrations ranging from 1.00 µg/mL to 32.00 µg/mL. Subsequently, the samples were subjected to analysis under conditions adapted from a previous study (Khadra et al., 2019), with the following conditions: column: Inertsil-ODS3 (4.6 × 250 mm I.D., 5 µm) (GL Sciences, Japan); flow rate: 1.0 mL/min; mobile phase: methanol (80): 0.1% acetic acid (20), adjusted to pH 4.0; oven temperature: 35°C; detector: diode array detector (DAD) set at 280 nm; injection volume: 10 µL. Fifty milligrams of the enteric DS microparticles were weighed and dissolved in methanol to a volume of 100 mL. The drug content was quantified and expressed in terms of loading capacity and loading efficiency, calculated using Eq. (1) and Eq. (2), respectively. The analysis was performed in triplicate for each sample.

$$\text{Loading capacity (\%)} = \frac{\text{Total amount of DS (mg) x 100}}{\text{Amount of microparticles (mg)}} \quad (1)$$

$$\text{Loading efficiency (\%)} = \frac{\text{Total amount of DS (mg) x 100}}{\text{Total amount of DS added initially (mg)}} \quad (2)$$

3.8 Dissolution study

The in vitro dissolution of enteric DS microparticles was conducted following the methodology outlined by Alotaibi et al., (2019) using a USP apparatus II dissolution tester (Dissolution system 2100B, Distek, USA) with a paddle speed of 50 rpm and a controlled temperature of 37±0.5°C. A two-stage biorelevant drug release study was employed, beginning with a 2-hour acid stage in 750 mL of pH 1.2 (0.1 N HCl), followed by transitioning to a pH 6.8 basic stage by introducing 250 mL of 0.2 M tribasic sodium phosphate for an additional 3 hours. At appropriate intervals, 5 mL samples were withdrawn and passed through a 0.22-µm filter before being replenished with 5 mL of dissolution media. The determination of DS quantity was conducted using the previously described HPLC conditions. Each sample was analyzed in triplicate.

3.9 Statistical analysis

All experiments were performed at least in triplicate. Results were represented as the average ± standard deviation and statistically evaluated using a t-test in Microsoft Excel, with significance set at a level of 0.05.

4. Results and discussion

4.1 Preparation of enteric DS microparticles

To prepare the aqueous solutions of Eudragit® L100, alkaline salts were employed to neutralize the acidic groups within the polymer, thereby facilitating the formation of soluble salt forms in the solutions. In accordance with preliminary investigations, a phosphate buffer at pH 7.0 was selected as the dispersion medium for Eudragit® L100. This decision was based on the finding that it represented the lowest pH at which a 1% w/v concentration of the polymer could achieve complete dissolution, thus reducing the necessity for supplementary additives in the formulation. In the system based on AHC, Eudragit® L100 demonstrated a more rapid dissolution compared to the phosphate buffer system. This could be explained by the elevated alkalinity of the AHC solutions, which had a pH level of 7.9. The polymer solution was blended with the fine DS particles and continuously stirred to achieve a homogeneous dispersion in the feed solution. In the Eudragit® L100 solutions based on phosphate buffer, DS particles dispersed rather than dissolved. In contrast, in the polymer solutions based on AHC, drug dissolution was observed. This was attributed to the drug's solubility, which increases under more basic conditions (Kincl et al., 2004). Notably, variations in the drug's solubility could potentially impact the characteristics of the microparticles. Since the drug dispersed within the feed dispersion without dissolving, it was anticipated that a core-shell particle structure would form. The drug particles could become trapped inside the polymeric shell (Galogahi et al., 2020). In contrast, for AHC-based formulations, where the drug was dissolved in the feed solution before the spray-drying procedure, the drug might potentially be present in a solid dispersion in its amorphous state (Paudel et al., 2013). The micro-particles obtained from the spray-drying process were observed to be white, fine powder in all formulations. The production yield of the process ranged from 60% to 70%, indicating effective spray-drying conditions, as the

yield exceeded 50% (Can Karaca et al., 2016; Tontul, & Topuz, 2017).

4.2 Particle morphology

The surface structure and morphology of the enteric DS microparticles were analyzed using a scanning electron microscope, as shown in Figure 1. The microparticles formulated based on phosphate buffer solution at pH 7.0 exhibited a spherical shape with smooth surfaces and a broad size distribution, ranging from 5 to 30 µm. Increasing the concentration of solids in the feed dispersions, from 1%w/v in the PB1 (Figure 1A) to 2%w/v in the PB2 (Figure 1B) resulted in improved yields while maintaining the spherical particle shape and similar particle sizes. However, irregular shapes and deteriorated microparticles were more commonly observed in the PB1-based micro-particles. This phenomenon was attributed to the low solids content, which led to a thinner shell, rendering it more flexible and fragile (Vicente et al., 2013). Moreover, no free DS crystals (Figure 1F) were found in either formulation; thus, the drug would be dispersed throughout the polymeric system. However, a further increase in the concentration of the solids to 4%w/v in the PB3 led to larger particles with increased aggregation (Figure 1C). The microparticles obtained from PB3 displayed irregular shapes, rough surfaces, and some exhibited characteristics resembling partially collapsed spheres, which arose from inadequate drying time and outlet temperature in the system unsuitable for feed dispersion with high solids concentration (Vicente et al., 2013; Vehring, 2008; Kusonwiriyawong, 2021).

Figure 1D and 1E show the morphology of microparticles prepared using AHC solutions as the dispersing medium in AHC1 and AHC2, respectively. It was found that the microparticles obtained exhibited spherical shapes with smooth surfaces and a wide range of size distribution. Less aggregation was observed compared to the particles prepared using phosphate buffer pH 7.0 as the solvent. This phenomenon might be attributed to the moisture absorption of the residual salt in the PB-based formulations, leading to cohesion between the microparticles. Furthermore, dimple-shaped microparticles and drug crystallization were noted in formulations AHC1 and AHC2, with a higher incidence in particles derived from AHC1. These indications imply that the concentration of AHC influenced the process of shell formation in microparticles. In contrast, isolated drug crystals were not observed in the PB-based microparticles. This could be attributed to the fact that some of the drug dissolved in AHC-based formulations crystallized independently of the polymer, while the drug in PB-based formulations could have been encapsulated by the polymer.

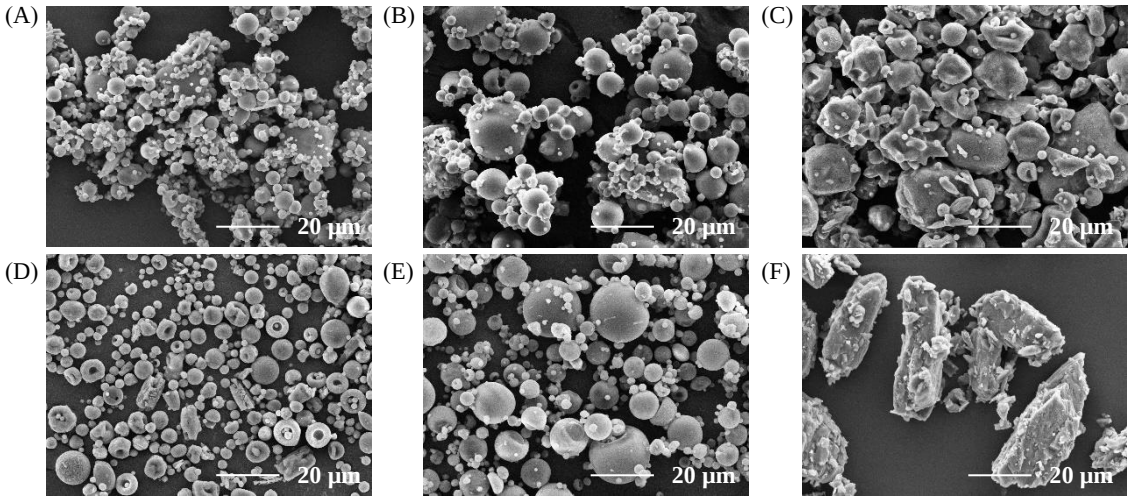

Figure 1 Scanning electron micrograph of enteric DS microparticles prepared from PB1 (A), PB2 (B), PB3 (C), AHC1 (D), AHC2 (E), and untreated DS (F)

4.3 FT-IR analysis

FT-IR spectra of the untreated DS, Eudragit® L100, and enteric DS microparticles are shown in Figure 2. The microparticles prepared based on the formulations PB2 and AHC2 were selected as representative formulations of the PB-based and AHC-based formulation, respectively. The FT-IR spectrum of the untreated DS showed peaks corresponding to the aromatic secondary amine functional group at a wavenumber of 3386 cm^{-1}, aliphatic C–H at 2969 cm^{-1}, asymmetric O=C–O– at 1573 cm^{-1}, metallic salt (Na^+) at 1452 cm^{-1}, C–N stretching of aromatic secondary amine at positions 1282 and 1305 cm^{-1}, and stretching of aromatic (C–Cl) at 745 cm^{-1}. In the case of Eudragit® L100, the spectrum revealed absorption bands in the range of 3100 – 3500 cm^{-1} corresponding to –OH stretching, absorptions at positions 2994 and 2950 cm^{-1} indicative of methylene –CH stretching, a peak at 1720 cm^{-1} representing carbonyl groups (C=O stretching), and a –C–O–C stretching vibration at 1159 cm^{-1} (Lin, & Yu, 1999).

The alteration in solids concentration within the feed dispersion from PB1 to PB3 demonstrated no discernible impact on the FT-IR spectra (data not shown). FT-IR spectra of the PB-based microparticles revealed major characteristic peaks similar to those of the polymer. The PB2 spectrum displayed absorptions at 1452 cm^{-1}, associated with Na^+, and at 745 cm^{-1}, indicating aromatic (C–Cl) stretching, thus revealing the presence of DS on the microparticle surface. Consequently, it was suggested that DS may not be entirely encapsulated within the polymer but rather dispersed as a solid dispersion within the polymer matrix. The occurrence of doublets within the absorption bands ranging from 909.54 to 1102.27 cm^{-1} in the PB2 spectrum was associated with the valence vibrations of the PO_4^{3-} functional group (Jančaitienė, & Šlinkšienė, 2016). This observation indicated the existence of residual phosphate salt within the microparticles. Additionally, the absence of new absorption peaks observed in this study indicated that no interaction occurred between the DS and Eudragit® L100 during the preparation of microparticles.

The AHC1 and AHC2 formulations showed no significant difference in the FT-IR absorption spectra. The AHC-based enteric DS microparticles displayed similar peak intensities in the FT-IR absorption spectrum to those observed in the physical mixture of DS and Eudragit® L100 at a 1:1 ratio. Notably, the microparticles exhibited a high-intensity absorption peak corresponding to the drug's functional group, indicating potential drug crystallization or incomplete coating of the drug. This phenomenon could lead to decreased drug encapsulation efficiency compared to PB-based microparticles. Furthermore, to investigate the presence of residual ammonium salt, the AHC-based microparticles were subjected to additional incubation at 70°C for 3 hours before being analyzed using FT-IR. The results showed no alteration in the peak intensity at the wavelength of 1550 cm^{-1}, indicative of residual ammonium salts possibly remaining from the manufacturing process (Alhnan et al., 2011). Thus, it can be concluded that the microparticle preparation process effectively removed excess ammonia without the need for additional heating.

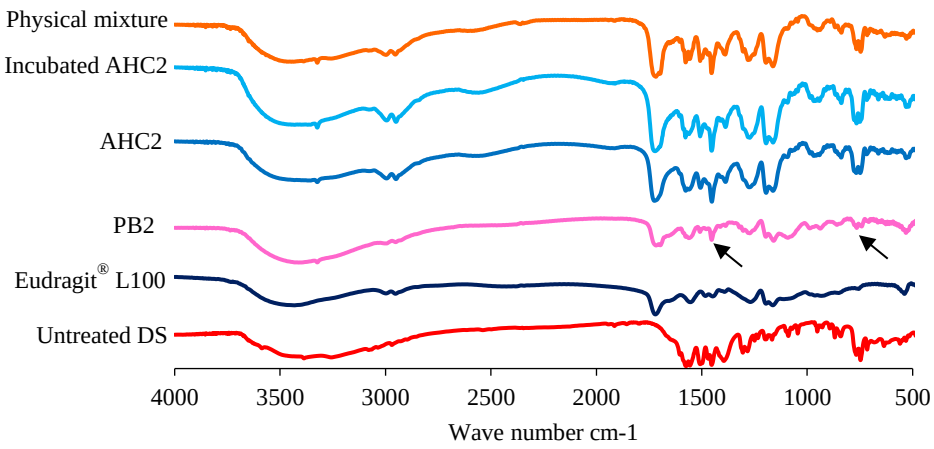

Figure 2 FT-IR spectra of untreated DS, Eudragit® L100, enteric DS microparticles PB2, AHC2 and incubated AHC2, and the physical mixture of DS: Eudragit® L100 (1:1)

4.4 Thermal properties

Differential scanning calorimetry (DSC) is an analytical methodology that investigates the reaction of a polymer or drug when subjected to heat. Figure 3 shows the DSC thermograms of untreated DS, Eudragit® L100, and enteric DS microparticles. Specifically, the investigation focused on the enteric DS microparticles derived from PB2 and AHC2, as they exhibited promising characteristics for development as enteric microspheres. The melting point of DS was determined to be 279ºC, exhibiting a sharp and narrow peak indicative of a high and distinct energy absorption capacity characteristic of a crystalline solid. In contrast, Eudragit® L100 displayed amorphous characteristics as no peak for energy absorption was observed. However, energy absorption was noted in the form of broad endothermic bands at temperatures below 100ºC, suggesting moisture loss, and at 200 - 225ºC, indicative of polymer degradation (Lin, & Yu, 1999). In contrast to untreated DS, the thermograms of the enteric DS microparticles did not show a sharp endothermic peak corresponding to the drug's melting point. Instead, a broad thermal absorption around 200 - 225ºC was observed. This observation implies a possible conversion of the drug's solid state from crystalline to amorphous, or the drug was entrapped in the microparticles (EL-Badry et al., 2010).

4.5 PXRD analysis

The PXRD patterns of untreated DS, Eudragit® L100, enteric DS microparticles PB2 and AHC2, and the physical mixture of DS: Eudragit® L100 (1:1) are shown in Figure 4. The diffraction pattern of DS exhibited sharp peaks characteristic of crystalline solids, with peaks observed at $2\theta =$ 6.62, 8.5, 10.24, 11.22, 15.18, 19.90, 21.04, 23.46, 25.92, 27.08, and 27.90°. In contrast, Eudragit® L100 clearly demonstrated a halo pattern typical of amorphous solids (Lin, & Yu, 1999). In comparison to the PXRD patterns of the physical mixture, the diffraction pattern of PB2 exhibited a slight displacement in the peaks of DS. This displacement might arise from alterations in the ionization state within the drug molecule during the spray-drying process, leading to the formation of diclofenac in its acidic form rather than as the sodium salt (Palomo et al., 1999). Consequently, this alteration could potentially reduce dissolution in gastric acid solution, although it does not affect dissolution in the neutral to alkaline conditions of the small intestine. In the case of AHC2, the diffraction peaks indicating DS shifted slightly, similar to that of PB2, but with lower peak intensity. This could be attributed to the lower crystallinity of DS in the AHC- based microparticles. The results regarding the dissolution of DS in the AHC-based medium resulted in the formation of amorphous solids after spray-drying (Singh, & Van den Mooter, 2016).

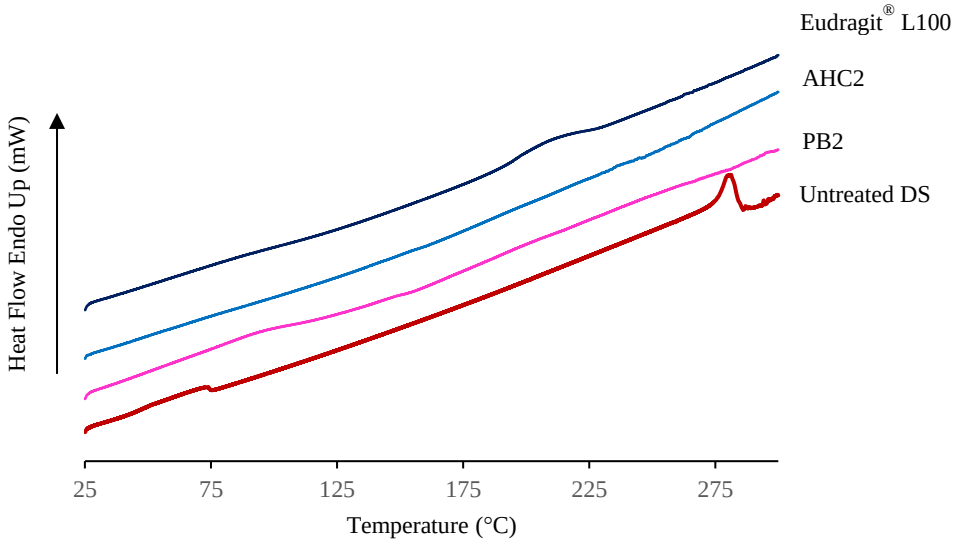

Figure 3 DSC thermogram of untreated DS, Eudragit® L100, enteric DS microparticles PB2 and AHC2

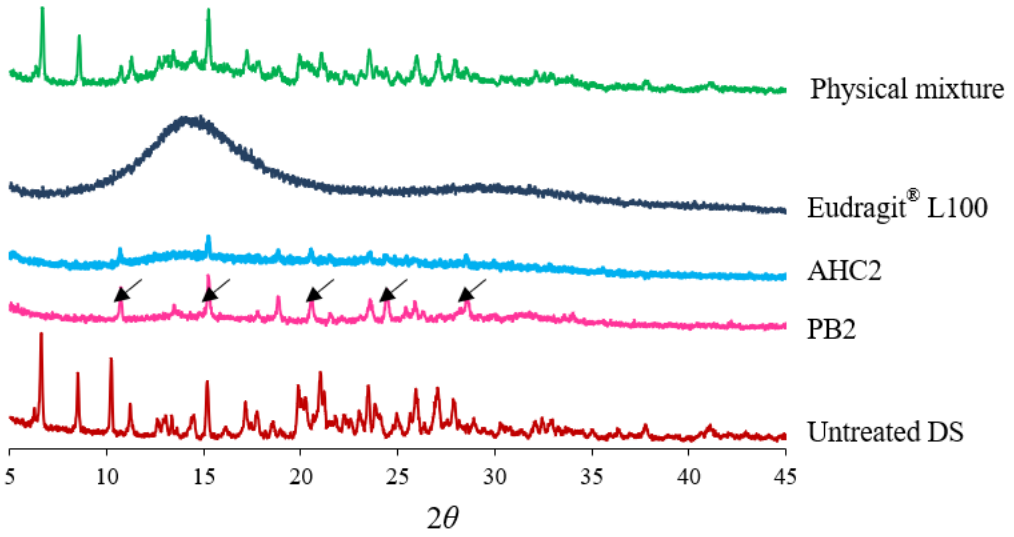

Figure 4 PXRD patterns of untreated DS, Eudragit® L100, enteric DS microparticles PB2 and AHC2, and the physical mixture of DS: Eudragit® L100 (1:1)

Table 2 Loading capacity (%) and loading efficiency (%) of the enteric DS microparticles

Formulation	Loading capacity (%)	Loading efficiency (%)
PB1	27.01 ± 0.69[a]	97.03 ± 2.50
PB2	35.04 ± 2.18[b]	98.00 ± 6.09
PB3	40.42 ± 1.04[c]	96.92 ± 2.48
AHC1	49.25 ± 1.12[d]	98.51 ± 2.24
AHC2	49.01 ± 0.62[d]	98.02 ± 1.25

[a-d]Values in each column which have different letters are significantly different ($p<0.05$)

4.6 Drug content

Loading capacity (%) and loading efficiency (%) of the enteric DS microparticles are shown in Table 2. The results suggested that employing the spray-drying technique with an aqueous-based feed dispersion could lead to the production of enteric microparticles with high drug loading efficiency. The type of dispersing medium and solids concentration did not cause a significant difference in the loading efficiency ($p>0.05$). Nevertheless, the loading capacity of individual enteric microparticles varied depending on the drug and polymer amounts presented in the feed dispersion. In addition to DS and Eudragit® L100, the PB-based formulations incorporated buffer salts like KH_2PO_4 and NaOH in the feed dispersion. As a result, in the PB1 formulation with limited drug and polymer quantities, the buffer salt proportion was relatively high. This resulted in diminished loading capacity of DS in PB1-based microparticles. Therefore, by increasing the quantities of both the drug and polymer in PB2 and PB3 formulations, the drug loading capacity was enhanced significantly ($p<0.05$). The utilization of an AHC solution as a feed dispersion medium left no residuals in the enteric microparticles, as it can completely evaporate during the drying process. Consequently, the drug loading capacity of AHC1 and AHC2 microparticles was higher than that of the PB formulations, in which the phosphate salt still persisted within the microparticles.

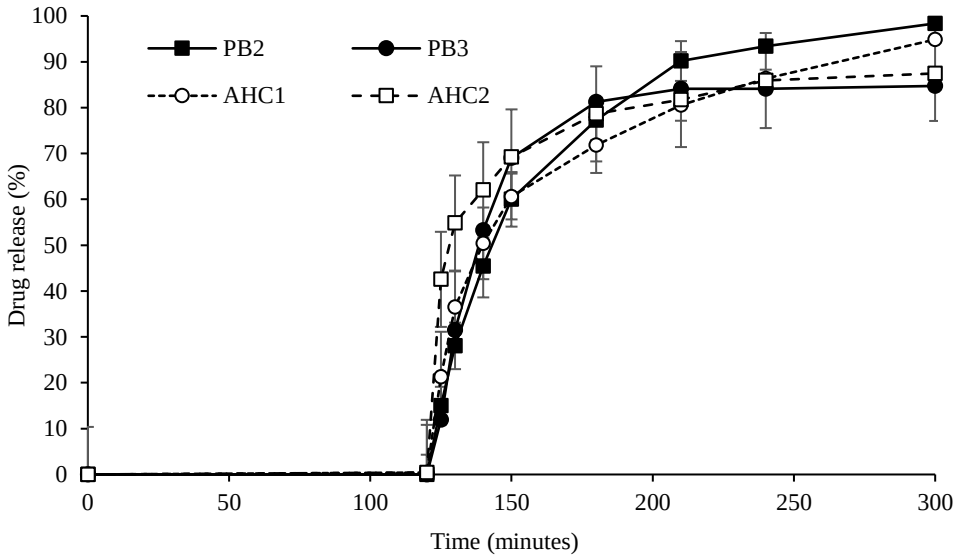

Figure 5 In vitro release profile of DS from enteric microparticles in two-stage biorelevant media

4.7 Dissolution study

Figure 5 shows the in vitro release profile of DS from the enteric DS microparticles. All enteric DS microparticles effectively prevented the dissolution of the drug in acidic conditions in the first 120 minutes, as none of the formulations exhibited drug dissolution exceeding the 10% threshold specified by the United States Pharmacopeial Convention Committee of Revision (2021b). The release of DS in the acidic environment from microparticles prepared with a PB-based feed dispersion was not detected. In the AHC-based formulations, drug dissolution was found to be less than 0.5% for both formulations. When adjusting the pH of the dissolution medium to 6.8, it was found that DS dissolved rapidly from all formulations. This is because Eudragit® L100 can freely dissolve in the medium, allowing the drug to be released from the microparticles. For the PB-based formulations, an increase in solids content in the feed dispersion to 4%w/v caused faster drug release. This might be due to incomplete coating, as observed in the SEM micrograph. In the AHC-based formulations, rapid drug release was observed at the onset of the basic dissolution phase. This could be attributed to the transformation of DS into amorphous solid within the AHC-based microparticles, making the drug readily available for dissolution. Increasing the concentration of AHC to 1.0% w/v in AHC2 resulted in faster drug release from the particles. This may be due to an increased amount of ammonia near the surface of the enteric particles, leading to the creation of porous structures which the dissolution medium can penetrate more easily, resulting in faster drug release. However, the microparticles based on PB3 and AHC2 exhibited reduced drug release, with approximately 85 - 87% of the drug dissolved at 300 minutes. These effects may arise due to the alteration of DS molecules, followed by the crystallization of DS after exposure to acidic condition followed by the phosphate buffer, serving as the biphasic dissolution media. As reported by Palomo et al., (1999), alterations in DS crystal properties were observed following exposure to 0.2M HCl and subsequently to phosphate buffer pH 6.8. They noted elevated levels of chloride (Cl) and phosphorus (P) in the drug molecule, accompanied by a decrease in sodium (Na) proportion, which could potentially influence the drug's solubility. Hence, both PB3-based microparticles, with high drug content and irregular shape morphology, and AHC2-based microparticles, exhibiting high surface porosity due to elevated AHC levels, may offer increased opportunities for DS exposure to acidic solution. Consequently, the drug molecules underwent alterations, leading to a decrease in drug dissolution.

5. Conclusion

Enteric microparticles containing diclofenac sodium, using Eudragit® L100 as the polymeric carrier, were successfully fabricated via the aqueous-phase spray-drying technique. Two alkaline solutions, phosphate buffer with a pH of 7.0 and AHC solution, were utilized as solvents for dissolving Eudragit® L100

based on the polymer's solubility characteristics. Even though the polymer completely dissolved in both solutions, DS displayed distinct behavior in each feed dispersion, leading to different levels of incorporation into the microparticles. Utilizing phosphate buffer at pH 7.0 as the dispersion medium resulted in the production of spherical microparticles with smooth surfaces. The morphology of these particles was greatly influenced by the solid's concentration. Employing a feed dispersion containing 2% w/v solids resulted in a high production yield of microparticles with suitable properties. The drug within the microparticles exhibited characteristics of a crystalline solid, which was partially entrapped within the polymer matrix and showed residual crystallinity as observed through PXRD analysis. Although residual phosphate salt was detected in the microparticles, it did not impact the acid protection efficiency, as no drug release was observed during the acid phase of the dissolution test. In AHC-based microparticles, DS was primarily dissolved in the polymer solution, resulting in the majority of the drug being dispersed in the polymer matrix as an amorphous solid after spray-drying. Due to the high temperature during the spray-drying process, no residual AHC was detected in the microparticles, as observed in the FT-IR spectra. However, dimple-shaped microparticles and drug crystallization were observed in the AHC-based formulations, which could lead to instability and uneven drug release from the microparticles. The enteric microparticles derived from both aqueous-based feed dispersions exhibited the capability to hinder drug dissolution in acidic conditions while promoting drug release in basic environments. These findings affirm the effectiveness of the aqueous-based spray-drying approach in the development of microparticles intended for use as an enteric drug delivery system.

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7. References

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