Synthesis, Characterization and In Vivo Assessment of Dexibuprofen-Eudragit Solid Dispersion Nanoparticles with Supercritical Antisolvent Technique

Muhammad AKHLAQ 1, Sattar BAKHSH 1, Muhammad SAFDAR 1, Sardar ALAM 1, Muhammad TARIQ 2 & Zeeshan ANWER 3

1 Faculty of Pharmacy, Gomal University D.I.Khan KPK, Pakistan
2 Department of Pharmacy, Dublin University, Ireland
3 Hayat Abad Medical Complex, Peshawar KPK, Pakistan

SUMMARY. The current study shows drug/polymer nanoparticles can raise the ratio and amount of oral absorption of a low solubility and high-permeability drug. Dexibuprofen-Eudragit solid dispersion nanoparticles less than 300 nm in size were effectively made using the supercritical antisolvent (SAS) technique with or without surfactant. The effect of different surfactants on nanoparticle formation and dissolution as well as on the oral absorption of Dexibuprofen-Eudragit E100 solid dispersion nanoparticles was examined. Powder X-ray diffraction and DSC analysis were also done. The dexibuprofen-Eudragit-TPGS solid dispersion nanoparticles considerably improved in vitro dissolution and oral absorption of dexibuprofen relative to that of the unprocessed form. The area under the concentration-time curve (AUC0-24 h) and peak plasma concentration Cmax increased 4.6 and 5.7 times respectively, with the dexibuprofen-Eudragit-TPGS formulation. This study established that the use the SAS technique for the formulation of dexibuprofen-Eudragit-TPGS solid dispersion nanoparticles is an enormously beneficial approach for improving the bioavailability of poorly water-soluble dexibuprofen.

RESUMEN. Este estudio demuestra que las nanopartículas de fármaco/polímero pueden elevar la proporción y cantidad de absorción oral de un fármaco de baja solubilidad y alta permeabilidad. Se realizaron con eficacia nanopartículas de dispersión sólida de dexibuprofeno-Eudragit de menos de 300 nm de tamaño utilizando la técnica de antidasolvente supercrítico (SAS) con o sin tensioactivo. Se examinó el efecto de diferentes tensioactivos sobre la formación de nanopartículas y su disolución, así como sobre la absorción oral de nanopartículas de dispersión sólida de dexibuprofeno-Eudragit E100. También se realizó la difracción por rayos X y el análisis por DSC del polvo. Las nanopartículas de dispersión sólida de dexibuprofeno-Eudragit TPGS mejoraron considerablemente la disolución in vitro y la absorción oral de dexibuprofeno con relación a la de la forma no procesada. El área bajo la curva de concentración-tiempo (AUC0-24 h) y la concentración plasmática máxima Cmax aumentaron 4.6 y 5.7 veces, respectivamente, con la formulación dexibuprofeno-Eudragit-TPGS. Este estudio estableció que el uso de la técnica SAS para la formulación de dexibuprofeno-Eudragit TPGS nanopartículas dispersión sólida es un enfoque enormemente beneficioso para mejorar la biodisponibilidad de dexibuprofeno poco soluble en agua.

INTRODUCTION
Dexibuprofen [2-(+)-isobutylphenyl] propionic acid] is a non-steroidal anti-inflammatory drug (NSAID) used widely in rheumatoid arthritis, osteoarthritis and a number of other painful conditions 1. Dexibuprofen or S (+)-ibuprofen is the pharmacologically active form and 160 times more potent than R (-)-ibuprofen. R (+)-ibuprofen is inverted to S (+)-ibuprofen in vivo to the extent of 57-69% 2-4. Dexibuprofen with an acid dissociation constant (pKa) of 4.5 belongs to the biopharmaceutics classification system (BSC) class II drug category because of its low solubility and high permeability 5. Various formulations of dexibuprofen such as controlled release matrix tablets, dry elixir, and film coated tablets have been studied to evaluate their potential to enhance dissolution and bioavailability of dexibuprofen 6-8. An excellent formulation system

KEY WORDS: antisolvent technique, bioavailability, dexibuprofen, nanoparticles, solid dispersion, supercritical.

* Author to whom correspondence should be addressed. E-mail: sardaralam754@gmail.com
for improving the bioavailability of poorly water-soluble APIs (active pharmaceutical ingredients) is solid dispersion. Generally, solid dispersions consist of an API and a hydrophilic polymer such as hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), Eudragit, or polyethylene glycol (PEG) 9-11. Most poorly water-soluble APIs exist in an amorphous form within the solid dispersion, thereby enhancing their dissolution and oral absorption by attaining a highly supersaturated state above their equilibrium solubility. Furthermore, ternary solid dispersions consisting of API, polymer, and surfactant can further enhance dissolution and in vivo performance of APIs compared to binary solid dispersions 12. Recently was reported that of the 71 combination formulations been evaluated, the most efficient ternary solid dispersion for enhanced bioavailability of sirolimus was the HPMC/TPGS followed by the HPMC/Sucroester 15 13. Solid dispersions containing polymer and/or surfactant can be manufactured on the principle of solvent evaporation, melting, and/or solvent-mediated melting. It has been reported that solid dispersion nanoparticles can be manufactured using supercritical fluid technology. Supercritical carbon dioxide (Pc = 7.38 MPa, Tc = 31.1 °C) is widely used as a solvent or antisolvent in the field of nanoparticle formation because it is non-toxic and non-flammable. The nanoparticle manufacturing process using supercritical carbon dioxide was developed based on the role of the supercritical carbon dioxide in the process as either a solvent (rapid expansion of supercritical solutions) or an antisolvent SAS. Yasuji et al. 14 reviewed particle design of poorly water-soluble APIs using supercritical fluid technologies.

Solid dispersion nanoparticles manufactured with hydrophilic polymers and surfactants using the SAS process significantly improved the solubility, dissolution, and oral bioavailability of poorly water-soluble APIs such as genistein, valsartan, dutasteride, lercanidipine, nilotinib, telmisartan, and azithromycin 15-22. The purpose of this study was to develop dexibuprofen-Eudragit solid dispersion nanoparticles with and without surfactant using the SAS process and to evaluate their potential to enhance the dissolution and oral bioavailability of dexibuprofen. Eudragit has been widely used to improve the solubility of poorly water-soluble drugs 23. Therefore, we used Eudragit E100 as a hydrophilic polymer in this study. The effect of different surfactants including gelucire 50/13, poloxamer 335, poloxamer 407, Ryoto sugar ester S-1670, and TPGS on the nanoparticle formation, dissolution, and oral absorption of dexibuprofen-Eudragit E100 solid dispersion nanoparticles was investigated. An in vitro-in vivo correlation (IVIVC) study was also conducted using the in vitro dissolution data and in vivo pharmacokinetic parameters.

MATERIALS AND METHODS

Dexibuprofen was obtained from Getz Pharma (VANIT, Pakistan). Gelucire 50/13 (melting point, 44 °C, Gattefosse, Saint-Priest, France), polyvinylpyrrolidone (PVP K30, BASF Co. Ltd., Ludwigshafen, Germany), poloxamer 335 (melting point: 52 °C, BASF Co. Ltd., Ludwigshafen, Germany), poloxamer 407 (melting point: 56 °C BASF Co. Ltd., Ludwigshafen, Germany), Ryoto sugar ester S1670 (melting point: 35-50 °C, Mitubishi-Kagaku Foods Co., Tokyo, Japan), and D-α-tocopheryl polyethylene glycol 2000 succinate (melting point: 37 °C, TPGS, Eastman Co., Kingsport, TN, USA) were used. Hydrochlorothiazide was purchased from Sigma-Aldrich Co. Ltd (St. Louis, MO, USA). Acetonitrile, ethanol, and methanol were of high-performance liquid chromatography (HPLC) grade.

Preparation of dexibuprofen-Eudragit E100 solid dispersion nanoparticles

Dexibuprofen solid dispersion nanoparticles were manufactured by the SAS process using Thar SAS 200 equipment (Thar Technologies, Pittsburgh, PA, USA) 24. To study the effect of the dexibuprofen/Eudragit E100 ratio, dexibuprofen-Eudragit E100 nanoparticles were fabricated with 20, 30, and 40% drug loading concentrations. The drug solution was first prepared by dissolving dexibuprofen and Eudragit E100 in methanol at 5% solute concentration. Once the particle precipitation vessel reached steady state (above critical temperature and pressure), the drug solution was introduced into the particle precipitation vessel by an HPLC liquid pump. The SAS process was then performed under the following conditions, based on preliminary experiments 15, temperature of precipitation vessel, 40 °C; pressure of precipitation vessel, 15 MPa; flow rate of drug solution, 1 mL/min; and flow rate of supercritical carbon dioxide, 11 g/min. To completely extract residual methanol, supercritical carbon dioxide was introduced into the precipitation vessel for 1 h, and the dexibuprofen solid dispersion nanopar-
articles were obtained from the precipitation vessel after depressurization to atmospheric pressure level. To investigate the effect of various surfactants on the dissolution and bioavailability of dexibuprofen, ternary solid dispersion nanoparticles of dexibuprofen-Eudragit E100 and surfactants were also prepared. Drug solutions were prepared by dissolving dexibuprofen, Eudragit E100, and the respective surfactant (with the exception of gelucire 50/13) in methanol at 5% solute concentration. For Gelucire 50/13, the drug solution was prepared using a 1:1 mixture of methanol and dichloromethane. Gelucire 50/13, poloxamer 335, poloxamer 407, Ryoto sugar ester S1670, and TPGS were tested as surfactants. The nanoparticles were manufactured under the same conditions as described above for the formulation without surfactant. The formulation characteristics of dexibuprofen solid dispersion nanoparticles are presented in Table 1.

Characterization of dexibuprofen-Eudragit E100 solid dispersion nanoparticles

The morphology of dexibuprofen-Eudragit E100 solid dispersion nanoparticles was examined using a scanning electron microscope (SEM, JSM-6300, Jeol Ltd., Tokyo, Japan). After suspension of the nanoparticles in mineral oil by sonication for 20 min, the particle size of dexibuprofen-Eudragit E100 solid dispersion nanoparticles was determined by the dynamic light scattering method using a laser particle analyzer (BI-9000; Brookhaven, NY, USA). The specific surface area (m²/g) of dexibuprofen-Eudragit solid dispersion nanoparticles was measured by the Brunauer, Emmett, and Teller (BET) method with nitrogen as the adsorption gas using an Autosorb-1 instrument (Quantachrome GmbH, Odelzhausen, Germany). The crystalline state of dexibuprofen within the solid dispersion nanoparticle was characterized using a differential scanning calorimeter (DSC, S-650 model, Sinco Co. Ltd., Seoul, Korea) and powder X-ray diffractometer (PXRD, D8 Advance X-ray diffraction system, Bruker AXS GmbH, Karlsruhe, Germany). DSC was calibrated for temperature and enthalpy using indium. The melting temperature and enthalpy of dexibuprofen and solid dispersion nanoparticles (2-5 mg) were then recorded at a heating rate of 5°/min under nitrogen purge (20 mL/min). Powder X-ray diffraction pattern was recorded from 5° to 50° of 2θ at a scanning rate of 3°/min. The dexibuprofen concentration within the solid dispersion nanoparticles was determined by dissolving about 30 mg of solid dispersion nanoparticles in 100 mL ethanol, filtering aliquots using a 0.45 µm syringe filter, and analyzing concentration with an HPLC system (Agilent 1100 Series, Agilent Technologies, Santa Clara, CA, USA). Chromatographic separation was performed with a CAPCELL PAK C18 UG120 (4.6 mm × 150 mm, 5 µm) reversed-phase column (Shiseido Fine Chemicals, Tokyo, Japan). Acetonitrile in water (60%) was used as the isocratic mobile phase at a flow rate of 1.0 mL/min. Dexibuprofen was detected by an ultraviolet (UV) detector at 239 nm. The drug content was calculated using the following equation: weight of the drug in nanoparticles/weight of the feeding excipients and drug × 100.

<table>
<thead>
<tr>
<th>Formulation (Weight)</th>
<th>Drug content (%)</th>
<th>Mean particle size (nm)</th>
<th>Specific surface area (m²/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexibuprofen: Eudragit E100 = 4:6</td>
<td>90.7 ± 1.5</td>
<td>158.4 ± 18.7</td>
<td>77.2 ± 1.2</td>
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<tr>
<td>Dexibuprofen: Eudragit E100 = 3:7</td>
<td>92.9 ± 2.3</td>
<td>145.2 ± 11.6</td>
<td>79.5 ± 1.5</td>
</tr>
<tr>
<td>Dexibuprofen: Eudragit E100 = 2:8</td>
<td>94.8 ± 2.9</td>
<td>155.4 ± 11.2</td>
<td>80.0 ± 2.0</td>
</tr>
<tr>
<td>Dexibuprofen: Eudragit E100: Gelucire 50/13 = 2:5:3</td>
<td>96.7 ± 3.2</td>
<td>612.2 ± 74.3</td>
<td>21.1 ± 1.9</td>
</tr>
<tr>
<td>Dexibuprofen: Eudragit E100:Poloxamer 335 = 2:5:3</td>
<td>95.5 ± 2.1</td>
<td>275.5 ± 34.5</td>
<td>40.2 ± 1.4</td>
</tr>
<tr>
<td>Dexibuprofen: Eudragit E100:Poloxamer 407 = 2:5:3</td>
<td>94.4 ± 2.4</td>
<td>282.8 ± 42.6</td>
<td>36.9 ± 1.4</td>
</tr>
<tr>
<td>Dexibuprofen: Eudragit E100:Ryoto Sugar ester S1670 = 2:5:3</td>
<td>95.9 ± 1.5</td>
<td>220.9 ± 24.6</td>
<td>49.8 ± 1.4</td>
</tr>
<tr>
<td>Dexibuprofen: Eudragit E100:TPGS = 2:5:3</td>
<td>95.2 ± 1.9</td>
<td>290.5 ± 45.8</td>
<td>29.2 ± 0.9</td>
</tr>
</tbody>
</table>

Table 1. Formulation, particle size, and specific surface area of dexibuprofen-Eudragit E100 solid dispersion nanoparticles prepared using the SAS process. * The dexibuprofen concentration within the solid dispersion nanoparticles was determined by dissolving about 30 mg of solid dispersion nanoparticles in 100 mL ethanol, filtering aliquots using a 0.45 µm syringe filter, and analyzing concentration with an HPLC system. The drug content (%) = weight of the drug in nanoparticles/weight of the feeding excipients and drug × 100. Data are expressed as the mean ± standard deviation (n = 3).
Dissolution tests for raw dexibuprofen and dexibuprofen-Eudragit E100 solid dispersion nanoparticles were performed in 300 mL of a dissolution medium containing hydrochloric acid (HCl) and sodium chloride (NaCl) at pH 1.2 and 37 °C using a USP rotating paddle apparatus at 50 rpm (non-sink condition). Samples equivalent to 60 mg of dexibuprofen were added to the dissolution tester (Electrolab, Mumbai, India). At predetermined time intervals, 2 mL of the medium was sampled, filtered using a 0.45 µm glass fiber syringe filter, diluted with methanol, and analyzed for dexibuprofen concentration by HPLC as described above. Dissolution tests were also performed using acetate buffer (pH 4.0), phosphate buffer (pH 6.8) and water under the same conditions.

Solubility of dexibuprofen in surfactant solution
To investigate the solubilization capability of gelucire 50/13, poloxamer 335, poloxamer 407, Ryoto sugar ester S1670, and TPGS, which were tested as surfactants, the solubility of dexibuprofen was measured in 1% surfactant solution at 37 °C. About 200 mg dexibuprofen was added to 5 mL of surfactant solution in glass vials. After sonication for 1 h, vials were placed in a shaking water bath at 100 rpm for 3 days. After setting solution aside for 4 h, 3 mL aliquots were filtered using a 0.45 µm syringe filter, diluted with methanol and then dexibuprofen concentration was analyzed by HPLC as described above.

Pharmacokinetic study in rats
The study protocol complied with the institutional guidelines for the care and use of laboratory animals, and it was approved by the ethics committee of Gomal University (No. 2012-04B). Oral bioavailability of dexibuprofen-Eudragit solid dispersion nanoparticles was evaluated in fasted Sprague-Dawley (SD) rats weighing 250 ± 10 g. Twenty SD rats were divided into four groups (n = 5), and the first group was orally administered raw dexibuprofen, while the remaining three groups received solid dispersion nanoparticles of dexibuprofen-Eudragit E100, dexibuprofen-Eudragit E100-poloxamer 407, or dexibuprofen-Eudragit E10-TPGS, using an animal feeding needle at a dose of 200 mg/kg of dexibuprofen. Prior to oral dosing, the samples were dispersed in distilled water. Following a predetermined time interval, about 0.35 mL of blood was drawn from the retro-orbital plexus of the rats, collected in heparinized tubes, and centrifuged at 10,000 rpm for 5 min at 4 °C to obtain the plasma. The plasma concentration of dexibuprofen was subsequently measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Sample preparation and conditions for analysis adhered to previously reported methods. For protein precipitation, 20 µL of a 20 µg/mL solution of hydrochlorothiazide (internal standard; IS) was added to 100 µL of heparinized plasma followed by 400 µL of acetonitrile. After vortexing briefly, the organic phase was separated from the aqueous phase by centrifugation at 13,000 rpm for 5 min. A 5 µL aliquot of the organic phase was injected into the LC-MS/MS system. Chromatographic separation was achieved using a ZORBAX® Eclipse XDB-C 18 column (4.6 × 50 mm, 1.8 µm, Agilent Technologies). The HPLC system was operated isocratically at 40 °C. The mobile phase consisted of 0.1% formic acid:acetonitrile (25:75, v/v). The mass spectrometer (Agilent technologies 6410 triple quadrupole mass spectrometer) was equipped with an electrospray source. The ions monitored using multiple reaction monitoring were m/z 380 (parent) and m/z 316 (product) for dexibuprofen, and m/z 296 (parent), and m/z 205 (product) for the IS. Pharmacokinetic analysis of the data was carried out with WinNonlin Standard Edition software, Version 5.3 (Pharsight Corp., St. Louis, MO, USA). The area under the curve (AUC0→24 h) was calculated using the trapezoidal method. The maximum concentration of dexibuprofen after oral administration (Cmax) and the time to reach the maximum concentration (Tmax) were determined from the experimentally obtained data.

Statistical analysis
The data were analyzed by a one-way analysis of variance (ANOVA) test followed by the Student-Newman-Keuls (SNK) and least-squares difference (LSD) tests using the SPSS 21.0 software (IBM SPSS Statistics, Armonk, NY, USA).

RESULTS AND DISCUSSION
In this study, dexibuprofen-Eudragit E100 solid dispersion nanoparticles were formulated using the SAS process with the aim of enhancing the dissolution and oral absorption of dexibuprofen. Fig. 1 shows the SEM images of the solid dispersion nanoparticles and Table 1 summarizes the mean particle size and specific surface area of solid dispersion nanoparticles. All dexibuprofen-Eudragit E100 solid dispersion
nanoparticles had regular spherical shape with particle size range of 145-159 nm and specific surface area of 77-80 m$^2$/g, indicating there was no significant difference between the dexibuprofen-Eudragit E100 solid dispersion nanoparticle formulations.

The ratio of dexibuprofen/Eudragit E100 also did not appear to influence the morphology and particle size of solid dispersion nanoparticles prepared by the SAS process. However, the mean particle size and specific surface area of solid dispersion nanoparticles were significantly affected by addition of the surfactant (Fig. 2).

In particular, the particles of the dexibuprofen-Eudragit E100-gelucire 50/13 solid dispersion nanoparticles had a regular spherical shape with mean particle size of 612.2 nm and specific surface area of 21.1 m$^2$/g. As shown in Table 1, the mean particle size and specific surface area of solid dispersion nanoparticles increased and decreased, respectively, following addition of the surfactant. The increased mean particle size and aggregation of solid dispersion nanoparticles might be due to the fusion of the surfactant, resulting in lower melting temperature. The melting points of all surfactants tested were below 57 °C as stated in the material and methods section. Similar results were previously reported [15-18]. Nevertheless, solid dispersion nanoparticles with surfactants (with the exception of gelucire 50/13) showed mean particle sizes below 300 nm. The crystal state of dexibuprofen within the solid dispersion nanoparticles was determined by DSC curves and PXRD patterns and is shown in Fig. 3. Raw dexibuprofen showed a sharp endothermic peak at about 152 °C. In addition, characteristic diffraction patterns indicating crystalline dexibuprofen were observed at 2θ values of 5.31°, 10.68°, 13.00°, 14.83°, 16.08°, 19.63°, 21.49°, 22.13°, 25.36°, and 29.48°. However, the melting peak and diffraction patterns of crystalline dexibuprofen were not observed for all solid dispersion nanoparticle formulations. In fact, dexibuprofen exists in the amorphous form in solid dispersion nanoparticle fabricated by the SAS process.

In the released studies (Fig. 4), raw dexibuprofen showed very low dissolution because of its poor water solubility. Although, the release of dexibuprofen was significantly increased by solid dispersion nanoparticles. The release of drug from dexibuprofen-Eudragit (2:8) solid dispersion nanoparticles had an extreme rate of 33.0% within 0.25 h, and slowly reduced to 26.3% after 2 h (Fig. 4).
The extreme release and release ratio of dexibuprofen at 2 h, enhanced with raising Eudragit ratio within nanoparticles, but there were no significant differences between Eudragit solid dispersion nanoparticles (4:6, 3:7, and 2:8). The enhanced release properties of dexibuprofen might be due to the formation of amorphous dexibuprofen in Eudragit solid dispersion nanoparticles developed by the SAS method and the specific interaction of Eudragit and dexibuprofen in forming hydrogen bonds. It has been previously reported that the solubility of amorphous dexibuprofen was 20.53 µg/mL in Eudragit aqueous solution and 4.57 µg/mL in water, indicating that Eudragit enhances solubilization and stabilization of amorphous dexibuprofen. The release of dexibuprofen was also enhanced by incorporated of surfactant within the solid dispersion nanoparticles. In particular, the maximum dexibuprofen release in dexibuprofen-Eudragit E100-TPGS solid dispersion nanoparticles was 67%, and dissolution at 2 h was 58%. The release percentage of dexibuprofen at 2 h ranked by the SNK test ranged as follows: dexibuprofen-Eudragit E100-poloxamer 335 < dexibuprofen-Eudragit E100-Ryoto sugar ester S1670 < dexibuprofen-Eudragit E100-poloxamer 407 < dexibuprofen-Eudragit E100-gelucre 50/13 < dexibuprofen-Eudragit E100-TPGS solid dispersion nanoparticle. In solubility and stabilization of amorphous dexibuprofen.
studies, the most effective surfactant tested was TPGS, followed by gelucire 50/13 and poloxamer 407, as shown in Table 2.

Release of dexibuprofen from solid dispersion nanoparticles with surfactant at 2 h was in fact related to the solubilization capability of the surfactant used. It has been revealed that the solubility of dexibuprofen was considerably increased by TPGS via micellar solubilization at a critical micelle concentration of 0.1 mg/mL. Moreover, it was reported that the recrystallization of dexibuprofen from amorphous state can be effectively inhibited by the combination of Eudragit and TPGS. Therefore, the significant enhancement in both the dissolution rate and extent of release of dexibuprofen can probably be attributed to the increased solubility induced by the Eudragit-TPGS stabilized amorphous form, the enhanced solubility by micellar solubilization of TPGS, and/or the improved wettability of particle surface by Eudragit and surfactant. Furthermore, dexibuprofen-Eudragit E100-TPGS solid dispersion nanoparticles showed higher release above 60% at different dissolution media pH (1.2, 4.0, 6.8 and water), as shown in Fig. 5.

Interestingly, the release of dexibuprofen from dexibuprofen-Eudragit E100-TPGS solid dispersion nanoparticles was not influenced by the pH of dissolution media. The solubility of dexibuprofen was not influenced by the physiological pH condition (1.0-7.5) since the pKa of dexibuprofen is 11.3. In fact, raw dexibuprofen showed very low release of below 3% in different pH dissolution media (pH 1.2, 4.0, 6.8, and water). To determine the IVIVC for dexibuprofen, the dissolution efficiency (DE%) as defined by Khan and Rhodes, was calculated using the dissolution profiles of dexibuprofen.

The DE for dexibuprofen-Eudragit solid dispersion nanoparticles was calculated from the area under the dissolution curves at 120 min and expressed as a percentage of the area of the rectangle resulting from 100% dissolution within the same period. As shown in Table 3, dexibuprofen-Eudragit E100-TPGS solid dispersion nanoparticles showed the highest DE%.

Table 2. Solubility of dexibuprofen in various surfactant solutions. * The solubility of dexibuprofen was measured in 1% surfactant solution at 37 °C. Data are expressed as the mean ± standard deviation (n = 3).

<table>
<thead>
<tr>
<th>Surfactant</th>
<th>Solubility (µg/mL) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw dexibuprofen</td>
<td>4.1 ± 0.3</td>
</tr>
<tr>
<td>Gelucire 50/13</td>
<td>3099.2 ± 64.9</td>
</tr>
<tr>
<td>Poloxamer 335</td>
<td>15.9 ± 4.0</td>
</tr>
<tr>
<td>Poloxamer 407</td>
<td>2100.8 ± 39.4</td>
</tr>
<tr>
<td>Ryoto Sugar Ester S1670</td>
<td>1401.1 ± 53.1</td>
</tr>
<tr>
<td>TPGS</td>
<td>6519.9 ± 26.1</td>
</tr>
</tbody>
</table>

Table 3. Dissolution efficiency of dexibuprofen-Eudragit solid dispersion nanoparticles prepared using the SAS process. Data are expressed as the mean ± standard deviation (n = 3).

<table>
<thead>
<tr>
<th>Formulation</th>
<th>DE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw dexibuprofen</td>
<td>2.0 ± 0.3</td>
</tr>
<tr>
<td>Dexibuprofen:Eudragit E100 = 2:8</td>
<td>30.2 ± 2.8</td>
</tr>
<tr>
<td>Dexibuprofen:Eudragit E100: Gelucire 50/13 = 2:5:3</td>
<td>44.9 ± 2.9</td>
</tr>
<tr>
<td>Dexibuprofen:Eudragit E100:Poloxamer 335 = 2:5:3</td>
<td>24.5 ± 1.9</td>
</tr>
<tr>
<td>Dexibuprofen:Eudragit E100:Poloxamer 407 = 2:5:3</td>
<td>36.8 ± 3.1</td>
</tr>
<tr>
<td>Dexibuprofen:Eudragit E100:Ryoto Sugar Ester S1670 = 2:5:3</td>
<td>30.4 ± 2.8</td>
</tr>
<tr>
<td>Dexibuprofen:Eudragit E100:TPGS = 2:5:3</td>
<td>60.2 ± 2.9</td>
</tr>
</tbody>
</table>
The bioavailability of dexibuprofen solid dispersion nanoparticles and raw dexibuprofen was determined in SD rats. As shown in the plasma concentration–time curves (Fig. 6), the $C_{\text{max}}$ of dexibuprofen from solid dispersion nanoparticles was significantly raised compared to raw dexibuprofen.

From the pharmacokinetic data, $C_{\text{max}}$ and AUC$_{0\rightarrow24\text{ h}}$ of raw dexibuprofen was 1.14 µg/mL and 14.42 µg·h/mL, respectively (Table 4). As predictable from the dissolution data, dexibuprofen-Eudragit E100-TPGS solid dispersion nanoparticles showed highest $C_{\text{max}}$ and AUC$_{0\rightarrow24\text{ h}}$ values and were 4.6 and 5.7 times higher, correspondingly, that shown by raw dexibuprofen. Additionally, ANOVA showed that there were significant differences among the samples ($p < 0.05$), which in order of increasing the $C_{\text{max}}$ of dexibuprofen, were ranked by the SNK test as follows: raw dexibuprofen < dexibuprofen-Eudragit E100 (2:8) < dexibuprofen-Eudragit E100-poloxamer 407 < dexibuprofen-Eudragit E100-TPGS solid dispersion nanoparticle.

Further studies of correlation between the $in\text{ vitro}$ dissolution data and $in\text{ vivo}$ pharmacokinetic parameters (Fig. 7) showed $in\text{ vitro}$ DE was well correlated to $in\text{ vivo}$ $C_{\text{max}}$ and AUC$_{0\rightarrow24\text{ h}}$ ($R^2 > 0.90$). In fact, $in\text{ vitro}$ dissolution of dexibuprofen was $C_{\text{max}}$ and AUC$_{0\rightarrow24\text{ h}}$ (Table 4). Pharmacokinetic parameters of dexibuprofen-Eudragit solid dispersion nanoparticles prepared using the SAS process. $^a$ indicates $p < 0.05$ vs. raw dexibuprofen; $^b$ indicates $p < 0.05$ vs. Dexibuprofen:PVP K30; $^c$ indicates $p < 0.05$ vs. dexibuprofen-Eudragit E100-Poloxamer 407. Data are expressed as the mean ± standard deviation ($n = 5$).

**Table 4.** Pharmacokinetic parameters of dexibuprofen-Eudragit solid dispersion nanoparticles prepared using the SAS process. $^a$ indicates $p < 0.05$ vs. raw dexibuprofen; $^b$ indicates $p < 0.05$ vs. Dexibuprofen:PVP K30; $^c$ indicates $p < 0.05$ vs. dexibuprofen-Eudragit E100-Poloxamer 407. Data are expressed as the mean ± standard deviation ($n = 5$).

**Figure 6.** Plasma concentration-time profile of dexibuprofen in rats after oral administration of the raw dexibuprofen and dexibuprofen-Eudragit E100 solid dispersion nanoparticles prepared using the SAS process. Data are expressed as the mean ± standard deviation ($n = 5$).

**Figure 7.** Correlation between the $in\text{ vitro}$ DE and $in\text{ vivo}$ pharmacokinetic parameters of dexibuprofen. A) Area under the curve (AUC) and B) $C_{\text{max}}$. 
ibuprofen was increased by solid dispersion nanoparticles, resulting in increased oral bioavailability. This also implies that the oral bioavailability of dexibuprofen can be controlled by the in vitro dissolution property. This correlation was similar to formerly reported IVIVC studies for dexibuprofen using self-microemulsifying Drug Delivery system (SMEDDS) design 31. As described in earlier studies, IVIVC study using DE is an effective technique for analyzing dexibuprofen in solid dispersion nanoparticles 30.

Generally, supersaturatable formulations such as solid dispersions, raise the highly supersaturated state of poorly water-soluble APIs above their equilibrium solubility in in vitro dissolution medium and in vivo in the gastrointestinal tract 32. To enhance the bioavailability of poorly water-soluble APIs by a supersaturatable system, the formulation must have the essential properties of generation and maintenance of the thermodynamically metastable supersaturated state 33. Therefore, the precipitation of APIs must be inhibited by using a hydrophilic polymer and surfactant. In this study, the enhanced solubility of dexibuprofen induced by dexibuprofen-Eudragit-TPGS solid dispersion nanoparticles resulted in enhanced oral absorption through the gastrointestinal epithelial membrane. This formulation can also be applied to potentially enhance the bioavailability of other poorly water-soluble APIs.

CONCLUSION

In the present study, spherical dexibuprofen solid dispersion nanoparticles smaller than 300 nm were successfully prepared using the SAS method. Among the preparations, dexibuprofen-Eudragit-TPGS solid dispersion nanoparticles showed significantly enhanced in vitro dissolution and oral absorption of dexibuprofen. Furthermore, in vitro dissolution efficiency was well correlated to in vivo pharmacokinetic parameters ($C_{\text{max}}$ and AUC). The current study thus confirmed that the formulation of dexibuprofen-Eudragit-TPGS solid dispersion nanoparticles utilizing the SAS method is an extremely effective approach for enhancing the bioavailability of poorly water-soluble dexibuprofen.

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