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Development of a novel celecoxib-loaded nanosuspension using a wet media milling process

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To develop a novel celecoxib (CXB)-loaded drug delivery system, numerous nanosuspensions were prepared with various polymers and surfactants using a wet media milling process, and their particle sizes were subsequently determined. A 2^4 full factorial design was used to identify the most appropriate preparation conditions. Pharmacokinetics of the selected nanosuspension were performed in rats and compared with those of a drug powder and a commercial CXB-loaded product. Among the carriers investigated, copovidone and sodium lauryl sulphate gave the smallest particle size of the drug in the nanosuspension. In particular, the nanosuspension prepared with 5% CXB, 4% copovidone, and 0.1% sodium lauryl sulphate, under the appropriate conditions, showed a particle size of approximately 190 nm, which was physically stable for at least 8 weeks. This nanosuspension provided a significantly higher plasma concentration and AUC in rats as compared with the drug powder and the commercial product. Thus, this novel CXB-loaded nanosuspension is a promising candidate with excellent stability and enhanced oral bioavailability.

1. Introduction

Celecoxib (4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzene sulphonamide; CXB), a selective cyclooxygenase-2 (COX-2) inhibitor, has been widely used for the treatment of osteoarthritis, rheumatoid arthritis, acute pain, and dysmenorrhea (Chakma et al. 2015). CXB is a Biopharmaceutics Classification System Class II drug due to its poor water solubility and high membrane permeability (Fong et al. 2015). Various approaches have been used in an attempt to increase the solubility and bioavailability of celecoxib, including solid dispersion (Knopp et al. 2016), microcapsules (Ha et al. 2015), cyclodextrin (Cannavà et al. 2013), lipid formulation (Nguyen et al. 2013), a self-emulsifying drug delivery system (Song et al. 2013), and nanocrystals (Nasr 2013).

A nanosuspension is a sub-micron colloidal dispersion of drug particles. These thermosdynamically unstable dispersion systems can be stabilised with polymers and/or surfactants (Chingunpituk 2007). Nanosuspensions provide a very large surface area, thereby increasing the dissolution and bioavailability for drugs with poor water solubility (Van Eerdenbrugh et al. 2008). Nanosuspension systems are advantageous for the pharmaceutical industry, since harsh chemicals and organic solvents can be avoided; and manufacturing and administration are easy, and the drug-loading capacity is high (Verma et al. 2011). Nanosuspensions are prepared either by changing a large particle to a nanoparticle (top-down approach) or by precipitating dissolved drugs into solid particles (bottom-up approach) (Van Eerdenbrugh et al. 2008; Knieke et al. 2013).

In this study, we aimed to develop a novel celecoxib (CXB)-loaded nanosuspension with improved dissolution and oral bioavailability. To achieve this, numerous CXB-loaded nanosuspensions were prepared with various polymers and surfactants using a wet media milling process, and their particle sizes were subsequently determined. The wet media milling process is a typical top-down approach, during which drugs with poor water solubility are mechanically pulverised in water by media milling pearls (Niwa et al. 2011). A 2^4 full factorial design with a selected CXB-loaded nanosuspension was used to identify the most appropriate preparation conditions. The crystallinity, dissolution, and oral bioavailability of the selected CXB-loaded nanosuspension were evaluated in rats and compared with those of the drug powder and the commercial CXB-loaded capsule.

2. Investigations, results, and discussion

2.1. Preparation of the CXB-loaded nanosuspension

Drug particle size in a nanosuspension system is important for absorption and physical stability. Thus, we aimed to reduce the CXB particle size by adding polymers and surfactants to CXB-loaded nanosuspensions.

Firstly, to select an appropriate polymer, the CXB-loaded nanosuspensions were prepared with various substances at a concentration of 4%, such as copovidone, polyvinylpyrrolidone (PVP) or hydroxypropylmethycellulose (HPMC), poloxamer 407, and poloxamer 188. The CXB and surfactant concentrations were fixed at 5% and 0.1%, respectively. The effect of the polymers on

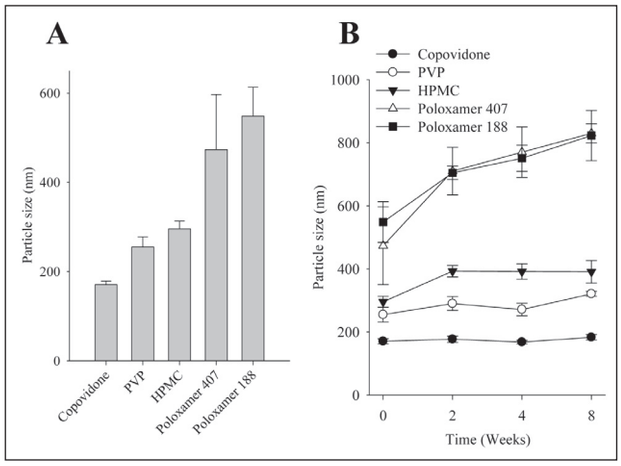

Fig. 1: Effect of the polymer on the particle size (A) and physical stability (B) of nanosuspensions. The nanosuspensions were prepared with 5 g CXB, 0.1 g SLS, and 4 g polymer in 100 mL distilled water. Each value represents the mean ± S.D. (n = 3).

CXB particle size in the nanosuspensions is shown in Fig. 1A. The particle size was significantly increased in the order of copovidone < PVP < HPMC < poloxamer 407 < poloxamer 188. Polymer-induced changes in CXB particle size were mainly dependent on the viscosity of the polymer (Murdande et al. 2015; Liu et al. 2011). The copovidone solution gave a lower viscosity than the PVP and HPMC solutions (Kim et al. 2014; Rashid et al. 2015); with the former providing significantly smaller particle sizes than the latter. Although the viscosities of the poloxamer 407 and 188 solutions were lower than those of the other polymer solutions, the CXB particle sizes were larger than those in the other polymer solutions. This is due to the fact that the viscosity of poloxamer solutions increases as the temperature increases, unlike with general polymer solutions (Din et al. 2017). The physical stabilities of the CXB-loaded nanosuspensions were evaluated over a period of 8 weeks by changing the particle size of the drug at 25 °C (Fig. 1B). There were no significant changes in the particle sizes of the nanosuspensions prepared with PVP or HPMC after 8 weeks; however, the drug particle size increased after 8 weeks in the poloxamer 407 and 188 nanosuspensions. Of the tested polymers, copovidone produced the smallest particle size as well as good drug stability, and was therefore chosen as the polymeric stabiliser. The nanosuspensions prepared with 3–5% copovidone were further tested to determine a suitable copovidone concentration. Those prepared with 3% and 4% copovidone gave significantly smaller particle sizes than that prepared with 5% copovidone; however, the particle size of the 3% copovidone nanosuspensions increased after the 8-week stability test (data not shown). Thus, 4% copovidone was chosen for use in subsequent experiments.

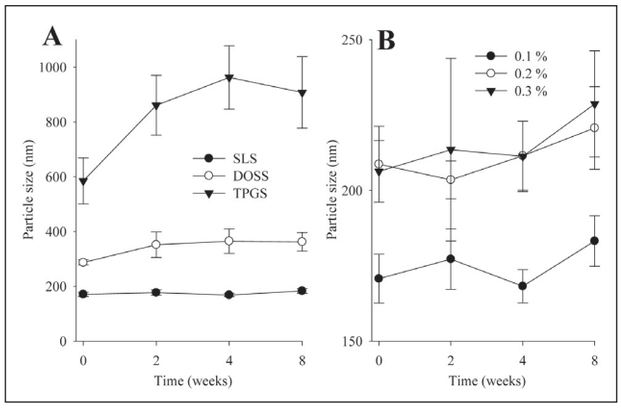

Fig. 2: Effect of the amount of surfactant (A) and SLS (B) on the physical stability of nanosuspensions. The nanosuspensions were prepared with 5 g CXB, 0.1 g surfactant (or 0.1–0.3 g SLS), and 4 g copovidone in 100 mL distilled water. Each value represents the mean ± S.D. (n = 3).

The CXB-loaded nanosuspensions were prepared with 5% CXB, 4% copovidone, and various surfactants at a concentration of 0.1%; sodium lauryl sulphate (SLS), docusate sodium (DOSS), and D-α-Tocopherol polyethylene glycol 1000 succinate (TPGS). The effects of the surfactants on CXB particle size and physical stability are shown in Fig. 2A. SLS and DOSS gave significantly smaller CXB particle sizes than TPGS. The electrostatic stabilisers (SLS and DOSS) have been reported to form more stable nanosuspensions than TPGS, which is a steric stabiliser (Ghosh et al. 2012; Verma et al. 2011). Moreover, a CXB-loaded nanosuspension supplemented with SLS was more stable than a DOSS-supplemented one. Ionic surfactants with a high HLB value increase the interaction with hydrophobic drugs, leading to enhanced stability of nanosuspensions (Kim et al. 2016; Owen et al. 2009). SLS, which has a relatively high HLB value, has been shown to be more effective at stabilising CXB-loaded nanosuspensions than DOSS, which has a relatively low HLB (George et al. 2013). Furthermore, while the drug particle sizes in nanosuspensions prepared with SLS and DOSS did not change over time, those in nanosuspensions prepared with TPGS increased over time. SLS has been frequently employed in the preparation of oral pharmaceutical products (Rashid et al. 2015); therefore, SLS was chosen as a suitable surfactant for the development of a CXB-loaded nanosuspension.

Nanosuspensions were prepared with 5% CXB, 4% copovidone, and 0.1–0.3% SLS, and their particle size and stability were subsequently investigated (Fig. 2B). The nanosuspensions prepared with 0.1% SLS provided significantly smaller particle sizes than those prepared with either 0.2% or 0.3% SLS. All particle sizes in the 0.1–0.3% SLS nanosuspensions were stable over an 8-week period; thus, 0.1% was chosen as the SLS concentration for subsequent nanosuspensions.

2.2. Analysis of the factorial design

A 2^4 full factorial design was used to select the most appropriate preparation conditions. This design has been widely used as a statistical approach for the planning and optimisation of experimental series. The nanosuspensions were prepared with 5 g CXB, 4 g copovidone, and 0.1 g SLS in 100 mL distilled water under various preparation conditions (independent variables), such as X_1 (agitator speed: 2000, 2500, or 3000 rpm), X_2 (milling time: 120, 150, or 180 min), X_3 (bead quantity: 450, 500, or 550 g/batch), and X_4 (suspension quantity: 300, 350, or 400 mL/batch), and their particle size were subsequently measured. To evaluate the individual effects of the independent variables (preparation conditions) on the response variable (particle size), the data were statistically analysed using the Design-Expert® software. The impact of the independent variables and their interaction with the response variables was determined using Pareto charts (Shah et al. 2010), as shown in Fig. 3. The non-significant response coefficients below the t-value limit line were deleted in the present study. The bars for four coefficients; agitator speed, milling time, bead quantity, and suspension quantity, extended above the Bonferroni limit

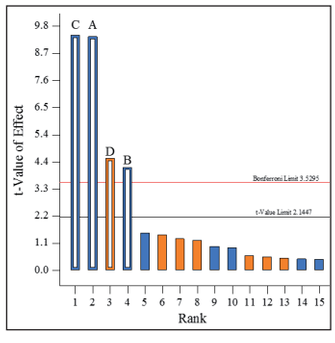

Fig. 3: Pareto charts of the effect of processing parameters on particle size: (A) agitator speed; (B) milling time; (C) bead quantity; (D) suspension quantity.

line for particle size, suggesting that these independent variables significantly impacted the particle size. The significant polynomial responses for the predicted particle size were as follows: particle size (nm) = 238.51 – 17.09X_1 – 7.54X_2 – 17.19X_3 + 8.17X_4. The relationship between the predicted and practical particle sizes (R^2 = 0.93; data not shown) showed good linearity, which is an indication of their excellent correlation.

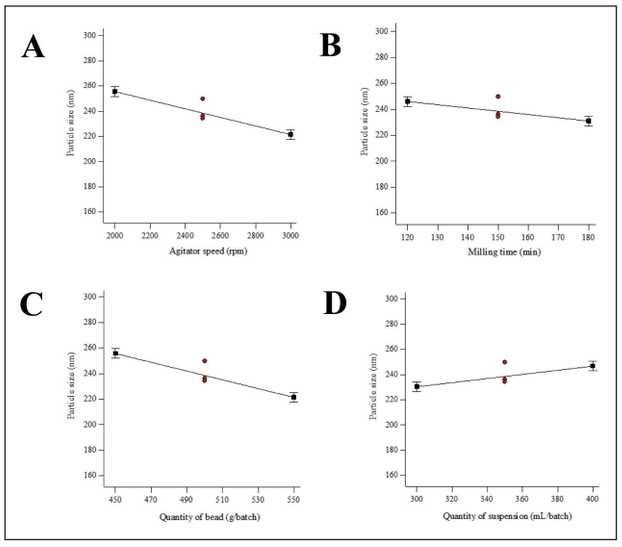

Fig. 4: Effect of the agitator speed (A), milling time (B), bead quantity (C), and suspension quantity (D) on the particle size.

Agitator speed, milling time, bead quantity, and suspension quantity significantly influenced the particle size (Fig. 4). Increasing the agitator speed resulted in a significantly decreased particle size (Fig. 4A) ($p < 0.0001$) (Hou et al. 2007). Moreover, as the milling time was increased, the particle size significantly decreased (Fig. 4B) ($p < 0.005$). The stress energy for the reduction of drug particle size can be varied by changing the tip speed of the agitator and grinding media size (Knieke et al. 2013; Toraman et al. 2011). A longer milling time causes the large particles to split into smaller ones and provides sufficient time for the stabiliser to absorb onto the drug particle surfaces (Verma et al. 2009; Liu et al. 2011). Moreover, the particle size was significantly decreased as the quantity of beads was increased (Fig. 4C) ($p < 0.0001$). An

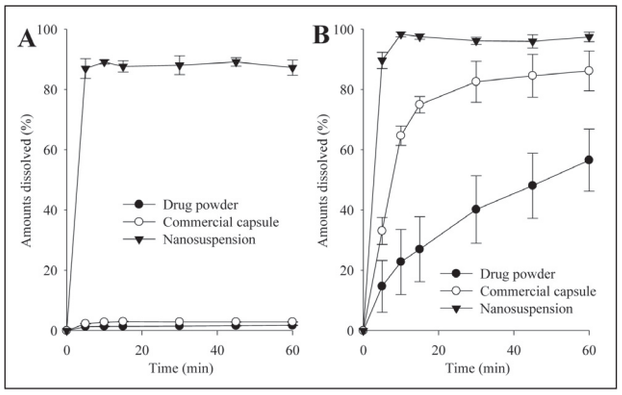

Fig. 5: Dissolution profiles of the drug from the drug powder, the commercial capsule, and the nanosuspension in distilled water (A) and 0.04 M tribasic sodium phosphate (pH 12.0) containing 1% sodium lauryl sulphate (B). Each value represents the mean ± S.D. (n = 6).

increase in the quantity of beads dramatically increases the bead-bead collisions, thus increasing the average number of compressed drug particles per unit time. Drug particles catch between the beads and experience contact fatigue damage that leads to particle fracture (Hou et al. 2007). Furthermore, increasing the quantity of suspension resulted in an increased particle size (Fig. 4D) ($p < 0.001$), since the increase in suspension quantity decreases the number of collided drug particles per bead (Kim et al. 2011). Based on the present data, an agitator speed of 3000 rpm, milling time of 180 min, bead quantity of 550 g/batch, and suspension quantity of 300 mL/batch were selected as appropriate preparation conditions, under which, the predicted value for the particle size of the nanosuspension was 188.5 nm. Moreover, the experimental value for the particle size determined by three confirmation batches was 188.8±1.0 nm. The similarity between the predicted and experimental values (1.02) indicates an excellent validity of the model.

2.3. Dissolution and pharmacokinetics

Drug dissolution from the CXB-loaded nanosuspension was compared with that of the drug powder and the commercially available CXB-loaded capsule in either distilled water or 0.04 M tribasic sodium phosphate (pH 12.0) containing 1% SLS (Fig. 5). The latter is an FDA-recommended dissolution medium for the commercial CXB-loaded capsules (Puri et al. 2011). In distilled water, the drug powder and the commercial capsule had dissolution rates of approximately 3% within 60 min, whereas the nanosuspension had a dissolution rate of approximately 90% within 5 min (Fig. 5A). In the FDA-recommended dissolution medium, the dissolution rates of the drug from the CXB-loaded nanosuspension was superior to the drug powder or the commercial capsule (Fig. 5B), at all times. In particular, the dissolution rates of the drug after 30 min from the drug powder, the commercial capsule, and the nanosuspension had dissolution rates of 40%, 80%, and 100%, respectively. Thus, our data suggest that the nanosuspension improved the dissolution of the relatively insoluble CXB to a greater degree than the commercial capsule due to its reduced particle size (Yousaf et al. 2015).

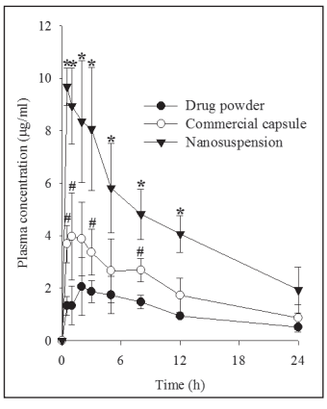

Fig. 6: Mean plasma concentration of the drug following oral administration of the drug powder, the commercial capsule, and the nanosuspension, to rats at a drug dose of 100 mg/kg. Each value represents the mean ± S.D. (n = 6). $^{\#}p < 0.05$ compared with the drug powder. $^{*}p < 0.05$ compared with the drug powder and commercial capsule.

The mean plasma concentration–time profiles of CXB following oral administration of the drug powder, the commercial capsule, or the nanosuspension to rats at the equivalent drug dose of 100 mg/kg are shown in Fig. 6. The CXB plasma concentrations were in the order as follows: drug powder < commercial capsule < nanosuspension. At 0.5, 1, 3, and 8 h, the CXB plasma concentrations were higher with the commercial capsule than with the drug powder. The nanosuspension gave significantly higher plasma concentrations than the commercial capsule and the drug powder up to 12 h post-dosing. The corresponding pharmacokinetic parameters are shown in the Table. The nanosuspension and the commercial capsule had significantly higher AUC and C_{max} values than the drug powder ($p < 0.05$). Moreover, the AUC and C_{max} values were higher for the nanosuspension than for the commercial capsule. The AUC value of the nanosuspension (109.9±15.8 μg/h/mL) was approximately 2.5- and 6-fold higher than that of the commercial capsule (41.9±15.9 μg/h/mL) and drug powder (18.8±10.1 μg/h/

Table: Pharmacokinetic parameters

Parameter	Drug powder	Commercial capsule	Nanosuspension
AUC (μg/h/mL)	18.76±10.12	41.89±15.85#	109. 89±15.78*
C_{max} (μg/mL)	2.06±0.47	3.97±0.93#	9.68±0.86*
T_{max} (h)	2.20±1.64	1.10±0.55	0.90±0.65
$t_{1/2}$ (h)	17.53±4.97	10.35±9.97	11.96±10.92
K_{el} (h^{-1})	0.04±0.03	0.07±0.04	0.06±0.03

Each value represents the mean ± S.D. (n = 6)
#$p < 0.05$ compared with the drug powder
*$p < 0.05$ compared with the drug powder and commercial capsule

mL), respectively. However, the T_{max}, $t_{1/2}$, and K_{el} values were not significantly different among the three drug preparations ($p > 0.05$). The present results suggest that the enhanced oral bioavailability of the CXB in nanosuspension is due to a marked increase in the CXB absorption rate as a result of particle size reduction (Kim et al. 2011). Further study regarding long-term stability and bioavailability in human subjects will be carried out with a view to developing this CXB-loaded nanosuspension as an alternative commercial product.

2.4. Conclusion

The CXB-loaded nanosuspension, with a weight ratio for CXB:copovidone:SLS:water of 5:4:0.1:100, milled using a top-down wet media milling method with an agitator speed of 3000 rpm, a milling time of 180 min, a bead quantity of 550 g/batch, and a suspension quantity of 300 mL/batch, provided a reduced particle size of approximately 190 nm. This nanosuspension was physically stable for 8 weeks. Furthermore, it gave higher a dissolution, plasma concentration, and AUC than either the drug powder or the commercial product due to its particle size reduction. Thus, this novel nanosuspension system is a promising candidate with excellent stability and enhanced bioavailability.

3. Experimental

3.1. Materials

Celecoxib (CXB) was procured from PharmaZell (Vizag, India). Copovidone (Kollidon® VA64), polyvinylpyrrolidone (PVP, Kollidon® K30), poloxamer 407, and poloxamer 188 were purchased from BASF (Ludwigshafen, Germany). Hydroxypropylmethycellulose (HPMC) was obtained from Shin-Etsu (Tokyo, Japan). Ibuprofen, sodium lauryl sulphate (SLS), docusate sodium (DOSS), and D-α-Tocopherol polyethylene glycol 1000 succinate (TPGS) were bought from Sigma-Aldrich Co. (St. Louis, MO, USA). Yttrium-stabilised zirconium oxide beads were provided by Tosoh (Tokyo, Japan). The commercial CXB-loaded capsule (Celebrex®; hard capsule form) was kindly supplied by Pfizer Korea Pharm. Co (Seoul, South Korea). All other chemicals and solvents were of reagent grade and were used without additional purification.

3.2. Animals

Male Sprague-Dawley rats (300±20 g) were provided with water and food *ad libitum*. Throughout the study, the animals were confined to cages under maintained environmental conditions (20–25 °C and 45–60% RH). The animal studies were consistent with NIH Policy and the Animal Welfare Act, and were approved by the Institutional Animal Care and Use Committee (IACUC) at Hanyang University.

3.3. Preparation

The CXB-loaded nanosuspensions were prepared using a wet media milling process. Various amounts of CXB, polymers, and surfactants were dispersed/dissolved in distilled water, and pulverised with beads (diameter 0.3 mm) for 3 h using a MiniCer® (Netzsch GmbH & Co., Selb, Germany) at an agitator speed of 3000 rpm and a pump speed of 40 rpm. During the wet milling process, each drug suspension was pumped into the milling chamber, passed through the screen, returned to the vessel, and re-circulated to the mill.

3.4. Particle size

The particle sizes of the CXB-loaded nanosuspensions were analysed by dynamic light scattering (DLS; Zetasizer Nano ZS; Malvern Instrument, Malvern, Worcestershire, UK). Each drop of nanosuspension sample (approximately 5 μL) was diluted with 50 mL distilled water. The cuvette was shaken for approximately 10 s and placed immediately inside the sample holder. Once the required intensity was reached, size distribution analysis was performed. The physical stabilities of the CXB-loaded nanosuspensions were evaluated over an 8-week period by changing the particle size of the drug at 25 °C.

3.5. Evaluation of the milling parameters using a 2^4 full factorial experimental design

The nanosuspensions were prepared with 5 g CXB, 4 g copovidone, and 0.1 g SLS in 100 mL distilled water under various preparation conditions (independent variables), such as X_1 (agitator speed), X_2 (milling time), X_3 (bead quantity) and X_4 (suspension quantity), and their particle sizes were subsequently assessed as described above. To select the most appropriate preparation conditions, a 2^4 full factorial experimental design was carried out using the Design-Expert® software (version 9, Stat-Ease Inc., city, Nation). ANOVA was used to evaluate the effects of the independent variables on the dependent variable (particle size), in addition to the interactions among these factors. The general form of the mathematical expression is given by the following equation: $Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_4X_4 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{14}X_1X_4 + b_{23}X_2X_3 + b_{24}X_2X_4 + b_{34}X_3X_4 + b_{123}X_1X_2X_3 + b_{124}X_1X_2X_4 + b_{234}X_2X_3X_4 + b_{1234}X_1X_2X_3X_4$, where Y is the dependent variable (mean particle size); X_1, X_2, X_3, and X_4 are the independent variables that affect the process; b_0 is the intercept; and b_1-b_{1234} are empirically derived coefficients that relate to the independent variables (X_1, X_2, X_3, and X_4) or their interaction with the dependent variable (Y). Moreover, the standardised influence of the independent variables and their interactions with the dependent variable was investigated using Pareto charts.

3.6. Dissolution

The dissolution behaviour of the drug powder, the commercial CXB-loaded capsule, and the CXB-loaded nanosuspension were investigated using the paddle method according to the USP dissolution apparatus II (paddle apparatus) (Vision® SR8Plus™; Hanson Research Co., Chatsworth, CA, USA). One litre distilled water or 0.04 M tribasic sodium phosphate (pH 12.0) containing 1% sodium lauryl sulphate (Puri et al. 2011) were used as dissolution media. The dissolution tests were performed at 37±0.5 °C using a paddle at a rotation speed of 50 rpm. At predetermined time intervals, 1 mL dissolution medium was withdrawn and filtered through a nylon syringe filter. The concentration of the drug in the filtrate (10 μL) was quantitated using an HPLC instrument consisting of a Waters 515 HPLC pump system, a 717 autosampler, and a 2487 dual λ absorbance detector (Waters Co., Milford, MA, USA). Using a Zorbax RX-C8 column (4.6 mm × 250 mm, 5 μm; Agilent Technologies, Santa Clara, CA, USA), the mobile phase, comprised of acetonitrile and 0.5% trimethylamine in phosphate buffer (pH 7.0) (55:45, v/v), was injected at a flow rate of 1.5 mL/min and a wavelength of 256 nm.

3.7. Pharmacokinetics in rats

Eighteen SD rats were divided into three groups (n = 6). The first group was administered the drug powder, and the other two groups received the CXB-loaded nanosuspension or the commercial CXB-loaded capsule, each at a drug dose of 100 mg/kg. These preparations were administered orally as a suspension in 0.25% sodium carboxyl methylcellulose utilizing an animal feeding needle. Following dose administration, 0.5 mL blood was collected from the cannulated right femoral artery at predetermined times (0.5, 1, 2, 3, 5, 8, 12, and 24 h) into glass tubes containing 5% EDTA (20 μL/mL blood). These blood samples were centrifuged at 5000 g for 20 min, and the collected plasma was stored at -20 °C until further use. A mixture of 25 μL internal standard (1 mg/mL ibuprofen in methanol), 25 μL phosphate buffer (pH 5.0; 0.5 M), and 1 mL chloroform were spiked with 250 μL plasma sample and the solution was vortex-mixed for 1 min, followed by centrifugation at 5000 g for 20 min. The upper layer was discarded, and the chloroform layer was transferred to a clean tube and evaporated to dryness at 50 °C under a stream of nitrogen. The residue was reconstituted in 100 μL mobile phase. With 50 μL final clear solution, CXB in plasma was quantitated by HPLC (Jalalizadeh et al. 2004). The HPLC system consisted of an Agilent 1260 Infinity (Agilent Technologies, Santa Clara, CA, USA) employing a Capcell Pak C18 column (4.6 mm ´ 250 mm, 5 μm; Shiseido, Tokyo, Japan). The mobile phase, comprised of acetonitrile and 0.1% acetic acid in distilled water (45:55, v/v) was injected at a flow rate of 1.0 mL/min, and UV-detection was performed at 260 nm.

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