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ORIGINAL ARTICLE

Sustained release dosage form of noscapine HCl using hot melt extrusion (HME) technique: formulation and pharmacokinetics

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Abstract

Sustained release formulation of noscapine (Nos) HCl could be useful in maintaining plasma Nos HCl level for prolonged period of time, which is important for chemo-sensitization. However, weakly basic drugs like Nos HCl have pH-dependent solubility. Therefore, the purpose of this study was to achieve pH-independent drug release by developing the sustained release dosage form of Nos HCl using biodegradable polymer Eudragit RLPO and FDA-approved pH modifier citric acid (CA) by hot melt extrusion (HME) technique. Nos HCl was successfully formulated using 10% CA with 91.2 ± 1.34% drug recovery through the extruder. X-ray diffraction (XRD) results showed that drug was completely dispersed in the polymer and changed to amorphous from its crystalline form. In vitro drug release studies in pH 6.8 buffer showed that formulation containing 10% CA released 70.99 ± 3.85% drug in 24 h after initial burst release of 40.04 ± 2.39% compared to formulation without CA. Furthermore, in vivo pharmacokinetic data showed the sustained release plasma concentration time curve with significant ($p < 0.05$) increase in area under curve (AUC) in Nos HCl extrudate compared to Nos HCl solution. Overall, HME can be used to enhance the bioavailability and achieve the pH-independent solubility of weakly basic drugs like Nos HCl.

Keywords Hot melt extrusion · Sustained release formulation · Noscapine HCl · Weakly basic drug · Solid dispersion

Introduction

Several drugs which are weak bases or their salts have pH-dependent solubility. Such drugs are less soluble in basic pH compared to acidic pH environment. Therefore, these drugs show the variability in their release pattern in different pH buffers in vitro. These variabilities are important in in vivo studies and may cause inter- and intra-individual differences in bioavailability and plasma profiles [1, 2]. Various researchers have reported that increased pH in GI tract results in incomplete absorption of several basic drugs including rifampicin, ketoconazole, and dipyridamole [2]. So far, numerous methodologies have been reported to address the issue of pH-dependent solubility of weakly basic drugs. Dashevsky et al. demonstrated that the use of extended and enteric release polymers as film-coating materials can attain pH-independent drug release in which they showed that enteric polymer has low solubility in acidic pH and it rapidly dissolves in basic pH which helps in enhancing the solubility of poorly soluble drug by increasing porosity of the film coat [3]. In another study by Takka et al., enteric polymer Eudragit L as a pH-dependent soluble filler was incorporated into hydroxypropyl methylcellulose (HPMC) matrix tablets which was dissolved and formed pores in basic pH to augment the drug release [4]. In many studies, organic acids (e.g., succinic or fumaric acid) have been used to generate a favorable pH microenvironment to attain improved release of weakly basic drugs or their salts irrespective of the pH environment [5–7]. Streubel et al. demonstrated the enhanced drug release of verapamil hydrochloride from matrix tablets containing HPMC or ethyl cellulose by using adipic, sorbic, or fumaric acid as a pH modifier [5]. Fumaric acid has also been used to achieve pH-independent release of weakly

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basic drug ZK 811752 from polyvinyl acetate/polyvinylpyrrolidone matrix tablets and polyvinyl acetate/polyvinylpyrrolidone-coated pellets respectively [8]. In addition to this, citric acid (CA) has also been used as a pH modifier by Nie et al. to increase the drug release of vinpocetine from HPMC matrices into phosphate buffer [9]. Noscapine (Nos) HCl, a phthalide isoquinoline alkaloid without sedative, euphoric, analgesic, or respiratory depressant properties, is used as an antitussive agent worldwide [10]. Recent studies have shown that Nos HCl is also tubulin-binding and can be used for its anticancer properties [11–17]. Nos HCl also acts as a potent chemosensitizer for various anticancer drugs including docetaxel and doxorubicin [18–27]. The oral route for drug delivery has been preferred because of its ease of administration and patient compliance. However, relatively high doses of the drug (ED50 300 mg/kg body weight) are essential for induction of anticancer activity. To date, development of oral formulations of the Nos has been limited because of the large dose required, poor absorption, low dissolution or aqueous solubility, and extensive first-pass metabolism [28]. HME has now been used more commonly in pharmaceutical industries for development of variety of dosage forms including tablets and pellets because of its numerous advantages including enhancing the solubility and bioavailability of poorly soluble drugs [29–31]. Eudragit RLPO has been reported as a chemically stable polymer with excellent extrudability and pH-independent properties. It is a copolymer of ethyl acrylate, methyl methacrylate, and a low content of methacrylic acid ester with quaternary ammonium groups. It has been reported that the presence of higher number of ammonium groups in the Eudragit RLPO structure helps the polymer to be more permeable [32]. It is also reported as a FDA-approved polymer and has been used in various studies including the study of Park et al. who reported the effect of Eudragit RLPO and RSPO on release of theophylline and carbamazepine from hot melt extruded formulations [33–35]. Eudragit RLPO has low glass temperature, high thermostability, excellent thermoplastic properties, and high miscibility with active pharmaceutical ingredients (APIs) and other excipients. Moreover, the use of CA as a plasticizer and pH modifier in the extrusion process has been reported in many studies [36, 37]. Sustained release formulation of Nos HCl could be useful in maintaining plasma Nos HCl levels for prolonged periods of time, which is important for chemosensitization [10]. Therefore, the purpose of this study was to achieve pH-independent drug release by developing the sustained release dosage form of Nos HCl using biodegradable polymer Eudragit RLPO and FDA-approved pH modifier CA by HME technique and to evaluate the pharmacokinetic characteristics of the formulation in Sprague-Dawley (SD) rats.

Materials

Eudragit RLPO was obtained from Evonik (Essen, Germany). Noscapine HCl was obtained from Sigma Aldrich and citric acid was obtained from spectrum chemicals. All the solvents used in HPLC were of HPLC grade. Hot melt extrusion equipment, model Omicron 10P (Steer America, OH, USA), was used for processing the formulation. Microfuge 22R Centrifugation equipment (Beckman Coulter, CA, USA) was used for the centrifugation process.

Methods

HME equipment

In this technique, the material is processed in the rotating screw at a set temperature, torque, and speed of the screw through a die having different configurations which results in a solid dispersion. HME equipment has three types of screw with outer diameter: inner diameter (DO:DI) ratio of 1.21, 1.55, and 1.71. It has five zones, namely feeder zone, conveying zone, melting zone, mixing zone, and discharge zone, through which the material passes and forms the extrudate. Screw speed rotation can be adjusted from 20 to 800 rpm depending on the requirement.

Formulation of Nos HCl formulation

As shown in Table 1, briefly, Nos HCl and Eudragit RLPO were triturated with and without CA. The powder mixture was then fed into the feeder of extruder (hot melt extruder, Steer America, OH, USA). The barrel temperature of 120 °C for the powder mixture with CA and 135 °C for the mixture without CA was maintained in all the five zones of extruder: feeder zone, conveying zone, melting zone, mixing zone, and discharge zone. Additionally, the materials were processed with three different screw configurations with different DO:DI ratios (1.21, 1.55, and 1.71). The extrudate was then collected from the discharge zone and pulverized into the ball

Table 1 Composition of Nos HCl formulation showing formulations from A1–A4 having variation in the concentration of Eudragit RLPO (%) and citric acid (%)

Formulation	Nos HCl (%)	Eudragit RLPO (%)	Citric acid (%)
A1	10	90	–
A2	10	87.5	2.5
A3	10	85	5
A4	10	80	10

mill (Retsch MM200, Glen Mills Inc., NJ, USA) which was further passed through sieve no. 80 (US standard sieve series, The W.S. Tyler Company, OH, USA) and was finally filled into size "0" HPMC capsules.

Drug assay using HPLC

Nos HCl analysis was carried out using the Waters HPLC alliance e2695 system with PDA detector at a wavelength of 232 nm. Acetonitrile (ACN) and 20 mM ammonium acetate (pH 4.5) at a ratio of 80:20 (v/v) were used as a mobile phase with the flow rate of 1.0 ml/min. The injection volume and the retention time were 50 μl and 4.45 min respectively. Data acquisition and analysis were performed using Empower software (Waters Corporation, MA). The calibration curve (peak area vs concentration) was generated over the range of 1–50 μg/ml and was found to be linear with a correlation coefficient of 0.9995 (Figs. 1 and 2 in the supplementary data). To determine the drug content in Nos HCl formulation, briefly, extrudate was dissolved in ACN:pH 4.5 buffer (mobile phase) in a 10-ml volumetric flask which was then vortexed to dissolve the drug completely. Furthermore, the solution was centrifuged, and supernatant was collected which was then analyzed by HPLC. Healthy untreated SD rat was used for the HPLC method development of Nos HCl. Briefly, blood was collected from healthy untreated rats using cardiac puncture method. The blood was then centrifuged to obtain plasma. The resultant plasma was further used in the HPLC method development.

Fourier transform infrared (FTIR)

Nos HCl extrudate was analyzed by FTIR using a Spectrum 100 PerkinElmer spectrophotometer (PerkinElmer, USA), which was equipped with crystal diamond universal ATR (UATR) sampling accessory. Spectra were obtained by the KBr disc method using a Thermo Scientific Nicolet iS5 FTIR instrument (Waltham, MA, USA). Briefly, the sample was dissolved in chloroform and was applied on the KBr disc. The disc was then placed in the FTIR instrument for analysis.

X-ray diffraction (XRD)

XRD of Nos HCl extrudate and Nos HCl API was performed using an automated X'Pert Pro diffractometer (PANalytical, Almelo, the Netherlands) in Bragg-Brentano geometry with a flat sample holder filled using the back-loading technique to minimalize preferred orientation. Diffractograms were collected using X'Pert Data Collector version 2.2.c (PANalytical, Almelo, Netherlands) in continuous scan mode with a scan region of 5° until 50° and a step size of 0.008°. The counting time was 40.005 s. Data visualization and treatment were done using X'Pert Data Viewer version 1.2.a (PANalytical, Almelo, the Netherlands) [38].

In vitro drug release study

In vitro release study of Nos HCl (crude drug) (control), Nos HCl without CA, and Nos HCl with 10% CA was performed using USP apparatus-I (basket) using acidic buffer pH 1.2 for 2 h. Briefly, 500 ml of buffer was placed in the flasks and the temperature was adjusted to 37 °C with 75 rpm speed. Capsules containing powdered extrudate of Nos HCl and crude drug (50 mg) (control) were then placed in the basket after the temperature was reached to the set value. Samples (0.3 ml) were collected after 0.5, 1, and 2 h and same quantity of fresh buffer was added in the flask to maintain the sink condition. In vitro release study was separately performed with the same setup using phosphate buffer pH 6.8 as dissolution medium. Samples (0.3 ml) were collected after 1, 2, 4, 6, 8, 12, and 24 h and same quantity of fresh buffer was added in the flask to maintain the sink condition. Furthermore, all the samples were centrifuged at 10,000 rpm for 15 min to obtain the clear supernatant. A total of 150 μl of supernatant was then mixed with same quantity of ACN:pH 4.5 buffer (mobile phase) and analyzed by HPLC.

Optimization of extruder parameters

Effect of different barrel configurations on drug release

Formulation was extruded with Eudragit RLPO by different barrel configurations 1.21, 1.55, and 1.77 (DO:DI ratio). Furthermore, the formulation was analyzed by in vitro drug release study. The barrel configuration which showed higher drug release was selected for further studies.

Effect of CA concentration on drug release

Nos formulation was extruded with different concentrations of CA (2.5, 5, and 10%). All the extrudates were analyzed by in vitro drug release study. CA concentration which showed enhanced drug release in a sustained manner from the Nos extrudate was selected for further studies.

In vivo pharmacokinetic study

Sprague-Dawley (SD) rats (body weight 250 ± 10 g, Charles River, USA) were housed in cages for a minimum of at least 3 days prior to beginning the study and had free access to food and water. Rats were randomly divided into two groups (n = 5): Nos HCl extrudate with 10% CA and Nos solution. As Nos HCl was readily soluble in water, Nos solution was prepared simply by dissolving the drug in distilled water. The rats were fasted for 12 h prior to the experiments, and after 2 h of dosing

of formulations, they were given access to food. A total of 50 mg/kg dose Nos HCl of Nos HCl extrudate and Nos solution was given orally by using oral gavage. Serial blood samples (200 μl) were taken from the tail vein at time points 0.5, 1, 2, 4, 6, 8, 10, 12, 24, and 48 h post-dosing. The whole blood was collected into heparin-coated tubes and centrifuged at 4 °C at 12,000 rpm for 5 min to obtain plasma. The plasma samples were kept frozen at − 80 °C until analysis [38, 39]. For the HPLC analysis, the plasma samples were mixed with same quantity of ACN:pH 4.5 buffer (mobile phase). All the samples were vortexed for 2 min to separate the drug from the plasma. They were then centrifuged at 14,000 rpm to obtain clear supernatant. The resultant supernatant was then injected in HPLC to determine the drug content. Animal protocol was approved by the Institutional Animal Care and Use Committee (IACUC) (protocol number: 020-04).

Statistical analysis

All the results of the study have been expressed as the mean ± standard deviation for at least three repetitions. One-way analysis of variance (ANOVA) analysis was used for the comparison among multiple groups followed by Tukey's multiple comparison test, while Student's *t* test analysis was used for the comparison between two groups. The mean differences were considered significant in all experiments valued at $*p < 0.05$, $**p < 0.01$, and $***p < 0.001$.

Results

Formulation of sustained release dosage form of Nos HCl

Nos HCl and Eudragit with and without CA were successfully extruded through an extruder at 120 °C and 135 °C respectively with a glassy extrudate. Data revealed that Nos HCl and Eudragit mixture, when extruded below 135 °C, Nos was not evenly distributed in the polymer, and extrudate was not glassy suggesting solid dispersion was not formed with the drug and polymer. Similarly, when Nos HCl and Eudragit were extruded with CA below 120 °C, solid dispersion was not formed and extrudate was not glassy. Addition of CA reduced the processing temperature from 135 to 120 °C.

Drug assay

All the Nos extrudates were analyzed for drug content to confirm if there was any drug loss in the process of formulation. Results revealed that all the extrudates showed 91.2 ± 1.34% of drug recovery.

In vitro drug release study

Data from in vitro release study in acidic pH 1.2 buffer showed that 81.59 ± 4.39%, 10.93 ± 2.97%, and 13.68 ± 3.24% drug was released from Nos HCl (crude drug) (control), Nos HCl without CA, and Nos HCl with 10% CA in 2 h (Fig. 1a). Furthermore, in vitro drug release of Nos HCl with 10% CA formulation in pH 1.2 was evaluated for drug release kinetics (zero order, first order, Higuchi, and Peppas as shown in Fig. 5a, b, c, and d in the supplementary data) to understand the drug release mechanism. Zero-order release pattern was observed with an R^2 value of 0.9805 for Nos with 10% CA formulation. In vitro drug release data in basic pH 6.8 buffer showed that Nos HCl (crude drug) (control), Nos HCl without CA, and Nos HCl with 10% CA released 4.68 ± 0.48, 22.25 ± 3.71, and 70.99 ± 3.85% drug respectively (Fig. 1b) in a 24-h study. Furthermore, in vitro drug release of Nos HCl formulation with 10% CA was evaluated for drug release kinetics (zero order, first order, Higuchi, and Peppas; Fig. 6a, b, c, and d in the supplementary data) to understand the drug release mechanism. Data showed that the Peppas release pattern was observed with an R^2 value of 0.9955 with Fickian diffusion drug release mechanism based on the *n* value (0.171) calculated using the Peppas equation.

Effect of different barrel configurations on drug release

Eudragit RLPO with CA 10% and 10% Nos HCl were processed in different barrel configurations (1.21, 1.55, 1.71) and evaluated for drug release from the extrudate. Results showed that extrudate processed using barrel 1.21 released 70.99 ± 3.85% of drug with an initial burst release of 40.04 ± 2.39 drug in pH 6.8 buffer (Fig. 2).

Effect of CA concentration on drug release

Results revealed that extrudate containing Nos HCl with Eudragit RLPO and CA 5% and 10% released 53.41 ± 2.45 and 70.99 ± 3.85% drug respectively within 24 h in pH 6.8 buffer (Fig. 3).

FTIR

Figure 3 shows the FTIR spectra of Nos HCl having characteristic peaks at 1670–1821 cm^{-1} for carbonyl (C=O) group, 1250–1340 cm^{-1} for cyanide (C–N), and 1180–1200 cm^{-1} for ether (C-O-C). Extrudate containing combination of Nos HCl with Eudragit RLPO and extrudate of Nos HCl dehydrate, Eudragit RLPO, and CA showed the presence of all the characteristic peaks present in the drug (Fig. 4).

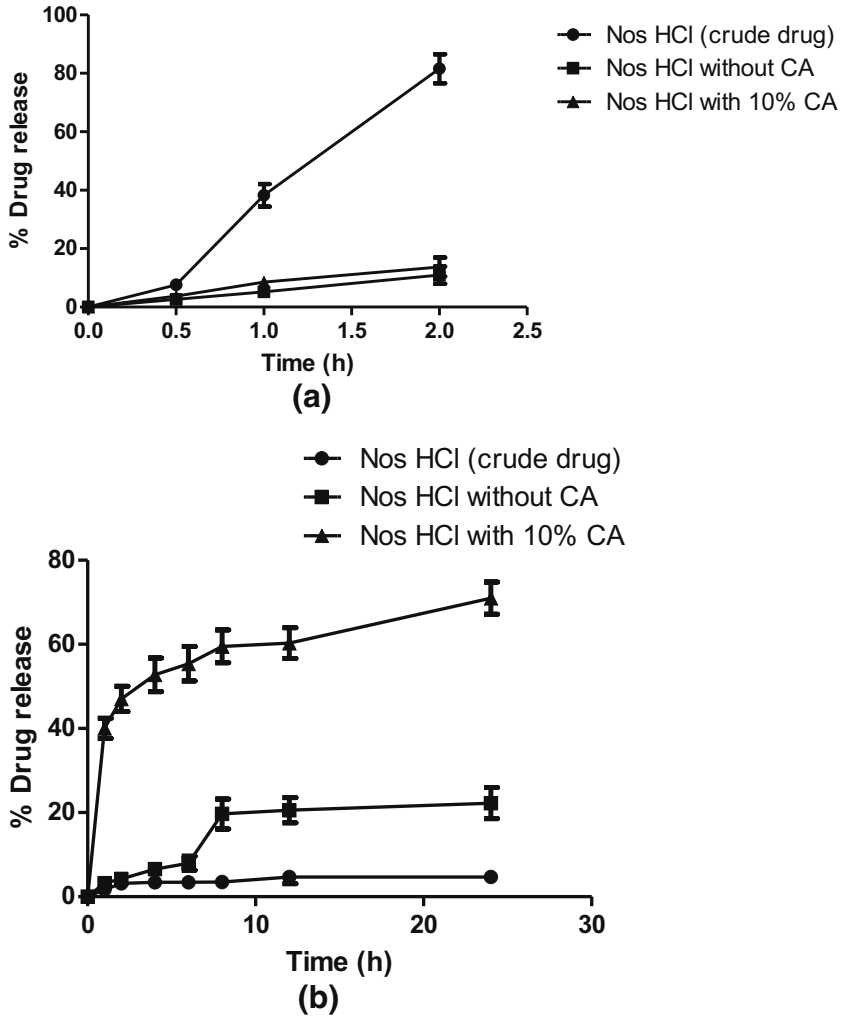

Fig. 1 **a** In vitro drug release study of Nos HCl (crude drug) in pH 1.2 buffer showing significant increase in drug release compared with Nos HCl without CA and with 10% CA formulations. **b** In vitro drug release study of Nos HCl with 10% CA in pH 6.8 buffer showing significant increase in drug release compared with control Nos HCl (crude drug) and Nos HCl without CA

X-ray powder diffraction

Figure 4 depicts the powder X-ray diffractograms of Nos HCl, extrudate of Nos HCl with Eudragit RLPO, and extrudate of Nos HCl dehydrate, Eudragit RLPO, and CA. Nos HCl diffractogram showed various diffraction peaks, whereas the extrudate did not show any peak in their diffractograms (Fig. 5).

In vivo pharmacokinetic study

Results from in vivo pharmacokinetic study in rats revealed that Nos HCl solution and Nos extrudate did not show significant difference in the C_{max} and T_{max}. C_{max} for Nos HCl solution and Nos extrudate were 21.35 ± 4.34 and 18.61 ± 4.72 μg/ml respectively. Furthermore, T_{max} for Nos HCl

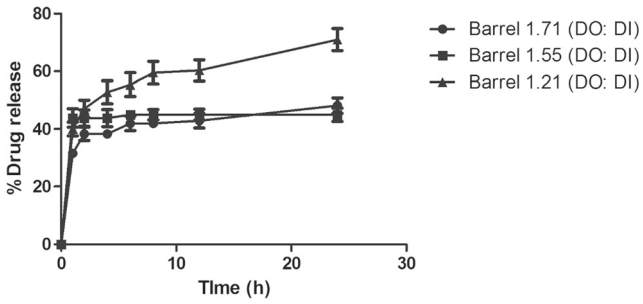

Fig. 2 In vitro drug release study of Nos HCl with different barrel configurations showing increased drug release in pH 6.8 buffer when the material extruded in barrel 1.21 (DO:DI) compared with barrels 1.55 and 1.71 (DO:DI)

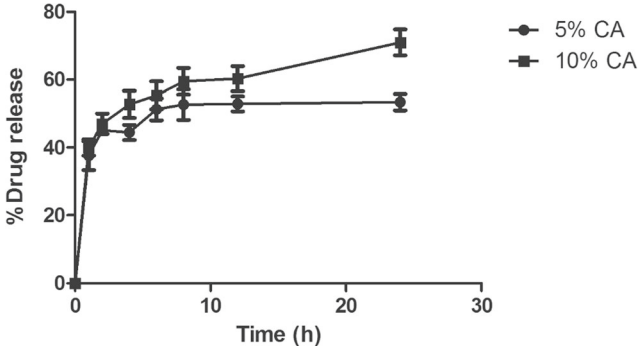

Fig. 3 In vitro drug release study of Nos HCl at different concentrations of CA showing enhanced drug release in pH 6.8 buffer when the drug was processed with 10% CA in the extruder in contrast to 5% CA

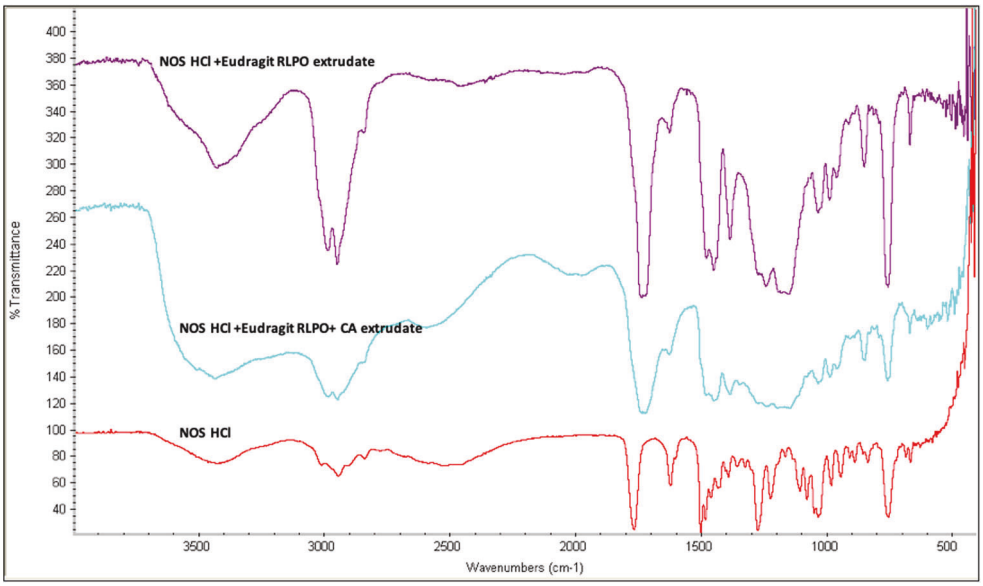

Fig. 4 FTIR spectra of Nos HCl (API), Nos HCl with Eudragit RLPO and CA extrudate, and Nos HCl with Eudragit RLPO extrudate showing presence of characteristic peaks for all the functional groups present in Nos HCl (API)

solution and Nos extrudate were 0.70 ± 0.27 and 0.80 ± 0.27 h respectively. However, Nos HCl extrudate showed a significantly ($p < 0.05$) high area under the curve ($AUC_{0–48}$) of 406.99 ± 179.81 (μg h/ml) in contrast to Nos HCl solution which showed an $AUC_{0–48}$ of 167.62 ± 35.82 (μg h/ml). Plasma-drug concentration curve also showed that Nos extrudate released the drug in a sustained pattern as compared with Nos HCl solution (Fig. 6; Table 2).

Discussion

Hypothesis of the present work was that HME-based solid dispersion technique along with pH modifier approach will enhance the bioavailability of Nos HCl and show the sustained release behavior of a drug from the formulation. In this study, we formulated sustained release dosage form of weakly basic drug Nos HCl and enhanced the bioavailability in contrast to Nos HCl solution. Preliminary studies revealed that Eudragit RLPO showed enhanced drug release compared with other Eudragit polymers which could be because of Eudragit RLPO characteristics which might have helped in releasing more drug in basic pH environment. Furthermore, all the parameters of HME including temperature, screw speed, and barrel configuration were optimized for the sustained release formulation of Nos HCl. CA was used as a pH modifier to control the release of drug from the formulation. CA has been widely used as an acidifying agent in solid oral dosage forms [1, 40, 41]. Solid dispersions of poorly soluble APIs in citric acid produced by co-melting techniques exhibited increased dissolution rates. Furthermore, the plasticizing effects of CA monohydrate (CA MH) on certain acrylic polymers including Eudragit® L 30D-55, Eudragit® S100, and Eudragit® RSPO have been previously demonstrated [37, 41]. Optimization of CA concentration study revealed 10% CA was found to be optimal to enhance the drug release in a sustained manner. We further confirmed the conversion of the amorphous form of the drug from its crystalline form by extrusion process using XRD analysis which showed the complete absence of drug peaks in the drug polymer mixture extrudate. The results are in concordance with the study by Chowdhury et al. where they demonstrated that the absence of the endothermic peak of resveratrol (RAS) and tamoxifen (TAM) in the extrudate consisting of combination of Soluplus as a polymer and TAM and RAS as drugs indicates that drugs were completely dispersed in the polymer and attained the amorphous form [38]. The study of Kate et al. also showed that HME-processed atovaquone resulted in the conversion of the crystalline form of the drug into amorphous form indicating enhanced bioavailability of the drug [42]. Park et al. have demonstrated that the crystalline form of both drugs in the extrudate containing theophylline (TP) and carbamazepine (CBZ) changed into the amorphous form in the HME process [35]. Furthermore, FTIR spectra showed the presence of carbonyl, cyanide, and ether functional groups in the drug polymer mixture extrudate proving that the drug was not degraded in the extrusion process which might be because the drug was extruded below its degradation temperature. Eudragit RLPO played a critical role in processing the material at low temperature, whereas CA further helped in lowering down the glass transition temperature. Many studies have shown that drugs remain stable when processed in HME process below their

Fig. 5 X-ray diffractograms of **a** Nos HCl (API), **b** Nos HCl with Eudragit RLPO extrudate, and **c** Nos HCl with Eudragit RLPO and CA extrudate showing presence of various diffraction peaks in Nos HCl (API), whereas no peak in the extrudates ▶

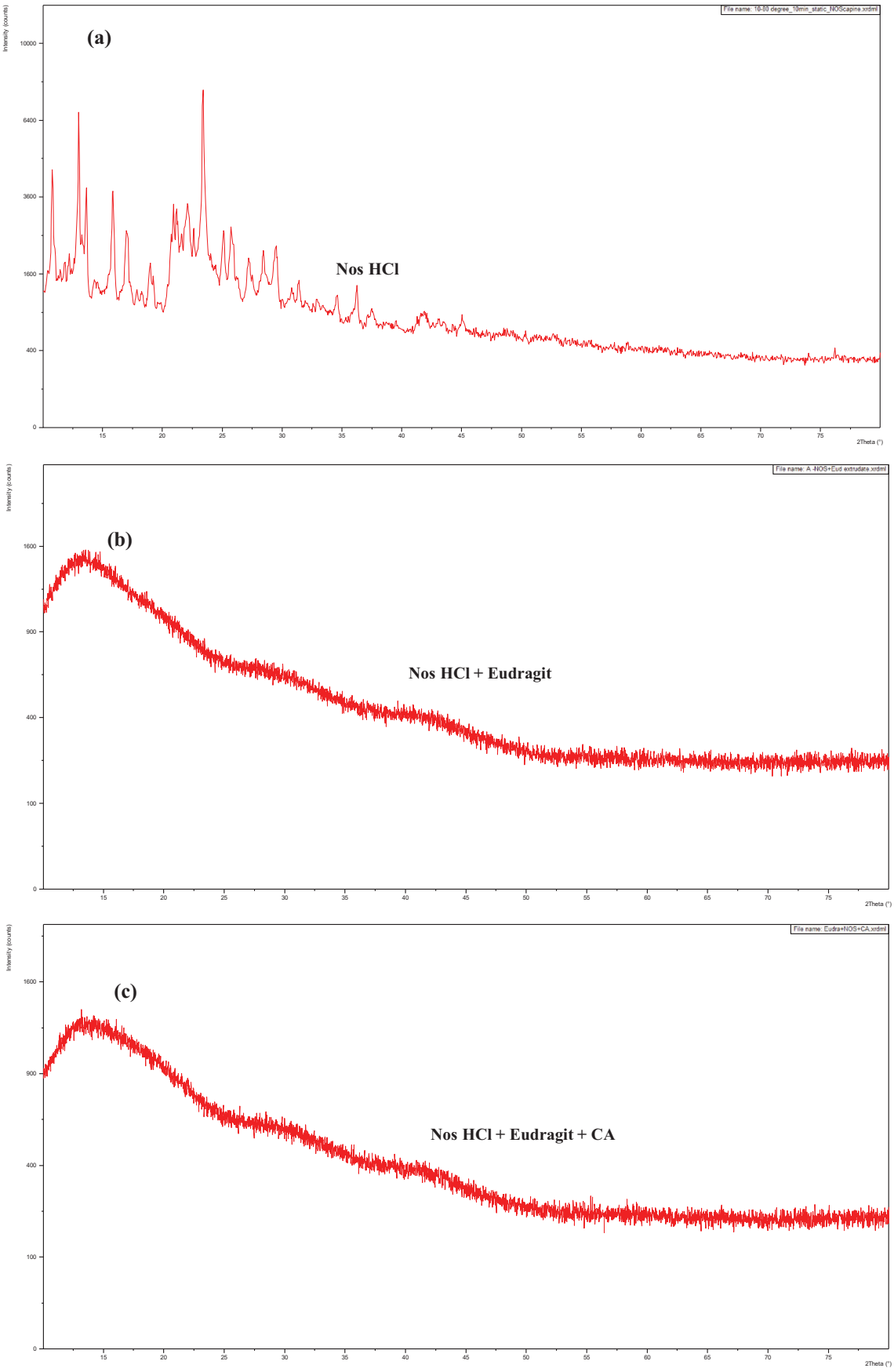
(a)
Nos HCl
(b)
Nos HCl + Eudragit
(c)
Nos HCl + Eudragit + CA
Intensity (counts)
2Theta (°)

Table 2 Pharmacokinetic parameters of Nos HCl solution and Nos extrudate after oral administration of 50 mg/kg dose of Nos HCl

Parameters	Nos HCl solution	Nos HCl extrudate
C_{max} (μg/ml)	21.35 ± 4.34	18.61 ± 4.72
T_{max} (h)	0.70 ± 0.27	0.80 ± 0.27
AUC_{0-48} (μg h/ml)	167.62 ± 35.85	406.99 ± 179.81

degradation temperature [36, 38, 43]. Effect of concentration of CA on percent drug release study revealed that, at low concentration of CA (2.5%), the material could not be processed which might be because of insufficient concentration of plasticizer present in the blend which could not reduce the glass transition temperature of polymer Eudragit RLPO. Furthermore, at 10% concentration of CA, formulation showed significant improvement in the drug release behavior which could be because CA successfully lowered down the glass transition temperature of polymer and the processing temperature as well. Many studies have shown that CA as a plasticizer helps in reducing the processing temperature and enhances the drug release in basic environment due to its pH-modifying characteristics [37]. Nos HCl formulation containing 10% of CA showed significant ($p < 0.05$) increase in drug release as compared with Nos HCl (crude drug) control and Nos HCl without CA formulation in vitro drug release in pH 6.8, suggesting that CA played an important role in enhancing the drug release from the drug polymer mixture extrudate in basic environment. Results revealed that Nos HCl formulation containing 10% of CA followed Peppas release pattern with Fickian diffusion drug release mechanism in basic dissolution medium and zero-order drug release pattern in acidic dissolution medium. Eudragit RLPO, a biodegradable polymer, was chosen in the formulation owing to its high

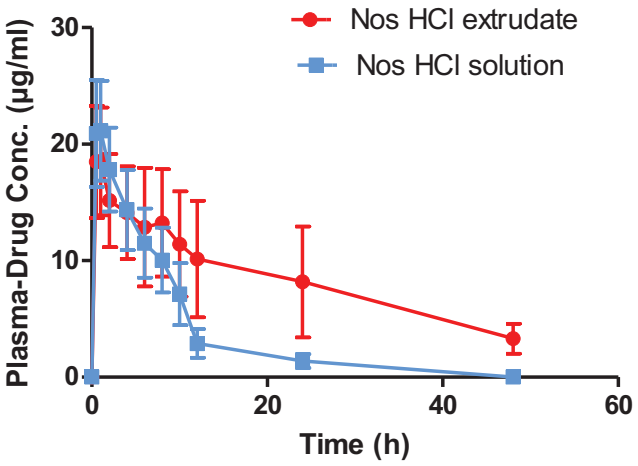

Fig. 6 Average plasma-drug concentration time profile of Nos HCl solution and Nos extrudate following oral administration of 50 mg/kg dose of Nos HCl (mean ± SD, $n = 5$)

chemical stability, good extrudability, and pH-independent properties and also has been used widely in the past by various researchers [33]. Park et al. studied the effect of hot melt extruded Eudragit RLPO and RSPO on the release of TP and CPZ where they showed increasing the proportion of RLPO in the formulation lead to increase in the percent drug release [35]. Pharmacokinetic data showed significant ($p < 0.05$) increase in AUC in Nos HCl extrudate formulation compared with Nos solution which suggested that bioavailability was significantly enhanced by the extrusion method along with pH modifier approach. Patil et al. demonstrated that HME process enhanced the bioavailability of fenofibrate solid lipid nanoparticle (SLN) formulation compared with marketed formulation and crude fenofibrate drug [39]. Kate et al. studied the formulation of solid dispersion of atovaquone using HME. They found that the formulation showed improved release in contrast to Malarone® tablets, and 3.2-fold and 4.6-fold higher bioavailability in contrast to Malarone® tablets and atovaquone respectively. The higher bioavailability also resulted in increase in anti-malarial activity to 100% in murine infection model at 1/8th therapeutic dose [42]. Bioavailability enhancement of Nos HCl using co-solvent and cyclodextrin-based approaches has been reported in the literature. In this study, inclusion complexes of the drug were prepared using hydroxypropyl-b-cyclodextrin and sulfobutyl ether cyclodextrins. Polyethylene glycol succinate, vitamin E tocopherol, and propylene glycol-based co-solvent formulations showed improved drug permeability coefficient. Also, the relative drug bioavailabilities with the cyclodextrin-based formulations and co-solvent were found to be similar [28]. Nos HCl bioavailability has also been enhanced by formulating hydroxypropyl methylcellulose–stabilized self-emulsifying solid dispersible carriers of Nos. In this study, stable self-microemulsifying dispersions (SMEDDs) at a SMEDD-to-water ratio of 1–3:7–9 parts by weight was developed by using oil/surfactant/co-surfactant mixture of Labrafil M1944, Tween-80, and Labrasol optimized at weight ratios of 62.8:9.30:27.90%. Pharmacokinetic study showed that Mann-Nos SESD was 40% more bioavailable as compared with Nos self-emulsifying solid dispersible microparticles (Nos SESDs) and was effective in sensitizing H1650 SP cells to cisplatin in vitro and in an orthotopic lung tumor model of H1650 SP origin. They also found that mannosylated noscapine self-emulsifying solid dispersions (Mann-Nos SESDs) are bioavailable and enhance the antineoplastic effect of cisplatin-based chemotherapy in cisplatin-resistant non-small-cell lung cancer (NSCLC) [10]. HME has also been reported in the literature for the enhancement of bioavailability of various drugs with solid dispersion technique and pH modifier approach [39]. Overall, in this study, we have enhanced the drug release of weakly basic drug noscapine HCl in basic pH environment and also achieved sustained drug release with enhanced bioavailability.

Conclusion

Nos HCl sustained release formulation was successfully optimized using HME and evaluated by XRD, FTIR, in vitro release study, and in vivo pharmacokinetic study. Bioavailability of Nos HCl was significantly enhanced, and pH-independent drug release was achieved by HME using Eudragit RLPO as a polymer and CA as a pH modifier.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Animal studies All institutional and national guidelines for the care and use of laboratory animals were followed. Animal protocol was approved by the Institutional Animal Care and Use Committee (IACUC) (protocol number: 020-04).

References

1. Ploen J, Andersch J, Heschel M, Leopold CS. Citric acid as a pH-modifying additive in an extended release pellet formulation containing a weakly basic drug. Drug Dev Ind Pharm. 2009;35(10):1210–8.
2. Siepe S, Lueckel B, Kramer A, Ries A, Gurny R. Strategies for the design of hydrophilic matrix tablets with controlled microenvironmental pH. Int J Pharm. 2006;316(1–2):14–20.
3. Dashevsky A, Kolter K, Bodmeier R. pH-independent release of a basic drug from pellets coated with the extended release polymer dispersion Kollicoat® SR 30 D and the enteric polymer dispersion Kollicoat® MAE 30 DP. Eur J Pharm Biopharm. 2004;58(1):45–9.
4. Takka S, Rajbhandari S, Sakr A. Effect of anionic polymers on the release of propranolol hydrochloride from matrix tablets. Eur J Pharm Biopharm. 2001;52(1):75–82.
5. Streubel A, Siepmann J, Dashevsky A, Bodmeier R. pH-independent release of a weakly basic drug from water-insoluble and-soluble matrix tablets. J Control Release. 2000;67(1):101–10.
6. Xu G, Sunada H. Influence of formulation change on drug release kinetics from hydroxypropylmethylcellulose matrix tablets. Chem Pharm Bull. 1995;43(3):483–7.
7. Thoma K, Ziegler I. The pH-independent release of fenoldopam from pellets with insoluble film coats. Eur J Pharm Biopharm. 1998;46(1):105–13.
8. Kranz H, Guthmann C, Wagner T, Lipp R, Reinhard J. Development of a single unit extended release formulation for ZK 811 752, a weakly basic drug. Eur J Pharm Sci. 2005;26(1):47–53.
9. Nie S, Pan W, Li X, Wu X. The effect of citric acid added to hydroxypropyl methylcellulose (HPMC) matrix tablets on the release profile of vinpocetine. Drug Dev Ind Pharm. 2004;30(6):627–35.
10. Andey T, Patel A, Marepally S, Chougule M, Spencer SD, Rishi AK, et al. Formulation, pharmacokinetic, and efficacy studies of mannosylated self-emulsifying solid dispersions of noscapine. PLoS One. 2016;11(1):e0146804.
11. Mahmoudian M, Rahimi-Moghaddam P. The anti-cancer activity of noscapine: a review. Recent Pat Anticancer Drug Discov. 2009;4(1):92–7.
12. Aneja R, Dhiman N, Idnani J, Awasthi A, Arora SK, Chandra R, et al. Preclinical pharmacokinetics and bioavailability of noscapine, a tubulin-binding anticancer agent. Cancer Chemother Pharmacol. 2007;60(6):831–9.
13. Landen JW, Lang R, McMahon S, Rusan NM, Yvon AM, Adams AW, et al. Noscapine alters microtubule dynamics in living cells and inhibits the progression of melanoma. Cancer Res. 2002;62(14):4109–14.
14. Chougule MB, Patel AR, Jackson T, Singh M. Antitumor activity of noscapine in combination with doxorubicin in triple negative breast cancer. PLoS One. 2011;6(3):e17733.
15. Chougule M, Patel AR, Sachdeva P, Jackson T, Singh M. Anticancer activity of noscapine, an opioid alkaloid in combination with cisplatin in human non-small cell lung cancer. Lung Cancer. 2011;71(3):271–82.
16. Jackson T, Chougule MB, Ichite N, Patlolla RR, Singh M. Antitumor activity of noscapine in human non-small cell lung cancer xenograft model. Cancer Chemother Pharmacol. 2008;63(1):117–26.
17. Chougule MB, Patel A, Sachdeva P, Jackson T, Singh M. Enhanced anticancer activity of gemcitabine in combination with noscapine via antiangiogenic and apoptotic pathway against non-small cell lung cancer. PLoS One. 2011;6(11):e27394.
18. Doddapaneni R, Patel K, Chowdhury N, Singh M. Noscapine chemosensitization enhances docetaxel anticancer activity and nanocarrier uptake in triple negative breast cancer. Exp Cell Res. 2016;346(1):65–73.
19. Doddapaneni R, Patel K, Chowdhury N, Singh M. Reversal of drug-resistance by noscapine chemo-sensitization in docetaxel resistant triple negative breast cancer. Sci Rep. 2017;7(1):15824.
20. Chougule MB, Patel AR, Patlolla R, Jackson T, Singh M. Epithelial transport of noscapine across cell monolayer and influence of absorption enhancers on in vitro permeation and bioavailability: implications for intestinal absorption. J Drug Target. 2014;22(6):498–508.
21. Andey T, Marepally S, Patel A, Jackson T,Sarkar S, O'Connell M, Reddy RC, Chellappan S, Singh P, Singha M Cationic lipid guided short-hairpin RNA interference of annexin A2 attenuates tumor growth and metastasis in a mouse lung cancer stem cell model. Journal of Controlled Release, 2014;184: 67–78.
22. Patel K, Chowdhury N, Doddapaneni R, Boakye CHA, Singh M Piperlongumine for enhancing oral bioavailability and cytotoxicity of docetaxel in triple-negative breast cancer. Journal of pharmaceutical sciences, 2015;104(12):4417–4426.
23. Patel AR, Chougule MB, Ian T, Patlolla R, Guangdi W, Singh M Efficacy of aerosolized celecoxib encapsulated nanostructured lipid carrier in non-small cell lung cancer in combination with docetaxel. Pharmaceutical research, 2013;30(5):1435–1446.
24. Andey T, Patel A, Jackson T, Safe S, Singh M 1,1-Bis (3′-indolyl)-1-(p-substitutedphenyl) methane compounds inhibit lung cancer cell and tumor growth in a metastasis model. European Journal of Pharmaceutical Sciences, 2013;50(2):227–241.
25. Andey T, Sudhakar G, Marepally S, Patel A, Banerjee R Lipid nanocarriers of a lipid-conjugated estrogenic derivative inhibit tumor growth and enhance cisplatin activity against triple-negative breast cancer: pharmacokinetic and efficacy evaluation. Molecular pharmaceutics, 2015. 12(4):1105–1120.
26. Doddapaneni R, Patel K, Owaid HI, Singh M Tumor neovasculature-targeted cationic PEGylated liposomes of gambogic acid for the treatment of triple-negative breast cancer. Drug Delivery, 2016. 23(4):1232–1241.

27. Haynes A, Shaik MS, Chatterjee A, Singh M Formulation and evaluation of aerosolized celecoxib for the treatment of lung cancer. Pharmaceutical Research, 2005. 22(3):427–439.
28. Sammeta SM, Wang L, Mutyam SK, O'Loughlin K, Green CE, Werner MH, et al. Formulation approaches to improving the delivery of an antiviral drug with activity against seasonal flu. Pharm Dev Technol. 2015;20(2):169–75.
29. Patil H, Tiwari RV, Upadhye SB, Vladyka RS, Repka MA. Formulation and development of pH-independent/dependent sustained release matrix tablets of ondansetron HCl by a continuous twin-screw melt granulation process. Int J Pharm. 2015;496(1):33–41.
30. Bagde A, et al. Formulation of topical ibuprofen solid lipid nanoparticle (SLN) gel using hot melt extrusion technique (HME) and determining its anti-inflammatory strength. Drug Deliv Transl Res. 2019:1–12.
31. Palekar S, Nukala PK, Mishra SM, Kipping T, Patel K. Application of 3D printing technology and quality by design approach for development of age-appropriate pediatric formulation of baclofen. Int J Pharm. 2019;556:106–116.
32. Mehta R, Chawla A, Sharma P, Pawar P. Formulation and in vitro evaluation of Eudragit S-100 coated naproxen matrix tablets for colon-targeted drug delivery system. J Adv Pharm Technol Res. 2013;4(1):31–41.
33. Konta AA, García-Piña M, Serrano DR. Personalised 3D printed medicines: which techniques and polymers are more successful? Bioengineering. 2017;4(4):79.
34. Thakral S, Thakral NK, Majumdar DK. Eudragit®: a technology evaluation. Expert Opin Drug Deliv. 2013;10(1):131–49.
35. Park J-B, Lee BJ, Kang CY, Tiwari RV, Repka MA. Process analytical quality control of tailored drug release formulation prepared via hot-melt extrusion technology. J Drug Deliv Sci Technol. 2017;38:51–8.
36. Agrawal AM, Dudhedia MS, Zimny E. Hot melt extrusion: development of an amorphous solid dispersion for an insoluble drug from mini-scale to clinical scale. AAPS PharmSciTech. 2016;17(1):133–47.
37. Schilling SU, Shah NH, Malick AW, Infeld MH, McGinity JW. Citric acid as a solid-state plasticizer for Eudragit RS PO. J Pharm Pharmacol. 2007;59(11):1493–500.
38. Chowdhury N, Vhora I, Patel K, Bagde A, Kutlehria S, Singh M. Development of hot melt extruded solid dispersion of tamoxifen citrate and resveratrol for synergistic effects on breast cancer cells. AAPS PharmSciTech. 2018;19(7):3287–97.
39. Patil H, Feng X, Ye X, Majumdar S, Repka MA. Continuous production of fenofibrate solid lipid nanoparticles by hot-melt extrusion technology: a systematic study based on a quality by design approach. AAPS J. 2015;17(1):194–205.
40. Nykänen P, Lempää S, Aaltonen ML, Jürjenson H, Veski P, Marvola M. Citric acid as excipient in multiple-unit enteric-coated tablets for targeting drugs on the colon. Int J Pharm. 2001;229(1–2):155–62.
41. Schilling SU, Bruce CD, Shah NH, Malick AW, McGinity JW. Citric acid monohydrate as a release-modifying agent in melt extruded matrix tablets. Int J Pharm. 2008;361(1–2):158–68.
42. Kate L, Gokarna V, Borhade V, Prabhu P, Deshpande V, Pathak S, et al. Bioavailability enhancement of atovaquone using hot melt extrusion technology. Eur J Pharm Sci. 2016;86:103–14.
43. Kuksal A, Tiwary AK, Jain NK, Jain S. Formulation and in vitro, in vivo evaluation of extended-release matrix tablet of zidovudine: influence of combination of hydrophilic and hydrophobic matrix formers. AAPS PharmSciTech. 2006;7(1):E1–9.