



Contents lists available at ScienceDirect

Chemical Engineering Research and Design

journal homepage: www.elsevier.com/locate/cherd

IChemE ADVANCING CHEMICAL ENGINEERING WORLDWIDE



Design and characterization of prednisolone-loaded nanoparticles fabricated by electrohydrodynamic atomization technique

Kampanart Huanbutta^{a,*}, Tanikan Sangnim^{b,c}, Sontaya Limmatvapirat^{b,c},
Jurairat Nunthanid^{b,c}, Pornsak Sriamornsak^{b,c}

^a Faculty of Pharmaceutical Sciences, Burapha University, Chonburi 20131, Thailand

^b Department of Pharmaceutical Technology, Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand

^c Pharmaceutical Biopolymer Group (PBiG), Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand

ARTICLE INFO

Article history:

Received 16 October 2015

Received in revised form 16

February 2016

Accepted 3 March 2016

Available online 9 March 2016

Keywords:

Electrohydrodynamic atomization

Nanoparticles

Prednisolone

ABSTRACT

Nanoparticles (NPs) have been used for colon-specific drug delivery system due to their specific accumulation in the inflamed tissue in the colon and prolong presence in colon for the treatment of inflammatory bowel disease. The present study aimed to design NPs for colon-specific drug delivery via electrohydrodynamic atomization (EHDA). The NPs were prepared by dissolving prednisolone and Eudragit® S100 (EDS) in different solvents using various EDS concentrations and prednisolone/EDS weight ratios. Then, the prepared solution was sprayed using the EHDA machine. The process parameters such as applied voltage, injected distance, feed rate, and drum collector rolling rate were carefully adjusted to obtain blank and drug-loaded NPs. The EDS solution prepared from methanol offered high conductivity (93.51 μS) with low viscosity (4.48 cP), resulting in spherical and small NPs with average diameter of 422 nm. The NPs prepared by using isopropanol and butanol as a solvent were irregular in shape. The sprayed products were changed from particle to fiber when using high concentration of EDS. High-fiber product was obtained when high applied voltage (20 kV) was applied. Size range of the NPs loaded with prednisolone at different concentrations (0.5–3.5%) was 448–660 nm. The maximum drug encapsulation was 91.50%. From the obtained results, the NPs were successfully fabricated by EHDA technique and this showed a promising potential for further drug delivery system development.

© 2016 The Institution of Chemical Engineers. Published by Elsevier B.V. All rights reserved.

1. Introduction

Electrohydrodynamic atomization (EHDA) has gained attention in the field of drug delivery in the past decade; it has been used to fabricate drug carriers including polymeric micro-particles, nanoparticles (NPs) and nanofibers used in various pharmaceutical applications (Kenawy et al., 2002; Shen et al., 2011). Theoretically, EHDA is a process where a liquid breaks

up into spray droplets under the drive of an electrical field. Various modes of EHDA were reported, of which the stable cone-jet is of specific interest (Xie et al., 2014). Under such mode, liquid flowing through a nozzle maintained at high potential is subjected to an electric field (Fig. 1), which leads to elongation of the meniscus to a form of jet and subsequently the jet deforms and breaks up into fine droplets. The small jet diameter allows rapid evaporation of the solvent and, as a

* Corresponding author. Tel.: +66 38102610; fax: +66 38102610.

E-mail address: kampanart@buu.ac.th (K. Huanbutta).

<http://dx.doi.org/10.1016/j.cherd.2016.03.004>

0263-8762/© 2016 The Institution of Chemical Engineers. Published by Elsevier B.V. All rights reserved.

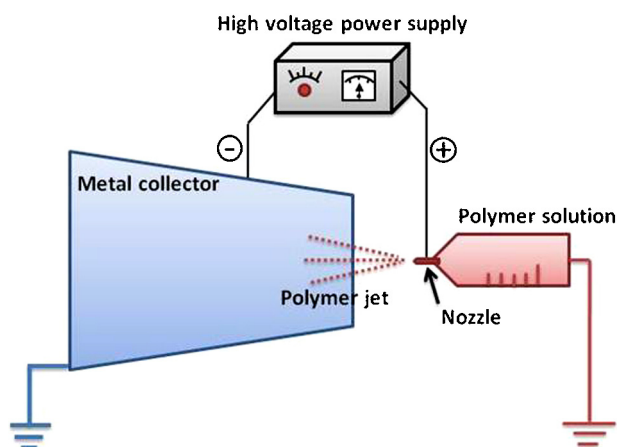


Fig. 1 – Schematic diagram showing nanoparticles fabrication by EHDA.

result, particles are deposited on the collector. Applied voltage, feed rate, distance from the nozzle to collector, drum collector rolling rate, charge and viscosity of sprayed solution are vital parameters to determine product characteristics (Xie et al., 2014). The principal advantages of this technique in drug delivery system are (i) to offer opportunity of heat sensitive drug loading, (ii) the relative rapid and simple way to prepare a several materials into NPs, and (iii) controllable operation factors.

Inflammatory bowel diseases (IBD) are relapsing and chronic inflammatory disorders of the intestinal mucosa, with an organ-susceptibility for the colon (Mowat et al., 2011). Conventional drug delivery systems are not completely successful when applied for the treatment of IBD (Friend, 2005). Aside from incidences where therapy fails due to insufficient drug deposition at the site of action, adverse drug effects have also limited therapeutic outcome. These adverse effects are thought to be related to the lack of selective drug release at the inflamed colon. Nanoparticulate systems for colonic drug delivery exhibit that size-dependency of particles impacts their epithelial uptake and a preferential accumulation in the inflamed colon has been found (Lamprecht, 2009). Lamprecht et al. (2001) demonstrated that high binding to the inflamed tissue of Lewis rat colon was found for 100-nm particles. This is because thicker mucus layer produced in the ulcerated regions increasing adherence of the small particles.

Prednisolone is a synthetic corticosteroid drug that is particularly effective as immunosuppressant and anti-inflammatory drug. It has been used to treat a number of different conditions such as IBD, inflammation (swelling), severe allergies, adrenal problems, arthritis and asthma (Gionchetti et al., 2002; Porter, 2011). For treatment of IBD, administration of prednisolone at a large and frequent dose for a long period causes significant and prolonged absorption of the drugs from the small intestine, often leading to toxic side effects (Campieri et al., 1997). Therefore, the specific delivery of drugs to diseased parts should be developed. Furthermore, prednisolone is a class II substance according to the Biopharmaceutics Classification System; it is a poorly water-soluble drug (Vogt et al., 2007). Consequently, the improvement of the dissolution rate of prednisolone by different techniques such as solid dispersion, nanoparticle preparation and liquisolid compacts can offer more rapid and complete absorption (Chen et al., 2015; Spireas and Sadu, 1998; Zakeri-Milani et al., 2011).

To extensively target drug to the colon, nanocarriers made of pH-dependent polymer have been applied. In the gastrointestinal tract, from the stomach to the colon, intraluminal pH varies progressively up to 7. In order to obtain pH-sensitive NPs, Eudragit® S, a polymer of methacrylic acid and methyl methacrylate, which dissolves when the pH is above 7, was used to control the release of entrapped drug (Damge et al., 2010; Makhlof et al., 2009). Therefore, the aim of this study was to design and optimize formulation and processing factors influencing the characteristics of NPs prepared by EHDA technique.

2. Materials and methods

2.1. Materials

Eudragit® S100 (EDS) (lot number B041005026) was a gift from Evonik Degussa (Thailand) Co., Ltd., Thailand. Methanol (lot number 14080041) was purchased from RCI Labscan Ltd., Thailand. Ethanol (lot number J32T04) was obtained from Mallinckrodt Baker, Malaysia. Butanol (lot number K35977190619) was purchased from Merck, Germany. Isopropanol (lot number V1A707131A) was received from Carlo Erba Reagents, France. Prednisolone (lot number R25301) was a gift from Bangkok Lab & Cosmetic Co., Ltd., Thailand. All other chemicals were of reagent grade and used without further purification.

2.2. Characterization of EDS solution

The prepared EDS solutions were characterized by several techniques to reveal the effect of the polymer solution properties on the NPs. The conductivity of each EDS solution was measured by conductivity meter (model ECtestr11+, Eutech Instruments Pte Ltd., Singapore). The viscosity was examined by viscometer (model DV-III Ultra, Brookfield, USA). The surface tension was measured by sessile drop method using a drop shape instrument (model FTA 1000, First Ten Angstroms, USA). All experiments were performed in triplicate.

2.3. Preparation of NPs

To prepare the blank NPs, various concentrations of EDS were dissolved in several solvents, including methanol, ethanol, isopropanol, butanol and mixtures of ethanol/water. The EDS solution was then sprayed using EHDA machine (Bangkok Cryptography, Thailand). For the drug-loaded NPs, prednisolone was dissolved in the EDS solution before spraying. The drug:EDS weight ratios were varied at 0.5:5, 1.5:5, 2.5:5 and 3.5:5. As presented in Table 1, the processing parameters such as applied voltage, injected distance, feed rate, and drum collector rolling rate were carefully adjusted to obtain blank

Table 1 – Conductivity, viscosity and interfacial tension of 5% (w/v) EDS in different solvents.

Solvent	Conductivity (μ S)	Viscosity (cP)	Interfacial tension (mN/m)
Methanol	93.51 $\pm$ 2.56	4.48 $\pm$ 1.10	22.82 $\pm$ 0.35
Ethanol	31.64 $\pm$ 0.74	5.76 $\pm$ 0.37	21.71 $\pm$ 0.19
2-Propanol	9.13 $\pm$ 0.09	10.88 $\pm$ 0.37	20.46 $\pm$ 0.25
t-Butanol	N/A ^a	N/A ^a	N/A ^a

^a EDS did not completely dissolve in t-butanol.

and drug-loaded NPs. The products were kept in desiccator for further investigation.

2.4. Morphology and particle size

Surface morphology of the prepared NPs was carried out using scanning electron microscope (SEM; model Maxim 2000S, CamScan Analytical, UK). Sample powders for SEM analyses were sprinkled on a stub and sputter-coated with gold to increase their conductance. Particle size and size distribution were analyzed by J MicroVision software (version 1.2.7).

2.5. Zeta potential determination

Zeta potential of the blank and drug-loaded NPs was monitored by zeta potential analyzer (model ZetaPlus, Brookhaven, USA) to evaluate the coating efficiency. The samples were diluted to 0.5% w/v using deionized water as a solvent and then agitated for 3 min before measuring. The average and standard deviation of the measurement of three batches of samples were reported.

2.6. Drug content and encapsulation efficiency

Drug content was determined by dispersing prednisolone-loaded NPs (2 mg) in methanol (10 mL), stirring for 24 h and then sonicating for 2 h before the dispersion was filtered through 0.45- μ m cellulose acetate membrane. The amount of prednisolone in the filtrate was quantified by high performance liquid chromatography (HPLC; model JASCO PU-2089plus quaternary gradient inert pump, and JASCO UV-2070plus multiwavelength UV-vis detector, Jasco, Japan) (Tobita et al., 2002). The analytical column used was a reverse phase Kinetex™ column (C18, 250 $\times$ 4.6 mm, pore size 5 μ m, Phenomenex, USA). The mobile phase was a mixture of methanol, tetrahydrofuran and water (at a ratio of 3:25:72). The column effluent was detected at 254 nm with a UV/vis detector. The calculation equation is as follows:

$$\text{drug content(\%)} = \frac{\text{amount of drug in nanoparticles}}{\text{weight of nanoparticles}} \times 100 \quad (1)$$

The encapsulation efficiency was defined as the ratio of actual and original amount of prednisolone encapsulated in NPs. The encapsulation efficiency was calculated using the following equation:

$$\text{encapsulation efficiency(\%)} = \frac{\text{actual amount of drug - loaded in nanoparticles}}{\text{initial amount of drug - loaded in nanoparticles}} \times 100 \quad (2)$$

2.7. Fourier transform infrared (FTIR) spectroscopy

To investigate the effect of the EHDA processing parameters on the drug-polymer interaction, prednisolone, EDS, their physical mixtures and prednisolone-loaded NPs were pulverized and blended with KBr and compressed. The measurement was carried out using a FTIR spectrophotometer (model Magna-IR system 750, Nicolet Biomedical Inc., USA).

2.8. Powder X-ray diffraction

Powder X-ray diffraction patterns of the stating materials, their physical mixtures and the NPs were analyzed by using a powder X-ray diffractometer (model D8, Bruker, Germany) under the following conditions: graphite monochromatized Cu K α radiation, voltage 45 kV, electric current 40 mA, slit: DS1°, SS1°, RS, 0.15 nm, and scanning ratio $2\theta = 5^\circ \text{ min}^{-1}$.

2.9. Differential scanning calorimetry (DSC)

DSC thermograms of the stating materials, their physical mixtures and the NPs were determined by a differential scanning calorimeter (model Sapphire, Perkin Elmer, USA) using indium as a standard. Each sample, 2–3 mg, was accurately weighed into a close aluminum solid pan. The scanning rate was run at 10 °C/min from 20 to 300 °C under nitrogen purge.

2.10. Statistical analysis

Analysis of variance (ANOVA) and Levene's test for homogeneity of variance were performed using SPSS version 11.5 for Windows (SPSS Inc., USA). Post hoc testing ($p < 0.05$) of the multiple comparisons was performed by either the Scheffé or Games-Howell test depending on whether Levene's test was insignificant or significant, respectively.

3. Result and discussion

3.1. Characterization of EDS solution

The conductivity, viscosity and interfacial tension of 5% w/v EDS in methanol, ethanol, 2-propanol or t-butanol are given in Table 2. EDS did not completely dissolve in t-butanol; therefore, characterization of the solution of EDS in t-butanol could not be conducted. In methanol, the viscosity of 5% (w/v) EDS was the lowest (4.48 cP) while the conductivity and interfacial tension were the highest, which were 93.51 μ S and 22.82 mN/m, respectively. This might be because methanol contains higher amount of hydroxyl group, at the same weight, compared to other alcohols. Therefore, high hydroxyl groups can increase conductivity of the solution (Sonkar et al., 2012). Furthermore, earlier studies have shown that viscosity affects conductivity; a decrease in viscosity results in the increase in the movement of the ions, so the conductance of the electrolyte increases from 2-propanol to methanol (Asif, 2009).

The interfacial tension is one of the crucial parameter to determine properties of the sprayed products (Ciach et al., 2003). High surface tension value of the solution can decrease size of the particles. The interfacial tension values all of the EDS solutions were slightly different ranging from 20.46 to 22.82 mN/m. EDS solution prepared from methanol gave the highest interfacial tension. This result is in agreement with the previous study (Ghahremani et al., 2012), which explained that the surface tension decreases with the length of the hydrocarbon tail.

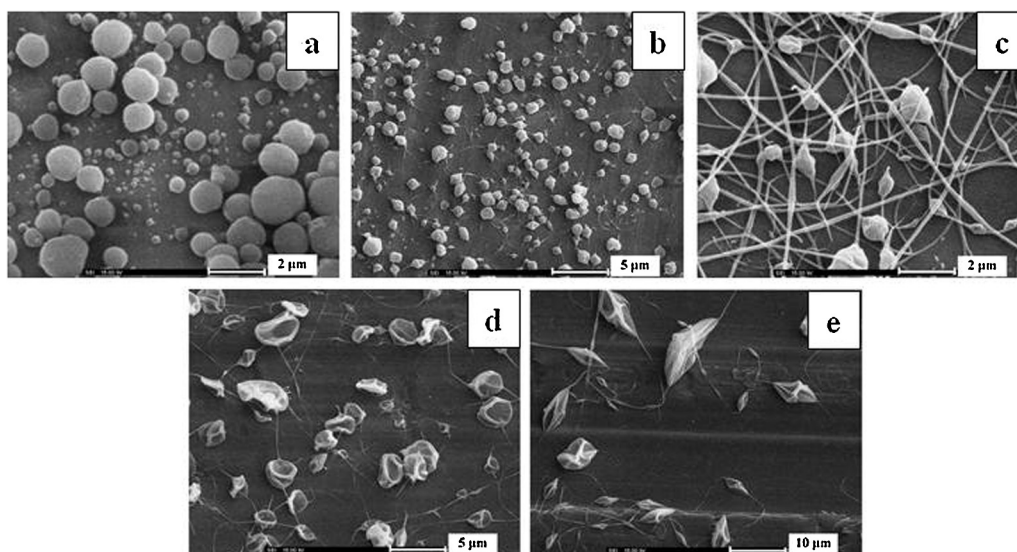
The conductivity of drug-loaded EDS solution slightly decreased when the drug loading was higher (Table 3). This is because prednisolone is nonpolar drug which can lowering conductivity of the solution (Rub et al., 2014). For Interfacial tension value, there were not different amount several drug concentrations.

Table 2 – Conductivity, viscosity and interfacial tension values of prednisolone-loaded EDS solution using methanol as dissolving solvent.

The EDS solution loaded with different prednisolone concentrations	Conductivity (μS)	Viscosity (cP)	Interfacial tension (mN/m)
0.5% prednisolone	97.03 ± 1.26	2.99 ± 0.37	21.60 ± 0.87
1.5% prednisolone	94.70 ± 2.86	4.05 ± 0.32	22.20 ± 0.17
2.5% prednisolone	92.41 ± 0.54	4.27 ± 0.37	22.28 ± 0.30
3.5% prednisolone	92.02 ± 0.54	4.91 ± 0.36	21.48 ± 0.23

Table 3 – Particle size and zeta-potential value of NPs containing different concentrations of prednisolone.

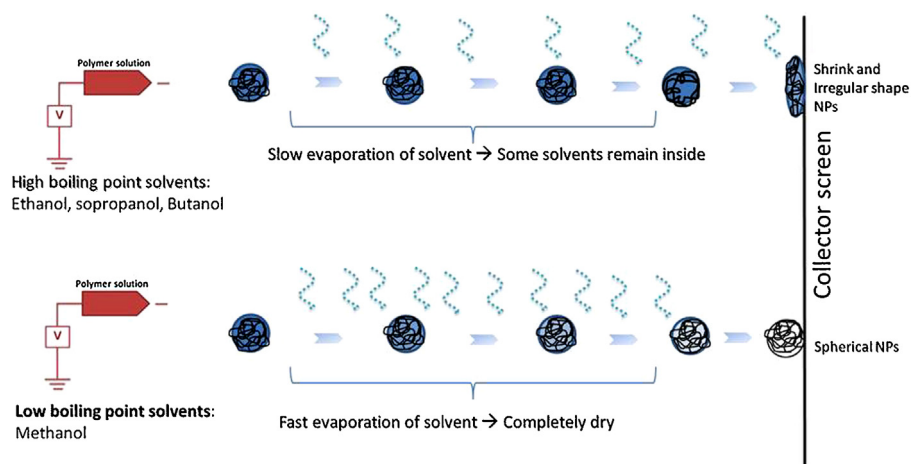
	Concentration of prednisolone in NPs			
	0.5% (w/v)	1.5% (w/v)	2.5% (w/v)	3.5% (w/v)
Particle size (nm)	448.6 ± 65.2	492.4 ± 69.9	661.0 ± 65.7	471.1 ± 59.3
Zeta-potential (mV)	-16.08 ± 0.24	-33.20 ± 0.46	-25.71 ± 0.78	-23.64 ± 0.76

**Fig. 2 – SEM images of the NPs prepared from EDS (5%, w/v) dissolved with different media; (a) methanol (5000 $\times$), (b) ethanol (2000 $\times$), (c) ethanol/water (70:30) (5000 $\times$), (d) 2-propanol (2000 $\times$) and (e) t-butanol (1000 $\times$).**

3.2. Morphology and particle size

The characterized blank and drug dissolved solutions were sprayed by EHDA to reveal the effect of the solution properties on appearance of the sprayed products. As shown in Fig. 2, the NPs prepared from EDS (5%, w/v in methanol) offered

spherical particles with diameter of 447.9 nm. The NPs prepared from EDS in ethanol and the mixture between ethanol and water (70:30) were spherical and fibrous as illustrated in Fig. 2b and c, respectively. The electrospayed products of EDS in isopropanol and t-butanol were collapsed particles (Fig. 2d and e). The proposed fabrication mechanism of the NPs by

**Fig. 3 – Proposed fabrication mechanism of the NPs by EHDA.**

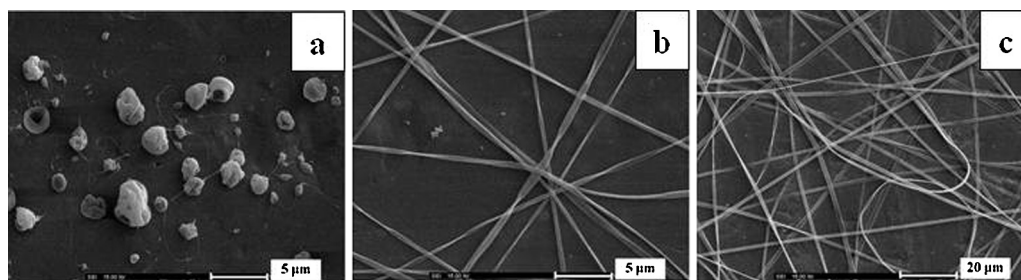


Fig. 4 – SEM images of the products prepared from (a) 5% (w/v) (2000×), (b) 7.5% (w/v) (2000×) and (c) 10% (w/v) (500×) EDS dissolved in ethanol under applied voltages of 10 kV.

EHDA is presented in Fig. 3. The boiling point of solvents may influence the evaporation of solvents. The boiling point of isopropanol and butanol are higher than those of methanol and ethanol; therefore, solvent evaporation may not complete during spraying. After that, the wet droplets hit the collector causing irregular and collapsed particles (United States Pharmacopeial, 2006). This phenomenon can be explained by Rayleigh's equation as shown in Eqs. (3) and (4).

$$X = \frac{CE}{2SE} = q^2(64\pi^2\varepsilon\gamma R^3) \quad (3)$$

where X is Rayleigh limit, CE is Coulomb energy, SE is surface free energy, q is the surface charge of the droplet, ε is the permittivity of the medium surrounding the droplet, γ is the surface tension of the liquid, and R is the radius of a droplet (Rayleigh, 1882; Taflin et al., 1989).

$$d_d = \alpha \left(\frac{Q^3 \varepsilon \rho}{\pi^4 \sigma \gamma} \right)^{\frac{1}{6}} \quad (4)$$

where d_d is droplet size of neat liquids, α is a constant depending on liquid permittivity, Q is the liquid flow rate, ε is the dielectric constant in a vacuum, ρ is the density of the liquid, γ is the surface tension of the liquid, and σ is the conductivity of the liquid (Gañán-Calvo, 1999).

From the characterization of the EDS solution results shown in Table 1, the EDS dissolved in methanol provided higher conductivity and surface tension with low viscosity, resulting in a high Rayleigh limit and low droplet size of neat liquids. Consequently, there is high possibility that the droplet breakup occurred, causing small spherical particles without fiber (Festag et al., 1997). On the other hand, EDS dissolved in ethanol and 2-propanol offered lower conductivity and

surface tension with high viscosity. These make high Rayleigh limit value, causing connected spraying liquid and connected fiber products.

The electrospayed products were changed from spherical particles to fibers when the spraying solution prepared from high concentration of EDS (Fig. 4). As explained in Eq. (3), a higher viscosity and lower surface tension of 10% (w/v) EDS (data not shown) resulted in the formation of smooth filaments or fiber. Figs. 4a and 5a and b illustrated the electrospayed products fabricated by 10, 15 and 20 kV of applied voltages, respectively. More fibrous products were obtained and the product size is smaller when applying higher voltages (15 kV and 20 kV). This is in agreement with previous research that the size of particle slightly decreases when voltage is increased (Bock et al., 2012; Hong et al., 2008). Moreover, Shenoy et al. (Gupta et al., 2005; Huang et al., 2003) stated that, since the voltage is increased, morphology changes from spherical particle to elongated particles or bended fiber to eventually only fiber. This might be due to the fact that high voltage accelerates the sprayed drop to elongate, resulting in connected fiber (Thammachat et al., 2010).

Particle morphology of prednisolone and the NPs loaded with different concentrations of prednisolone is demonstrated in Fig. 6. It is observed that sprayed prednisolone without EDS was irregular in shape with the size ranged from 5 to 10 μm (Fig. 6a). All of the NPs (Fig. 6b–e) were spherical in shape with average size ranged from 448.60 to 660.98 nm (see Table 3). The particle size was not significantly different among the NPS containing different drug concentrations. This result could be explained by the conductivity, viscosity and interfacial tension of EDS solutions loaded with different prednisolone concentrations (Table 2), which were slightly different, resulting in a slight difference in size and shape (Gañán-Calvo, 1999).

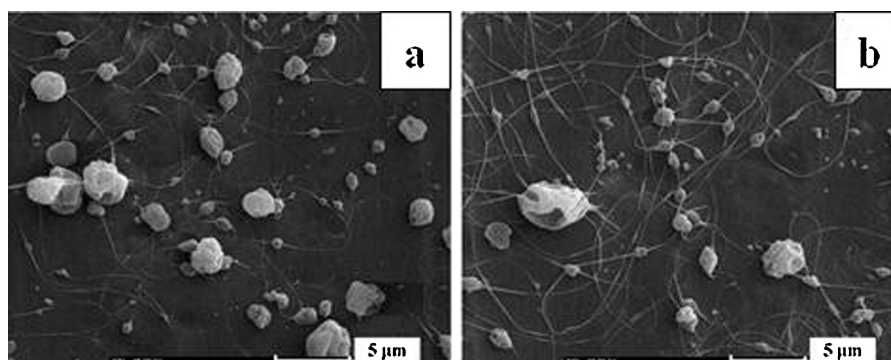


Fig. 5 – SEM images of the products prepared from 5% (w/v) EDS dissolved in ethanol under applied voltages of (a) 15 kV and (b) 20 kV.

Table 4 – Drug loading and encapsulation efficiency of NPs containing different concentrations of prednisolone.

The NPs loaded with different prednisolone concentrations	Drug loading (%)	Encapsulation efficiency (%)
0.5%	6.58 ± 0.06	72.35 ± 0.63
1.5%	17.27 ± 0.28	74.84 ± 1.23
2.5%	30.86 ± 0.54	92.65 ± 1.61
3.5%	37.68 ± 0.85	91.50 ± 2.07

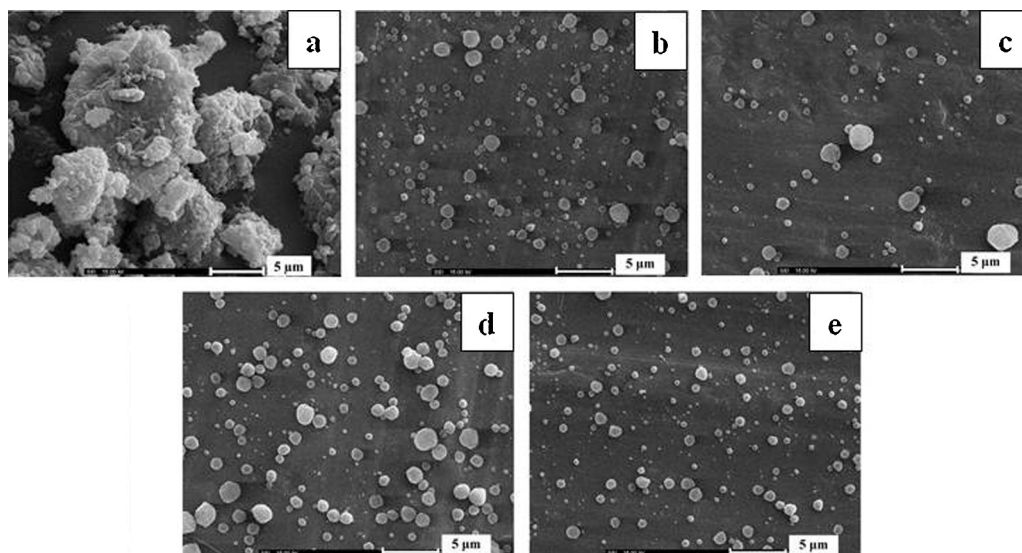


Fig. 6 – SEM images at magnification of 2000× of the (a) sprayed prednisolone, and prednisolone-loaded NPs containing (a) 0.5% (w/v), (b) 1.5% (w/v), (c) 2.5% (w/v) and (d) 3.5% (w/v) prednisolone, using 5% (w/v) EDS in methanol under applied voltage of 10 kV.

Furthermore, the irregular shaped particles were not found for all prednisolone-loaded NPs. This could confirm that all prednisolone was loaded in the NPs (Huanbutta et al., 2013).

3.3. Zeta-potential determination

Table 3 shows the particle size and zeta-potential value of NPs containing different concentrations of prednisolone. Particle size of the NPs ranged from 448.6 to 671.1 nm. The zeta potential value of all NPs was negative, resulting from the negative charge of carboxylic moiety in the EDS structure (Huanbutta et al., 2013). The results indicated the encapsulation of prednisolone in EDS.

3.4. Drug loading and encapsulation efficiency

Drug loading and encapsulation efficiency of NPs containing different concentrations of prednisolone are shown in Table 4. The percentage of drug loading ranged from 6.58% to 37.68% and the encapsulation efficiency ranged from 72.35% to 92.65%. The encapsulation efficiency of the NPs depended on concentration of prednisolone in the NPs. High portion of prednisolone (2.5% and 3.5% prednisolone in 5% w/v EDS) provided high drug loading and encapsulation efficiency. Such an effect on encapsulation of drug is quite commonly reported (Wischke and Schwendeman, 2008). The increase in encapsulated drug might rise the viscosity of the EDS solution. This makes the EHDA product larger resulting in higher drug encapsulation.

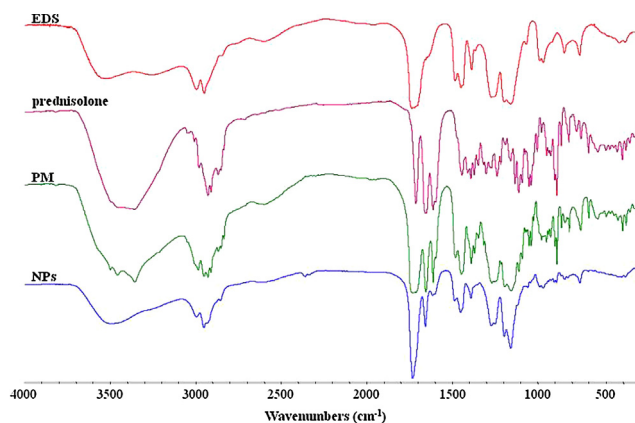


Fig. 7 – FTIR spectra of prednisolone, EDS, physical mixture of prednisolone and EDS (PM) and prednisolone-loaded NPs.

3.5. Fourier transform infrared (FTIR) spectroscopy

FTIR spectra of the starting materials (EDS and prednisolone), their physical mixture and the NPs loaded with 2.5% prednisolone are illustrated in Fig. 7. The spectrum of prednisolone showed the characteristic stretching vibration of C=O at 1700 cm⁻¹ and C=C from cyclohexadiene at 1660 cm⁻¹. The FTIR spectrum of EDS exhibited peaks at 1731 and 1159 cm⁻¹ due to C=O stretching of carboxylic acid and C–O stretching of ester, respectively. The spectra of physical mixture of EDS and prednisolone showed peaks at similar wave number as the starting materials. However, strong peak of prednisolone at 1700 cm⁻¹ was covered by broad peak of

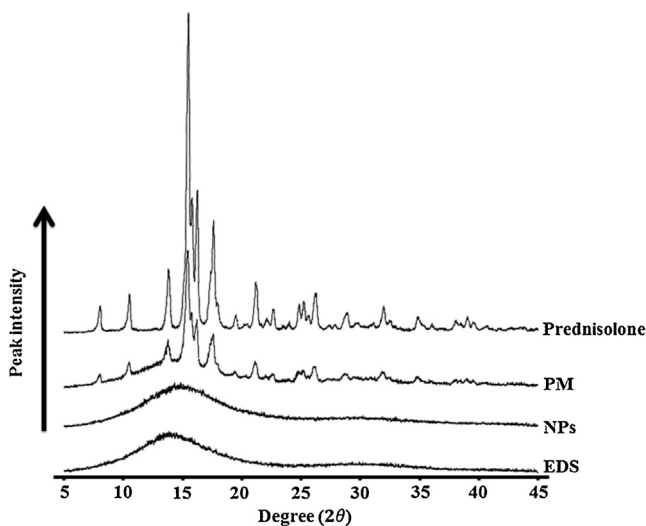


Fig. 8 – Powder X-ray diffractograms of prednisolone, EDS, physical mixture of prednisolone and EDS (PM) and prednisolone-loaded NPs. The PM was prepared at the same drug:polymer ratio as NPs.

EDS. The IR absorption of NPs showed the same pattern as prednisolone and EDS but peaks at 1605 and 891 cm^{-1} were weaker, which could be attributed to the encapsulation a drug molecule inside the polymer and led to the low IR absorption of prednisolone (Li et al., 2009).

3.6. Powder X-ray diffraction

Fig. 8 illustrated the powder X-ray diffractograms of the starting materials (EDS100 and prednisolone), their physical mixture and the NPs loaded with 2.5% prednisolone. The powder X-ray diffraction pattern of EDS exhibited typical halo patterns of amorphous structure while prednisolone revealed sharp crystalline peaks (Auda et al., 2010; Sahin and Arslan, 2007). The NPs demonstrated broad peaks at 14.82° due to the EDS while PM expressed sharp peaks at 7.72° , 10.36° , 13.74° , 15.22° , 17.74° and 21.00° , which appeared at the same positions as prednisolone. This indicated that prednisolone dispersed molecularly in EDS.

3.7. Differential scanning calorimetry (DSC)

The DSC thermograms of prednisolone, EDS, their physical mixture and the NPs loaded with 2.5% prednisolone are shown in Fig. 9. The thermogram of EDS showed a broad endothermic peak representing amorphous state of the polymer (Auda et al., 2010). The DSC thermogram of prednisolone expressed an endothermic characteristic peak at 240°C assigned to its melting point (Sahin and Arslan, 2007). The DSC thermogram of physical mixture of prednisolone:EDS (1:2) showed that the endothermic peak of the drug existed at lower temperature compared to prednisolone alone and lost its sharpened appearance. This observation suggested the presence of an interaction between prednisolone and the polymer at high temperature. For the NPs, no melting peak of prednisolone was found. It is indicated that prednisolone has been highly dispersed in the NPs by EHDA fabrication technique (Maghsoodi, 2009).

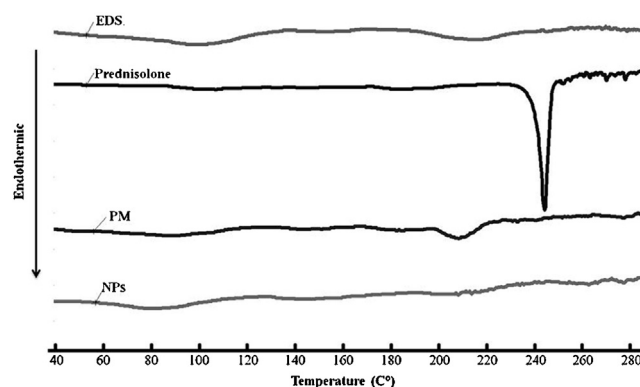


Fig. 9 – DSC thermograms of prednisolone, EDS, physical mixture of prednisolone and EDS (PM) and prednisolone-loaded NPs. The PM was prepared at the same drug:polymer ratio as NPs.

4. Conclusion

EHDA technology can be applied for the fabrication of EDS-based NPs containing prednisolone. Properties of the sprayed solution are crucial factors to determine characteristic of the EHDA products. The spherical NPs were obtained from 5% (w/v) EDS dissolved in methanol under conditions of 10 kV applied voltage. Moreover, prednisolone can be loaded in the NPs with high encapsulation efficiency. This nanoparticulate system expresses possibility to fabricate colon-specific drug delivery system.

Acknowledgements

The authors acknowledge the Thailand Research Fund (MRG56800086) and Faculty of Pharmaceutical Sciences, Burapha University for financial support. We also thank Degussa Thailand Co. Ltd. for supplying Eudragit® S100.

References

- Asif, M., 2009. Relationship between viscosity and conductivity for tokamak plasmas. *Braz. J. Phys.* 39, 60–61.
- Auda, S.H., Ahmed, M.M., El-Rasoul, S.A., Saleh, K.I., 2010. Formulation and physicochemical characterization of piroxicam containing polymer films. *Bull. Pharm. Sci.* 33, 33–42.
- Bock, N., Dargaville, T.R., Woodruff, M.A., 2012. Electrospraying of polymers with therapeutic molecules: state of the art. *Prog. Polym. Sci.* 37, 1510–1551.
- Campieri, M., Ferguson, A., Doe, W., Persson, T., Nilsson, L.G., 1997. Oral budesonide is as effective as oral prednisolone in active Crohn's disease. *The Global Budesonide Study Group. Gut* 41, 209–214.
- Chen, X.-Y., Shang, Y.-L., Li, Y.-H., Wang, J.-X., Maimouna, A.G., Li, Y.-X., Zou, D., Foster, N.R., Yun, J., Pu, Y., 2015. Green preparation of uniform prednisolone nanoparticles using subcritical water. *Chem. Eng. J.* 263, 20–26.
- Ciach, T., Diaz, L., van den Ijssel, E., Marijnissen, J.M., 2003. Application of electro hydrodynamic atomisation in the production of engineered drug particles. In: Gradoñ, L., Marijnissen, J. (Eds.), *Optimization of Aerosol Drug Delivery*. Springer, Netherlands, pp. 189–204.
- Damge, C., Socha, M., Ubrich, N., Maincent, P., 2010. Poly(epsilon-caprolactone)/eudragit nanoparticles for oral delivery of aspart-insulin in the treatment of diabetes. *J. Pharm. Sci.* 99, 879–889.

- Festag, R., Alexandratos, S.D., Cook, K.D., Joy, D.C., Annis, B., Wunderlich, B., 1997. Single- and few-chain polystyrene particles by electrospray. *Macromolecules* 30, 6238–6242.
- Friend, D.R., 2005. New oral delivery systems for treatment of inflammatory bowel disease. *Adv. Drug Deliv. Rev.* 57, 247–265.
- Gañán-Calvo, A.M., 1999. The surface charge in electrospraying: its nature and its universal scaling laws. *J. Aerosol Sci.* 30, 863–872.
- Ghahremani, H., Moradi, A., Abedini-Torghabeh, J., Hassani, S.M., 2012. Measuring surface tension of binary mixtures of water + alcohols from the diffraction pattern of surface ripples. *Der Chem. Sin.* 2, 212–221.
- Gionchetti, P., Amadini, C., Rizzello, F., Venturi, A., Campieri, M., 2002. Review article: treatment of mild to moderate ulcerative colitis and pouchitis. *Aliment. Pharm. Ther.* 4, 13–19.
- Gupta, P., Elkins, C., Long, T.E., Wilkes, G.L., 2005. Electrospinning of linear homopolymers of poly(methyl methacrylate): exploring relationships between fiber formation, viscosity, molecular weight and concentration in a good solvent. *Polymer* 46, 4799–4810.
- Hong, Y., Li, Y., Yin, Y., Li, D., Zou, G., 2008. Electrohydrodynamic atomization of quasi-monodisperse drug-loaded spherical/wrinkled microparticles. *J. Aerosol Sci.* 39, 525–536.
- Huanbutta, K., Sriamornsak, P., Luangtana-anan, M., Limmatvapirat, S., Puttipatkhachorn, S., Lim, L.-Y., Terada, K., Nunthanid, J., 2013. Application of multiple stepwise spinning disk processing for the synthesis of poly(methyl acrylates) coated chitosan–diclofenac sodium nanoparticles for colonic drug delivery. *Eur. J. Pharm. Sci.* 50, 303–311.
- Huang, Z.-M., Zhang, Y.Z., Kotaki, M., Ramakrishna, S., 2003. A review on polymer nanofibers by electrospinning and their applications in nanocomposites. *Compos. Sci. Technol.* 63, 2223–2253.
- Kenawy, E.-R., Bowlin, G.L., Mansfield, K., Layman, J., Simpson, D.G., Sanders, E.H., Wnek, G.E., 2002. Release of tetracycline hydrochloride from electrospun poly(ethylene-co-vinylacetate), poly(lactic acid), and a blend. *J. Control. Release* 81, 57–64.
- Lamprecht, A., 2009. Drug delivery concepts in nanoscience. In: Lamprecht, A. (Ed.), *Nanocarriers in the Therapy of Inflammatory Disease*. Pan Stanford Publish Pte. Ltd., Singapore, pp. 261–276.
- Lamprecht, A., Schafer, U., Lehr, C.M., 2001. Size-dependent bioadhesion of micro- and nanoparticulate carriers to the inflamed colonic mucosa. *Pharm. Res.* 18, 788–793.
- Li, F., Jin, L., Han, J., Wei, M., Li, C., 2009. Synthesis and controlled release properties of prednisone intercalated Mg–Al layered double hydroxide composite. *Ind. Eng. Chem. Res.* 48, 5590–5597.
- Maghsoodi, M., 2009. Physicomechanical properties of naproxen-loaded microparticles prepared from Eudragit L100. *AAPS PharmSciTech* 10, 120–128.
- Makhlof, A., Tozuka, Y., Takeuchi, H., 2009. pH-Sensitive nanospheres for colon-specific drug delivery in experimentally induced colitis rat model. *Eur. J. Pharm. Biopharm.* 72, 1–8.
- Mowat, C., Cole, A., Windsor, A., Ahmad, T., Arnott, I., Driscoll, R., Mitton, S., Orchard, T., Rutter, M., Younge, L., Lees, C., Ho, G.T., Satsangi, J., Bloom, S., 2011. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 60, 571–607.
- Porter, R.S., 2011. *The Merck Manual of Diagnosis and Therapy*. Wiley.
- Rayleigh, L., 1882. On the equilibrium of liquid conducting masses charged with electricity. *Philos. Mag. Ser. 5* (14), 184–186.
- Rub, M.A., Asiri, A.M., Khan, J.M., Khan, F., Khan, R.H., Kabir ud, D., 2014. A study of interaction between antidepressant drug nortriptyline hydrochloride with gelatin. *J. Taiwan Inst. Chem.* 45, 2068–2074.
- Sahin, N.O., Arslan, H., 2007. Inclusion complex of prednisolone with skimmed milk. Part I: Physicochemical characterization. *Yakugaku Zasshai* 127, 1255–1261.
- Shen, X., Yu, D., Zhu, L., Branford-White, C., White, K., Chatterton, N.P., 2011. Electrospun diclofenac sodium loaded Eudragit L 100-55 nanofibers for colon-targeted drug delivery. *Int. J. Pharm.* 408, 200–207.
- Sonkar, P.A., Suryavanshi, P.S., Sutar, S.H., Shukla, S.T., 2012. Effect of solvent properties on equivalent conductivity of electrolytes. *J. Chem. Pharm. Res.* 4, 1978–1982.
- Spireas, S., Sadu, S., 1998. Enhancement of prednisolone dissolution properties using liquid compact. *Int. J. Pharm.* 166, 177–188.
- Taflin, D.C., Ward, T.L., Davis, E.J., 1989. Electrified droplet fission and the Rayleigh limit. *Langmuir* 5, 376–384.
- Thammachai, T., Sriamornsak, P., Luangtana-Anan, M., Nunthanid, J., Limmatvapirat, C., Limmatvapirat, S., 2010. Preparation and characterization of shellac fiber as a novel material for controlled drug release. *Adv. Mater. Res.* 152–153, 1232–1235.
- Tobita, T., Senarita, M., Hara, A., Kusakari, J., 2002. Determination of prednisolone in the cochlear tissue. *Hear. Res.* 165, 30–34.
- United States Pharmacopeial Convention, 2006. *USP 30. United States Pharmacopeial Convention*.
- Vogt, M., Derendorf, H., Krämer, J., Junginger, H.E., Midha, K.K., Shah, V.P., Stavchansky, S., Dressman, J.B., Barends, D.M., 2007. Biowaiver monographs for immediate release solid oral dosage forms: prednisolone. *J. Pharm. Sci.* 96, 27–37.
- Wischke, C., Schwendeman, S.P., 2008. Principles of encapsulating hydrophobic drugs in PLA/PLGA microparticles. *Int. J. Pharm.* 364, 298–327.
- Xie, J., Jiang, J., Davoodi, P., Srinivasan, M.P., Wang, C.-H., 2014. Electrohydrodynamic atomization: a two-decade effort to produce and process micro-/nanoparticulate materials. *Chem. Eng. Sci.* 125, 32–57.
- Zakeri-Milani, P., Hallaj Nezhadi, S., Barzegar-Jalali, M., Mohammadi, L., Nokhodchi, A., Valizadeh, H., 2011. Studies on dissolution enhancement of prednisolone, a poorly water-soluble drug by solid dispersion technique. *Adv. Pharm. Bull.* 1, 48–53.