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Wittava Nakachon

Garnpiniol C.

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Wittaya Nakachon[1] and Garnpimol C. Ritthidej[1]

[1] *Department of Pharmaceutics and Industrial Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10330, Thailand.*

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INTRODUCTION

Intranasal administration has extensively gained interest in recent years for delivery of therapeutically active drugs not only small molecules but also peptides and proteins[1, 2]. It can be used in delivery therapeutic drugs for treatment local, systemic and central nervous disorders as well as for vaccination[3]. Intranasal delivery also has several advantages such as non-invasive route, self and easy administration, rapid onset of action, lack first pass hepatic metabolism, rich vascular submucosa and lymphatic system, bypass of the blood brain barrier, and probable direct pathways to the brain[1, 4, 5]. However, one of the principal drawbacks of nasal delivery system is rapidly cleared from the nose by mucociliary clearance, a defend mechanism of upper respiratory tract to prevent the body against any noxious inhaled substances[6]. Powder formulations can solve such disadvantage and improve bioavailability of drug, based on deceleration of mucociliary clearance rate[7]. Moreover, dry powder formulations can offer essential advantages over liquid formulations in terms of enabling higher drug payload and increasing drug product stability[8].

The aim of the present study was to develop dry powder formulation by using liquid-free film casting technique followed by jet milling process for intranasal drug delivery. Additionally, physicochemical evaluations including mucoadhesive property were determined.

MATERIALS AND METHODS

Materials Polyvinyl caprolactam - polyvinyl acetate - polyethylene glycol graft copolymer (Soluplus®) was a generous gift form BASF chemical company (Ludwigshafen, Germany). Eudragit® E PO was purchased from Evonik industries (Darmstadt, Germany). Chitosan (low molecular weight, 75-85% deacetylation) and Poly(ethylene glycol) (PEG: molecular weight 3350) were procured from Sigma-Aldrich, Co. (St. Louis, MO, USA).

Methods

Powdered-film preparation Soluplus®, PEG, low molecular weight chitosan, and Eudragit® E PO were mixed with appropriated ratio into 6 formulations. The ratios of mixtures of Soluplus® to chitosan or Eudragit® E PO were ranged from 0.5 – 1.0, and amount of PEG was 20-80% of the aforementioned polymer mixtures. The powder blends were cast on the Teflon sheets mounted on a leveled glass plate and stored in hot air oven at 65 °C for 3-4 hr.

Nasal powder preparation The obtained polymeric films were coarsely ground by granulator with 30-mesh sieve (Erweka FGS, Germany) and then pulverized by a jet mill machine (Current Jet; model CJ-10, Nisshin Engineering Co., Ltd., Japan). The collected powders were kept in a dessicator at room temperature until further used.

Particle morphology, size and size distribution evaluation Particle morphology was characterized by using a scanning electron microscope (SEM; JEOL, JSM-6400 Scanning Microscope, Tokyo, Japan) and particle size and size distribution of powder formulations were determined by a Mastersizer 2000 (Malvern Instrument, Herrenberg, Germany) equipped with Scirocco 2000 dispersion unit.

Physicochemical characterizations Differential scanning calorimeter (DSC: model DSC822e, Mettler Toledo, Switzerland) and attenuated total reflectance Fourier transform infrared spectroscopy (ATR-FTIR; Spectrum One FT-IR Spectrometer, PerkinElmer, USA) were performed.

In vitro evaluation of mucoadhesive property This method was adapted from Harikarnpakdee et al. (2006). The intestine obtained from a local authorized slaughterhouse was kept in ice pack and used within 1 hour from killing. A 5-centimeter long intestine was cut, then incised along, and cleaned by washing with 0.9% normal saline. After that, the tissue was placed on glass Petri dish installed in the funnel with an angle of 40° relative to the horizontal plane. An accurate weight of powder formulations incorporated Brilliant Blue as indicator was applied on mucosal surface. A pH 6.0 simulated nasal fluid (SNF) was warmed at 32±1°C and peristaltically pumped at a rate of 5 ml/min over the mucosa tissue. The washed was collected at 10, 20, 30, 60, 90, and 120 minutes and analyzed by UV spectrophotometer (model UV-1800, Shimaszu, Japan).

RESULTS

Dry powder formulations were prepared by 3-step methods consisting of film casting, coarsed grinding, and pulverizing. All obtained powder formulations were characterized their morphology under SEM. The results demonstrated that all formulations had irregular shape with round edge. Their average sizes (d(0.5)) were between 6 and 10 micron with narrow span values of 1.3 – 2.2.

DSC and ATR-FTIR were performed to elucidate physicochemical interaction among excipients used and influence of production processes. According to DSC thermograms, formulation no. 2 both film and powder exhibited two enderthermic peaks. The first sharp peak and the second broad peak appeared at around 58°C and 320°C which may be the melting point peak of PEG and the degradation of polymers, respectively, as shown in Figure 1. Moreover, other formulations also showed similar results. The FI-IR spectra of physical mix, film cast, and powder of formulation no. 2 (Figure 2) demonstrated the dominant peak of Soluplus® and PEG such as the C=O-stretching around 1732-1733 and 1632-1633 cm^{-1} of Soluplus® as well as the CH-stretching around 2883-2886 and 2861 cm^{-1} of PEG. In addition, the intensity of the peak appearing around 1731-1733 cm^{-1} in formulation no. 6 was higher than that around 1632-1634 cm^{-1} (data not shown), while other formulations had opposite result. This effect may be the influence of amount of Eudragit® E PO in the formulation.

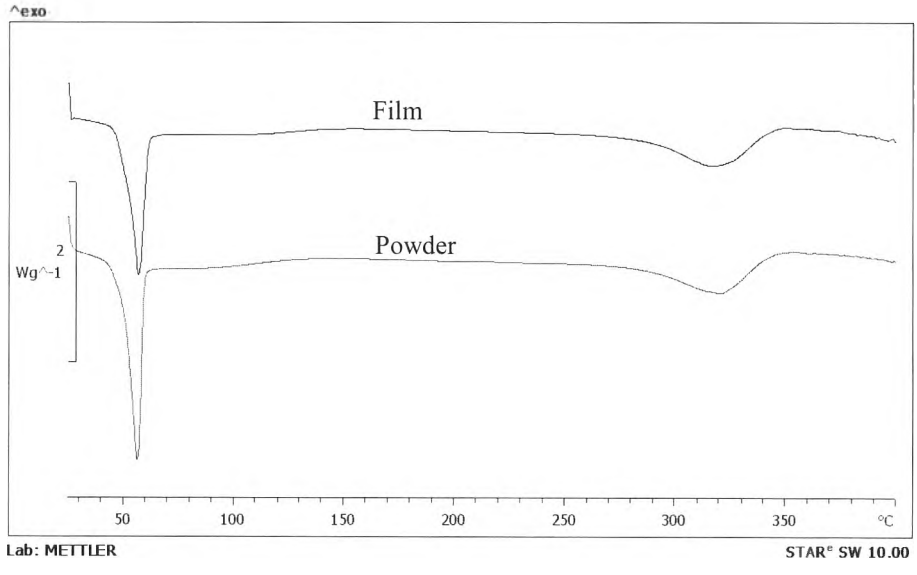

Figure 1 DSC thermogram of film and powder of formulation no. 2.

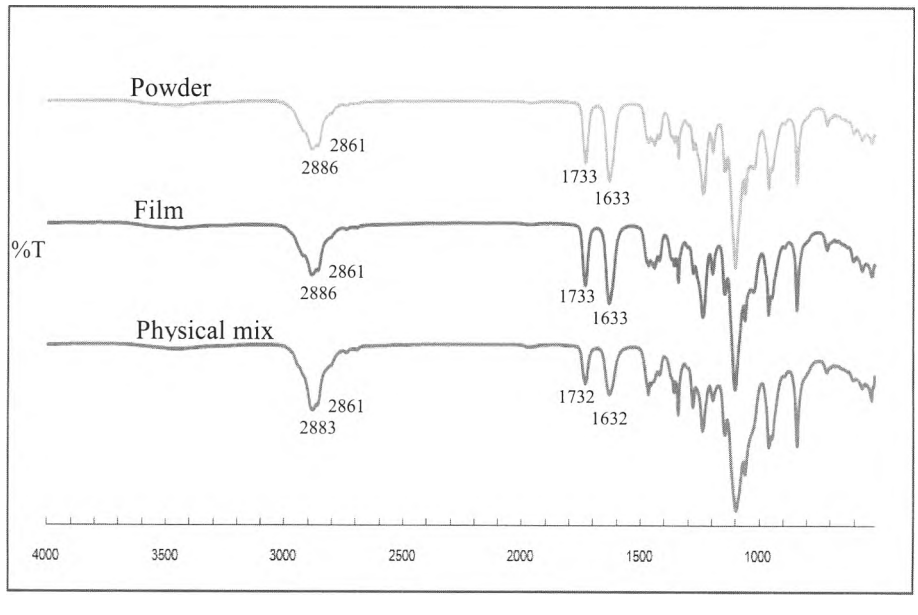

Figure 2 FT-IR spectra of physical mix (bottom line), film (middle line), and powder (upper line) of formulation no. 2.

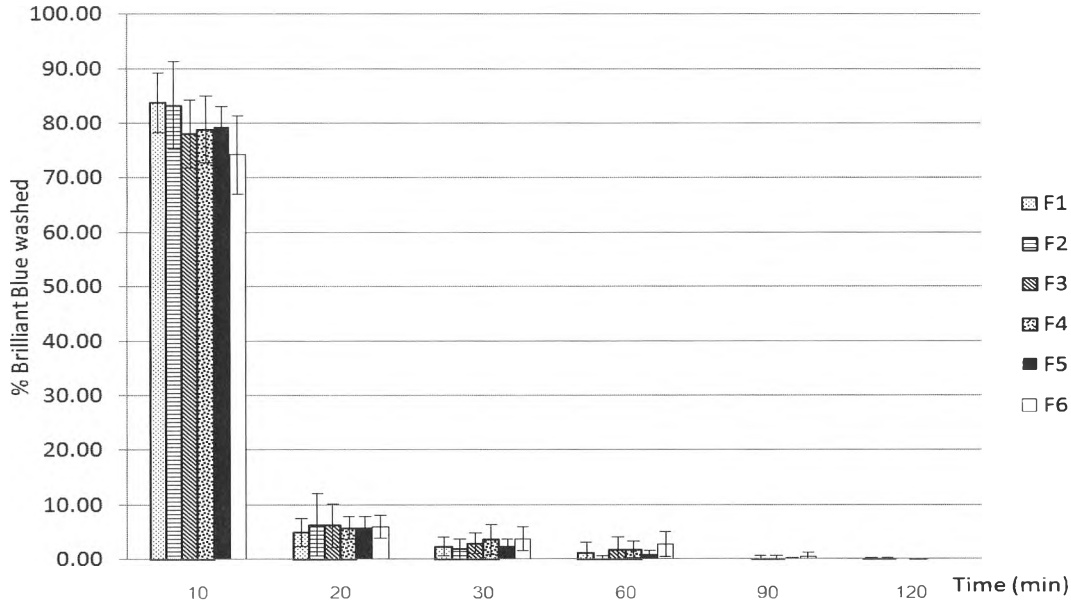

Figure 3 The percent of Brilliant Blue washed from porcine intestinal mucosa of powder formulations no.1-6.

The mucoadhesive property was determined by observing capability of powder adhering on porcine intestinal mucosa. All powder formulations could retain on the mucosa for 60 minutes. However, it can be seen in the figure 2 that more than75% of dye in all formulations was washed within 10 minutes. At the first 10 minutes, although there was no significantly different among formulations, formulation no. 3-6, containing chitosan or Eudragit® E PO, had a tendency to better adherence to the mucosa than the others.

DISCUSSION

The results of the present study may be summarized by pointing out, firstly, that powder formulations which were prepared by liquid-free film casting technique and pulverized by jet milling process could produce particle size with range of 6-10 micron. This size of particles is appropriate for nasal drug delivery which requires size range about 5-120 micron[8, 10, 11]. In order to determine their mucoadhesion, the formulations consisting of low molecular weight chitosan and Eudragit® E PO were likely to better adhere to the mucosa. As there are many proposed mucoadhesive theories used to explain this phenomena such as electronic theory, wetting theory, adsorption theory, diffusion theory, mechanical theory, and fracture theory, but this process of mucoadhesion cannot be described by just one of these theories[12]. In this case, it can be explained by assuming that electronic interaction may play a role in adhesion by interacting between positive charge of polymer and negative charge of mucin on mucosal surface. On the DSC and FT-IR data, there was no new peak or significant peak shift observing in the thermograms and spectrums. The results suggested that compatibility of polymers were accepted, and the effect of production processes to polymer interactions was scared.

CONCLUSION

According to the results of this study, dry powder formulations prepared by liquid-free film casting technique and jet milling process showed a suitable particle size range with narrow size distribution as well as polymer and process compatibility. Furthermore, positively charged formulations were likely to improve mucoadhesive property. Therefore, the dry powder formulations developed in this study may be a novel and promising candidate for intranasal delivery system. However, further study on permeation and stability of the formulations incorporating drug should be performed.

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REFERENCES

1. J.J. Lochheadand R.G. Thorne. Intranasal delivery of biologics to the central nervous system. *Adv Drug Deliv Rev.* 64:614-628 (2012).
2. H.R. Costantino, L. Illum, G. Brandt, P.H. Johnson, and S.C. Quay. Intranasal delivery: Physicochemical and therapeutic aspects. *Int J Pharm.* 337:1-24 (2007).
3. L. Illum. Nasal drug delivery: new developments and strategies. *Drug Discov Today.* 7:1184-1189 (2002).
4. K.L. Berensand T.R. Sullivan. Advances in intranasal therapeutics - Delivery of dry powder pharmaceuticals and biologics. *Touch Briefings* (2007).
5. S.V. Dhuria, L.R. Hanson, and W.H. Frey. Intranasal delivery to the central nervous system: Mechanisms and experimental considerations. *J Pharm Sci.* 99:1654-1673 (2010).
6. N.M. Schipper, J.C. Verhoef, and F.H.M. Merkus. The nasal mucociliary clearance: Relevance to nasal drug delivery. *Pharm Res.* 8:807-814 (1991).
7. C. Callens, E. Pringels, and J.P. Remon. Influence of multiple nasal administrations of bioadhesive powders on the insulin bioavailability. *Int J Pharm.* 250:415-422 (2003).
8. T. Keldmann. Advanced simplification of nasal delivery technology: Anatomy+innovative device=added value opportunity, *ONdrugDelivery Magazine*, ONdrugDelivery Ltd, West Sussex, 2005, pp. 4-7.
9. S. Harikarnpakdee, V. Lipipun, N. Sutanthavibul, and G. Ritthidej. Spray-dried mucoadhesive microspheres: Preparation and transport through nasal cell monolayer. *AAPS PharmSciTech.* 7:E79-E88 (2006).
10. M. Copleyand P. Kippax. From actuation to deposition: Particle sizing techniques for characterizing nasal drug delivery systems. *Inhalation* (2012).
11. Draft guidance for industry: Sinusitis: designing clinical development programs of non antimicrobial drugs for treatment US. FDA; Center for Drug Evaluation and Research (CDER) 2006.
12. J.D. Smart. The basics and underlying mechanisms of mucoadhesion. *Adv Drug Deliv Rev.* 57:1556-1568 (2005).

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