The Thai Journal of Pharmaceutical Sciences

Volume 38
Issue 0 *supplement issue*

Article 70

1-1-2013

PHYSICOCHEMICAL PROPERTIES OF PSEUDOLATEX SYSTEMS PREPARED FROM PARA RUBBER SHEET AND PRELIMINARY DRUG LOADING FOR DRUG DELIVERY

Wiwat Pichayakom

Rungtiwa Waiprib

Isara Lueanpaen

Jirapomchai Suksaeree

Wirach Taweepreda

PHYSICOCHEMICAL PROPERTIES OF PSEUDOLATEX SYSTEMS PREPARED FROM PARA RUBBER SHEET AND PRELIMINARY DRUG LOADING FOR DRUG DELIVERY

Wiwat Pichayakorn[1, 2, *], Rungtiwa Waiprib[1], Isara Lueanpaen[1], Jirapornchai Suksaeree[1], and Wirach Taweepreda[2,3]

[1]*Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences,*
[2]*Medical Products Innovations from Polymers in Clinical Use Research Unit, Prince of Songkla University, Songkhla 90112, Thailand.*
[3]*Department of Materials Science and Technology, Faculty of Science, Prince of Songkla University, Songkhla 90112, Thailand.*
[*]*Corresponding author: wiwat.p@psu.ac.th*

KEYWORDS: Pseudolatex, Para rubber sheet, Drug delivery

INTRODUCTION

Applying the products onto the skin is the simplify method and much attractive for both topical and systemic approaches in drug and cosmetic delivery. Many types of particulated systems, such as liposomes, polymeric micelles, micro/nanoemulsions, and polymeric micro/nanoparticles have been developed to gain the different formulations such as conventional topical products and the novel dosage forms as reservoir-type transdermal patches or film forming polymeric solutions[1]. Some of these particulated carriers can also control the release and permeation rates of active ingredients into the deeper layers of the skin or into the blood circulation[2]. Pseudolatex system, the colloidal aqueous dispersions of hydrophobic polymers, is one of these particulated carriers that can also be used in the same purpose. In general, pseudolatex has been prepared from any existing thermoplastic water-insoluble polymers such as several types of acrylate polymers[3,4], ethyl cellulose[5], and cellulose acetate[6]. Oil-in-water emulsification is the common technique to prepare these pseudolatexes as aqueous polymeric dispersions[3,6].

Cis 1,4-polyisoprene, the natural hydrophobic polymer obtained from the tapping process of the bark of Para rubber tree (Hevea brasiliensis), has much interesting characteristics such as excellent elasticity and flexibility, and ease for film forming. Our research group has successfully developed several products from this polymer to use in transdermal drug delivery, such as matrix films[7-10], reservoir patches[11], and film forming polymeric solution[12]. The initial raw material to prepare these products is fresh natural rubber latex. However, this fresh latex cannot be kept in several days for commercially due to its instability since the droplet coagulation and microbial contamination are the main stability problems. Normally, in Thailand, this polymer is primary transformed into the Para rubber sheet for commercial. However, there is no report to use Para rubber sheet as raw material in drug delivery. Therefore, this study aimed to preliminary prepare the pseudolatex systems from Para rubber sheet for drug delivery and to investigate the effects of various parameters in preparation process on properties of pseudolatexes. Lastly, the feasibility of drug loading in these pseudolatex systems was evaluated.

MATERIALS AND METHODS

Materials Para rubber sheet was kindly gifted from the farmer in Songkhla province, Thailand. The other chemicals and model drugs were pharmaceutical or analytical grade and used without further modification.

Preparation of drug-free pseudolatex systems Organic phase and aqueous phase were separately prepared. A 3.5 g of Para rubber sheet was dissolved in 200 mL dichloromethane and mixed with 4% dibutyl phthalate (DBP) and 2-8% mineral oil, and used as organic phase. In the other phase, surfactants (5-15% Tween80 or 1-2% sodium lauryl sulfate [SLS]), thickeners (0.16-0.30% hydroxypropyl methylcellulose [HPMC] or 0.08-0.24% methylcellulose [MC]), and preservative (2% Uniphen P-23) were dissolved in distilled water to the final volume of 100 mL. Then, the aqueous phase was poured into the organic phase under a high speed homogenizer (IKA, Germany) at ambient temperture to obtain oil-in-water emulsions. The speed and time of homogenization were varied in the ranges of 12,000, 16,000, 20,000 rpm and 10, 15, 20 minutes, respectively. Finally, the oil-in-water emulsion was evaporated by rotary evaporator to remove the dichloromethane. The formed pseudolatex was filled in the well-close container and kept at ambient temperature for further evaluations. The pseudolatex formulations are presented in Table 1.

Preparation of drug loaded pseudolatex systems Five model drugs were separately loaded in the selected pseudolatex base formulation. For water-insoluble drugs, either indomethacin or lidocaine was dissolved in the organic phase before emulsification process. For water soluble drugs, in contrast, either propranolol HCl, lidocaine HCl, or vitamin C was dissolved in the water phase before emulsification process. Then,

both phases were further mixed and pseudolatex systems were formed according to the selected optimal condition.

Physicochemical characterizations of pseudolatex systems The pseudolatex systems were optically observed for their appearances and redispersibilities. Particle size was measured by a laser particle size analyzer (Coulter, USA). Particle shape was studied under a light microscope (Olympus, Japan). The pH value was performed by a pH meter (Mettler Toledo, Switzerland). Rhelogical behavior was measured by a programmable rheometer (Brookfield DV-III Ultra, Brookfield Engineering Laboratories Inc., USA) fitted with a spindle SC4-31 while set at different spindle speeds at 50-250 rpm, and the viscosity was calculated. The protein remaining in pseudolatex systems was analyzed as total nitrogen content by Kjeldahl method[13].

Table 1 Formulations of pseudolatex bases prepared with various parameters.

Parameters	Formulations (%)														
	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15
Para rubber sheet	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
DBP	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Mineral oil	2	4	2	4	2	4	2	2	4	6	4	4	4	4	6
Tween80	15	15	10	10	5	5	-	-	-	-	-	-	-	-	-
SLS	-	-	-	-	1	1	2	1	1	1	1	1	1	1	2
HPMC	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.16	0.30	-	-	-	-
MC	-	-	-	-	-	-	-	-	-	-	-	0.08	0.16	0.20	0.24
Uniphen P-23	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2

RESULTS AND DISCUSSION

Effects of compositions on the properties of drug-free pseudolatex systems

Amount of Para rubber sheet In preliminary step, the Para rubber sheet could dissolve in dichloromethane but only in a limited level that might affect the evaporation process in the last step. Higher amount of Para rubber sheet required the higher amount of dichloromethane, then, it took more time in preparation process and increased the production cost. The 3.5 g of Para rubber sheet could be dissolved in 200 mL dichloromethane that be an optimum level of organic solvent used and the appropriate time to evaporate it. Therefore, the formulations P1-P15 were then developed (Table 1). The fixed preparation parameters at 20,000 rpm homogenization speed and 10 minutes homogenization time were used.

Type and amount of surfactants Tween80 was firstly chosen as surfactant because it is commonly used in oil-in-water emulsion formulations in pharmaceuticals. In this study, however, it caused the aggregation of rubber polymer after evaporation process. Although the level of Tween80 was reduced from 15% (P1-2) to 10% (P3-4) and 5% (P5-6), the un-appropriate products were also formed. Therefore, SLS was then used instead of Tween80 as showed in P7-15. It was found that 1-2% SLS could be formed the appropriate pseudolatex systems. Higher amount of SLS revealed the higher smooth dispersion.

Amount of mineral oil Mineral oil amount also affected the pseudolatex stability (P8-10). Increase amount of mineral oil revealed more stable systems that took the longer time to phase separation occur.

Type and amount of thickeners Both HPMC and MC could stabilize the obtained pseudolatex systems. The higher amount of thickeners revealed more stable systems. Moreover, MC resulted in the higher product stability than HPMC formulations.

In this study, therefore, the P15 was chosen for the further studied.

Effects of preparation parameters on the properties of drug-free pseudolatex systems

Homogenization speed All the P15 formulations prepared by different homogenization speeds of 12,000, 16,000, and 20,000 rpm, and the homogenization time of 10 minutes provided the similar appearance of pseudolatex systems. The white-color polymeric dispersions without any aggregation were obtained. After 2 months of storage at ambient temperature, however, the separation of upper white emulsion and lower clear slight-yellowish solution occurred that could be easily dispersed by hand-shaking. The viscosity behaviors of all formulations revealed the Newtonian properties. The pH, percentage of separation level after storage, particle size and viscosity before and after storage are shown in Figure 1

(top). The pH values were not different, the %separation and droplet size slightly decreased, and the viscosity slightly increased in increasing homogenization speed. After storage, the droplet size and viscosity also decreased.

Homogenization time All the P15 formulations prepared by different homogenization times of 10, 15, and 20 minutes, and the homogenization speed of 20,000 rpm also provided the similar appearance of pseudolatex systems. The results also provided the similar trends. The pH, percentage of separation level after storage, particle size and viscosity before and after storage are shown in Figure 1 (bottom). The pH values were not different, the %separation and droplet size slightly decreased, and the viscosity slightly increased in increasing homogenization time. After storage, the droplet size and viscosity also decreased. The deviation of all data at 15 minutes homogenization time was the lowest. In this study, therefore, the optimum preparation parameters at 20,000 rpm homogenization speed and 15 minutes homogenization time were chosen for the further studied.

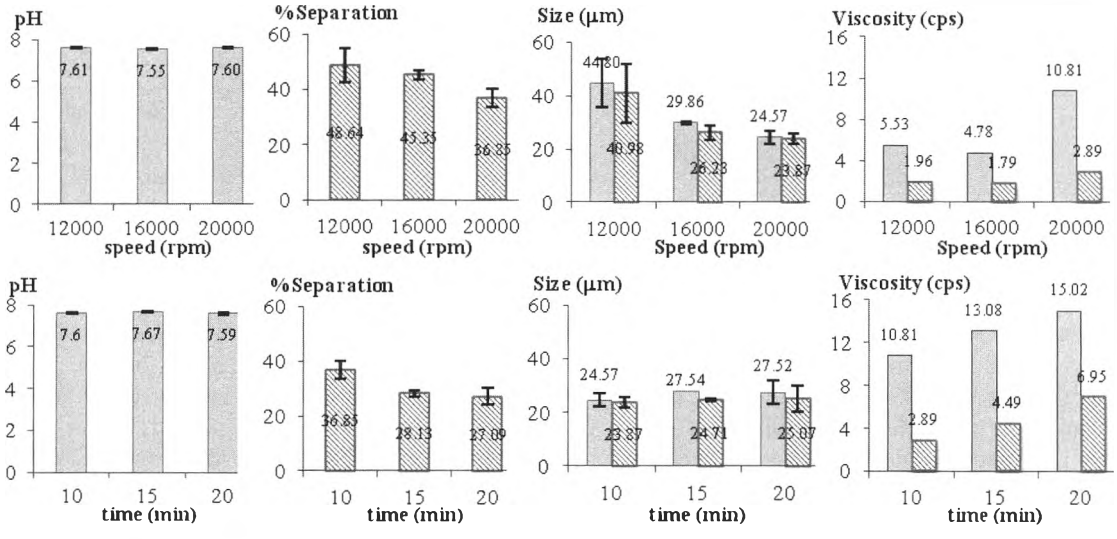

Figure 1 Effects of (top) homogenization speed and (bottom) homogenization time on the properties of drug-free pseudolatex systems (▭) at initial and (▨) after storage at ambient temperature for 2 months.

Effects of stabilizers on the properties of drug-free pseudolatex systems at the optimum preparation parameters

SLS amounts The 1, 1.5, and 2% SLS were further confirmed again in the optimum preparation parameters. The pH, percentage of separation level after storage, particle size and viscosity before and after storage are shown in Figure 2 (top). The %separation and droplet size slightly decreased, and the pH and viscosity slightly increased in increasing SLS amounts. After storage, the droplet size and viscosity also decreased. The 2% SLS obtained the highest pseudolatex stability.

Mineral oil amounts The 4, 6, and 8% mineral oil were further confirmed again in the optimum preparation parameters. The pH, percentage of separation level after storage, particle size and viscosity before and after storage are shown in Figure 2 (bottom). The pH values were not different, but the %separation and droplet size slightly decreased, and the viscosity significantly increased in increasing mineral oil amounts, especially in 8% that could not determine in the same condition due to the very high viscosity. After storage, the droplet size and viscosity also decreased. The 6% mineral oil obtained the highest pseudolatex stability.

Therefore, the best pseudolatex formulation contained 3.5% block rubber, 0.24% MC, 6% mineral oil, 4% DBP, 2% SLS, and 2% Uniphen P-23 using the speed and time of homogenizer as 20000 rpm and 15 minutes, respectively. The protein content of this best drug-free pseudolatex system decreased from 2.56% to 0.32. This indicated that the risk of contact allergy of this product caused by the protein allergens could decrease. The droplet morphology under optical microscope presented as the multiple emulsion with various size distributions (figure was not shown).

PT - 36

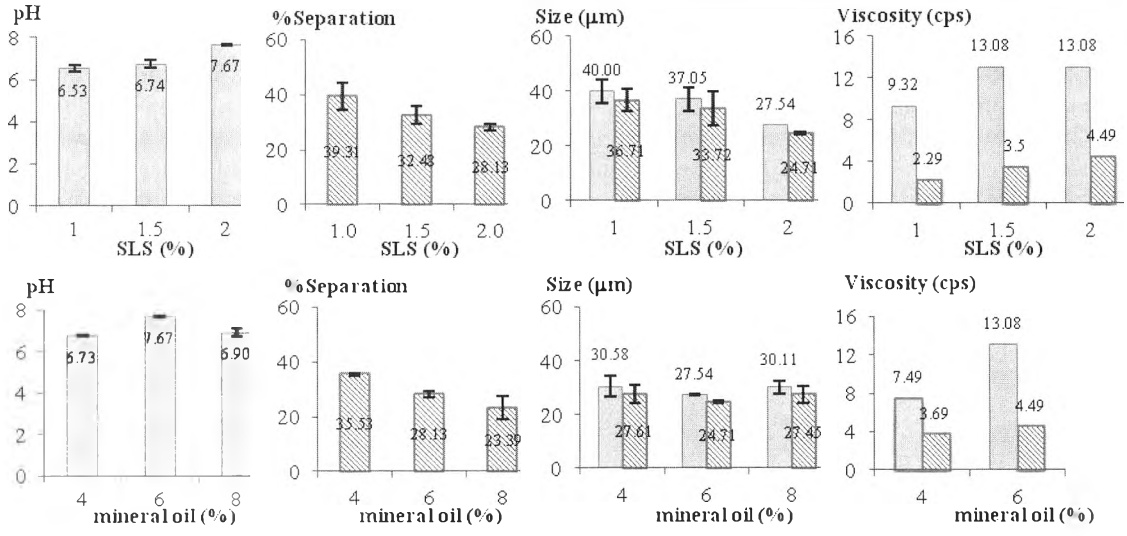

Figure 2 Effects of amounts of (top) SLS and (bottom) mineral oil on the properties of drug-free pseudolatex systems ( ) at initial and ( ) after storage at ambient temperature for 2 months.

Drug-loaded pseudolatex systems

Only 2% lidocaine could be loaded into the pseudolatex system with the good physical appearances. The white stable dispersion was obtained. The particle size of lidocaine loaded pseudolatex (26.73±11.87 μm) was not different from the pseudolatex base (27.54±0.23 μm) but with larger size distribution. The pH increased to 9.12±0.03 due to the basic properties of drug. The viscosity quite increased and its behavior changes to pseudoplastic flow that the viscosity decreased when the shear force increased. Unfortunately, the 1, 2, and 4% indomethacin and vitamin C were also loaded into the pseudolatex systems, but the aggregation of drug and polymer droplets was found especially in the higher drug amounts due to their acidic properties that incompatible to rubber polymer. Propranolol HCl and lidocaine HCl precipitated in the pseudolatex systems and some polymer aggregations occurred. These might be due to the complex incompatibility between HCl salts and SLS resulting in the lower stabilizer activity. Therefore, the property of drug was the important factor that should be considered for loading into this pseudolatex system.

CONCLUSION

Pseudolatex systems could be developed from Para rubber sheet. The preparation parameters in both compositions and emulsification process directly affected the properties of pseudolatex systems. Some drugs could be loaded into this system to form the good properties. However, many drugs could not be applied in this system. Therefore, it should be further studied to find out the flexible condition for use this system in widely types of drug delivery.

ACKNOWLEDGEMENTS

The authors would like to express their gratitude to the Faculty of Pharmaceutical Sciences, Prince of Songkla University, for financial supports.

REFERENCES

1. Schröeder IZ, Franke P, Schaefer UF, et al. (2007) Delivery of ethinylestradiol from film forming polymeric solutions across human epidermis *in vitro* and *in vivo* in pigs. J Controlled Release 118: 196-203.
2. Barry BW (2001) Novel mechanisms and devices to enable successful transdermal drug delivery. Eur J Pharm Sci 14: 101-114.
3. Quintanar-Guerrero D, Allémann E, Fessi H, et al. (1999) Pseudolatex preparation using a novel emulsion–diffusion process involving direct displacement of partially water-miscible solvents by distillation. Int J Pharm 188: 155-164.

4. Panigrahi L, Pattnaik S, Ghosal SK (2005) The effect of pH and organic ester penetration enhancers on skin permeation kinetics of terbutaline sulfate from pseudolatex-type transdermal delivery systems through mouse and human cadaver skins. AAPS PharmSciTech 6: 167-173.

5. Morales ME, Ruiz MA, López G, et al. (2010) Development of oral suspensions of microparticles of ethylcellulose with tramadol. Drug Dev Ind Pharm 36: 885-892.
6. Sastry SV, Wilber W, Reddy IK, et al. (1998) Aqueous-based polymeric dispersion: preparation and characterization of cellulose acetate pseudolatex. Int J Pharm 165: 175-189.
7. Suksaeree J, Boonme P, Taweepreda W, et al. (2012) Characterization, *in vitro* release and permeation studies of nicotine transdermal patches prepared from deproteinized natural rubber latex blends. Chem Eng Res Des 90: 906-914.
8. Pichayakorn W, Suksaeree J, Boonme P, et al. (2012) Preparation of deproteinized natural rubber latex and properties of films formed by itself and several adhesive polymer blends. Ind Eng Chem Res 51: 13393-13404.
9. Pichayakorn W, Suksaeree J, Boonme P, et al. (2012) Deproteinized natural rubber latex/hydroxypropyl methylcellulose blending polymers for nicotine matrix films. Ind Eng Chem Res 51: 8442-8452.
10. Pichayakorn W, Suksaeree J, Boonme P, et al. (2012) Nicotine transdermal patches using polymeric natural rubber as the matrix controlling system: Effect of polymer and plasticizer blends. J Membr Sci 411-412: 81-90.
11. Pichayakorn W, Suksaeree J, Boonme P, et al. (2013) Deproteinised natural rubber used as a controlling layer membrane in reservoir-type nicotine transdermal patches. Chem Eng Res Des 91: 520-529.
12. Pichayakorn W, Suksaeree J, Boonme P, et al. (2013) Deproteinized natural rubber film forming polymeric solutions for nicotine transdermal delivery. Pharmaceut Dev Tech 18: 1111-1121.
13. ASTM International (2001) Standard test method for rubber-nitrogen content D3533. West Conshohocken, Pennsylvania, United States.