Effect of Formulation Composition on Particle Size and Surface Charge of Eudragit-based Film Forming Polymeric Dispersions

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Abstract

This study evaluated the effect of formulation composition such as the amount of absolute ethanol, amount of glycerin, and ratio of Eudragit RL 30D to Eudragit RS 30D on particle size and surface charge of Eudragit-based film forming polymeric dispersions. Thirteen formulations containing Eudragit RL 30D, Eudragit RS 30D, glycerin, and absolute ethanol were prepared using simple mixing method. Three formulation compositions including the amount of absolute ethanol, amount of glycerin, and ratio of Eudragit RL 30D to Eudragit RS 30D were studied. Particle size, polydispersity index, and particle surface charge (zeta potential) of the preparations were determined using particle size and zeta potential analyzer. Most of the formulations had particle size approximately 150 to 500 nm, except formulation containing Eudragit RL 30D and Eudragit RS 30D in the ratio of 30:0 had the largest size, 1,100 nm. Particle size increased with an increment of absolute ethanol amount. Increasing of glycerin amount, particle size was decreased. However, constant particle size was observed when low to medium amount of glycerin was used. The increment of Eudradit RS 30D caused the particle size to decrease. Furthermore, all formulations had polydispersity index lower than 0.5 with zeta potential ranged from +28.98 to +58.63 mV. All three formulation compositions affected particle size of Eudragit-based film forming polymeric dispersions. Conversely, polydispersity index and surface charge were independent from formulation compositions. In conclusion, formulation compositions should be optimized to get the desired particle size of the formulation.

Keywords**:** *Eudragit, film forming polymeric dispersion system, particle size, particle surface charge, skin drug delivery*

บทคัดย่อ

การศึกษานี้มีวัตถุประสงค์เพื่อประเมินผลของส่วนประกอบในตำรับ ได้แก่ ปริมาณของเอทานอล ปริมาณของกลีเซอรีน และสัดส่วนของยูดราจิต อาร์แอล 30 ดีและยูดราจิต อาร์เอส 30 ดี ต่อขนาดอนุภาคและประจุไฟฟ้าที่ผิวอนุภาคของระบบกระจายตัวของพอลิเมอร์ก่อฟิล์มที่เตรียมจากยูดราจิต การศึกษานี้ได้เตรียมสูตรตำรับระบบกระจายตัวของพอลิเมอร์ก่อฟิล์มทั้งสิ้น 13 สูตร ด้วยวิธีการผสมแบบธรรมดา สูตรตำรับประกอบด้วยยูดราจิต อาร์แอล 30ดี ยูดราจิต อาร์เอส 30ดี กลีเซอรีน และเอทานอล โดยปรับเปลี่ยนส่วนประกอบของสูตรตำรับ 3 ประการ ได้แก่ ปริมาณของเอทานอล ปริมาณของกลีเซอรีน และสัดส่วนของยูดราจิต อาร์แอล 30ดีและยูดราจิต อาร์เอส 30ดี จากนั้นวิเคราะห์ขนาดอนุภาค ดัชนีการกระจายขนาด และประจุไฟฟ้าที่ผิว (ศักย์ซีต้า) ด้วยเครื่องวิเคราะห์ขนาดอนุภาคและศักย์ซีต้า ผลการศึกษา พบว่า สูตรตำรับที่เตรียมขึ้นส่วนใหญ่มีขนาดอนุภาคประมาณ 150 ถึง 500 นาโนเมตร ยกเว้นสูตรตำรับที่เตรียมจากยูดราจิต อาร์แอล 30ดีและยูดราจิต อาร์เอส 30ดีในสัดส่วน 30:0 มีขนาดอนุภาคใหญ่ที่สุด คือ 1,100 นาโนเมตร ขนาดของอนุภาคจะเพิ่มขึ้นเมื่อใช้เอทานอลในปริมาณมากขึ้น การเพิ่มขึ้นของปริมาณกลีเซอรีนทำให้ขนาดอนุภาคลดลง แต่อย่างไรก็ตามการใช้กลีเซอรีนปริมาณต่ำถึงปานกลางไม่ได้ส่งผลต่อขนาดอนุภาคมากนัก การเพิ่มขึ้นของสัดส่วนยูดราจิต อาร์เอส 30ดี ส่งผลให้อนุภาคมีขนาดลดลง นอกจากนี้สูตรตำรับที่เตรียมขึ้นมีดัชนีการกระจายขนาดต่ำกว่า 0.5 และมีศักย์ซีต้าอยู่ในช่วง +28.98 ถึง +58.63 มิลลิโวลต์ การศึกษานี้สามารถสรุปได้ว่า ส่วนประกอบของสูตรตำรับทั้งสามประการส่งผลต่อขนาดอนุภาคของระบบกระจายตัวของพอลิเมอร์ก่อฟิล์มที่เตรียมจากยูดราจิต ในขณะที่ส่วนประกอบของสูตรตำรับไม่ได้ส่งผลต่อดัชนีการกระจายขนาดและประจุไฟฟ้าที่ผิวอนุภาค ดังนั้นจะต้องมีการหาค่าที่เหมาะสมของส่วนประกอบของสูตรตำรับเพื่อที่จะให้สูตรตำรับมีขนาดอนุภาคตามที่ต้องการ

คำสำคัญ: *ยูดราจิต ระบบกระจายตัวของพอลิเมอร์ก่อฟิล์ม ขนาดอนุภาค ประจุไฟฟ้าที่ผิวอนุภาค การนำส่งยาทางผิวหนัง*

1. Introduction

The skin is the largest organ of the human body, accounting for more than 10% of body weight. The skin is a natural barrier of human body act as a defensive barrier of the body from external environment (Walters & Roberts, 2007). The skin consisted of two major layers: epidermis (nonviable and viable

epidermis) and dermis. Which, the outer layer of the skin called stratum corneum plays an important role on preventing of drug penetration through the skin (Parhi, Suresh, & Patnaik, 2015).

Drug delivery via skin offers several advantages over oral route. It is useful for vomiting and unconscious patients that cannot be swallowed. It can avoid first pass metabolism by the liver. It is also useful for significantly metabolized drugs. It has a potential for sustained release thus useful for short biological half-life drug. It also has advantages compared with injections. It is painless because it is non-invasive manner, lack of infection due to the inappropriate injection procedure. In addition, it is a self-administered system which unnecessary to use well-trained healthcare personnel. In the case of toxicity occurrence, it can easily be removed by the patients. However, the only partial number of drugs can transport via this route (Prausnitz & Langer, 2008; Ruby, Pathak, & Aggarwal, 2014).

Generally, a drug with low molecular weight (less than 500 Da), octanol-water partition coefficient (P) between 10-10,000 or log P between 1-4, and daily dose less than 20 mg will be appropriated for skin drug delivery. However, a high log P drug, buprenorphine (log P = 4.98), can also penetrate through the skin (Wiedersberg & Guy, 2014). In 1979, the first transdermal patch for treatment of motion sickness, scopolamine patch, is approved by the United States Food and Drug Administration. After that, several drugs are approved such as nitroglycerin, clonidine, estradiol, fentanyl, nicotine, lidocaine, methylphenidate, selegiline, etc. (Prausnitz & Langer, 2008).

The film forming polymeric dispersions are novel skin drug delivery system. This system consists of an active pharmaceutical ingredient, film forming polymer, plasticizer, and other additives. When the film forming polymeric dispersions are firstly applied to the skin, the preparation is in liquid form. And then, the solvent is evaporated from their preparation, *in situ* film is formed, the obtained film is adhered to the skin to release active compound (Zurdo Schroeder et al., 2007a). Several active pharmaceutical ingredients can be delivered to the skin using the film forming polymeric dispersions such as ethinylestradiol (Zurdo Schroeder et al., 2007a), nicotine (Pichayakorn et al., 2013; Pichayakorn et al., 2015), and betamethasone-17-valerate (Frederiksen, Guy, & Petersson, 2015; Garvie-Cook et al., 2015). According to these studies, several film forming polymers are used including acrylates copolymer, Eudragit E 100, Eudragit S 100, chitosan, polyvinylpyrrolidone, polyvinylpyrrolidone-vinyl acetate copolymer, polyisobutylene, polyvinyl alcohol (Zurdo Schroeder et al., 2007b), Eudragit RL PO, polyurethane-14 and AMP-acrylates copolymer, hydroxypropyl cellulose, silicone gum (Zurdo Schroeder et al., 2007a; Zurdo Schroeder et al., 2007b), deproteinized natural rubber latex mixed hypromellose (Pichayakorn et al., 2015), deproteinized natural rubber latex mixed methyl cellulose, deproteinized natural rubber latex mixed polyvinyl alcohol, deproteinized natural rubber latex mixed sodium alginate (Pichayakorn et al., 2013), Eudragit RS PO, Eudragit NE 40D, and acrylate/octylacrylamide copolymer (Frederiksen, Guy, & Petersson, 2015; Garvie-Cook et al., 2015; Zurdo Schroeder et al., 2007b).

Our previous work was to develop film forming polymeric dispersions based on Eudragit RL 30D and Eudragit RS 30D (Monton & Suksaeree, 2016). Particle size and surface charge are important factors affected the stability of dispersion system (Tadros, 2006). Therefore, the particle size and the zeta potential should be monitored to understand the relationship between formulation composition and particle size and the surface charge of Eudragit-based film forming polymeric dispersions.

2. Objective

The objective of the study was to evaluate the effect of formulation composition such as the amount of absolute ethanol, amount of glycerin, and ratio of Eudragit RL 30D to Eudragit RS 30D on particle size and surface charge of Eudragit-based film forming polymeric dispersions.

3. Materials and methods

3.1 Materials

Two polymethacrylates; Eudragit RL 30D (poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.2) and Eudragit RS 30D (poly(ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1) (Evonik Industries, Germany) were gifted from the Jebsen and Jessen NutriLife Co, Ltd., Thailand. Glycerin was purchased from Sigma, USA. Absolute ethanol was purchased from Honeywell-Burdick & Jackson, USA.

3.2 Preparation of film forming polymeric dispersions

Eudragit RL 30D and Eudragit RS 30D (as the film forming polymers), glycerin (as the plasticizer), and absolute ethanol (as the solvent) were used to prepare the film forming polymeric dispersions. Formulations 1-13 were coded as P1 to P13. Amount of absolute ethanol, amount of glycerin, and ratio of Eudragit RL 30D to Eudragit RS 30D were varied, shown in Table 1. Film forming polymeric dispersions was prepared by simple mixing method using magnetic stirrer (CMAG HS7, Ika, Germany). Eudragit RL 30D and Eudragit RS 30D were mixed together until dispersions were homogeneous. Then, glycerin was added and mixed. Finally, absolute ethanol was also added and mixed. Schematic of preparation method is shown in Figure 1.

Table 1 Formulation composition of Eudragit-based film forming polymeric dispersions

Formulation	Formulation composition (g)			
	Eudragit RL 30D	Eudragit RS 30D	Glycerin	Absolute ethanol
P1	15	15	1	0
P2	15	15	1	4
P3	15	15	1	6
P4	15	15	1	8
P5	15	15	1	10
P6	15	15	2	10
P7	15	15	4	10
P8	15	15	6	10
P9	15	15	8	10
P10	30	0	8	10
P11	20	10	8	10
P12	10	20	8	10
P13	0	30	8	10

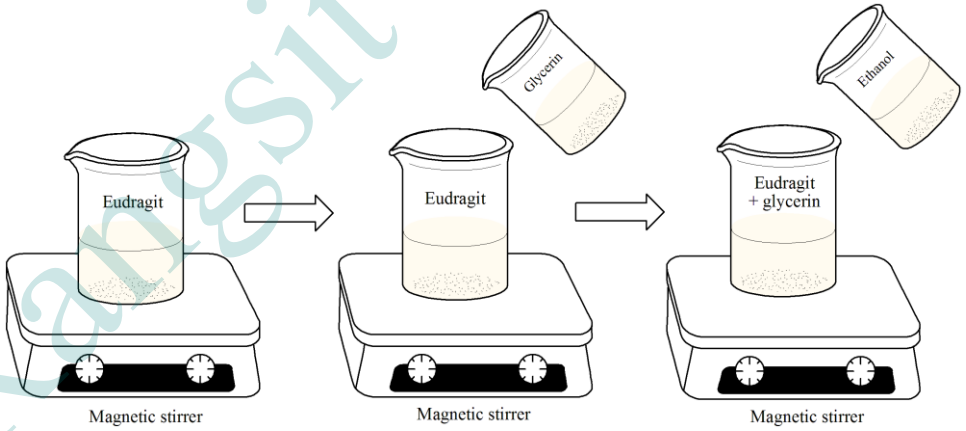

Figure 1 Schematic of film forming polymeric dispersion preparation

3.3 Evaluation of particle size, polydispersity index, and surface charge

Each formulation was diluted with deionized water before analysis of particle size and surface charge. Particle size with polydispersity index and zeta potential was analyzed by photon correlation spectroscopy and electrophoretic light scattering technique, respectively. The analysis was performed using NanoPlus-3 (Micromeritics, USA). The temperature was controlled at 25 ºC. Each formulation was performed in five replicates. Mean and standard deviation were reported.

4. Results

Three factors of formulation composition were studied. Particle size of dispersions increased with an increment of absolute ethanol amount (P1-P5). P1 had the smallest size, 149 nm, and P5 had the largest

size, 449 nm. Increasing the amount of glycerin from 1 to 4 g (P5-P7), particle size gradually increased from 449 nm to 486 nm. While increasing the amount of glycerin from 4 to 8 g (P7-P9), particle size was decreased remarkably to 286 nm. Alteration of the ratio of Eudragit RL 30D to Eudragit RS 30D (P9-P13) was also affected particle size. The increment of Eudradit RS 30D, particle size was decreased. P10 which contained Eudragit RL 30D and Eudragit RS 30D in the ratio of 30:0, the largest particle size was observed at approximately 1,100 nm. According to P9 and P11-P13, P11 had the largest particle size (349 nm) and P13 had the smallest particle size (155 nm). These results indicated that all three formulation factors affected particle size of Eudragit-based film forming polymeric dispersions. Results of particle size of each formulation are shown in Figure 2.

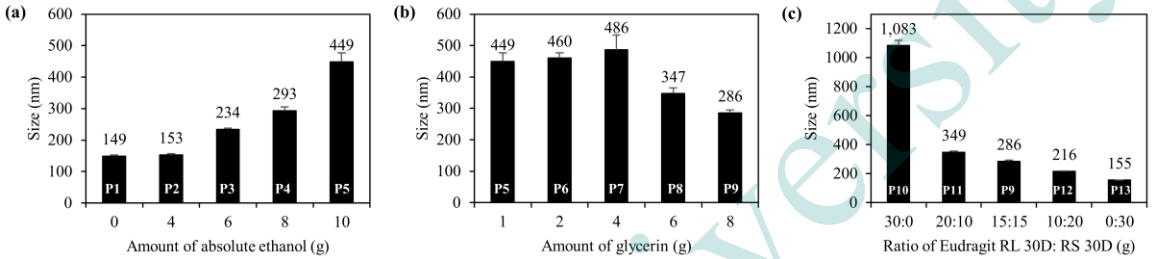

Figure 2 Particle size of formulation containing different (a) amount of absolute ethanol (P1-P5), (b) amount of glycerin (P5-P9), and (c) ratio of Eudragit RL 30D to Eudragit RS 30D (P10, P11, P9, P12, and P13), respectively

Polydispersity index of all 13 formulations was ranged from 0.18 to 0.50, which P12 and P10 had the lowest and the highest polydispersity index, respectively. Results of polydispersity index are shown in Figure 3. Furthermore, all 13 formulations had positive surface charge; zeta potential was ranged from +28.98 to +58.63 mV, which P2 and P12 had the lowest and the highest zeta potential, respectively. Results of zeta potential are shown in Figure 4.

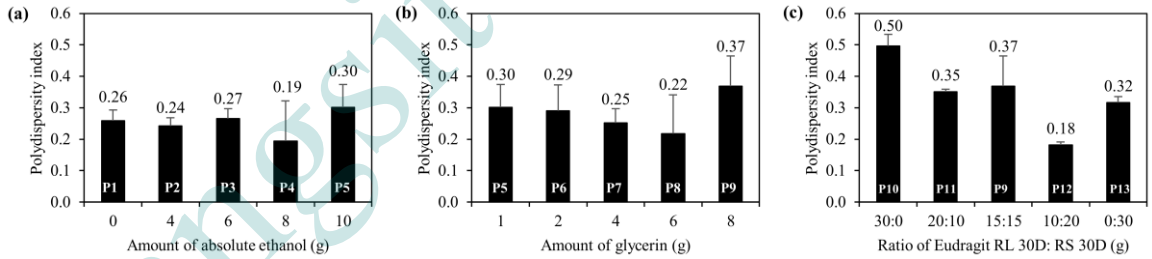

Figure 3 Polydispersity index of formulation containing different (a) amount of absolute ethanol (P1-P5), (b) amount of glycerin (P5-P9), and (c) ratio of Eudragit RL 30D to Eudragit RS 30D (P10, P11, P9, P12, and P13), respectively

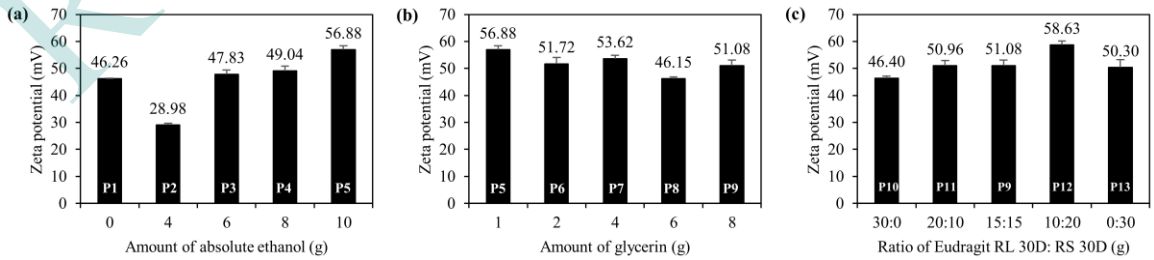

Figure 4 Zeta potential of formulation containing different (a) amount of absolute ethanol (P1-P5), (b) amount of glycerin (P5-P9), and (c) ratio of Eudragit RL 30D to Eudragit RS 30D (P10, P11, P9, P12, and P13), respectively

5. Discussion

According to our preliminary study, the particle size of Eudragit RL 30D and Eudragit RS 30D raw materials were 189.5±2.2 and 123.7±1.2 nm, respectively. Furthermore, homogeneous size was observed, which polydispersity indexes were 0.21±0.01 and 0.18±0.01, respectively. Figure 2 showed that P1 which containing no ethanol had particle size approximately 150 nm, which closed to the average value of these two Eudragits (155 nm). Increasing of ethanol to 4 g in the formulation, particle size remained closed to 155 nm. Major alteration of particle size was observed when ethanol was added at least 6 g. Eudragit RL 30D and Eudragit RS 30D had high and low permeability properties, respectively (Rowe, Sheskey, & Quinn, 2009). The increment of ethanol amount might be affected Eudragit RL 30D, a high permeable polymer, more than Eudragit RS 30D. Ethanol might be permeated to Eudragit RL 30D particle, so polymer particle swell. However, clarified mechanism of this phenomenon was not reported elsewhere. This hypothesis was related to the result of particle size of P10 which containing Eudragit RL 30D and Eudragit RS 30D in the ratio of 30:0; the largest particle size was observed. When the ratio of Eudragit RL 30D to Eudragit RS 30D was altered from 20:10 to 0:30, particle size was decreased. This phenomenon clarified that ethanol had less effect on particle size of Eudragit RS 30D.

Alteration of particle size of dispersion systems under ethanol-consisted formulation was reported in the previous publication. Suksaeree et al. (2014) stated that addition of ethanol into ketoprofen pseudolatex gel prepared from deproteinized natural rubber latex and ethyl cellulose caused increased of particle size. After 3 months storage, the particle size of a formulation containing ethanol slightly increased (Suksaeree et al., 2014). This previous work had the same result with our recent work. Particle size was increased from 149 to 449 nm when ethanol amount increased.

Most of polymers used in pharmaceutical film coatings including Eudragit RL 30D and Eudragit RS 30D are amorphous in nature. The modification of polymer properties using plasticizer is necessary (Porter & Bruno, 1990). The plasticizer has a primary role in improving the flexibility and processability of amorphous polymers by lowering the glass transition temperature (Snejdrova & Dittrich, 2012). In our work, glycerin, a clear and water and ethanol soluble compound (Rowe, Sheskey, & Quinn, 2009), was used as a plasticizer for the formulation. Increasing of glycerin from 1 to 4 g, particle size slightly increases, remarkably changing was not found. The high amount of glycerin caused particle size decreased remarkably. This phenomenon was previously reported by Purmová et al. (n.d.). The addition of plasticizer could decreased particle size of polyvinyl chloride (Purmová et al., n.d.). In addition, plasticizer could also decreased particle size of aqueous ethyl cellulose dispersions (Vesey, Rizzo, & Rajabi-Siahboomi, 2006). The mechanism of the decreasing of particle size by plasticizer might be related to decreasing of dynamic surface tension of film forming polymers. Zelkó et al. (2002) reported that 5% to 20% plasticizer, dibutyl sebacate, could be decreased the dynamic surface tension of Eudragit L 30D and Eudragit RL 30D aqueous colloidal polymer dispersions at 25.0, 27.5, 30.0, and 32.5 ºC (Zelkó et al., 2002).

According to Figure 3 and 4, formulation composition was unaffected by polydispersity index and zeta potential value. Zeta potential was related to electrostatic repulsion of the colloidal system. An appropriate zeta potential value could be prevented particle agglomeration and provided stability of the colloidal system. Generally, 30 mV was accepted as the threshold for stability in several colloidal systems. When zeta potential was higher than the threshold, strong electric repulsion force was obtained, resulting in an increase in dispersion stability (Xu, 2002). Eudragit RL 30D and Eudragit RS 30D were polymethacrylates, a synthetic cationic polymer (Larsson, Abrahmsén-Alami, & Juppo, 2008). A preliminary study showed that Eudragit RL 30D and Eudragit RS 30D had a zeta potential of +62.24±0.45 and +50.94±0.67 mV, respectively. All formulations had a positive charge due to the cationic property of these two Eudragits. Thus, Eudragit-based film forming polymeric dispersions might be stable, it could be warranted from zeta potential value.

6. Conclusion

Effect of formulation composition including an amount of absolute ethanol, amount of glycerin, and ratio of Eudragit RL 30D to Eudragit RS 30D on particle size and surface charge of Eudragit-based film forming polymeric dispersions were evaluated in this work. Formulation composition was highly affected the particle size of the formulation. Neither polydispersity index nor surface charge was unaffected by the

three formulation factors. In conclusion, formulation compositions should be optimized to get the desired particle size of the formulation.

7. Acknowledgements

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