ระบบยูเทกติกเพื่อเป็นระบบนำส่งยาสำหรับรักษาโรคปริทันต์อักเสบ

ศรัณย์ ตันตะราวงศา[1*], จงจันท์ มหาดเล็ก[1], ธวัชชัย แพชมัด[2]

Received: 31 January 2017 **Accepted:** 4 April 2017

บทคัดย่อ

บทนำ: ระบบยูเทกติกของพิมเสนเกร็ดและการบูร เป็นตัวทำละลายที่เหมาะสมสำหรับระบบนำส่งยาเฉพาะที่เพื่อรักษาโรคปริทันต์อักเสบเนื่องจากมีฤทธิ์เป็นยาชาเฉพาะที่และฤทธิ์ต้านเชื้อจุลชีพ ไอบูโปรเฟนเป็นหนึ่งในยาตัวเลือกสำหรับการรักษาโรคปริทันต์อักเสบเนื่องจากฤทธิ์ต้านการอักเสบและบรรเทาปวด ระบบนำส่งยาเฉพาะที่ของยาไอบูโปรเฟนที่มีสมบัติการปลดปล่อยยายาวนานจึงถูกพัฒนาขึ้น **วิธีดำเนินการวิจัย:** ไอบูโปรเฟนถูกบรรจุในระบบยูเทกติกของพิมเสนเกร็ดและการบูร สำหรับรักษาโรคปริทันต์อักเสบ สูตรตำรับไอบูโปรเฟนที่บรรจุในระบบยูเทกติกได้รับการพัฒนาขึ้น ทำการประเมินสมบัติทางกายภาพและการปลดปล่อยยา **ผลการวิจัย**: ตัวทำละลายที่เลือกใช้ในการศึกษานี้คือพิมเสนเกร็ด:การบูร อัตราส่วน 5:5 สารละลายยูเทกติกที่บรรจุไอบูโปรเฟนมีความหนืดเพิ่มขึ้นตามความเข้มข้นของไอบูโปรเฟนและมีรูปแบบการไหลแบบนิวโตเนียน สารละลายยูเทกติกของไอบูโปรเฟนบรรจุพอลิเมอร์ที่ประกอบด้วย ไอบูโปรเฟน 10 % และยูดราจิต อี พีโอ 30 % ในตัวทำละลายยูเทกติกมีค่าความหนืดที่สูงขึ้นมากและมีรูปแบบการไหลแบบนิวโตเนียน การเกิดระบบยูเทกติกนี้สามารถยืนยันผลจากพฤติกรรมการหลอมจากการศึกษาการเปลี่ยนแปลงภายใต้กล้องจุลทรรศน์ โดยตัวทำละลายยูเทกติกมีจุดหลอมเหลวที่ต่ำกว่าพิมเสนเกร็ดและการบูร การศึกษาค่าการละลายของไอบูโปรเฟนพบว่าในไดเมทิลซัลฟอกไซด์มีค่าการละลายสูงที่สุด แต่อย่างไรก็ตามค่าการละลายของยาไอบูโปรเฟนในตัวทำละลายยูเทกติกเพิ่มสูงขึ้นอย่างมากเมื่อเทียบกับค่าการละลายในน้ำหรือสารละลายฟอสเฟตบัฟเฟอร์ พีเอช 6.2 สารละลายยูเทกติกที่บรรจุไอบูโปรเฟนและสารละลายยูเทกติกของไอบูโปรเฟนบรรจุพอลิเมอร์ที่เตรียมขึ้นมีสมบัติเป็นระบบนำส่งยาแบบออกฤทธิ์เนิ่น **สรุปผลการวิจัย**: ระบบนำส่งยาของไอบูโปรเฟนในรูปแบบยูเทกติกที่เตรียมขึ้นมีศักยภาพที่จะนำไปใช้สำหรับการรักษาโรคปริทันต์อักเสบ มีสมบัติการออกฤทธิ์เนิ่นและตัวทำละลายมีฤทธิ์เป็นยาชาเฉพาะที่และต้านเชื้อจุลชีพ

คำสำคัญ: ยูเทกติก, พิมเสนเกร็ด, การบูร, ไอบูโปรเฟน, โรคปริทันต์อักเสบ

วารสารเภสัชศาสตร์อีสาน 2560; 13 (ฉบับพิเศษ): 89-96

[1] Ph.D., อาจารย์, หน่วยภูมิปัญญาทางเภสัชศาสตร์ "ประโชติ เปล่งวิทยา" คณะเภสัชศาสตร์ มหาวิทยาลัยศิลปากร อ.เมือง จ.นครปฐม
[2] Ph.D., รองศาสตราจารย์, ภาควิชาเทคโนโลยีเภสัชกรรม, คณะเภสัชศาสตร์ มหาวิทยาลัยศิลปากร อ.เมือง จ.นครปฐม
* **ติดต่อผู้นิพนธ์:** ศรัณย์ ตันตะราวงศา คณะเภสัชศาสตร์ มหาวิทยาลัยศิลปากร อ.เมือง จ.นครปฐม 73000
โทร. 034-244-462 e-mail: tuntarawongsa_s@su.ac.th

Eutectic system as drug delivery for periodontitis treatment

Sarun Tuntarawongsa[1*], Jongjan Mahadlek[1], Thawatchai Phaechamud[2]

Abstract

Introduction: Eutectic system of menthol (M) and camphor (C) was suitable as solvent for local delivery system for periodontitis treatment because local anesthetic and antimicrobial activities. Ibuprofen is one of drugs of choice for periodontitis treatment as anti-inflammation and pain managements. The local administration of ibuprofen with prolong released property was developed. **Methods:** Ibuprofen was loaded into eutectic system of M:C as the delivery system for periodontitis treatment. Ibuprofen-loaded eutectic system was developed. Their physical properties and drug released profile were investigated. **Results:** The 5:5 M:C was selected as solvent in this study. The viscosity of ibuprofen-loaded eutectic (iES) was increased as concentration of ibuprofen increased and exhibited the Newtonian flow. Ibuprofen-loaded polymeric eutectic solution (PES) containing 10% ibuprofen and 30% Eudragit® E PO in eutectic solvent showed high viscosity apparently and exhibited Newtonian flow. The eutectic formation was confirmed with melting behavior study under hot stage microscope. Melting point of 5:5 M:C was lower than that of individual menthol and camphor. The highest solubility of ibuprofen was obtained in dimethyl sulfoxide; however, solubility of ibuprofen in eutectic solvent was markedly higher than those of water or phosphate buffer solution pH 6.2. The ibuprofen release could be sustainable from iES and PES. **Conclusion:** The developed eutectic drug delivery system of ibuprofen was potentially for periodontitis treatment which prolong released property and the eutectic solvent was local anesthetic and antimicrobials agent

Keywords: Eutectic, Menthol, Camphor, Ibuprofen, Periodontitis

IJPS 2017; 13 (Supplement): 89-96

[1] Ph.D. (Pharmaceutical technology), Lecturer, Pharmaceutical Intelligence Unit Prachote Plengwittaya, Faculty of Pharmacy, Silpakorn University, Nakhon Pathom, Thailand

[2] Ph.D. (Pharmaceutical technology), Associate Professor, Department of Pharmaceutical Technology, Faculty of Pharmacy, Silpakorn University, Nakhon Pathom, Thailand

* **Corresponding author:** Sarun Tuntarawongsa, Pharmaceutical Intelligence Unit Prachote Plengwittaya, Faculty of Pharmacy, Silpakorn University, Nakhon Pathom, Thailand 73000 Tel: 034-244462 Fax: 034-244462 e-mail: tuntarawongsa_s@su.ac.th

Introduction

The eutectic system is the mixture which exhibits melting point suppression since the total entropy of system is increased (Bi et al., 2003; Woolfson et al., 2000). The local anesthetic and antimicrobial properties of menthol and camphor (Al-Bayati, 2009; Patel et al., 2007; Shunying et al., 2005; Chang, 2004) are interesting for the periodontitis treatment. Moreover, eutectic system has been increased the dissolution, permeation and absorption of some active compounds (Lazerges et al., 2010; Yong et al., 2004; Stott et al., 2001, 1998). Local periodontal pocket drug delivery has been gained the interest for periodontitis treatment (Esteban et al., 2009). Ibuprofen is nonsteroidal anti-inflammatory drugs (NSAIDs) which widely used to control the painful of dental disease (Alessandro et al., 2011). NSAIDs gel significantly reduced of plaque index, bleeding on probing and probing pocket depth (Amirhossein et al., 2016, Esteban et al., 2009). The prolonged release of local administration of NSAIDs solubilized in the pharmaceutical active solvent such as eutectic system is interesting. In this study, the local eutectic drug delivery system consisting of menthol, camphor and ibuprofen was developed and characterized as the potential drug delivery system for periodontitis treatment.

Materials and Methods

Materials

Menthol (M), camphor (C) and ibuprofen were purchased from P. C. Drug Center Co., Ltd., Bangkok, Thailand. Eudragit® E PO was purchased from Rohm GmbH & Co. KG, Pharma Polymers, Darmstadt, Germany. Methanol was purchased from SK chemicals Co., Ltd., Ulsan, Korea. Dimethyl sulfoxide (DMSO) was purchased from Fluka Chemie GmbH, Switzerland, N-methyl-2-pyrrolidone (NMP) was purchased from Sigma-Aldrich Co., Missouri, USA, Potassium dihydrogen phosphate and Sodium hydroxide were purchased from QReC, New Zealand.

Preparation of eutectic solvent

The 10 g of eutectic system comprising various ratios of menthol:camphor (M:C) (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1) were prepared in glass bottle and stirred on magnetic stirrer for 12 h. The physical appearance of each eutectic system was observed. The obtained clear eutectic systems were investigated their viscosity and rheology. The eutectic system which exhibited the lowest viscosity was selected as eutectic solvent in this study.

Preparation of ibuprofen eutectic solution (iES)

The 10%, 20% and 30% w/w ibuprofen in selected eutectic solution were prepared in glass bottle and stirred on magnetic stirrer for 12 h

Preparation of ibuprofen-loaded polymeric eutectic solution (PES)

30% w/w Eudragit® E PO and 10% w/w ibuprofen were loaded in eutectic solvent in glass bottle and stirred on magnetic stirrer for 12 h.

Viscosity and rheology measurements

Eutectic solvent and ibuprofen eutectic

solution were determined their viscosity and rheology behaviors using Brookfield viscometer (DV-III Ultra programmable rheometer, Brookfield engineering laboratories, Inc., Middleboro, USA) with a cone No.40. The viscosity of each system was collected at second 5 at room temperature (n=3). The rheology was run at room temperature using cone-and-plate geometry with a cone No. 40 (n=3).

Hot stage microscopy (HSM)

Melting behavior of menthol and camphor was investigated using hot-stage microscope (stage made by Mettler Toledo on an Olympus microscope) at magnification of 100x. Fine powder of each sample was placed onto a glass slide and covered with a cover slip. Measurement temperature was in range of 30^{O}C to 200^{O}C with heating rate of 10^{O}C/min.

Solubility of ibuprofen in various solvents

The solubility of ibuprofen in phosphate buffer solution (PBS) pH 6.2, distilled water, DMSO, NMP and eutectic solvent was investigated. Ibuprofen was added in each solvent until obtained saturated solutions. The supernatant of each system was diluted and measured amount of ibuprofen using UV spectrophotometer (Perkin-Elmer, Germany) at 220 nm (n=3). The solubility of ibuprofen in each solvent was calculated as mg of ibuprofen in 1 ml of solvent (mg/ml).

Drug release study

Ibuprofen eutectic solution and ibuprofen-loaded polymeric eutectic solution (0.5 g) was evaluated for drug release by dialysis tube method using shaking incubator (NB-205, N-Biotek, Korea) (n=3) at 50 rpm and 37°C. The 100 ml phosphate buffer solution pH 6.2 was used as release medium. The amount of drug released at specific time interval was measured using UV spectrophotometer at 220 nm.

Statistical study

All results were reported as mean and standard deviation.

Results

The clear liquid eutectic was obtained for the mixture of M:C in the ratio of 5:5 to 8:2. The 5:5 M:C exhibited the lowest viscosity as showed in Figure 1 because this ratio was the eutectic point exhibiting the lowest melting point of this system (Phaechamud et. al, 2015). The system of M:C at ratio 5:5 was selected as eutectic solvent in this study. This solvent consisted of the compounds which synthesized mimic the natural compound that low toxicity and edible thus this solvent was introduced as the green solvent (Parjikolaei et al., 2015).

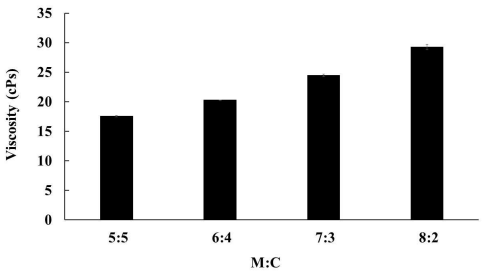

Figure 1 Viscosity of M:C eutectic system

Viscosity and rheology

Viscosity of iES was increased as concentration of ibuprofen increased. The PES exhibited high viscosity as showed in Figure 2 because eudragit® E PO is viscosity inducing agent. However all system showed the Newtonian flow behavior thus administration of this system was easily performed.

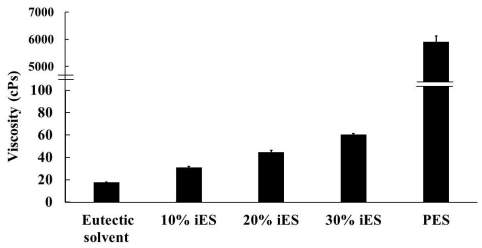

Figure 2 Viscosity of eutectic solvent, iES and PES

Hot stage microscopy (HSM)

The melting point of menthol demonstrated around 40°C as shown in Figure 3. The transformation from powder into melted menthol was evident. However, menthol and melted menthol sublimated and evaporated while melting.

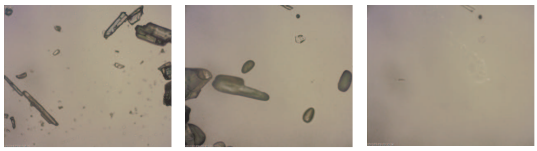

Figure 3 Melting behavior of menthol under HSM at magnification of 100x

Nevertheless the melting behavior of camphor could not be detected because camphor had high sublimation rate thus sublimating behavior was observed before their melting. Melting point of camphor was reported around 175°C (Phaechamud et. al, 2015). The sublimation of camphor is shown in Figure 4. Melting point of menthol and camphor was higher than room temperature (28°C) but the mixture of 5:5 M:C melted at room temperature indicating the behavior of the eutectic mixture.

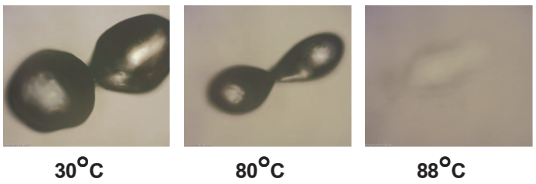

Figure 4 Sublimation behavior of camphor under HSM at magnification of 100x

Solubility of ibuprofen in various solvents

Solubility of ibuprofen in different solvents is presented in Table 1. The solubility of ibuprofen was as following: DMSO > NMP > eutectic solvent, respectively. However, solubility of ibuprofen in eutectic solvent was significantly higher than that in water. Solubility of ibuprofen in water and PBS pH 6.2 was less than 2 mg/ml.

Table 1 Solubility of ibuprofen in various solvents

Solvent	Solubility (mg/ml) ± SD
Eutectic solvent	501.36±12.00
Water	0.20±0.00
PBS pH 6.2	1.77±0.06
DMSO	1,369.77±3.17
NMP	1,247.47±10.35

Eutectic solvent containing menthol and camphor could load high amount of ibuprofen notably. This solvent was interesting for local treatment of periodontitis because menthol and camphor have local anesthetic and antimicrobial activities as reported previously (Al-Bayati, 2009; Patel et al., 2007; Shunying et al., 2005; Chang, 2004).

Drug released

The iES and PES prolonged the ibuprofen release as showed in Figure 5. The release rate of ibuprofen was higher in the systems with lower viscosity. The lowest drug release rate was obtained from PES because this system had eudragit® E PO to retard the diffusion of drug release because eudragit® E PO is water insoluble polymer (Flora et al., 2008). The drug release rate from PES was slower when concentration of ibuprofen was decreased. The success of topical subgingival gels treatment with 2.5 %w/w ibuprofen gel has been reported recently (Amirhossein et al., 2016). This study indicated that eutectic mixture containing eudragit® E PO could be used as local drug delivery system with adjustable released rate of drug for periodontitis treatment.

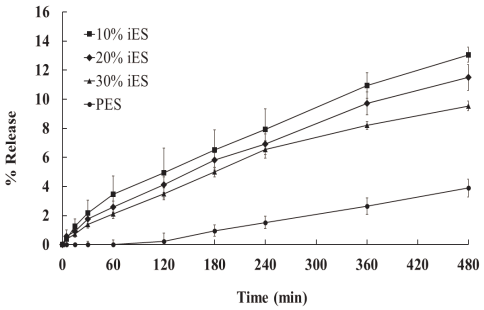

Figure 5 Release of ibuprofen from iES and PES

Discussions and Conclusion

The eutectic solvent comprising 5:5 M:C could be used as eutectic solvent for ibuprofen. The addition of eudragit® E PO into this system could modulate the drug release. The achievement for sustainable drug release using this eutectic system should be applicable for periodontitis treatment. Moreover, menthol and camphor used as eutectic compounds have local anesthetic and antimicrobial activities thus this

ibuprofen-loaded eutectic system exhibited as the potential delivery system for periodontitis treatment.

Acknowledgements

This research work was kindly supported by Faculty of Pharmacy, Silpakorn University and Thailand and the National Nanotechnology Center, National Science and Technology Development Agency (Grant P-11-00226).

References

Al-Bayati FA. Isolation and identification of antimicrobial compound from *Mentha longifolia* L. leaves grown wild in Iraq. *Ann Clin Microbiol Antimicrob*. 2009, 8:20 doi : 10.1186/1476-0711-8-20.

Alessandro P, Luca G. Pain management for dentists: the role of ibuprofen. *Annali di Stomatologia.* 2011, 2(3-4): 3-24.

Amirhossein F, Ferena S, Bahareh JE. Clinical efficacy of subgingivally delivered 2.5% ibuprofen gel in chronic periodontitis: a randomized controlled clinical trial. *J Int Oral Health*, 2016, 8(6): 651-656.

Bi M, Hwang S, Morris K. Mechanism of eutectic formation upon compaction and its effects on tablet properties. *Thermochim Acta*. 2003, 404, 213-226.

Biswal B, Karna N, Nayak J, Joshi V. (2014). Formulation and evaluation of microemulsion based topical hydrogel containing lornoxicam. *J Applie Pharm Sci*. 2014, 4, 77-84.

Chang CP, Leung TK, Lin SM, Hsu CC. Release properties on gelatin-gum arabic microcapsules containing camphor oil with added polystyrene. *Colloids Surf B*. 2006, 50(2): 136–140.

Esteban RF, Livia E, Lorella M. The use of topical subgingival gels of non-steroidal anti-inflammatory drugs (NSAIDs) as an adjunct to non-surgical management of chronic periodontitis. *Acta Odontol Latinoam*. 2009, 22: 215-219.

Flora JRV, Baker B, Wybenga D, Zhu H, Aelion CM. Preparation of acidic and alkaline macrocapsules for pH control. Chemosphere. 2008, 70(6): 1077–1084.

Gohel M, Nagori S. Fabrication and Evaluation of Hydrogel Thickened Microemulsion of ibuprofen for topical delivery. *Indian J Pharm Educ*. 2010, 44: 189-196.

Lazerges M, Rietveld I, Corvis Y, Céolin R, Espeau P. Thermodynamic studies of mixtures for topical anesthesia: lidocaine-salol binary phase diagram. *Thermochim Acta*. 2010, 497: 124-128.

Parjikolaei B, El-Houri R, Fretté X, Christensen K. Influence of green solvent extraction on carotenoid yield from shrimp (*Pandalus borealis*) processing waste. *J Food Eng*. 2015, 155: 22-28.

Patel T, Ishiuji Y, Yosipovitch, G. Menthol: A refreshing look at this ancient compound. *J Am Acad Dermatol*. 2007, 57(5): 873-878.

Phaechamud T, Tuntarawongsa S, Charoensuksai P. Evaporation Behavior and Characterization of Eutectic Solvent and Ibuprofen Eutectic Solution, *AAPS PharmSciTech*. 2016: 1213-1220.

Shunying Z, Yang Y, Huaidong Y, Yue Y, Guolin Z. Chemical composition and antimicrobial activity of the essential oils of Chrysanthemum. *indicum J Ethnopharmacol*. 2005, 96(1-2): 151–158.

Stott P, Williams A, Barry B. Mechanistic study into the enhanced transdermal permeation of a model β-blocker, propranolol, by fatty acids: a melting point depression effect. *Int J Pharm*. 2001, 219: 161-176.

Stott P, Williams A, Barry B. Transdermal delivery from eutectic systems: enhanced permeation of a model drug ibuprofen. *J Control Rel*. 1998, 50: 297–308.

Tyagi S, Panda A, Khan S. Formulation and evaluation of diclofenac diethylamine microemulsion incorporated in hydrogel. *World J Pharm Res*. 2012, 1: 1298-1319.

Woolfson A, Malcolm R, Campbell K, Jones D, Russell J. Rheological, mechanical and membrane penetration properties of novel dual drug systems for percutaneous delivery. *J Control Rel*. 2000, 67, 395-408.

Yong C, Oh Y, Jung S, Rhee J, Kim H, Kim C, Choi H. Preparation of ibuprofen-loaded liquid suppository using eutectic mixture system with menthol. *Eur J Pharm Sci*. 2004, 23: 347-353.