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Polymeric Eutectic Drug Delivery System

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Abstract

Eutectic system is the mixture of at least two substances that suppresses melting point for each of them. The viscosity enhancement of liquid eutectic by polymer addition might increase the viscous environment for retardation of drug release. Typically, there are rare polymers that can dissolve in the liquid eutectic. The aim of this study was to develop the polymeric eutectic delivery system for controlling the drug delivery. Liquid eutectic used as vehicle was prepared by mixing menthol and camphor in various ratios. The obtained lowest viscosity liquid eutectic was used as vehicle in this study. Various polymers were attempted to dissolve in this vehicle to prepare the polymeric eutectic system. Different physical properties of selected polymeric eutectic system were evaluated. Viscosity and rheology were evaluated by brookfield viscometer. Contact angle on glass slide and polydimethylsiloxane (PDMS) coated slide and interfacial tension were measured by goniometer. The polymeric eutectic system selected for controlling the drug delivery contained 30%w/w eudragit® EPO in 1:1 menthol:camphor. This system could be injectable with the newtonian flow property. Contact angle and interfacial tension indicated the hydrophobic characteristic of developed system which it was suitable to sustain the drug release. Various drugs were tested for incorporating in this developed liquid eutectic. Ibuprofen was the most suitable drug because of its high solubility in this system. Solubility of ibuprofen in liquid eutectic was higher than that in water about 1.1×10^4 folds. Viscosity of liquid eutectic increased as a function of ibuprofen concentration with the newtonian flow behavior. Drug released from this polymeric eutectic system were tested by dialysis tube method at 50 rpm and 37°C. The sustainable drug release could be obtained longer than 7 days with release kinetics primarily as diffusion control. Therefore this developed polymeric liquid eutectic was suitable as the new controlled drug delivery system such as for periodontitis treatment and other injectable dosage forms.

Keywords: Eutectic mixture, menthol, camphor and polymer

Introduction

Eutectic system is a two or more composition mixture that suppress the melting point of each pure compound due to the increased total entropy of systems.[1,2] For pharmaceutical field, the eutectic system has been applied in many proposes such as increase of drug solubility, permeation and absorption[3-6] or applying as oil phase in emulsion system.[7,8] In addition, the system of liquid eutectic consisting of quaternary ammonium salts and organic compound has been used as deep eutectic solvent (DES)[9-12] that was less toxic, cheap, biodegradable and non flammable[9]. Menthol has typically used as eutectic components having the pharmaceutical actions such as local anesthetic, pain reliever, antipuritic, antiflatulent[13] and antimicrobials.[14] Moreover, menthol is a permeation enhancer.[13] Menthol could form the liquid eutectic at room temperature with camphor that is the active agent for analgesic, anti-inflammatory, carminative[15] and antimicrobials.[16-17] In our previous work, the mixture between menthol-camphor, menthol-borneol, menthol-*N*-Ethyl-5-methyl-2-(1-methylethyl) cyclohexane-carboxamide (WS-3) were tested for their eutectic formation behavior.[18] The liquid eutectic delivery system such as liquid suppository could increase the drug bioavailability.[5] To prolong drug release the polymer could be alternatively incorporated in the delivery system for retardation of drug diffusion. The attempt of this study is to investigate the suitable polymeric material and drug which can dissolve in the selected eutectic mixture. The sustainable release property of incorporated drug with the obtained system was tested. To develop the polymeric eutectic drug delivery system, various polymers and drugs were incorporated in liquid eutectic containing menthol

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and camphor. The physical properties, released test and release mechanism of developed system were evaluated.

Materials and Experimental Procedures

Materials

Menthol (M) and camphor (C) were purchased from P. C. Drug Center Co., Ltd., Bangkok, Thailand. Poly(butylenes succinate) (PBS), polylactic acid (PLA), poly-3-hydroxy butyrate-co-valerate (PHBV) were kindly provided by SCG, Rayong, Thailand. Ethylene-vinyl acetate (EVA) was kindly provided by Shelic, Bangkok, Thailand. Eudragit® L100, eudragit® S100, eudragit® RL PO, eudragit® RS PO and eudragit® EPO were purchased from Rohm GmbH & Co. KG, Pharma Polymers, Darmstadt, Germany. Sylgard® 184 polydimethylsiloxane (PDMS) was purchased from Dow corning corporation, Midland, USA. N-methyl-2-pyrrolidone (NMP) was purchased from Acros organics (Geel, Belgium). Ibuprofen paracetamol, chloramphenical, dichlofenac sodium, piroxicam, aspirin, indomethacin and clotrimazole were supplied by P.C.Drug Center Co., Ltd., Thailand. Nevirapine and azithromycin were kindly supported by The Government Pharmaceutical Organization (GPO), Bangkok, Thailand.

Methods

Preparation of Liquid Eutectic

The liquid eutectic was prepared by gentlely mixing menthol and camphor in various ratio (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1) in beaker at room temperature. The physical appearance and viscosity were determined. Viscosity and rheology at room temperature were evaluated using brookfield viscometer (DV-III Ultra programmable rheometer, Brookfield engineering laboratories, Inc., Middleboro, USA) performed in a cone-and-plate geometry with a cone no.40 or 50 for low viscosity and high viscosity, respectively. The shear rates ranged from 0.1 up to $100s^{-1}$ (n=3). The prepared liquid eutectic exhibiting lowest viscosity was selected for further study as vehicle for polymer solubilization.

Preparation of Polymeric Solution

Poly(butylenes succinate) (PBS), polylactic acid (PLA), poly-3-hydroxy butyrate-co-valerate (PHBV), ethylene-vinyl acetate (EVA), eudragit® L100 (L100), eudragit® S100 (S100), eudragit® RL PO (RL), eudragit® RS PO (RS), eudragit® E PO (E) of 1% w/w were added in eutectic system comprising 1:1 menthol:camphor. Physical appearance of the prepared systems was visually observed. The selected soluble polymer was dissolved with higher concentration in liquid eutectic and evaluated for their physical appearance, viscosity, rheology, contact angle and surface tension. The contact angle onto the glass slide (hydrophilic surface) and PDMS coated slide (hydrophobic surface) of each system was measured by sessile drop technique (n=3), contact time at 5 sec after dropping. The pendant drop technique was used for surface tension determination using goniometer (FTA 1000, First Ten Angstroms, USA) (n=3).

Selection of Model Drug

Ibuprofen, paracetamol, chloramphenical, dichlofenac sodium, piroxicam, aspirin, indomethacin, clotrimazole, nevirapine and azithromycin of 1% w/w for each of them were individually dissolved in selected liquid eutectic. The higher amount of soluble drug was loaded in this selected eutectic system.

Preparation of Polymeric Eutectic Drug Delivery System

The selected polymer and drug were used to prepare the polymeric eutectic drug delivery system by using the liquid eutectic as vehicle. The viscosity, rheology, drug solubility and released test of prepared systems were evaluated.

Drug Solubility Test

The excess drug was added in liquid eutectic or water and kept at ambient condition for 24 hours. The supernatant of saturated drug solution was measured for the drug content by High performance liquid chromatography (HPLC) (Agilent 1100, Agilent, Germany) (n=3) with UV detector at 264 nm using ACE C-18 PEP column and acetonitrite (ACN) : 0.001 M H_2PO_3 in ratio of 50:50 as medium, flow rate of 1 ml/min.

Drug Released Test

The polymeric eutectic drug delivery system (1 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 6.8 was used as release medium. The same concentration of active compound in liquid eutectic and NMP were used as control. The amount of drug released at specific time interval was measured by HPLC method with the condition as same as that from solubility test. Least square fitting the experimental released data to the mathematical expressions (power law, first order, Higuchi's and zero order) were carried out using Scientist® 2.1 program to investigate the release mechanism. The coefficient of determination (r^2) and model selection criterion (msc) were used to indicate the goodness of curve fitting.

Results and Discussion

Preparation of Polymeric Solution

The liquid eutectic was obtained for the mixture of menthol:camphor in the ratio of 5:5 to 8:2 whereas the other ratios were solid combined with liquid like. The ratio of 5:5 showed the lowest viscosity and all obtained liquid systems showed Newtonian rheological behavior as our previous work reported.[18] The liquid eutectic in ratio 5:5 was selected as vehicle since its low viscosity was suitable for employing as injectable vehicle.

Eudragit® E PO and eudragit® RS PO could dissolve in selected liquid eutectic but eudragit® RS PO had to be stirred over night to completely dissolve them whereas other polymers could not dissolve. Therefore the selected polymer was eudragit® E PO. This polymer is aminoalkyl methacrylate copolymers with dimethyl aminoethyl functional group[19] that could be used in pharmaceutical filed to prolong the drug release[20] and to improve the adhesiveness of some dosage forms[21]. The viscosity of polymeric system was increased as polymer concentration was increased as shown in Figure 1 therefore this polymer could promote the viscous environment of liquid eutectic. Typically, the lower contact angle on glass slide related with hydrophilic property of liquid whereas the lower contact angle on PDMS coated slide related with hydrophobic property of the test liquid. By comparison with selected liquid eutectic, an addition of eudragit® E PO that is pH dependent water soluble polymer could increase the hydrophilic property of this system when the polymer concentration was lower than 20% w/w. The system exhibited high viscosity and decreased the hydrophilic property with higher contact angle than selected liquid eutectic. When compared with water, the hydrophilicity of the selected liquid eutectic and low viscosity polymeric system was not different. The hydrophilic property of high viscosity polymeric system (more than 20% w/w eudragit® E PO) was dropped and the hydrophobic property of selected liquid eutectic system and polymeric system was higher than water as shown in Figure 2. The interfacial tension of selected liquid eutectic and the polymeric system was not different as function of polymer concentration as shown in Figure 3. From rheological study, this polymeric system showed the Newtonian flow (data not shown). From contact angle and interfacial tension determinations the developed system demonstrated the high hydrophobic property that was suitable for prolongation of drug release into aqueous medium. The 30% w/w eudragit® E PO was selected as polymer in delivery system comprising 5:5 menthol:camphor, since the higher amount polymer was necessary for the formation of the dense matrix or gel to prolong the drug release. The higher concentration of polymer in this eutectic mixture could not be prepared owing to the limitation of polymer solubility in this system. Some polymeric solution which are injectable system have been used as delivery system for treatment periodontitis by intracanal route.[22-27]

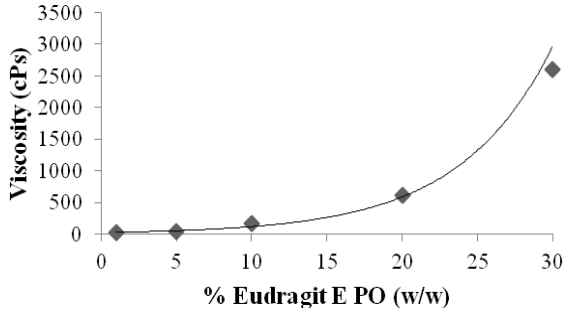

Figure 1. Viscosity of liquid eutectic comprising different amounts of eudragit® E PO

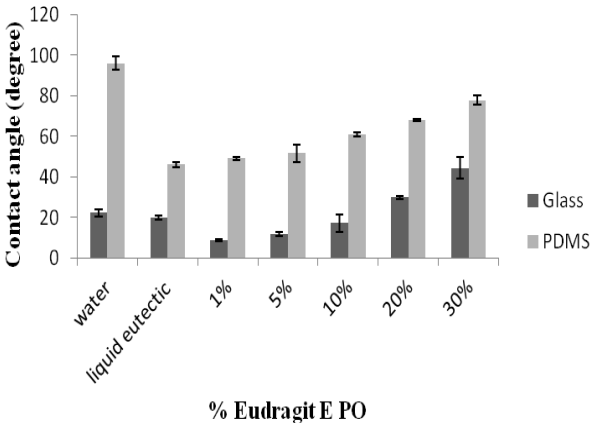

Figure 2. Contact angle of liquid eutectic containing different amounts of eudragit® E PO.

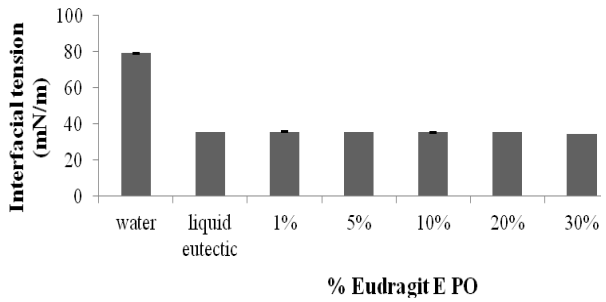

Figure 3. Interfacial tension of liquid eutectic containing eudragit® E PO.

Selection of Model Drug

The drugs that could dissolve in selected liquid eutectic were ibuprofen and azithromycin. Ibuprofen could dissolve up to 30% w/w and azithromycin could dissolve up to 20% w/w whereas the other drugs could not dissolve. Ibuprofen was selected as a model drug in this study. Many research developed the system of ibuprofen for transdermal[3] and rectal delivery.[5] Administration of ibuprofen as eutectic system could increase bioavailability. Ibuprofen was notably used in dentistical field[28] due to anti-inflammatory effect and delaying destruction of jaw[29,30]. Water solubility of ibuprofen was 0.02±0.00 mg/ml and liquid eutectic solubility of this drug was 292.13±6.77 mg/ml that more than water solubility about $1.5x10^4$ times therefore this liquid eutectic performed as DES for ibuprofen. The viscosity of liquid eutectic increased as ibuprofen concentration increased as showed in Figure 4 whereas the rheological behavior of all systems exhibited as Newtonian flow.

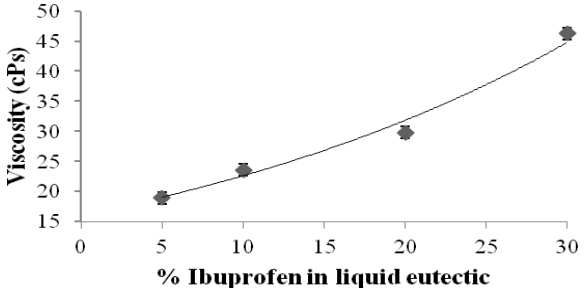

Figure 4. Viscosity of liquid eutectic (5:5 menthol : camphor) containing different amount of ibuprofen.

Drug Release Test

The polymeric eutectic drug delivery system containing 10% w/w ibuprofen, 30% w/w eudragit® E PO in 5:5 menthol:camphor was prepared by mixing all of them in beaker at room temparature. The 10%w/w ibuprofen for cream and gel are the commercial products in the market. This delivery system was injectable solution with viscosity of 12426.75 ± 20.21 cPs and Newtonian flow behavior. The dissolution profile of drug from this polymeric eutectic system, liquid eutectic and NMP are showed in Figure 5. The polymeric eutectic delivery system could extend drug release longer than liquid eutectic and NMP, respectively. Ibuprofen in NMP completely released within 44 hours. The hydrophobic property of liquid eutectic could retard the drug release which the 54.78±0.63% drug was released at 152 hours. The polymeric eutectic delivery system liberated 28.13±2.43% of drug at 152 h because of the controlled released property of eudragit® E PO as described previously[19,20] and also the hydrophobic property of employed eutectic system. The addition of eudragit® E PO could promote the viscous environment therefore the diffusion of drug molecule into the release medium was slower. Drug dissolution profiles fitting indicated the best fitting of drug released with Higuchi's model as present in Table 1 and the drug release kinetics primarily as diffusion control while ibuprofen in NMP showed the best fitting with first order model and the drug release kinetics primarily as anomalous mechanism with concentration dependent.

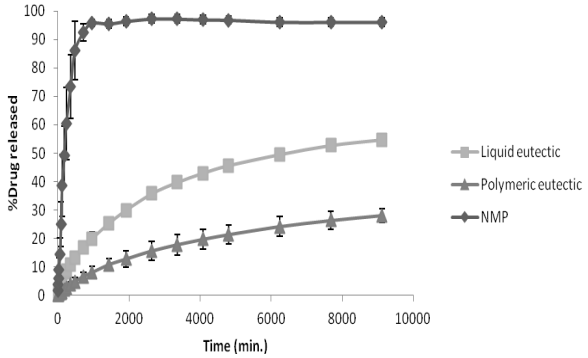

Figure 5. Dissolution profile of ibuprofen form liquid eutectic, NMP and polymeric eutectic delivery system

Table 1. The coefficient of determination (r^2) and model selection criterion (msc) from curve fitting of drug dissolution profiles with release equation.

Sample	Best fitting model	Model selection criterion (msc)	Coefficient of determination (r^2)
Polymeric eutectic	Higuchi's	5.81	0.9977
Liquid eutectic	Higuchi's	4.09	0.9865
NMP	First order	4.60	0.9939

Conclusion

Polymeric liquid eutectic comprising eudragit® E PO dispersed in 5:5 menthol:camphor was employed as vehicle for ibuprofen loading. This polymeric eutectic drug delivery system was injectable solution that could prolong drug released longer than 7 days because of hydrophobic property of liquid eutectic and controlled release property of eudragit® E PO. This system could apply to delivery ibuprofen for long time treatment in some case such as periodontitis treatment by intra-canal drug delivery route.

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References

1. Woolfson, A.D., Malcolm, R.K., Campbell, K., Jones, D.S. and Russell, J.A. (2000). Rheological, mechanical and membrane penetration properties of novel dual drug systems for percutaneous delivery. *J. Control. Rel.* **67(2-3)** : 395-408.

2. Bi, M., Hwang, S.J. and Morris, K.R. (2003). Mechanism of eutectic formation upon compaction and its effects on tablet properties. *Thermochim. Acta.* **404(1-2)** : 213-226.

3. Stott, P.W., Williams, A.C. and Barry, B.W. (1998). Transdermal delivery from eutectic systems: enhanced permeation of a model drug, ibuprofen. *J. Control. Rel.* **50(1-3)** : 297– 308.

4. Stott, P.W., Williams, A.C. and Barry, B.W. (2001). Mechanistic study into the enhanced transdermal permeation of a model β-blocker, propranolol, by fatty acids: a melting point depression effect *Int. J. Pharm.* 219(1-2) : 161-176.

5. Yong, C.S., Oh, Y.K., Jung, S.H., Rhee, J., Kim, H., Kim, C. and Choi, H. (2004). Preparation of ibuprofen-loaded liquid suppository using eutectic mixture system with menthol. *Eur. J. Pharm. Sci.* **23(4-5)** : 347-353.

6. Lazerges, M., Rietveld, I.B., Corvis, Y., Céolin, R. and Espeau, P. (2010). Thermodynamic studies of mixtures for topical anesthesia: Lidocaine–salol binary phase diagram. *Thermochim. Acta.* **497(1-2)** : 124-128.

7. Wahlgren, C.F. & Quiding, H. (2000). Depth of cutaneous analgesia after application of a eutectic mixture of the local anesthetics lidocaine and prilocaine (EMLA cream). *J. Am. Acad. Dermatol.* **42(4)** : 584-588.

8. Nazzal, S., Smalyukh, I.I., Lavrentovich, O.D. and Khan, M.A. (2002). Preparation and in vitro characterization of a eutectic based semisolid self-nanoemulsified drug delivery system (SNEDDS) of ubiquinone: mechanism and progress of emulsion formation. *Int. J. Pharm.* **235(1-2)** : 247-265.

9. Morrison, H.G., Sun, C.C. and Neervannan, S. (2009). Characterization of thermal behavior of deep eutectic solvents and their potential as drug solubilization vehicles. *Int. J. Pharm.* **378(1-2)** : 136-139.

10. Lindberg, D., Revenga, M. and Widersten, M. (2010). Deep eutectic solvents (DESs) are viable cosolvents for enzyme-catalyzed epoxide hydrolysis. *J. Biotechol.* **147 (2010)** : 169-171.

11. Miller, R.F. (2009). Deep eutectic solvents and applications. *US patent 20090247432*.

12. Domınguez de Marıa, P. and Maugeri, Z. (2011). Ionic liquids in biotransformations: from proof-of-concept to emerging deep-eutectic-solvents. *Curr. Opin. Chem. Biol.* **15(2)** : 220-225.

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

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

15. Chang, C.P., Leung, T.K., Lin, S.M. and Hsu, C.C. (2006). Release properties on gelatin-gum arabic microcapsules containing camphor oil with added polystyrene. *Colloids. Surf. B.* **50(2)** : 136–140.

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

17. Kotan, R., Kordali, S., Cakir, A., Kesdek, M., Kaya, Y. and Kilic, H. (2008). Antimicrobial and insecticidal activities of essential oil isolated from Turkish *Salvia hydrangea* DC. ex Benth. *Biochem. Syst. Ecol.* **36(5-6)** : 360-368.

18. Phaechamud, T. and Tuntarawongsa, S. (2012). Menthol, borneol, camphor and WS-3 eutectic mixture. *Adv. Mat. Res.* **506** : 355-358.

19. Evonik Röhm GmbH Pharma Polymers. *EUDRAGIT® Acrylic Polymers for Solid Oral Dosage Forms* : 1-14.

20. Flora, J.R.V., Baker, B., Wybenga, D., Zhu, H. and Aelion, C.M. (2008). Preparation of acidic and alkaline macrocapsules for pH control. *Chemosphere.* **70(6)** : 1077–1084.

21. Elgindy, N. and Samy, W. (2009). Evaluation of the mechanical properties and drug release of cross-linked Eudragit films containing metronidazole. *Int. J. Pharm.* 376(1-2) : 1-6.

22. Scherlund, M., Welin-Berger, K., Brodin, A. and Maimsten, M. (2001). Local anaesthetic block copolymer system undergoing phase transition on dilution with water. *Eur. J. Pharm. Sci.* **14(1)** : 53-61.

23. Kelly, H.M., Deasy, P.B., Ziaka, E. and Claffey, N. (2004). Formulation and preliminary in vivo dog studies of a novel drug delivery system for the treatment of periodontitis. *Int. J. Pharm.* **274(1-2)** : 167-183.

24. Chotichanapibal, B. (1998). *Clinical effects of the intra-pocket irrigation with tetracycline hydrochloride solution as an adjunct to root planning in adult periodontitis [dissertation]*. Bangkok: Chulalongkorn University.

25. Norling, T., Loding, P. and Engstrom, S. (1992). Formulation of a drug delivery system based on a mixture of monoglycerides and triglycerides for use in the treatment of periodontal disease. *J. Clin. Peridontol.* **19(9)** : 687-692.

26. Van Steenberghe, D. (1994). Antibiotic gels for periodontal disease. *Drug and Therapeutic Bulletin.* **32(6)** : 43-44.

27. Friskopp, J., Nilsson, M. and Isacsson, G. (2001). The anesthetic onset and duration of a new lidocaine/prilocaine gel intra-pocket anesthetic (Oraqix®) for periodontal scaling/root planing. *J. Clin. Periodontol.* **28(5)** : 453-458.

28. Hargreaves, K. and Abbott, P.V. (2005). Drugs for pain management in dentistry. *Aust. Dent. J. Suppl.* **50(4)** : S14-S22.

29. Parirokh, M., Ashouri, R., Rekabi, A.R., Nakhaee, N., Pardakhti, A. and Askarifard, S. (2010). The effect of premedication with ibuprofen and indomethacin on the success of interior alveolar nerve block for teeth with irreversible pulpitis. *J. Endod.* **36(9)** :1450-1454.

30. Williams, R.C. (2008). Host modulation for the treatment of periodontal diseases. *Compend. Contin. Educ. Dent.* **29(3)** : 160-168.