Thermal Properties and Rheological Behaviors of the Anesthetic Gel Containing Lidocaine and Prilocaine

นิพนธ์ต้นฉบับ **Original Article**

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บทคัดย่อ

วัตถุประสงค์: เพื่อพัฒนาสูตรตำรับเบื้องต้นของยาชา ลิโดเคน (lidocaine) และพริโลเคน (prilocaine) ในรูปแบบเจล และประเมินคุณสมบัติเชิงความร้อนและพฤติกรรมการไหล **วิธีการศึกษา:** ศึกษาคุณสมบัติเชิงความร้อนของสารด้วยเครื่องดิฟเฟอเรนเชียลสแกนนิงแคลอริมิเตอร์ การละลายของยาในระบบตัวทำละลายร่วม หาสารก่อเจลที่เหมาะสม และศึกษาพฤติกรรมการไหลของตำรับ **ผลการศึกษา:** ผลคุณสมบัติเชิงความร้อนของสารพบว่า การผสมยาลิโดเคนต่อพริโลเคนที่อัตราส่วน 1:1 ทำให้เกิดระบบสารผสมยูเทกติกขึ้นได้ ระบบตัวทำละลายร่วมที่เหมาะสมในการละลายยาทั้งสองชนิดคือสารละลายแอลกอฮอล์ในน้ำความเข้มข้นร้อยละ 35 โดยน้ำหนัก สารก่อเจลในตำรับที่เหมาะสมคือคาร์โบพอล 940 (carbopol 940) เมื่อเทียบกับครีมยาชาที่มีขายในท้องตลาด (EMLA® cream) พบว่าเจลที่พัฒนาขึ้นมีการไหลที่คล้ายคลึงกันเป็นแบบซูโดพลาสติกคือยิ่งให้แรงยิ่งไหลง่าย และพบว่าการเปลี่ยนแปลงอุณหภูมิขณะทำการทดสอบไม่มีผลต่อรูปแบบการไหลของตำรับ **สรุป:** การพัฒนาสูตรตำรับและการประเมินเจลยาชาลิโดเคนและพริโลเคนในเบื้องต้นนี้ สามารถนำไปพัฒนาต่อยอดให้เกิดเป็นสูตรตำรับที่เหมาะสมต่อไปได้ในอนาคต

คำสำคัญ: ลิโดเคน, พริโลเคน, เจล, สารผสมยูเทกติก, คุณสมบัติเชิงความร้อน, พฤติกรรมการไหล

Abstract

Objectives: To develop a gel containing lidocaine and prilocaine and to characterize its thermal and rheological properties. **Methods:** The thermal property by differential scanning calorimeter (DSC), solubility of the drugs in co-solvent system, suitable gelling agent and rheological behavior were evaluated. **Results:** DSC study revealed that lidocaine:prilocaine at the ratio of 1:1 could form a eutectic mixture. The co-solvent system, 35% w/w ethanol was used to dissolve these drugs. The 1% w/w carbopol 940 was an appropriate gelling agent. The developed gel and EMLA® cream showed a comparable pseudoplastic flow (shear thinning system). In addition, the changing of temperature did not affect the gels' rheological behavior. **Conclusion:** This study of the lidocaine-prilocaine gel formulation can be useful for the further development.

Keyword: lidocaine, prilocaine, gel, eutectic mixture, thermal properties, rheological behaviors

Introduction

Periodontitis is the inflammation and infection of the ligaments and bones that support the teeth. Loss of support causes the teeth to become loose and eventually fall out.[1] The treatment of advanced periodontitis may require dental surgery that local anesthetics may be needed. Local anesthetics commonly used in dentistry include lidocaine, mepivacaine, prolocaine, and prilocaine. Lidocaine or lignocaine is amide type local anesthetics with a fast onset of action, medium duration of action, and low toxicity. Because of its good properties, lidocaine is also widely used to relieve skin pain caused by skin irritation such as sun burn, insect bite, climber or tree poisoning, small injury, bruise/scratch, and hemorrhoids and pain in oral cavity. In addition, lidociane is used as an anesthetic to the gum in dental procedures and the skin in surgical procedures. Prilocaine is amide type local anesthetics which has pharmacokinetic and pharmacodynamic profile similar to lidocaine. The onset of action of prilocaine is fast; however the duration of action is longer than lidocaine. Another advantage of prilocaine over lidocaine is its lower toxicity with a faster excretion and a higher volume of distribution. The combination of lidocaine and prilocaine provides a good local anesthetic effect with low toxicity.[2-4] The mean onset time of surgical analgesia of both lidocaine and prilocaine is 10 min.[5] Lidocaine is eliminated with a terminal elimination phase half-life ($t_{½\,\beta}$) of 2.9 hrs. The total body clearance of lidocaine is 68 L/h. While prilocaine is rapidly eliminated with a $t_{½\,\beta}$ of 2.1 hrs which is somewhat comparable to that of lidocaine; the total body clearance of prilocaine (150 L/h) was higher than that of lidocaine. Both compounds demonstrate a comparable volume of distribution (V_d); while both the volume of distribution at steady-state (V_{ss}) and the

volume of distribution in the second compartment (V_β) values of prilocaine are 1.6 times higher than those of lidocaine.[5]

Both lidocaine and prilocaine separately are solid bases. However, when they are mixed together, the eutectic mixture is formed from solid to oil without the use of any solvent. The melting point of lidocaine-prilocaine eutectic mixture is lower than those of the individual components and in liquid form. Therefore, the mixture was definitely homogeneously incorporated into the gel base.[6,7]

This study aimed to develop the local anesthetics gel containing lidocaine and prilocaine, and to characterize the thermal and rheological properties of the prepared gel. The thermal property of the drugs, gelling agent and mixtures were determined. The solubility of the drug and eutectic mixture were evaluated. The suitable kind of gelling agent and the rheological behavior of developed gels were examined.

Materials and Methods

Materials

Lidocaine, prilocaine and EMLA® cream (AstraZeneca Canada Inc., Ontario, Canada) were kindly supported from T. Man Pharma Limited Partnership. Poloxamer 407, carbopol 940, carbopol ultralize, hydroxyethyl cellulose (HEC) and hydroxypropyl methylcellulose (HPMC) were purchased from VITA Co., Ltd, Bangkok, Thailand. Polyethylene oxide (polyox 303) (Lot. No. GA263364, Colorcon Asia Pacific Pte., Ltd, Singapore), polyox N12K (Lot. No. GA229281, Colorcon Asia Pacific Pte., Ltd, Singapore), sepigel 305 (B/No. T52135, Adinop Co., Ltd.), sepiplus 265 (B/No. T44031, Adinop Co., Ltd.), sepiplus 400 (B/No. T43131), simulgel EG (B/No. T51411) and simulgel NS (B/No. T40641) were purchased from Adinop Co., Ltd., Bangkok, Thailand. Ethanol, *N*-methyl pyrrolidone, triethanolamine, propylene glycol and hydrochloric were purchased from PC drug, Bangkok, Thailand.

Methods

Thermal analysis

The differential scanning calorimeter (DSC) (Pyris Sapphrie DSC, Standard 115V, Perkin Elmer instruments, Japan) was used to investigate the melting temperature of prilocaine, lidocaine, carbopol 940 and poloxamer 407 and thermal behavior of the mixture of lidocaine:prilocaine at the ratios of 1:1, 1:9 and 9:1, lidocaine:carbopol 940 at the ratio of 1:1, prilocaine:carbopol 940 at the ratio of 1:1 and lidocaine:prilocaine:carbopol 940 at the ratio of 1:1:2, lidocaine:poloxamer 407 at the ratio of 1:1, prilocaine:poloxamer 407 at the ratio of 1:1 and lidocaine:prilocaine:poloxamer 407 at the ratio of 1:1:2. The DSC was operated under N_2 atmosphere and heated from 10 to 200 °C at a heating rate of 10 °C/min.

Solubility study of prilocaine and lidocaine

Lidocaine:prilocaine at a ratio of 1:1 for 5% w/w was used for solubility study. The co-solvent systems of ethanol-water and NMP-water at 2, 4, 6, 8, 10, 15, 20, 30, 35 and 50% w/w of ethanol and NMP were used. The drugs were mixed into each co-solvent system and the clarity of those solutions was investigated.

The selection of suitable gelling agent

Gels were prepared by various gelling agents such as poloxamer 407, carbopol 940, carbopol ultralize, HEC, HPMC, polyox 303, polyox N12K, sepigel 305, sepiplus 265, sepiplus 400, simulgel EG and simulgel NS. These gelling agents at various concentrations were dispersed into water to form gel bases. The viscosity and clarity of gels were investigated. The pH of suitable gel bases was adjusted by concentrated HCl and triethanolamine to pH 9 to allow for the penetration of the local anesthetic agents.[8]

Preparation of lidocaine and prilocaine gel

2.5% w/w lidocaine and 2.5% w/w prilocaine were prepared by dissolving the two compounds in 35% w/w ethanol. 1% w/w of carbopol 940 and 15% w/w of propylene glycol, as gelling agents, were prepared by dissolving the two substances in purified water. These two systems were further mixed together and the pH was adjusted to 9 with triethanolamine.

Rheological behavior study

The rheological behavior of gels containing lidocaine and prilocaine was investigated and compared with that of EMLA® cream by determining their shear stress as a function of shear rate in a Brookfield DV-III Ultra programmable rheometer (HADV-III U CP, Brookfield Engineering Laboratory, USA). The effect of temperature on

rheological behavior of gels was tested. The measurements were conducted at three different temperatures, specifically 4, 28 and 35 °C.

Results and Discussions

Thermal properties

DSC is a method to determine the melting temperature and incompatibility of substances. DSC thermograms in Figure 1 show the melting points of pure lidocaine (1a), pure prilocaine (1b) and pure poloxamer 407 (1d) with the endothermic peaks at 66.5, 37.9 and 53.1 °C, respectively. However, the carbopol 940 showed a broad endothermic peak of dehydration at 61.7 °C (Figure 1c).

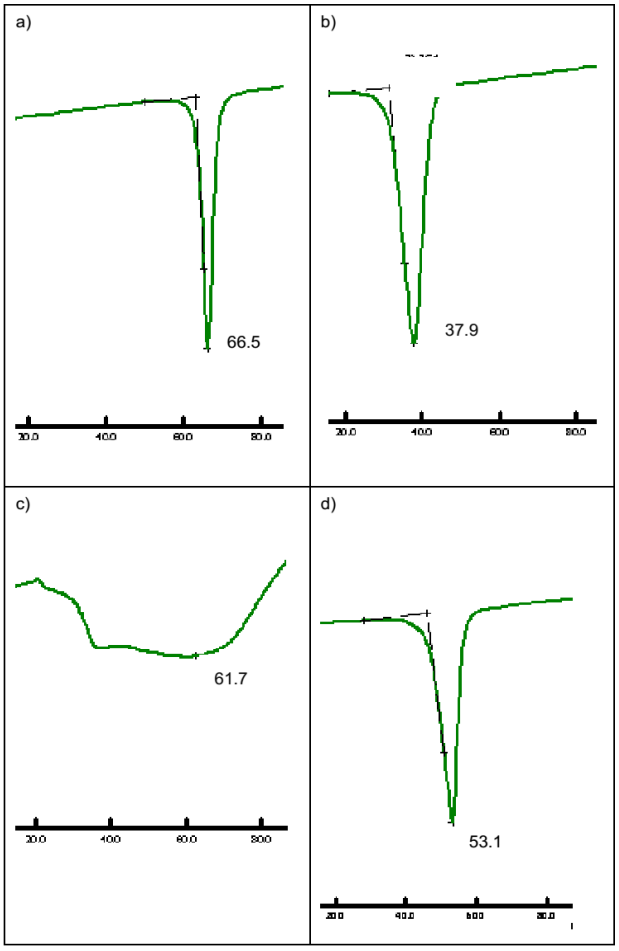

Figure 1 DSC thermograms of a) lidocaine, b) prilocaine, c) carbopol 940 and d) poloxamer 407.

DSC thermogram of lidocaine:prilocaine at the ratio of 1:1 showed the eutectic behavior that the mixture became a liquid form at room temperature and the melting point was lower than that of pure drugs (Figure 2a). The eutectic mixture system could promote the solubility and absorption of the drugs.[9] Similarly,1:1 eutectic mixture of lidocaine and prilocaine emulsified in water was investigated with a poly (dimethylsiloxane) membrane partition model.[10] The major advantages of using the emulsion formulation based on a eutectic mixture include the presence of local anesthetic bases in their permeable uncharged forms and the use of a low water content system (poor water) as the vehicle which could provide a saturated system at low concentrations. The droplets consist of a dissolvable drug and act as reservoirs to obtain steady-state release and the fluid state of the excess drug provides a dissolution rate higher than that from a solid state.[10] On the other hand, Chun *et al.* found that the eutectic mixture could be formed with the ratio of 3:1 (lidocaine:prilocaine) by DSC study. The permeation of both lidocaine and prilocaine increased; however crystallization was observed.[11] The melting points of lidocaine:prilocaine mixtures at the ratios of 1:9 and 9:1 revealed the endothermic peaks at 33.2 °C of prilocaine (Figure 2b) and 58.4 °C of lidocaine (Figure 2c), respectively.

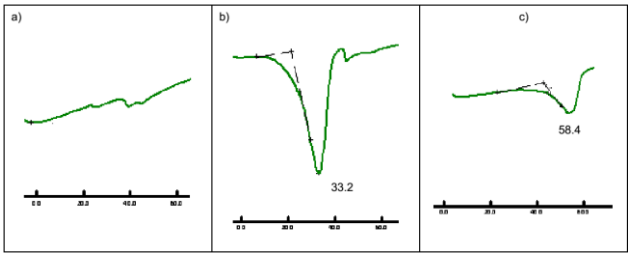

Figure 2 DSC thermogram of lidocaine:prilocaine at the ratio of a) 1:1 b) 1:9 and c) 9:1.

However, the eutectic mixture did not occur with these ratios. The DSC thermogram of 1:1 lidocaine:carbopol 940 only exhibited the melting point of lidocaine (Figure 3a) and that of 1:1 prilocaine:carbopol 940 only exhibited the melting point of prilocaine (Figure 3b). DSC thermogram of 1:1:2 lidocaine:prilocaine:carbopol 940, with carbopol mixed with each drug before mixing altogether, showed individual melting points of both prilocaine and lidocaine (Figure 3c). These result indicated that the components in the mixture were intact because the melting point of each substance was not changed.[12] Since lidocaine and prilocaine were separately enwrapped by carbopol 940 polymer before the final mixing, the contact of the two anesthetic agents was thus prevented. The eutectic formation was therefore disturbed by carbopol 940. On the other hand, with lidocaine and prilocaine mixed together before the final mixing with

carbopol 940, DSC thermograms of 1:1:2 lidocaine: prilocaine:carbopol 940 exhibited only the melting point of the eutectic mixture (Figure 3d). This result indicated that the eutectic behavior was detectable.

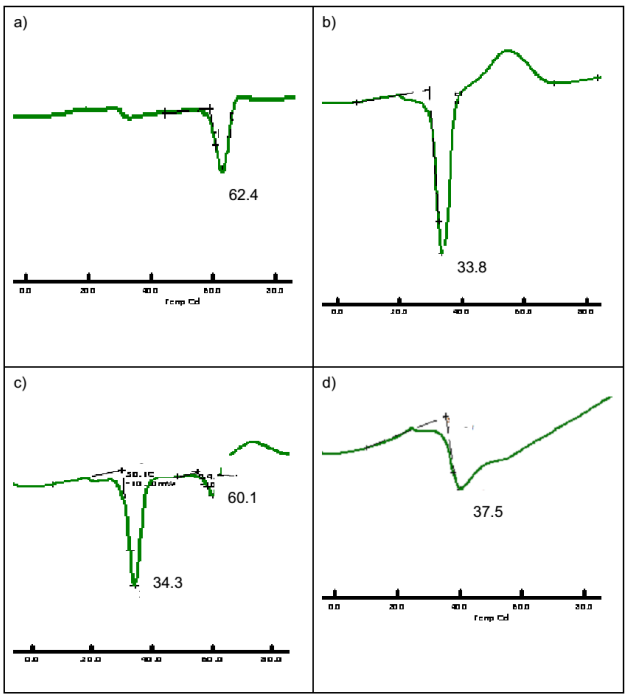

Figure 3 DSC thermograms of a) 1:1 lidocaine:carbopol 940, b) 1:1 prilocaine:carbopol 940, c) 1:1:2 lidocaine: prilocaine: carbopol 940 when carbopol was mixed with the single pure drug before mixing the other drug and d) 1:1:2 lidocaine:prilocaine:carbopol 940 when both of pure drugs were mixed before mixing with carbopol.

DSC thermograms of 1:1 lidocaine:poloxamer 407 and 1:1 prilocaine:poloxamer 407 exhibited two distinct melting points of the two anesthetic agents (Figures 4a and 4b, respectively). As expected, DSC thermograms of 1:1:2 lidocaine:prilocaine:poloxamer 407, with both drugs mixed before the final mixing with poloxamer, showed only the melting point of the eutectic mixture (Figure 4c). This finding could also be explained as previously mentioned that mixing individual anesthetic agents with the polymer before the final mixing could prevent the formation of eutectic mixture. The contact of the two drugs in their solid state induced the melting point depression and mutually dissolve with each other in the liquid state because of an entropy-driven phenomenon.[13] The intimate contact and mutual solubility between eutectic-forming materials are the necessary and sufficient criteria for eutectic formation.[14]

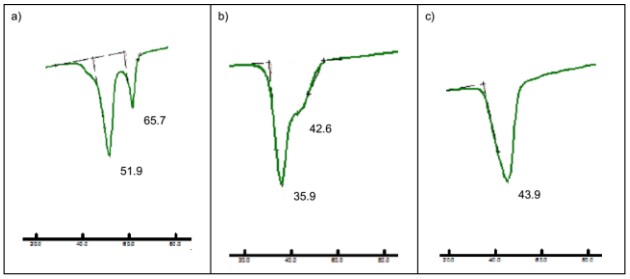

Figure 4 DSC thermograms of a) 1:1 lidocaine:poloxamer 407, b) 1:1 prilocaine:poloxamer 407 and c) 1:1:2 lidocaine: prilocaine:poloxamer 407.

Solubility of prilocaine and lidocaine

Lidocaine and prilocaine at a ratio of 1:1 could form a eutectic mixture when they were mixed together at room temperature. The oily liquid of eutectic mixture mixed easily with the gel although it was immiscible to water. Therefore, the solubility of the drug and the mixture was tested. Both drugs were soluble in ethanol and NMP, but were insoluble in water.[15] The co-solvent system was applied to dissolve the drugs. The results showed that each of the two drugs was separated from NMP-water phase at all NMP concentrations (2, 4, 6, 8, 10, 15, 20, 30, 35 and 50% w/w). On the other hand, the drugs could be dissolved in ethanol-water system. The clarity of solutions increased when the amount of ethanol increased, and became a clear solution when 35% w/w ethanol was used.

The suitable gelling agent

Most of all, 1% w/w carbopol 940 was the suitable gelling agent for the local anesthetic gel. In accordance with other research, the carbopol gel displayed a clear homogeneous texture[16,17] and exhibited a proper viscosity at pH 9. The clarity, viscosity and pH of 1% w/w carbopol 940 increased when triethanolamine was added. However, the viscosity of that gel slightly decreased when the system pH was adjusted to 9. All local anesthetics are bases and their pKa values are greater than 7.4, the physiologic pH.[18] Therefore, at pH 9, a greater proportion of the molecules exist in the free base forms which are lipophilic and able to penetrate the stratum corneum.[19]

Rheological behavior

Rheological behavior of lidocaine-prilocaine gel (Figure 5) was compared with that of EMLA® cream (Figure 6)

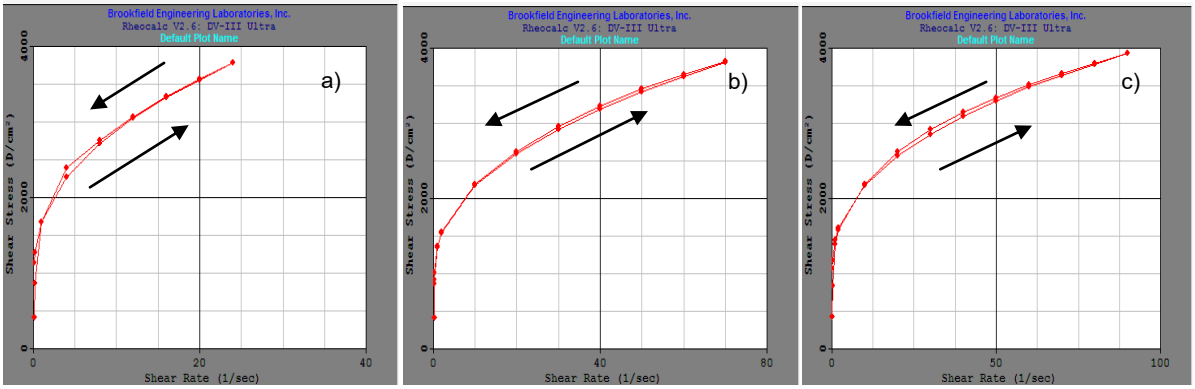

Figure 5 Rheological behavior of lidocaine-prilocaine gel at a) 4 °C, b) 28 °C and c) 35 °C.

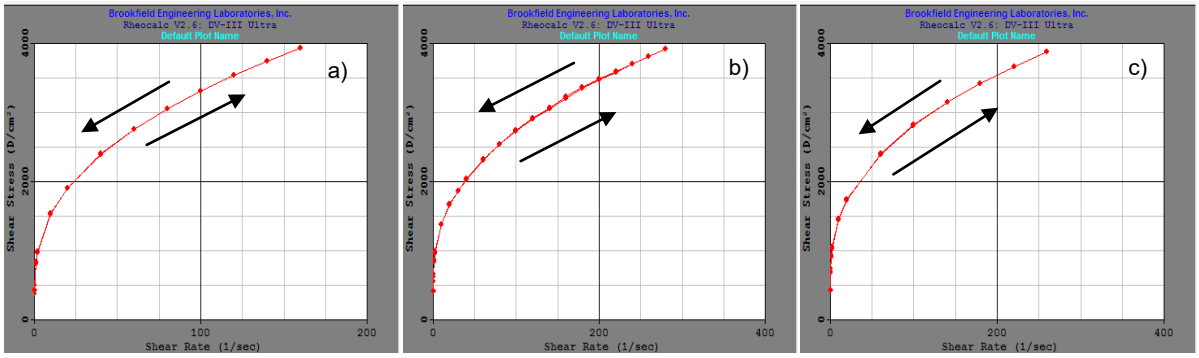

Figure 6 Rheological behavior of EMLA® cream at a) 4 °C, b) 28 °C and c) 35 °C.

All preparations showed comparable rheological behaviors. The shear rate was increased with the increasing shear stress; however, such association was in a nonlinear fashion. This non-linear relationship was considered a pseudoplastic flow, or shear thinning system, which was usually found in the system using both natural and synthetic polymers.[20-22] In accordance with previous research, these results indicated that the changing of temperature did not affect the rheological behavior of the gel formulation.[1]

Conclusion

The DSC thermogram of lidocaine:prilocaine at the ratio of 1:1 showed the eutectic behavior that could promote the solubility and absorption of the drugs. With the formula of lidocaine:prilocaine:carbopol 940 at the ratio of 1:1:2, carbopol was separately mixed with the single drugs before the final mixing. DSC thermograms showed that the melting point of each substance did not change. This indicated that each component in the mixture was compatible. However, the eutectic mixture could not be formed. On the other hand, the eutectic mixture occurred when lidocaine was mixed with prilocaine before the final mixing with the polymer. The intimate contact of the two drugs was necessary for eutectic formation. Carbopol 940 was the suitable gelling agent for the gel formulation. For rheological behavior, the gel containing lidocaine and prilocaine exhibited the pseudoplastic flow (shear thinning system). The changing of temperature did not affect the rheological behavior of the developed lidocaine-prilocaine gel. These results were useful for further development of the lidocaine-prilocaine gel formulation.

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References

1. Mariotti A, Hefti AF. Defining periodontal health. *BMC Oral Health* 2015;15(1):1-18.
2. Fee JPH, Bovill JG. Pharmacology for anesthesiologists. London, England. Taylor & Francis group, 2005.
3. Pinnock C, Lin T, Smith T. Fundamentals of anaesthesia. 2nd ed. Cambridge, England. Cambridge University Press, 2002.
4. Craig CR, Stitzel RE. Modern pharmacology with clinical applications. 6th ed. Philadephia, U.S.A. Lippincott Williams & Wilkins, 2003.
5. Simon MAM, Vree TB, Gielen MJM, Booij LHDJ, Lagerwerf AJ. Comparison of the effects and disposition kinetics of lidocaine and (±) prilocaine in patients undergoing axillary brachial plexus block during day case surgery. *Clin Drug Invest* 1998;16(3):241-250.
6. EMLA® cream (lidocaine 2.5% and prilocaine 2.5%) [online]. (Accessed on Jul. 13, 2016, at http://www.drugs.com /pro/emla.html)
7. Hallen B. Does lidocaine-prilocaine cream permit painfree insertion of IV catheters in children. *Anesthesiology* 1982;57:340-342.
8. Emla Cream 5%, Astra Pharmaceuticals Ltd. ABPI data sheet compendium. London. Datapharm Publications, 1993.
9. Stott PW, Williams AC, Barry BW. Transdermal delivery from eutectic systems: enhanced permeation of a model drug, ibuprofen. *J Control Release* 1998;50:297-308.
10. Nyqvist-Mayer AA, Brodin AF, Frank SG. Drug release studies on an oil–water emulsion based on a eutectic mixture of lidocaine and prilocaine as the dispersed. *J Pharm Sci* 1986;75(4):365-373.
11. Chun MK, Hossain K, Choi SH, Ban SJ, Moon H, Choi HK. Development of cataplasmic transdermal drug delivery system containing eutectic mixture of lidocaine and prilocaine. *J Pharm Investig* 2012;42(3):139-146.
12. Brown ME. Determination of purity by differential scanning calorimetry (DSC). *J Chem Educ* 1979;56(5):310.
13. Tantarawongsa S, Phaechamud T. Eutectic system in pharmaceutical applications. *Thai Pharm Health Sci J* 2011;6(1):66-72.
14. Bi M, Hwang SJ, Morris KR. Mechanism of eutectic formation upon compaction and its effects on tablet properties. *Thermochim Acta* 2003;404:213-226.
15. United States Pharmacopeial Convention. USP 29: U.S. Pharmacopeia and the National Formulary (USP 29/NF 24). Rockville, MD. United States Pharmacopeial Convention, 2006.
16. Sareen R, Kumar S, Gupta GD. Meloxicam carbopol-based gels: characterization and evaluation. *Curr Drug Deliv* 2011;8(4):407-415.
17. Dantas MG, Reis SA, Damasceno CM, et al. Development and evaluation of stability of a gel formulation containing the monoterpene borneol. *Sci W J* 2016;2016:1-4.
18. Becker DE, Reed KL. Essentials of local anesthetic pharmacology. *Anesth Prog* 2006;53(3):98-109.
19. Kumar M, Chawla R, Goyal M. Topical anesthesia. *J Anaesthesiol Clin Pharmacol* 2015;31(4):450–456.
20. Ortan A, Parvu CD, Ghica MV, Popescu IM, Ionita L. Rheological study of a liposomal hydrogel based on carbopol. *Rom Biotech Lett* 2011;16(1):47-54.
21. Islam MT, Rodríguez-Hornedo N, Ciotti S, Ackermann C. Rheological characterization of topical carbomer gels neutralized to different pH. *Pharm Res* 2004;21(7):1192-1199.
22. Zakaria R, Ahmad AH. Rheology behaviour of modified silicone-dammar as a natural resin coating. AIP Conf Proc. 2015:1674. (doi: http://dx.doi.org/10.1063/1.4928839)

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