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INTRODUCTION

For matrix membrane in transdermal drug delivery systems, the drug is dispersed or dissolved in a polymer. This membrane is attached to an adhesive layer and directly applied to the skin which can act as an adhesive layer by itself [1, 2]. Ketoprofen is a potent nonsteroidal anti-inflammatory drug and is practically insoluble in water. It is commonly used for the treatment of musculoskeletal disorders such as osteoarthritis and rheumatoid arthritis, as well as for symptoms of trauma [3]. Pseudolatex systems are prepared in colloidal aqueous dispersions that are water-based after solvent evaporation by the emulsification–evaporation technique which employs surfactant as stabilizers [4]. They can also be useful in mediating drug release [5-7].

The main objective of this work was to prepare ketoprofen matrix membrane made from ethyl cellulose (EC) and different amounts of deproteinized natural rubber latex (DNRL). Polyvinyl alcohol was used as the surfactant and stabilizer of these systems. Glycerine was used as a skin humectant, dibutyl phthalate as a plasticizer, and polyvinyl pyrrolidone as the channeling agent. Then, the matrix membrane for ketoprofen transdermal patches was produced by solvent evaporation using a hot air oven. The physical appearance and mechanical properties were characterized. Consequently, the *in vitro* studies of ketoprofen were also performed.

MATERIALS AND METHODS

Materials The DNRL was prepared by W. Pichayakorn's laboratory [8-10]. It was collected from *Hevea brasiliensis*: RRIM 600 clones and deproteinized by enzyme and centrifugation method. EC, ketoprofen (98 % purity, M*w* = 254.28 g/mol), polyoxyethylene-20 oleyl ether, polyvinyl pyrrolidone, glycerine, polyvinyl alcohol (M*w* = 31,000 g/mol), dibutyl phthalate were obtained from Sigma-Aldrich (USA). The other chemicals were of analytical grade.

Preparation and physical appearance of the EC-DNRL pseudolatex systems Ketoprofen matrix membrane was prepared by EC-DNRL pseudolatex systems composing of organic phase and aqueous phase. The EC and dry DNRL were dissolved in 500 mL of dichloromethane by using a magnetic stirrer until it was a clear, slightly yellow solution. After that, 6%w/w dibutyl phthalate and 2 g ketoprofen (20 mg/mL) were mixed together into this pseudolatex systems. For the aqueous phase, the 14%w/w polyvinyl alcohol and 4%w/w polyvinyl pyrrolidone, used as surfactant and channeling agent, respectively, were dissolved in 100 mL of water and stirred until completely dissolved. Then, 6%w/w glycerine as the skin humectant was mixed into this solution. The two phases were mixed together by homogenization method for 30 minutes until an emulsion-like system occurred. Dichloromethane was then removed under vacuum by rotary evaporator with bath temperature of 40 ± 2 °C for 5 hours. Finally, these pseudolatex systems were adjusted to 100 mL with water. Zeta potential and particle size were measured by ZetaPALS (Brookhaven, Germany) at 25 ± 2 °C, and presented as the effective diameter, polydispersity index (PI), and zeta potential, respectively. The pH of the pseudolatex systems was measured by a S220 SevenCompact™ pH/Ion pH meter (Mettler Toledo, Switzerland) at room temperature. The pH meter was calibrated by using pH 4.0, 7.0, and 10.0 standard buffers.

Preparation and mechanical properties of ketoprofen matrix membrane Fifteen mL of EC-DNRL pseudolatex systems preparation were poured into a Petri-dish. This was dried in a hot air oven at 70 ± 2 °C until a complete membrane containing 4 mg/cm^2 of ketoprofen was formed. Subsequently, the dry and complete ketoprofen matrix membranes were peeled from the Petri-dish and kept in desiccators. Then, the mechanical properties for their tensile strength (ultimate tensile strength [UTS] and elongation at break),

and the adhesion properties (T-peel strength and loop tack adhesion), were tested using the Universal Testing Machine Model QC-508E (Cometech, Taiwan) with a 500 N loaded cell [8, 9,11].

In vitro studies The *in vitro* study of ketoprofen was performed using a modified Franz-type diffusion cell with a diffusion area of 1.77 cm^2. The pseudolatex-membranes were cut into 4 cm^2 containing 16 mg of ketoprofen (4 mg/cm^2). The receptor compartment was filled with 12 mL of 0.5 w/v of polyoxyethylene-20 oleyl ether in pH 7.4 isotonic phosphate buffer solution controlled with a water jacket at 37 ± 0.5 °C, and constantly stirred at 300 rpm with a magnetic stirrer. A 1 mL sample of isotonic phosphate buffer solution was withdrawn at 0.5, 1, 2, 4, 6, 8, and 12 hour intervals, and an equal volume of fresh isotonic phosphate buffer solution was then added as a replacement [12]. For the *in vitro* release, the pure ketoprofen was applied to cellulose membrane (*Mw* cut-off 3,500 g/mol). The ketoprofen matrix membrane was directly applied to the donor compartment. The *in vitro* permeation of ketoprofen formulation was determined using pig skin and directly applied to the pig skin. The samples collected from the *in vitro* study were analyzed by the HPLC system (Agilent 1260 series, USA) with an Agilent C18 analytical column 4.6 mm × 150 mm. The mobile phases used were 0.025% v/v trifluoroacetic acid in water (solvent A) and acetonitrile (solvent B), and they were run at a gradient of 70:30 for 5 min, then 10:90 for 8 min followed by 0:100 (solvent A:B, respectively) with a flow rate of 1 mL/min. Ketoprofen content in the samples was determined at 255 nm. The ketoprofen content was calculated by comparing with the validated calibration curve. The HPLC method provided good accuracy (97.28-102.17%), precision (0.62-1.17), and linearity in the required concentration range of 10-50 µg/mL of pure ketoprofen in isotonic phosphate buffer solution.

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RESULTS AND DISCUSSION

Physical appearance of the EC-DNRL pseudolatex systems The DNRL material was confirmed to be a suitably safe polymer to apply on the skin and used in this work [8, 9, 11]. Ketoprofen in its solid form could be completely dissolved in EC-DNRL pseudolatex systems, and exhibited equally sticky emulsion. They were yellowish pseudolatex mixtures due to the color of ketoprofen and DNRL, with good homogeneity and smooth texture. The pH, effective diameter, polydispersity index, and zeta potential values of the pseudolatex systems indicated their safety and ease to be applied directly on the skin. They had pH values in range of 6.04 to 6.19 and they were safe for use on the skin with no irritation [13]. The effective diameter, polydispersity index, and zeta potential values of ketoprofen pseudolatex mixtures were 542.23 to 787.54, 0.11 to 0.17, and -35.18 to -51.55, respectively.

Mechanical properties of ketoprofen matrix membrane The mechanical properties of ketoprofen matrix membranes are shown in Figures 1 and 2. We found these membranes had significantly increased softness and flexibility. They were decreased in UTS and increased percentage of elongation at break when the DNRL was mixed into their formulation. This is directly related to the individual property of DNRL that is very stretchy and flexible [14, 15], therefore more flexible and viscous membranes were produced. In addition, the ketoprofen matrix membrane was improved adhesion properties that significantly increased the T-peel and tack adhesion values. The membranes made using polyvinyl alcohol showed significantly higher adhesive properties, i.e., T-peel strength and tack adhesion of the *in situ* membranes.

In vitro studies The ketoprofen pseudolatex matrix membrane was made from EC and DNRL at ratio of 1:1 was selected for *in vitro* studies and compared to pure ketoprofen. The pseudolatex systems could enhance the poor water solubility of ketoprofen. These systems significantly increased ketoprofen release profile and skin permeation profile from pseudolatex formulations (Figure 3 and 4).

CONCLUSION

We have prepared the ketoprofen matrix membrane from EC-DNRL pseudolatex systems. They had good physical appearance and mechanical properties that were appropriate to be developed and produced suitable ketoprofen matrix membrane. The *in vitro* study results showed that increased ketoprofen from ketoprofen matrix membrane of 1:1 ratios of EC:DNRL. Thus, this work successfully prepared ketoprofen matrix membrane for ketoprofen formulation development in skin applications.

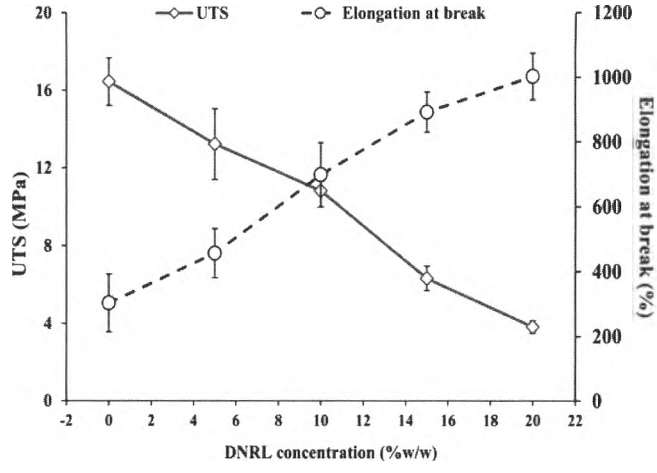

Figure 1 The UTS and elongation at break values of ketoprofen matrix membrane (mean ± SD, n=5)

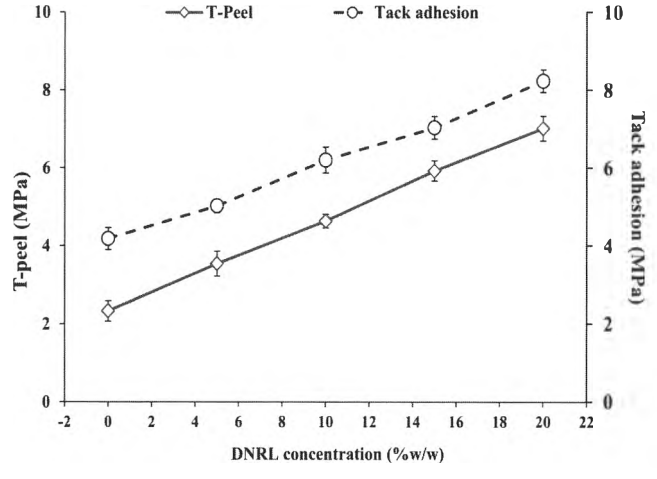

Figure 2 The T-peel strength and tack adhesion values of ketoprofen matrix membrane (mean ± SD, n=5)

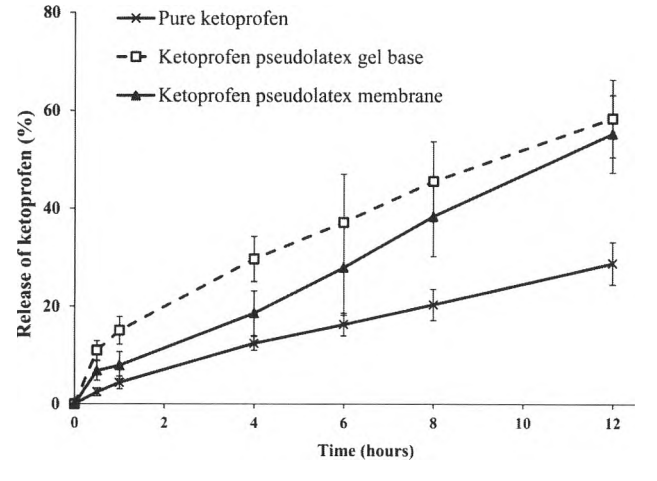

Figure 3 The *in vitro* release profile of ketoprofen matrix membrane at EC:DNRL=1:1 (mean ± SD, n=3)

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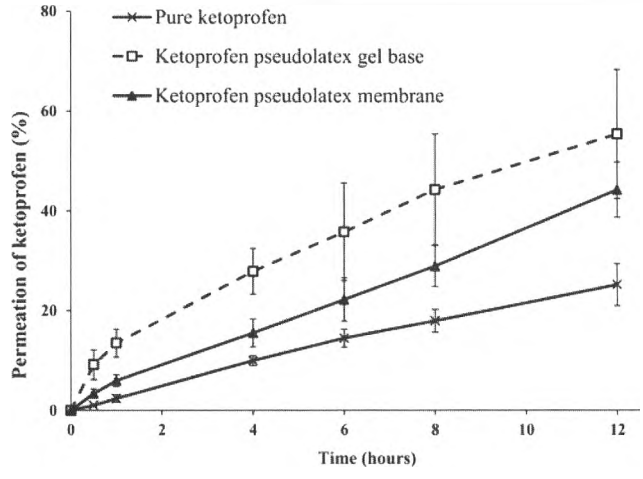

Figure 4 The *in vitro* skin permeation profile of ketoprofen matrix membrane at EC:DNRL=1:1 (mean ± SD, n=3)

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