Development of Topical Gel-Based Formulation for Enhancing Transdermal Delivery of Capsaicin: Physical properties characterization

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Introduction
Capsaicin extract are known for its various biological and physiological activities including physiological and pharmacological effects on the cardiovascular system and gastrointestinal track, anti-oxidants, anti-cancers and anti-inflammatories. In pharmaceutical research fields, the more the capsaicin, the hotter the pepper, and the higher the antioxidant level have been suggested. However, the potential applications of capsaicin were restricted by its strong pungency and irritation. The proper strategy to drive the research for capsaicin as drug delivery systems was desirable.

The research and development of novel drug delivery systems were still interested and attracted increasing. Our previous research have shown that the capsaicin can be delivered into the skin via various novel drug delivery systems such as microemulsions, solid lipid nanoparticles (SLN), liposomes. To date, novel formulation such as microemulsions, liposomes, SLNs loaded capsaicin was not available as commercial product. The primary consideration in the development of all pharmaceutical products, the efficacy, the safety and the stability of basic topical formulation (gels- and creams-based) should be concerned. The intrinsic properties of basic topical formulation may improve the activity of capsaicin by promoting the efficacy, the safety and the stability of the novel formulations.

The topical gels-based of carbopol have been not only to enhance the stability of liposome formulation, but also serve the efficacy of the liposome loaded paracetamol formulation. Due to carbopol may provide the key mechanical strength to the vesicle formulation. The aim of this study was to develop gel-based formulation for enhancing transdermal delivery of capsaicin. The gel-based formulation was performed to fine the optimal type and concentration of gelling agent to enhance the stability and to prove the efficacy of the novel formulations in promoting the activity of capsaicin. The 0.5-2.0 %w/w of gelling agent were varied. The physical appearance, pH, spreadability, rheology and drug content of capsaicin gel formulation were investigated.
Materials and Methods

Preparation of capsaicin gel formulation

Preparation of capsaicin gel formulation was two steps. Firstly, an aqueous dispersion of gelling agents (e.g., carbopol 934, carbopol 940, carbopol 1342, carbopol ultrez 10, carbopol ultrez 21 and carbopol ETD 2020) in deionized water, propylene glycol 400, preservative and ethanol was prepared. The gelling agent was varied at 0.5, 1.0, 1.5 and 2.0 %w/w. To this mixture 3%w/w of capsaicin resin (0.0125 %w/w capsaicin) in oil phase (vitamin E, methyl salicylate and various types of terpens) was dropped wise along with constant agitation on magnetic stirrer. Secondly, the dispersion was neutralized using triethanolamine for pH adjusting and viscosity enhancement.

Characterization of capsaicin gel formulation

The capsaicin gel was characterized for pH, spreadability, rheology, and drug content through standard methods. The measurement of pH, spreadability, rheology, and drug content of each sample was done at least in triplicate.

pH and rheology

The pH values of the gel was measured by a Digital pH meter (Mettler Toledo™ FE20 FiveEasy™ Benchtop pH Meter, Fisher Scientific, USA). The measurement of viscoelastic properties of prepared gels was carried out with the HAAKE™ MARS™ Rheometers (Thermo Fisher Scientific Inc, USA).

Spreadability

The spreadability represents the extent of area to which the gels readily spread on application to skin. The spreadability measurement was followed as described in previous study. Briefly, the gel formulation was placed over one of the slides, The other slide was placed on the top of the gels that the gels was sandwiched between the two slides in an area occupied by the distance of 10 cm of the slide. The weight of 125 g was placed upon the upper slides for 30 sec then the weight was removed. The distance of the spread gel was measured and calculated for the spreadability,

\[
S = \frac{U \times L}{T}
\]

Where \(U\) = weight tied to upper slide, \(L\) = length of glass slides, \(T\) = time taken to separate the slides.

Drug content

The concentration of capsaicin in all gel samples was analyzed using a HPLC (ThermoScientific™ Dionex™ UltiMate 3000 LC systems, Thermo Fisher Scientific Inc, USA). After disruption of the capsaicin formulations with methanol, the samples were centrifuged at 10,000 rpm at 25 °C for 20 min. The supernatant was filtered with a 0.45 µm nylon syringe filter. A Luna Omega C18 reversed-phase column (Phenomenex®, Phenomenex distributor, Thailand) with dimensions of 5 µm, 4.6×250 mm was utilized. The mixture of acetonitrile and 0.01%w/w phosphoric acid (50:50) was used as the mobile phase. A UV detector was set at 227 nm for capsaicin detection at ambient temperature. The flow rate was 1.0 mL/min and the injection volume was 20 µL. The calibration curve for CAP was in the range of 1-100 µg/mL with a correlation coefficient of 0.999. The data were reported as mean ± SD (n=3) and statistical analysis of the data was carried out using paired t-test. A p-value of less than 0.05 was considered to be significant.

Results and discussion

The appearances of all capsaicin carbopol gels are orange as the color of capsaicin resin. The 0.5%w/w of all carbopols capsaicin gels were homogenous. The appearances of the capsaicin gels were more viscous when the gelling agent concentration was increased. The pH of all capsaicin carbopol gels was ranging from 3.72±0.01 to 7.52±0.02 (Figure 1A), which the pH of gels about 4.0-7.0 was found to be acceptable for the skin. The spreadability of all capsaicin carbopol gels was in the range of 3.07±0.12 to 5.03±0.12 g/cm/sec (Figure 1B). The 0.5%w/w of all gelling agents was more high spreadability indicated the gels had low viscosity and could easily apply to skin. The efficacy of the capsaicin gels depends on their spread, The gel spreading assisted in the uniform application to the skin, therefore the prepared gels must have a good spreadability and fulfill the ideal quality in topical application.
The viscoelastic properties such as storage modulus (G') and loss modulus (G'') of these capsaicin carbopol gels were measured using the HAAKE™ MARS™ Rheometers. The viscoelastic properties of the capsaicin carbopol gels at different types and concentrations of gelling agents are shown in Figure 2. It was observed that G'' increased with an increase gelling agent concentration. For 0.5%w/w, the elastic modulus (G') of carbopol 940, carbopol 1342, carbopol ultrez 21 and carbopol ETD 2020 were greater than loss modulus (G'') with a good distance between them, indicating strong thickening or solidifying behavior. A crossover of G' and G'' was starting at the frequency about 10 rad/sec, the capsaicin gels started to break down, the lower frequency was a desirable feature since it simulated the onset of spreading of gel on the skin. Some capsaicin carbopol gels did not cross between G' and G'' until the frequency about 70 rad/sec, indicating that the structures of gels were strong thus the greater frequency was needed to spread the gels. However, the higher frequency was not suitable in topical preparation. Drug content of the capsaicin gels was nearly one-hundred percent by HPLC analysis. The incorporation of ethanol resulted in the successful in the loading of capsaicin resin in carbopol gel formulation.

**Figure 1.** pH (A) and spreadability (B) of the capsaicin gel formulations: Carbopol 934, Carbopol 940, Carbopol 1342, Carbopol Ultrez 10, Carbopol Ultrez 21 and Carbopol ETD 2020. (the bars represent the standard deviations of three replicates)

**Figure 2.** Angular frequency dependence of storage modulus (G', open symbols) and loss modulus (G'', closed symbols) for the capsaicin gels: (A) Carbopol 934, (B) Carbopol 940, (C) Carbopol 1342, (D) Carbopol Ultrez 10, (E) Carbopol Ultrez 21 and (F) Carbopol ETD 2020 at different concentrations (0.5%w/w, triangles; 1.0%w/w, squares; 1.5%w/w, circles; 2.0%w/w, diamonds).

**Conclusion**

The physical structure characterization of the carbopol gel based was investigated using physical appearance, pH, spreadability, rheology and drug content. The suitable gelling agent concentration of all carbopol types were 0.5-1.0 %w/w. These properties could serve as a suitable pre-formulation for enhancing transdermal delivery of capsaicin. To evaluate the potential of optimal gel-based formulation formulation (such as microemulsions, liposomes, SLNs) loaded in optimal gel based formulation should be performed in further study.

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