Preparation and Evaluation of Mefenamic Acid Transdermal Patches Prepared from Pressure Sensitive Adhesive

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Abstract. The pressure sensitive adhesive is interesting to apply in pharmaceutical and medical products. It composed of STR 5L block rubber which has high uniformity and very low impurity. Thus, it was used to prepare the transdermal patches for mefenamic acid delivery. The mefenamic acid powder was loaded in pure STR 5L block rubber and pressure sensitive adhesive. The pressure sensitive adhesive was the STR 5L block rubber mixed with hydroxyethyl cellulose and white oil which were used as tackifier and softener, respectively. The preparation of mefenamic acid loaded in transdermal patches were crushed by melt blending technique with two-roll mill machine. The mefenamic acid could be mixed into pure STR 5L block rubber and pressure sensitive adhesive to be the homogeneous transdermal patches. The percentages of moisture uptake and swelling ratio were less than 5% and 15%, respectively. The mefenamic acid was entrapped in the range of 75-90%. However, the content of mefenamic acid from transdermal patches was a low cumulative release (less than 60% of cumulative drug release). Therefore, this preparation of mefenamic acid loaded in transdermal patches might be developed to increase the release of mefenamic acid from transdermal patches in further study.

1. Introduction

The natural rubber exhibits various outstanding properties such as excellent resilience, high elongation at break and tensile strength because it presents the high stretching and ease of patch formation but it has a low adhesion and tack properties. The main component of natural rubber latex is rubber particle in the concentration of 30−40% in aqueous serum that is difficult to storage because it has the bulk volume or microbial contamination in their serum [1, 2]. The various publication reported the usage natural rubber latex as a controlled-release membrane in pharmaceutical and medical products for controlled drug release of nicotine [3-8], ketoprofen [9, 10], naproxen [11], sulindac [12], etc.

The block rubber is one choice as interesting material for the controlled-release membrane. Because it is formed as a solid stage and high stability when compared to natural rubber latex. The
Standard Thai Rubber (STR) of block rubber in Thailand are graded into 8 types that are STR 5, STR 5L, STR 5CV, STR 10, STR 10CV, STR 20, STR 20CV, and STR XL [13]. However, the STR 5L is the best material with the great potential to be used as a controlled-release membrane in pharmaceutical and medical products due to its quality latex and low impurity. Recently, the STR 5L block rubber is reported that can be prepared for transdermal patches preparation [14–16]. Thus, this work interested to use the STR 5L block rubber as a controlled-release membrane for transdermal patches preparation of mefenamic acid delivery.

This aim of the study was to formulate mefenamic acid loaded in transdermal patches using pure STR 5L block rubber and pressure sensitive adhesive. The pressure sensitive adhesive was the STR 5L block rubber mixed with hydroxyethyl cellulose and white oil which were used as tackifier and softener, respectively and to evaluate the moisture uptake, swelling ratio, and in vitro drug release from the transdermal patches.

2. Experimental Works

2.1 Preparation of mefenamic acid loaded in transdermal patches
For mefenamic acid loaded in a transdermal patch made from STR 5L, 100 phr of STR 5L block rubber was crushed with a two-roll mill machine (191-TM, Yasuda Seiki Seisakusho, Japan). The gap of the machine was set at 0.5 mm and the mixing time was 15 min. The mefenamic acid powder was added at 5% w/w and crushed to combine with STR-5L block rubber for 15 min.

For mefenamic acid loaded in a transdermal patch made from pressure sensitive adhesive, 100 phr of STR 5L block rubber was crushed with a two-roll mill machine (191-TM, Yasuda Seiki Seisakusho, Japan). The gap of the machine was set at 0.5 mm and the mixing time was 15 min. The white oil and hydroxyethyl cellulose were used as a softener and tackifier, respectively. The mefenamic acid powder was added at 5% w/w and crushed to combine with pressure sensitive adhesive for 15 min.

2.2 Percentage of moisture uptake
The study of moisture uptake of mefenamic acid loaded in transdermal patches stored the samples in a desiccator which was equilibrated with saturated NaCl solution at room temperature under the condition of 75% relative humidity. Every week, the samples of each mefenamic acid loaded in transdermal patches were weighed until constant. The percentage of moisture uptake was calculated as the difference of the percentage between the increased weight of the sample and the initial weight of the sample. The percentage of moisture uptake was tested in triplicate.

2.3 Percentage of swelling ratio
The study of the swelling ratio of mefenamic acid loaded in transdermal patches used the distilled water as a solvent. The samples were immersed in 10 mL of distilled water and kept at room temperature. The samples of each mefenamic acid loaded in transdermal patches were weighed every hour until constant. The percentage of swelling ratio was calculated as the difference of the percentage between the increased weight of the sample and the initial weight of the sample. The percentage of swelling ratio was tested in triplicate.

2.4 Determination of drug entrapment efficacy in transdermal patches
The transdermal patches were cut in small pieces and extracted in ethyl acetate under sonication for 3 hrs. The extracted solution was diluted and adjusted to the determined volume. The content of mefenamic acid that entrapped in transdermal patches was assayed by a high performance liquid chromatography (HPLC) instrument. The analyzed mefenamic acid content was compared with the peak area of the linearity of the standard curve. The determination of drug content in transdermal patches was assayed in triplicate. The percentage of drug entrapment efficacy of mefenamic acid in transdermal patches was calculated as the percentage of the analyzed mefenamic acid content in the
patch compared to the theoretical mefenamic acid content. The percentage of drug entrapment efficacy was carried out in triplicate.

2.5 In vitro release evaluation of mefenamic acid from transdermal patches

The cumulative release of the drug from the transdermal patches was studied under USP dissolution apparatus V. 900 mL of 2% w/v sodium dodecyl sulfate in distilled water was selected as a receptor medium. Because the previous study reported the 2% w/v of sodium dodecyl sulfate could improve the solubility of mefenamic acid in water at 37ºC [17]. The temperature of the water bath was set at 37±0.5ºC with stirring constantly at 100 rpm. At sampling time 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hrs, the receptor medium was withdrawn and then replaced with the equal volume of fresh receptor medium. The content of mefenamic acid in each sampling time was analyzed by HPLC assay and compared to the calibration curve. The samples for each sample were evaluated in triplicate.

2.6 Analytical Method

The HPLC instrument from Agilent Technologies, USA, model Agilent 1260 Infinity system was used for drug analysis. A reverse-phase ACE Generix5 C18 with 4.6 mm × 150 mm, 5 µm particle size from DV12-7219, USA was used to separate the mefenamic acid. The ratio between methanol and acetate buffer pH 4.1 at 95:5 was used as a mobile phase with 5 minutes run-time. The flow rate was 1 mL/min. The solution of the sample was injected at 10 µL. The UV detection was set at 285 nm. The required concentration of pure mefenamic acid for validation was in the range of 5-50 µg/mL. The limits of detection and quantification, linearity, accuracy, and precision were observed. The limit of detection and limit of quantification were 1.10 µg/mL and 3.33 µg/mL, respectively. The calibration curve was good linearity with R² more than 0.9997. The accuracy was found in a range of 103-107% and had a good precision (less than 2% RSD for both intra- and inter-day analysis).

3. Results and discussion

Figure 1 and 2 showed the controlled-release membrane for mefenamic acid loaded in transdermal patches that made from STR 5L block rubber and pressure sensitive adhesive, respectively. Figure 1 showed the unevenness of the patch while Figure 2 showed the smoothness of the patch. The mefenamic acid powder could homogeneously disperse in a controlled-release membrane made from pressure sensitive adhesive more than controlled-release membrane made from STR 5L block rubber. This was due to the transdermal patch in Figure 1 composed only STR 5L block rubber while the transdermal patch in Figure 2 had various fillers such as white oil and hydroxyethyl cellulose as a softener and tackifier, respectively.

![Figure 1. Mefenamic acid loaded in a transdermal patch made from STR 5L block rubber.](image1)

![Figure 2. Mefenamic acid loaded in a transdermal patch made from pressure sensitive adhesive.](image2)

The moisture uptake and swelling ratio of mefenamic acid-loaded STR 5L block rubber and loaded pressure sensitive adhesive are shown in Figure 3 and 4, respectively. The mefenamic acid-loaded pressure sensitive adhesive patch showed the high moisture uptake value than mefenamic acid-loaded STR 5L block rubber patch. This was due to the mefenamic acid-loaded pressure sensitive
adhesive patch composed the ingredient in formulation more than mefenamic acid-loaded STR 5L block rubber patch. However, the swelling ratio values of both mefenamic acid-loaded STR 5L block rubber and -loaded pressure sensitive adhesive were not significant.

**Figure 3.** Percentage of the moisture uptake of mefenamic acid loaded in transdermal patches.

**Figure 4.** Percentage of the swelling ratio of mefenamic acid loaded in transdermal patches.

The mefenamic acid could be loaded in transdermal patches at 1.90±0.13 and 2.27±0.13 mg/cm² for mefenamic acid-loaded STR 5L block rubber and -loaded pressure sensitive adhesive, respectively (Figure 5). The percentages of drug entrapment efficacy in STR 5L block rubber and pressure sensitive adhesive were 76.16±5.11% and 90.67±5.03%, respectively (Figure 6). Thus, the pressure sensitive adhesive could entrap the mefenamic acid in their patch more than STR 5L block rubber.

**Figure 5.** Drug loading in transdermal patches.
The cumulative release of mefenamic acid from the controlled-release membrane was studied under USP dissolution apparatus V using 900 mL of 2% w/v sodium dodecyl sulfate in distilled water as a receptor medium [17]. The times for sample collection was 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hrs. Each sample collection was analyzed by HPLC assay and compared to the calibration curve. The percentages of cumulative release of mefenamic acid from the controlled-release membrane that prepared from STR 5L block rubber were 0%, 5.33±0.12%, 9.96±2.63%, 15.68±3.68%, 19.89±2.65%, 25.63±5.53%, 29.32±9.64%, 34.36±8.94%, 42.59±9.33%, 44.95±8.30%, 48.63±9.78%, and 52.36±8.32%, respectively. The percentages of cumulative release of mefenamic acid from the controlled-release membrane that prepared from pressure sensitive adhesive were 0%, 6.98±0.22%, 11.70±2.70%, 19.62±3.85%, 22.65±3.36%, 28.31±7.89%, 33.67±6.88%, 39.87±5.97%, 44.29±11.64%, 49.65±7.64%, 53.96±12.63%, and 60.39±8.63%, respectively (Figure 7).

**Figure 6.** Percentage of drug entrapment efficacy in transdermal patches.

**Figure 7.** Percentages of the cumulative release of mefenamic acid from the controlled-release membrane that prepared from STR 5L block rubber and pressure sensitive adhesive.

### 4. Conclusions

The mefenamic acid could be successfully loaded into pure STR 5L block rubber and pressure sensitive adhesive to be the homogeneous transdermal patches. The percentages of moisture uptake and swelling ratio for both preparations were less than 5% and 15%, respectively. The percentage of mefenamic acid entrapment efficacy was in the range of 75-90%. However, the cumulative drug release of mefenamic acid from transdermal patches was a low cumulative release (less than 60%). Therefore, this preparation of mefenamic acid loaded in transdermal patches might be developed to increase the release of mefenamic acid from transdermal patches in further study.

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