

DEVELOPMENT OF NEW FORMULATION AND STUDY ON RELEASE OF CAPSAICIN FROM TRANSDERMAL PATCH

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ABSTRACT: The aim of this research was to develop a capsaicin transdermal patch to reduce skin irritation while still controlling pain with a formulary concentration of 0.025% as used commercially. The study began by researching polymer varieties and plasticizer proportions that were suitable for transdermal patches. It was found that a polymer of ethyl cellulose with 60% triethyl citrate as a plasticizer had the appropriate physical properties, being clear, elastic and adhesive. Varying the proportion of triethyl citrate from 50% to 70% produced a film that had similar physical properties to a patch with 60% triethyl citrate. The films were analyzed by UV-VIS Spectrophotometer. It was shown that 60% triethyl citrate released the highest level of capsaicin so this formulation was developed as a non-irritating patch. Glycerin was used as an anti-irritant in the proportions of 10%, 15% and 20%. It was observed that the formulated capsaicin transdermal patch containing ethyl cellulose with 60% triethyl citrate, and 20% glycerin delivered the highest amount of capsaicin while producing less skin irritation compared to the product currently marketed.

Keywords: Capsaicin, Transdermal patch, formulation, release

INTRODUCTION: Capsaicin, a pungent substance derived from the plants of the Solanaceae family, has long been used as an analgesic because of its selective action on the small diameter afferent nerve fibers, or C fibers, which are believed to mediate pain¹. From studies in animals, capsaicin appears to trigger C fiber membrane depolarization by opening cation selective channels for calcium and sodium. Although the detailed mechanisms are not yet known, capsaicin mediated effects include: (I) activation of nociceptors in peripheral tissues; (II) eventual desensitization of peripheral nociceptors to one or more stimulus modalities; (III) cellular degeneration of sensitive unmyelinated C fiber afferents; (IV) activation of neuronal proteases; (V) blockage of axonal transport; and (VI) a decrease in the absolute number of C fibers without affecting the number of myelinated fibers. The properties of capsaicin make it an option for relieving pain associated with osteoarthritis, rheumatoid arthritis, and diabetic neuropathy. Capsaicin is used to relieve muscle pain, joint pain and nerve pain. Many researchers have reported capsaicin's efficacy and safety. However, capsaicin is actually an irritant to human skin, producing a burning sensation. Transdermal

capsaicin patches are becoming popular products because they have increased patient compliance. However, these products may cause irritation and burn the skin.

MATERIALS AND METHODS:

Materials

Capsaicin extract was kindly provided by Bangkok Lab and Cosmetic Co.,Ltd. Ethyl cellulose (EC), Polyvinylpyrrolidone (PVP K-30), Geletin, Glycerin, Triethyl citrate (TEC), and Polyethylene glycol (PG) were received from Namsiang Co., Ltd. All solvents and chemicals were of pharmaceutical and analytical grade.

Preparation of transdermal patches

The formulated transdermal patches were modified by solvent casting technique used in previous studies.²⁻³ Transdermal patches were formulated by incorporating EC or PVP K-30 as the polymer along with TEC or PG as the plasticizer with 95% ethanol as the casting solvent. The casting solutions were prepared by dissolving the appropriate polymer and plasticizer in casting solvent using a homogenizer. Capsaicin extract was added slowly to the solution and dissolved by continuous stirring for 30 min.

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Aluminum foil was spread uniformly on a glass petri dish to make a frame. The mould was kept on a horizontal surface. About 25 ml of the solution was poured onto the foil (80 cm²) in the lab hood for 6 h and dried in a hot air oven at 45°C for 24 h. The dried cast film was then detached from the aluminum foil and cut into pieces to produce 4.0x4.0 cm transdermal patches. For the fabrication of capsaicin transdermal patches, the film was attached to adhesive plaster. The fabricated patch was wrapped in an aluminum foil and stored in a dessicator at room temperature for further use.

Evaluation of transdermal patch

The formulated transdermal patch was evaluated for % weight change, tensile strength, elastic modulus, and % elongation at break. To determine the tensile strength, the film was pulled by means of a pulley system. Weights were gradually added to the pan to increase the pulling force until the film ruptured. The skin permeation study was approved by the Institutional Ethics Committee at Faculty of Pharmacy, Srinakharinwirot University on January 2009.

The *in-vitro* permeation study of fabricated transdermal patches was carried out using excised newborn pig skin and an enhancer cell. The pig skin was inserted between the donor and receptor compartments of the enhancer cell. A 2 cm diameter patch was applied to the stratum corneum side of the skin. The top side of the enhancer cell was placed in the dissolution chamber which was filled with 250 ml phosphate buffer at pH 7.4. The dissolution apparatus was operated with a paddle stirrer and a temperature of 37°C was maintained throughout the experiment. The 5 ml resulting solutions were withdrawn through the sampling port at different time intervals for a period of 10 h, simultaneously replacing an equal volume with phosphate buffer pH 7.4. The samples were then analyzed for capsaicin content at 280 nm using a UV/VIS spectrophotometer.

RESULTS:

Preparation of transdermal patch

The preliminary batches of capsaicin transdermal patches were formulated using the polymer varieties and plasticizer proportions as

shown in Table 1. It was shown that EC as a polymer with 60% TEC as a plasticizer had the appropriate physical properties, being clear, elastic and adhesive. Varying the proportion of TEC to 50% and 70% produced a film that had similar physical properties to a film with 60% TEC.

Evaluation of transdermal patch

The physicochemical properties of the formulated transdermal patch were evaluated for % weight change, tensile strength, elastic modulus, and % elongation at break. The results are shown in Table 2. The weight change varied from -0.479% to 7.243%. The tensile strength of the films varied from 1.50 to 11.00 N/mm². Elastic modulus varied from 23 to 293 N/mm². The percentage of elongation at break varied from 3.30 to 18.10.

The formulated transdermal patches containing EC and TEC showed higher tensile strength and elastic modulus compared to patches containing PVP and PG. The percentage of elongation at break of transdermal patches containing EC and TEC was lower than for patches containing PVP

Table 1 Composition of preliminary batches of capsaicin transdermal patches

No.	Polymer	Plasticizer* (%w/w)	Casting Solvent
1	EC	TEC 20%	Ethanol
2	EC	TEC 30%	Ethanol
3	EC	TEC 40%	Ethanol
4	EC	TEC 60%	Ethanol
5	PVP K-30	PG 20%	Ethanol
6	PVP K-30	PG 30%	Ethanol
7	PVP K-30	PG 40%	Ethanol
8	PVP K-30	PG 60%	Ethanol

* %plasticizer (%w/w) is based on polymer weight.

Table 2 Percentage weight change, tensile strength, elastic modulus, and percentage of elongation at break of preliminary batches of capsaicin transdermal patches

No.	Composition	% Weight change	Tensile strength (N/mm ²)	Elastic modulus (N/mm ²)	% Elongation at break
1	EC+TEC20%	-0.479	11.00	293	3.30
2	EC+TEC30%	-0.358	9.70	259	4.80
3	EC+TEC40%	-0.281	5.50	119	10.50
4	EC+TEC60%	-0.281	1.83	38	14.80
5	PVP+PG20%	1.522	1.70	102	3.46
6	PVP+PG30%	2.670	1.69	55	5.20
7	PVP+PG40%	5.096	1.55	35	12.65
8	PVP+PG60%	7.243	1.50	23	18.10

and PG as shown in Figure 1.

A capsaicin transdermal patch was then developed in order to reduce skin irritation while still controlling pain with the formulary concentration of 0.025% as used commercially. Glycerin was used as an anti-irritant in the proportions of 10%, 15% and 20%. The optimized compositions of capsaicin transdermal patches are described in Table 3.

An *In-vitro* permeation study was carried out

for 10 h and the cumulative percentage permeated was calculated based on the amount of capsaicin in the patch. It was shown that 60% TEC released the highest level of capsaicin compared to 50% and 70% TEC. In addition, it was demonstrated that the formulated capsaicin transdermal patch containing EC with 60% TEC, and 20% GLY released the optimum amount of capsaicin while reducing skin irritation compared to the marketed product as shown in Figure 2.

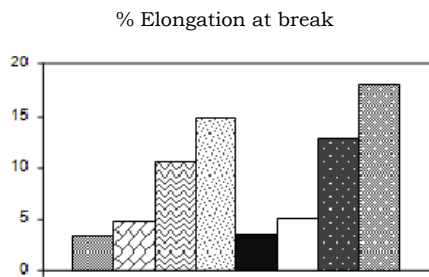
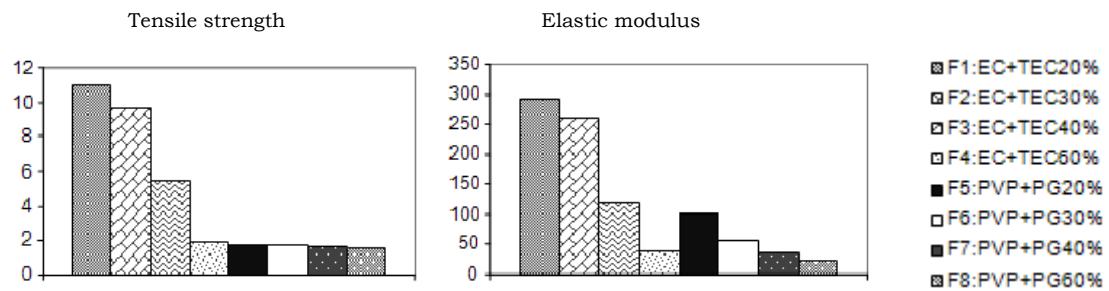


Figure 1 Tensile strength, elastic modulus and percentage of elongation at break of preliminary batches of capsaicin transdermal patches

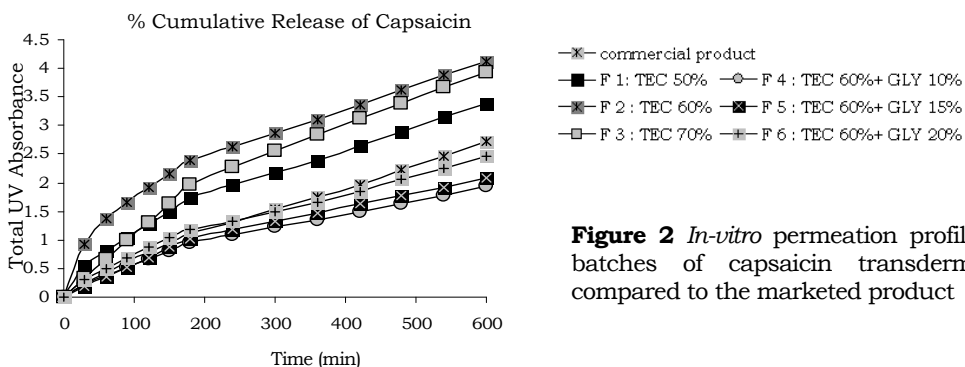
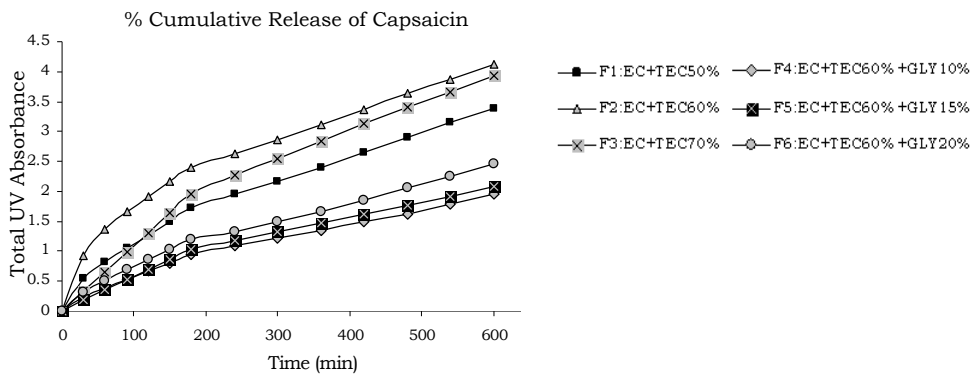


Figure 2 *In-vitro* permeation profile of optimal batches of capsaicin transdermal patches compared to the marketed product

Table 3 Optimal composition of batches of capsaicin transdermal patches

No.	Polymer	Plasticizer (%w/w)*	Glycerin	Capsaicin (%w/w)
1	EC	TEC 50%	-	0.025
2	EC	TEC 60%	-	0.025
3	EC	TEC 70%	-	0.025
4	EC	TEC 60%	GLY 10%	0.025
5	EC	TEC 60%	GLY 15%	0.025
6	EC	TEC 60%	GLY 20%	0.025

* % plasticizer (%w/w) is based on polymer weight.

DISCUSSION: According to the advantage of transdermal delivery system, the capsaicin formulations were packaged to produce the “drug in matrix type” transdermal patches⁴. Matrix patches were particularly preferred embodiments than reservoir patches and were more comfortable and convenient to apply⁵. Mechanical properties of the polymeric patches were conveniently determined by measuring their tensile strength⁶. The drug-free patches containing EC as the polymer with 60% TEC as the plasticizer showed the appropriate physical properties being clear, elastic and adhesive with optimal tensile strength (1.83 N/mm²), elastic modulus (38 N/mm²), and % elongation at break (14.80). The capsaicin patches was formulated by containing 0.025% capsaicin as the active ingredient with EC as the polymer, 60% TEC as the plasticizer, and 20% GLY as the anti-irritant. The capsaicin patches released the optimum amount of capsaicin as shown as % cumulative release of capsaicin within 10 h (64%).

CONCLUSION: This study determined the most suitable concentrations of polymer, plasticizer and anti-irritant for a transdermal drug delivery

system for capsaicin. The physicochemical characteristics of the optimized batches were satisfactory with respect to tensile strength, elastic modulus, and % elongation at break and *in-vitro* permeation profile. The non-irritating formulation of the capsaicin transdermal patch containing EC with 60% TEC, and 20% GLY produced the highest cumulative release of capsaicin while still controlling the pain with a formulary concentration of 0.025% as used commercially.

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