A COMPARISON OF THE EFFICACY OF STEROID PATCH CONTAINING BETAMETHASONE17 ,21DIPROPIONATE TO TOPICAL BETAMETHASONE17 ,21DIPROPIONATE TO TREAT IN CHRONIC HAND ECZEMA

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BY

SIRINAN THAITIRAROT

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Chronic hand eczema is a common inflammatory skin condition with a range of physical, social, and psychological effects on patients. Topical corticosteroids are recommended as a first line treatment as medical studies showed its beneficial and occlusive effect on chronic hand eczema. However, a few of the randomized clinical trials were investigated and none were performed transdermal patch containing steroid used to treat chronic hand eczema. This study aims to compare the efficacy of transdermal patch containing betamethasone17 ,21dipropionate and the topical betamethasone17 ,21dipropionate ointment to be treated in chronic hand eczema. The prospective randomized assessor-blind controlled trial was conducted with 56 patients, who had been diagnosed with mild to moderate chronic hand eczema. They were divided into two groups to be treated with steroid patches and topical corticosteroid by evaluating the result after two, four and eight weeks to determine the clinical severity by using Hand eczema severity index (*HECSI*) and *Physician Global Assessment* (PGA) score. The subjective assessment consisted of patient compliance, patient satisfaction, quality of life, and side effects. After 8-week study was done, none of statistically significant difference in HECSI and PGA score was found with *P*-value 0.314 and 0.394 respectively. Furthermore, statistical difference in quality of life and side effects were not discovered. However, the transdermal patch group showed better compliance than the topical corticosteroid ointment group with higher patient satisfaction. Critical adverse effects were not reported in both groups. The transdermal patch can effectively decrease clinical severity in the patients with chronic hand eczema. Therefore, it can be applied as one of the alternative treatments for improving treatment quality.

Keyword : Hand eczema, Chronic hand eczema, Steroid patches, Topical Corticosteroids, Treatment

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Introduction

Background and Significance of the Research

Hand eczema is a general found skin condition and also known as hand dermatitis which mainly affects the palms and other part of hands. Due to a chronic course and high relapse rates, it may cause significant impacts on daily activities[1]. Chronic hand eczema refers to an eczematous process that lasts for more than three months or relapses twice or more often per year[2].

Over the past 30 years, numerous papers have published data about work-related hand eczema. In addition, various surveys were also conducted by Meding, et al[3-7] to intensively study on hand eczema in industrial workers. Many different types of hand eczema found in an industrial city are reported, and the most common diagnosis is irritant contact dermatitis[3]. Furthermore, hand eczema is generally occurred more often in women than men by involving with wet work[6].

Hand eczema epidemiology research from 1964 to 2007 found that in general population, point prevalence is around 4%, 1-year prevalence is nearly 10%, lifetime prevalence reaches 15%, and median incidence rate is 5.5 cases-out of 1000 persons per years. Particularly, the research also stated that it mostly found in women having allergy or atopic dermatitis history, and wet work exposure[8]. Currently, new updated data estimates prevalence and incidence of hand eczema in general population from 2007 to 2020 that point prevalence, 1-year, and pooled of lifetime are 4.0%, 9.1%, and 14.5% respectively. For median incidence rate, the study reported 7.3 cases out of 1000 persons per years with 2 times higher occurrence in females[9]. The updated data also provides the most tendency towards higher pooled prevalence of hand eczema is occupation frequent contacting dermatitis with approximately 70%[10].

In Thailand, hand eczema associations and professions have analyzed that hand eczema is also related to certain occupations. For instance, in 2019, a study determined prevalence of hand dermatitis among food handlers in Department of

Medical Service Hospital and Hospital in Central Region of Thailand is 11%[11]. The following year, hand eczema is around 14.4% among spa massage therapists in Bangkok and vicinities[12]. During this time, an ongoing pandemic caused by the coronavirus disease (COVID-19), it is widely accepted that proper hand hygiene is one of the main preventives against COVID-19 transmission. However, frequent handwashing may affect hand skin barrier and incite hand eczema as the latest studies showed high prevalence in study population among health care workers in China[13], Turkey[14], and Thailand[15] at 74.5%, 79.3%, and 20.87%(in study population) respectively.

Hand eczema is heterogenous disease connected to several different etiologies[16]. A multifactorial etiology can be broadly divided into two groups which are exogenous and endogenous causes[17]. It can be acute or chronic stage and the severity ranges from mild to severe symptom[18] that persistently appears for 10 to 15 years after onset[19]. Regarding to eight-year follow up hand eczema study in 2008[20], there is a high risk of acute stage converted to chronic stage up to 67.6%. For example, occupational hand dermatitis had the poor long-term prognosis[19] due to continuous exposure with substances that would be one of the main reasons to reasonably sustain the treatment.

Treatments of chronic hand eczema require complex managements to be successful. The main purpose to achieve completely successful treatment is to identify and avoid causative exogenous factors.Based on European Society of Contact Dermatitis guideline treatment of hand eczema 2017[18], topical corticosteroids is recommended as first-line treatment. Besides, an apparent partial response or failure of treatment are often mentioned in chronic hand eczema patients. If ineffectiveness of treatments is suspected, several possible causes will be considered as well. For instance, patients may concomitant with atopic eczema[21], or topical therapy may be underestimated by patients and physicians[22]. For chronic hand eczema, regimens such as administration of potent corticosteroids only on weekend or everyday are required

long time series treatment (up to 36 weeks) for long-term maintenance[23]. However, patients would have poor adherence with topical treatment[24].

It is commonly known that thick palm skin might affect drug penetration, so using topical corticosteroids under occlusion has been recommended[25]. Occlusion is a technique to increase topical corticosteroids absorption by applying drug to affected area and then wrapping with plastic. As hands play importance functions whether held, grip, and grasp an object, patients have poor adherence to this treatment because of inconvenience in their daily lives[24]. Owing to the previously published studies, it could summarize that occlusion can enhance drug penetration to skin[26]. However, only few patients can tolerate because of long term treatment and loose-fitting plastic wrap.

Chronic hand eczema has substantial negative effects on the physical, social, and psychological of patients[27, 28]. The Swedish study reported undesirable consequences of chronic hand eczema patients, 81% experienced some degree of disturbance in daily lives, 8% change jobs, 21% take sick leave at least once, and 54% report frequent itching[4]. In 2002, the survey study in Denmark found prolong sick leave around 20.1% in wet occupations[29]. Moreover, it reported percentage of patients lost their job at least once during the past 12 months due to occupational hand eczema is about 23%. Apart from physical and social affects, psychological problems are also be triggered by chronic hand eczema. Higher anxiety levels corresponded to a greater impairment reported that 20% of occupational hand eczema patients have a positive anxiety score, and 14% of them have a positive depression score[29].

Transdermal drug delivery system[30] is a physicochemical technologies. This system is beneficial because it mainly involves local administration, can prevent local buildup in drug concentration and nonspecific delivery to tissues not targeted by the drug. It has significantly affected in various therapeutic agents such as pain management[31] and hormonal therapy[32]. The vehicle for drug delivery which is suitable for hand eczema is hydrogel patches, due to high water content, biocompatibility, and flexibility[33]. In 2013, there was a pilot study of Park K. et al[34] that showed the efficacy of triamcinolone (TAC) 0.1% cream compared with a new hydrogel patch to treat in atopic

dermatitis. Recently, a study of Rana K. et al[35] in 2022 reported the effectiveness of hydrogel-mediated topical delivery of steroids alleviating the clinical severity of psoriasis.

From aspects mentioned above, one of the main motivations to accomplish this thesis is to discover a better treatment for hand eczema patients by developing a new helpful invention called transdermal patch in order to improve efficacy of the treatment. Generating transdermal drug delivery system is a technique used to deliver drug throughout patient skin. It is convenient as doing in one-step process.

Research Questions

Primary Research Question

1. Does usage of transdermal patch containing 0.05%betamethasone17 ,21dipropionate be one of modalities in treatment of patients with chronic hand eczema compared to 0.05%betamethasone17 ,21dipropionate ointment by reducing Hand Eczema Severity Index (HECSI) score and Physician Global Assessment (PGA) score in patients with chronic hand eczema?

Secondary Research Questions

1. Does usage of transdermal patch containing 0.05%betamethasone17 ,21dipropionate in patients with chronic hand eczema have different side effects from using topical 0.05%betamethasone17 ,21dipropionate ointment?

2. Does usage of transdermal patch containing 0.05%betamethasone17 ,21dipropionate in patients with chronic hand eczema have different compliance comparison from using topical 0.05%betamethasone17 ,21dipropionate ointment?

3. Does satisfaction of patients with chronic hand eczema using transdermal patch containing 0.05%betamethasone17 ,21dipropionate differ from using topical 0.05%betamethasone17 ,21dipropionate ointment?

4. Does quality of life of patients with chronic hand eczema using transdermal patch containing 0.05%betamethasone17 ,21dipropionate differ from using topical 0.05%betamethasone17 ,21dipropionate ointment?

Research Objectives

Primary Objective

1 To compare efficacy of transdermal patch containing 0.05% betamethasone17 ,21dipropionate in patients with chronic hand eczema versus topical 0.05%betamethasone17 ,21dipropionate ointment by assessment of HECSI and PGA score.

Secondary Objectives

1. To compare safety of transdermal patch containing 0.05%betamethasone17 ,21dipropionate in patients with chronic hand eczema versus topical 0.05%betamethasone17 ,21dipropionate ointment.

2. To compare compliance in patients with chronic hand eczema by using transdermal patch containing 0.05%betamethasone17 ,21dipropionate versus topical 0.05% betamethasone17 ,21dipropionate ointment.

3. To compare satisfaction in patients with chronic hand eczema by using transdermal patch containing 0.05%betamethasone17 ,21dipropionate versus topical 0.05% betamethasone17 ,21dipropionate ointment.

4. To compare quality of life in patients with chronic hand eczema by using transdermal patch containing 0.05%betamethasone17 ,21dipropionate versus topical 0.05% betamethasone17 ,21dipropionate ointment.

Research Hypotheses

Primary Hypothesis

1. Usage of transdermal patch containing 0.05%betamethasone17 ,21dipropionate has superior efficacy in treatment of patients with chronic hand eczema compared to topical 0.05%betamethasone17 ,21dipropionate ointment.

Secondary Hypothesis

1. Usage of transdermal patch containing 0.05%betamethasone17 ,21dipropionate in patients with chronic hand eczema does not cause different adverse effects from using topical 0.05%betamethasone17 ,21dipropionate ointment.

2. The patients with chronic hand eczema using transdermal patch containing 0.05%betamethasone17 ,21dipropionate have more compliance than using of topical 0.05%betamethasone17 ,21dipropionate ointment.

3. The patients with chronic hand eczema using transdermal patch containing 0.05%betamethasone17 ,21dipropionate have more satisfaction than using of topical 0.05%betamethasone17 ,21dipropionate ointment.

4. The quality of life of patients with chronic hand eczema using transdermal patch containing 0.05%betamethasone17 ,21dipropionate is higher than using of topical 0.05%betamethasone17 ,21dipropionate ointment.

Research Aims

To perform transdermal patch containing with 0.05%betamethasone17 ,21dipropionate and assess efficacy, safety, compliance, and satisfaction in treatment of Thai chronic hand eczema patients.

Research Design

The study is a randomized-control trial in Thai chronic hand eczema patients who have not attended successful treatment for more than 3 months or their diseases have been relapsed twice or often per year. The age of target population is between 18 to 60 years old. The overall number of patients is approximately 50. They will be randomized into two groups which are 0.05%betamethasone17 ,21dipropionate cream group and 0.05%betamethasone17 ,21dipropionate transdermal patch group. Patients will have regular appointments to follow up at week 2, 4, and 8. They will be assessed clinical outcome by Hand Eczema Severity Index (HECSI) score. Estimated time to study is approximately 8 weeks at Skin SWU Center, Srinakharinwirot (SWU) University, Sukhumvit21, Bangkok, Thailand.

Expected Benefits

1. Efficacy and safety of transdermal patch containing 0.05%betamethasone17 ,21dipropionate will be accessed in treatment of patients with chronic hand eczema.

2. Outcomes of interventions may provide in clinical practice in order to develop new treatment guideline of chronic hand eczema for best practices and to ensure high-quality patient care.

3.Treatment compliance of patients with chronic hand eczema might be increased.

4. The satisfaction and quality of life of patients with chronic hand eczema could be better than in the past.

Definitions of Terms

1. Point Prevalence

refers to the prevalence measured at a particular point in time. It is the proportion of persons with a particular disease or attribute on a particular date[36].

2. Contact Irritant Dermatitis

is caused by the non–immune-modulated irritation of the skin by a substance, leading to skin changes[37].

3. Allergic Contact Dermatitis

is a delayed hypersensitivity reaction in which a foreign substance comes into contact with the skin[37].

4. Atopic Dermatitis

is a chronic, highly pruritic (itchy) inflammatory skin disease[38]

Conceptual Framework

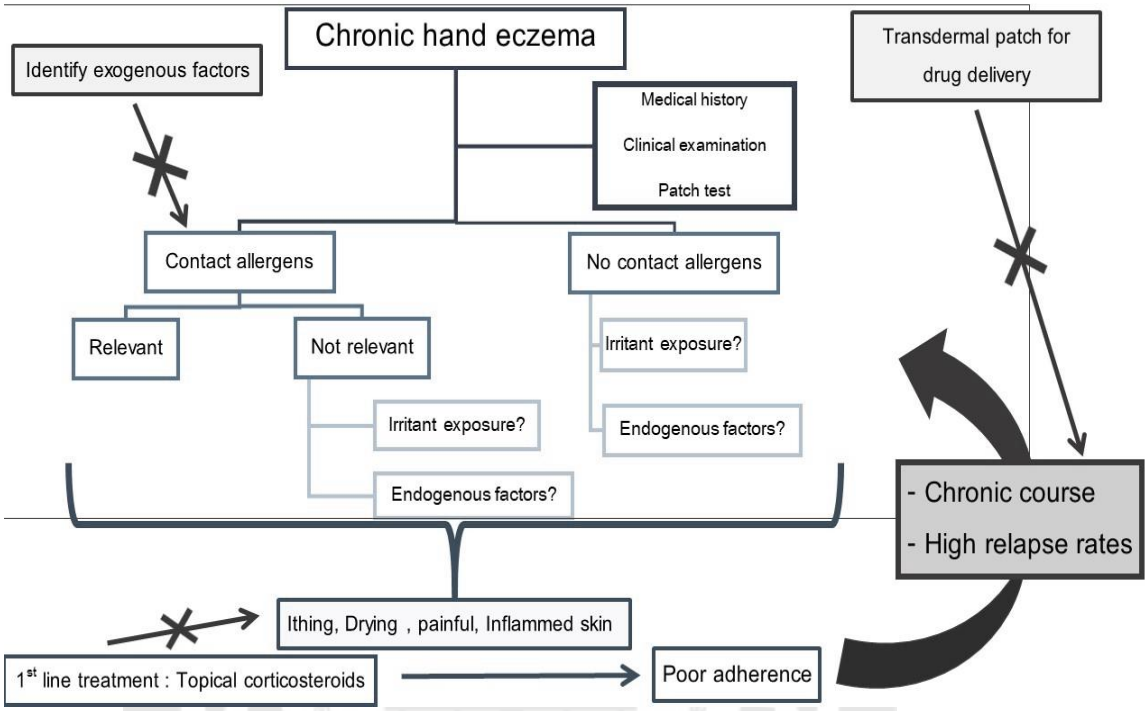


Figure 1 Conceptual Framework

Chapter 2

Literature Review'

Following literature and research have been reviewed,

1. Introduction and Subtypes of Hand Eczema
2. Pathogenesis of Hand Eczema
3. Diagnosis of Hand Eczema
4. Effect of Hand Eczema
5. Treatment of Hand Eczema
6. Role of Occlusive Dressings in Hand Eczema
7. History and Development of transdermal patches
8. Outcome Measurement of Hand Eczema

1. Introduction and Subtypes of Hand Eczema

Dermatitis or eczema is the most common inflammatory skin disorders[18] consists of many subgroup terms, but all of disorders perform common histological and clinical patterns depending on clinical stages such as acute, subacute, and chronic. These two aspects are different words but present the same thing. Dermatitis located on hands is known as “hand dermatitis or hand eczema”. Approximately 20% to 35% of hand eczema is highly associated with occupational skin disease[39].

The clinical stages are divided into three stages comprising of acute, subacute, and chronic. Acute and subacute stage are localized on hands that lasts for less than three months and it does not occur more than once a year. In acute stage, the usual findings are vesicles, erythema, edema, itching, or burning sensation. On the other hand, chronic stage lasts for more than three months or presents twice or more often per year. In many cases, it usually finds scaling, fissures, and hyperkeratosis[18].

“Hand eczema or hand dermatitis” is caused by multifactorial factors separated into two groups by causative condition, which are endogenous or exogenous condition. Endogenous condition possibly can be split further into atopic disease and pompholyx.

Exogenous condition is solely related to contact dermatitis. Moreover, contact dermatitis can be further allocated into irritant and allergic contact dermatitis as shown in figure2[39].

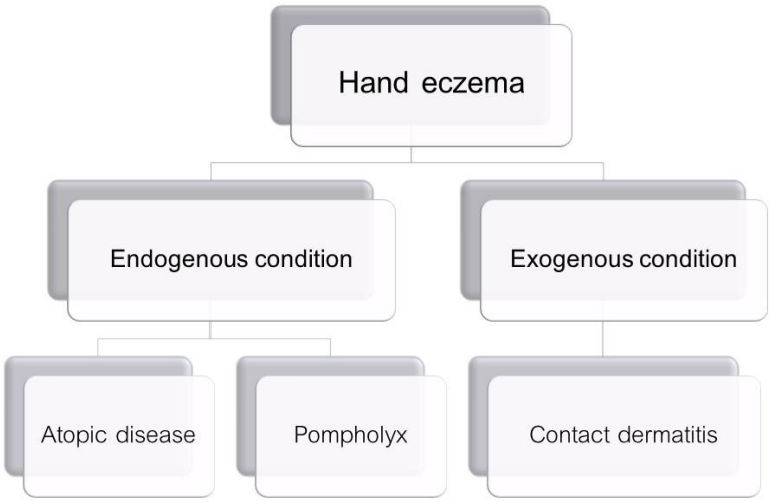


Figure 2 Classification of Hand Eczema

Practically, hand eczema is classified in six subtypes including allergic contact dermatitis, irritant contact dermatitis, atopic hand eczema, contact urticaria, hyperkeratotic endogenous eczema, and pompholyx[40]. However, there is no evidence regarding the categorization since morphology of hand eczema is not totally related to etiology, Besides, there is also no specific pattern mentioned. The study in 2015 performed data that more than half of patients had one or more additional diagnoses illustrates[40]. The most common subtype of hand eczema is irritant contact dermatitis, followed by allergic contact dermatitis, and atopic hand eczema[18]. There is approximately 30% eczema on feet and hand occur simultaneously that frequently coexists with hyperkeratotic and pompholyx[40].

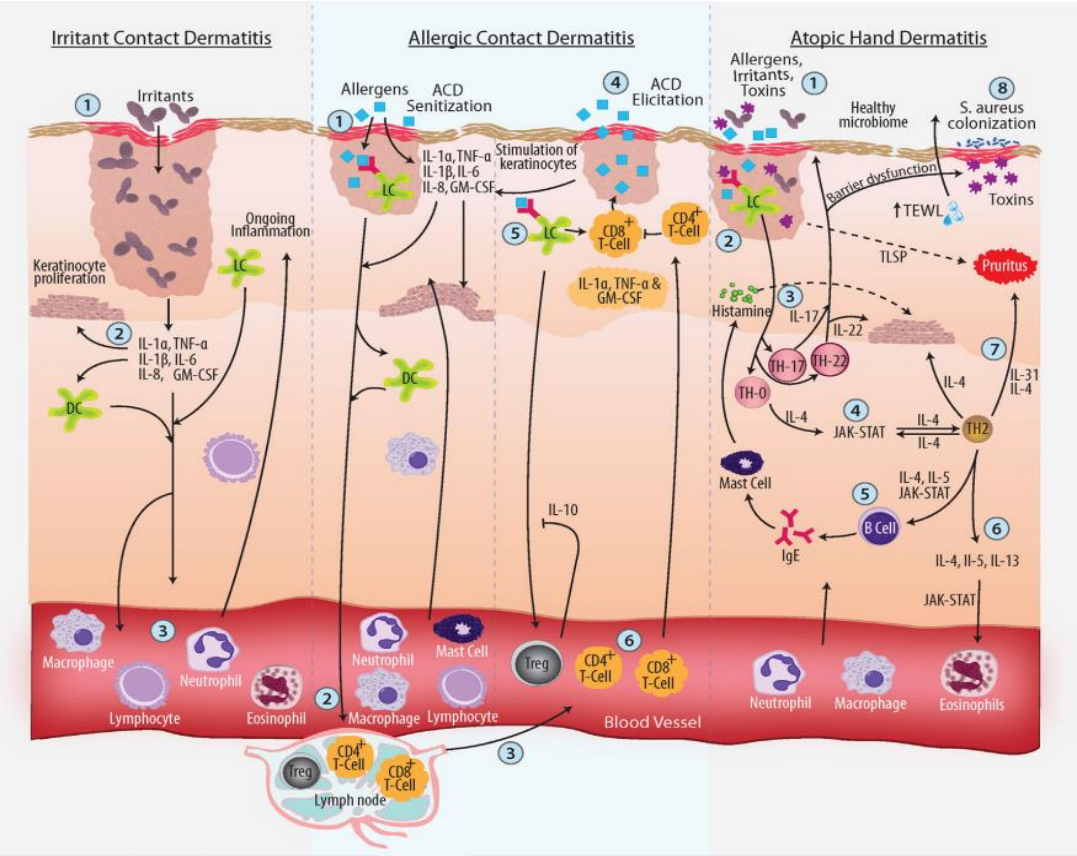
Table 1 Definition of Subtypes of Hand Eczema[18]

Subtypes of Hand Eczema	Definitions
Allergic Contact Dermatitis	Caused by contact allergens or identified cross-reactions by patch testing.
Irritant Contact Dermatitis	Documented irritant exposure, which is quantitatively likely to cause dermatitis. No current exposure to allergens which the patient has reacted positive in patch test.
Contact Urticaria/ Protein Contact Dermatitis	Exposed to proteins (food, latex and other biological material) with a positive prick test, or proven specific IgE, to suspected items.
Atopic Hand Eczema	Documented with a medical history of atopic eczema. No documented irritant exposure and/or relevant contact allergen.
Pompholyx (Vesicular Endogenous Eczema)	Recurrent HE with vesicular eruptions. No relevant contact allergy or documented irritant exposure likely to cause dermatitis.
Hyperkeratotic Eczema (Hyperkeratotic Dermatitis of the palms)	Chronic eczema with hyperkeratosis in the palms and no documented of irritant exposure to the involved skin areas.

*HE = Hand eczema

2. Pathogenesis of Hand Eczema[41]

Corresponding to the three most common subtypes, irritant contact dermatitis, allergic contact dermatitis, and atopic hand dermatitis, the pathogenesis generally combines exogenous (i.e., irritants, allergens) and endogenous parts (i.e., barrier defects, microorganism of skin). Subtypes of hand eczema are results of shared and distinct pathways. The figure below exhibits three most common subtypes.



ACD	Allergic Contact Dermatitis	JAK-STAT	The Janus kinase (*JAK*)-signal transducer and activator of transcription (*STAT*) pathway
LC	Langerhans cells	TNF-α	*Tumor Necrosis Factor alpha*
DC	Dendritic cells	GM-CSF	Granulocyte-macrophage colony-stimulating factor
TH-	T Helper Cells	IL-	*Interleukin-*
B Cell	B lymphocytes	$CD8^+$ T-Cell	Cytotoxic *T lymphocytes* (CTLs) that express the *CD8* co-receptor
S. aureus	Staphylococcus aureus	$CD4^+$ T-Cell	Cytotoxic *T lymphocytes* (CTLs) that express the *CD4* co-receptor
TEWL	Transepidermal water loss	Treg	*regulatory T* cells
TLSP	Thymic stromal lymphopoietin	IgE	Immunoglobulin E

Figure 3 Pathogenesis of Hand Eczema[41]

Panel 1: Irritant Contact Dermatitis

As irritants contact to skin, it is attached on keratinocytes causing toxic effects by massive releasing of various cytokines such as IL-1b, IL-6, IL-8, and GM-CSF. Dendritic cells, lymphocytes, neutrophils, macrophages, and mast cells are stimulated by these cytokines. Then, all activated cells will infiltrate the exposed site leading to inflammation by releasing the inflammatory mediators.

Panel 2: Allergic Contact Dermatitis

There are two steps in this process comprising sensitization and elicitation phases. The mechanism of sensitization phase is similar to irritant contact dermatitis, but different in memory T cells. In the sensitization phase, allergen exposures and activates innate immunity through keratinocyte release of massive cytokines, IL-1a, IL-1b, TNF-a, and GM-CSF, causing activation of leukocytes and dendritic cells. Subsequently, Langerhans cells and dendritic cells encounter allergens and migrate to lymph nodes to activate specific CD4+, CD8+, and regulatory T-cells. Furthermore, T-cells are proliferated and differentiated into effector and memory T cells. The individual memory T cells is sensitized to allergen and subsequent exposures, the same allergen induces a challenge called the elicitation phase[42]. Re-exposure of sensitized individuals with same allergen leads to rapidly allergic response. Allergens attack skin and it is taken up by skin cells expressing major histocompatibility complex (MHC) proteins classes I and/or II[43]. Above and beyond, specific T lymphocytes are activated in dermis and epidermis and then trig the inflammatory process.

Panel 3: Atopic Hand Dermatitis Panel

Apart from contacting dermatitis subtypes, atopic hand dermatitis has a unique barrier dysfunction characteristic of filaggrin mutations, decreased lipids, and increased TEWL. By these issues, allergens, irritants, and toxins are more easily penetrated to skin. Consequently, all of triggers are taken up by Langerhans cells expressed to TH-0, TH-17, and TH-22. Massive cytokines such as IL-17, and IL-22 are released leading to severe skin permeability. Then, TH-0 cells are differentiated into TH-2 cells via the JAK-STAT pathway and later release IL-4 and IL-5. Simultaneously, IgE synthesis of B-cells is stimulated and produced histamines and multiple inflammatory

mediators. Regarding to releasing of IL-4 and IL-5, neutrophils, macrophages, and eosinophils will be enhanced infiltration. Moreover, another inflammatory mediator such as IL-31 is released from keratinocytes leading to pruritus. Owing to chronic skin barrier dysfunction, the secondary infection probably begins.

3. Diagnosis of Hand Eczema

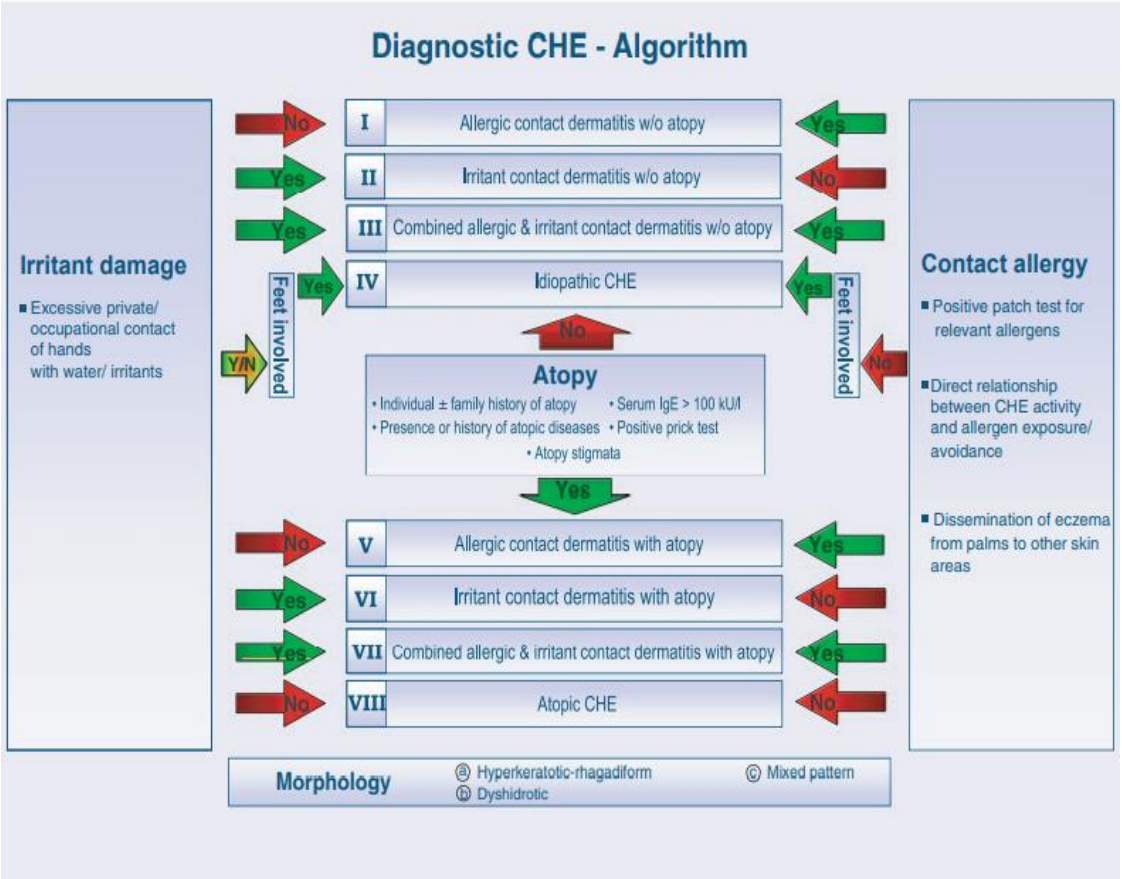


Figure 4 Diagnostic Algorithm of Chronic Hand Eczema[44]

Previously, information including morphology, exposure to allergen or irritant, results of patch testing, and atopy history have been used to clarify classifications of hand eczema[45]. As a result, it is vitally important to distinguish different classifications of hand eczema as it regularly dictates the diagnostic approach.

The study in Germany, 2010[46], discovered a short and new graphical algorithm that is helpful to identify various types of chronic hand eczema in clinical practices. According to the figure 4, chronic hand eczema is classified into three types which are irritant skin damage, contact allergy, and atopy. This criterion is carried out in a two-answer algorithm. Foot eczema is suspected of idiopathic eczema if contacting allergy and atopy absent. Clinical morphology is divided into three classifications that are hyperkeratotic, dyshidrotic, and mixed pattern.

4. Effects of Hand Eczema

Hand eczema has several symptoms such as erythema, itching, painful, or fissuring that consist negative impact on daily living. Treatment course is generally long-lasting, so prognosis is not quite well. Following, chronic hand eczema has effect on physical, social, and psychological of patients[27]. In 1990[4], the study performed undesirable consequence data of chronic hand eczema patients that 81% of patients experienced some degree of disturbance in their daily life, 8% changed jobs, 21% sick leave at least once, and 54% reported frequent itching. Besides, the survey study in Denmark,2002[47] found 20.1% prolonged sick leave in wet occupations. The survey in 2006[27] showed impact of chronic hand dermatitis on quality of life, work productivity, activity impairment, and medical costs in the United State population. They reported that quality of life, along with work productivity and activity impairment are significantly worse for patients owing chronic hand dermatitis. Furthermore, total medical costs are increased about 25% which translated to $70 per patient per month. However, there is no significant difference in work time missed. The cross-sectional study in 2016[48] also mentioned about patient cohort, *83*.4% of patients are employed and 70.1% of them are exposed to wet work. In the past 12 months, 37.3% of patients has been on sick leave due to their chronic hand eczema, 14.8% of has changed or given up their occupation. For assessment the burden of chronic hand eczema, the report uses the *Dermatology Life Quality Index (DLQI), with 39.4% of large effect.* Additionally, the recent study in a European dermatological multicenter,2018[49], showed that female patients with hand

eczema had higher Hospital Anxiety and Depression Scale (HADS) scores for anxiety and depression. The high psychological impact is significantly found in patients who are widowed or divorced, high suicidal ideation, and with low socioeconomic status.

Table 2 Effect of Chronic Hand Eczema Review of Literature

First Author	Year	Study Population	Method	Outcome	Measurement
K. Politiek [50]	2019 Denmark Netherlands	n=168 Female 56%	Cross-sectional questionnaire study	HRQoL was moderately impaired,	A structured questionnaire
S.E.Marron [49]	2018 Multicenter study	n=3635	Cross-sectional questionnaire study	- The most prevalent comorbidity was cardiovascular disease (15.3%) -Patients with high suicidal ideation, with low socioeconomic status and widowed or divorced are more likely to fulfil the HADS criteria for anxiety	A structured questionnaire

Table 2 (Cont.)

First Author	Year	Study Population	Method	Outcome	Measurement
S.E.Marron [49]	2017 Multicenter study	n=143 -Female 60%, -Mean age 45.5 years	Cross-sectional questionnaire study	Females have higher Hospital Anxiety and Depression Scale (HADS) scores for anxiety (n = 86, median = 7.0) than controls (n = 900, median = 5.0, p = 0.02)	A structured questionnaire
S. Cazzaniga [48]	2016 Switzerland	n=199 patients (mean age 40.4 years, 50.8% female)	Cross-sectional questionnaire study	-Moderate health impairment about 33.7% -Factors associated with a high (male sex, lesions on back of the hands and pruritus	-Dermatology life quality index (DLQI) -Structured questionnaire

Table 2 (Cont.)

First Author	Year	Study Population	Method	Outcome	Measurement
J.F.Fowler [27]	2006 The United State of America	n=507 n=140 CHE	Cross-sectional questionnaire study	-Quality of life, Work productivity and activity impairment are significantly worse -No significant difference in work time missed -Incremental cost of $70 per patient per month	-Structured questionnaire -Dermatology specific quality-of-life

*CHE = Chronic Hand Eczema, *HRQoL = Health-Related Quality of Life

5. Treatment of Hand Eczema

The treatment of hand eczema should consider appropriately in each stage of disease, etiology, morphology, and location. The treatment goals are the identification and avoidance causative factors (exogenous, and endogenous factors). According to the European Society of Contact Dermatitis (ESCD) guidelines,2017[18], the most effective treatment to prevent relapses is topical corticosteroids and emollients.

Moreover, the process should be started rapidly and strongly to prohibit the development of chronic hand eczema.

However, in chronic hand eczema, the treatment is more difficult than acute stage. Therefore, it requires complex managements as mentioned in figure 5. Therapeutic options can be divided to two groups, pharmacology, and non-pharmacology. Previously, there are topical and systemic therapy including emollients, topical corticosteroids, topical calcineurin inhibitors, Methotrexate, and Alitretinoin. For non-pharmacology, there is phototherapy, and skin protection program.

Topical therapy should always be prescribed as a part of treatment regimen, even combined with systemic therapies[51] as stated in figure 6. The appropriate choice of vehicle should relatively consider to skin condition. In general, the principles 'moist on moist', 'greasy on dry' mean using hydrating vehicles on acute lesions and lipid-rich vehicles on chronic ones. A topical therapy -based preparations, emollients, or moisturizer, is a key treatment in all types of eczema. Basic topical therapy relieves inflammation and itching and also promotes epidermal barrier recovery. In chronic hand eczema, keratolytic, anti-proliferative and moisturizing effects are needed to combine with keratolytic ointments (containing salicylic acid up to 20% if necessary, urea 10–20%) and lipid-rich ointments.

Topical corticosteroids are the first-line treatment of hand eczema. Many commercial topical corticosteroids products are generally available. According to adverse effects of long-term use of glucocorticoids as mentioned in figure 7, it is crucial consideration in steroid potency, duration of treatment, and frequency of administration before prescribing to patients. For chronic hand eczema, recommended steroid[52] is high potency for examples, Amcinonide 0.1%, Betamethasone dipropionate 0.5%, Desoximetasone, and Fluocinonide 0.05%. Patients should apply steroids once- or twice a day with roughly 0.5 fingertip unit (1 fingertip unit = approximately 0.5 g) on one hand (one side). Negative effects rarely cause if it is has been used less than 3 months[53]. For supporting its efficacy, the recent Cochrane review evaluated topical corticosteroids as the main intervention. Clobetasol propionate 0.05% foam and mometasone furoate

cream can probably control of symptoms. An open-label study in 2011[54] mentioned, clobetasol propionate 0.05% cream shows efficacy after being treated for 15 days with efficacy about 96.7%. Moreover, the recent published meta-analysis, 2021 studied on topical 0.05% clobetasol cream for chronic hand eczema in 8 databases found proportion of patients achieve more than 75% reduction in signs and symptoms according to the Hand Eczema Severity Index (HECSI)[55]. As results of topical corticosteroids to chronic hand eczema are well control, but few of patients are satisfied with this currently therapy. The web-based survey in the United States queried pre-identified patients with severe chronic hand eczema reveals only 15% of patients reported being very satisfied[56]. For other topical therapies and topical calcineurin inhibitors, the study in 2004, revealed a greater improvement in Investigator Global Assessment (IGA) of 294 patients with chronic hand dermatitis by using pimecrolimus 1% cream twice a day for 3 weeks compared to vehicle control[57]. Furthermore, a study in Germany,2008 reported 29 patients with occupational hand dermatitis with satisfied results in hand eczema score by applying tacrolimus ointment 0.1% twice a day for 2 months[58].

Regarding systemic therapy[51], there are acitretin, alitretinoin, cyclosporin, methotrexate, and systemic corticosteroid. Systemic corticosteroids may be usually required in severe acute hand eczema and exacerbations of chronic disease, with usually short-term 0.5–1 mg/kg/day prednisolone. A large trial of 1032 patients with chronic hand eczema assessed two dosages of alitretinoin (30 or 10 mg/day) against placebo up to 24 weeks are achieved up to 48%[59]. For Cyclosporine, there is a study comparing cyclosporin and topical betamethasone dipropionate 0.05% for 6 weeks in 41 patients with chronic hand eczema that published equal effectiveness of both treatments[60].

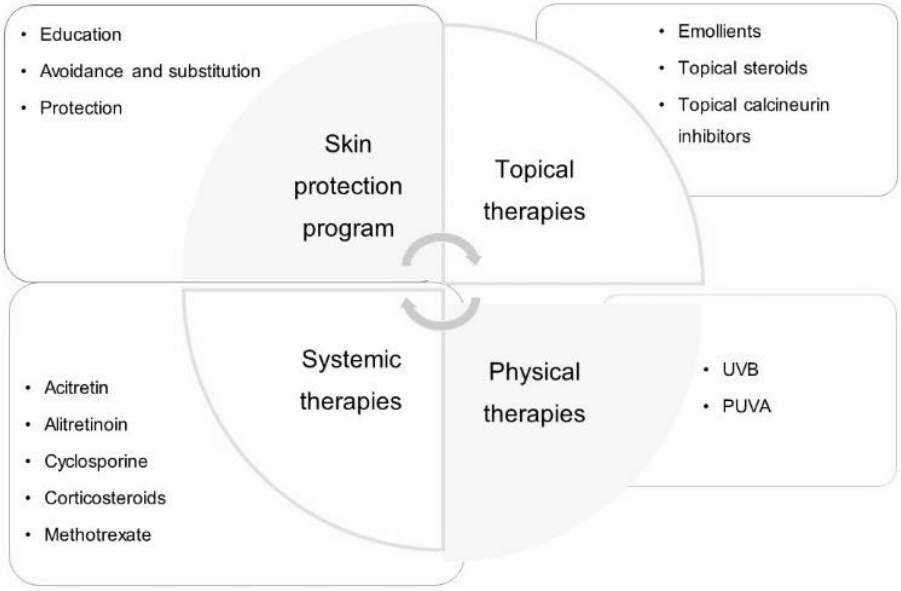


Figure 5 Treatment Options of Chronic Hand Eczema[18]

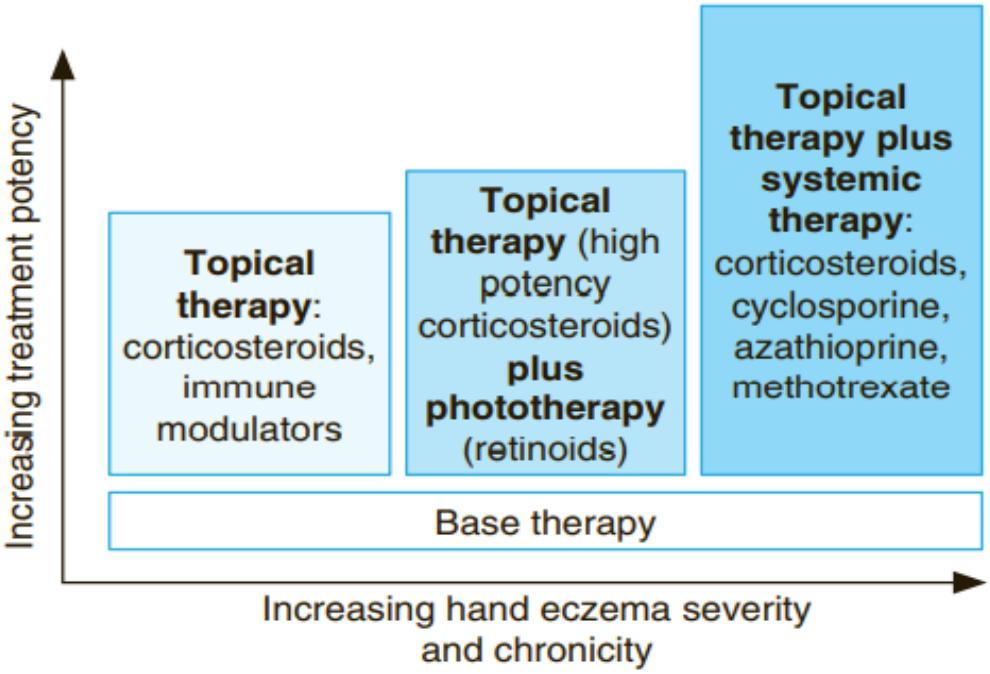


Figure 6 Treatment Options for Hand Eczema Depending on Disease Severity and Chronicity[16]

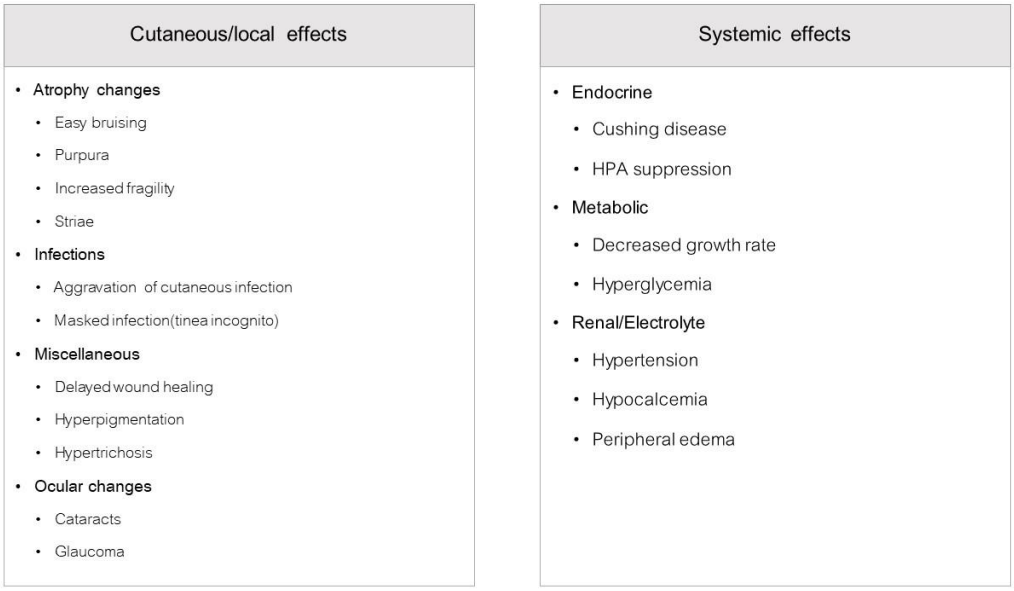


Figure 7 Potential Side Effects of Topical Corticosteroids[52]

Table 3 Corticosteroids Treatment of Hand Eczema Review of Literature

First Author	Year	Study Population	Method	Outcome	Measurement
P. Juntongjin[61]	2019 Thailand	n=13 Chronic Hand Eczema	-All recruited subjects underwent patch testing -One hand - application of 0.005% calcipotriol ointment on one hand -The other hand- application of 0.25%	-Mean HECSI scores reduced about 75% in both treatments ($p < .001$) without significant differences between the	-HECSI score

Table 3 (Cont.)

First Author	Year	Study Population	Method	Outcome	Measurement
			desoximetasone ointment -Both ointments are applied twice a day on the lesions for 8 weeks	groups (p > .05) -Equally effective both treatments	
U.S. Agarwal [62]	2013 India	n=91 18-65 years old	-Group A =46 Applied topical clobetasol propionate 0.05% cream twice daily only -Group B= 45 plus oral azathioprine 50 mg daily	-There was a significant improvement in both the scores -After 24 weeks → Gr.A improves 64.66% →Gr.B improves 91.29%	-HECSI score

Table 3 (Cont.)

First Author	Year	Study Population	Method	Outcome	Measurement
G Faghihi [63]	2006 Iran	n=47 Chronic Hand Eczema	-Group A Applied 0.05% Clobetasol + 2.5% zinc sulphate' cream -Group B Applied 0.05% Clobetasol alone cream twice a day for 2 weeks	-Group A was more effective than Group (P < 0.05) - The recurrence rate of eczema was significantly lower in group treated with this combination treatment (P < 0.05)	-Clinical severity score
N.K.Veivn [23]	1998	n=120 Chronic Hand Eczema -Above 17 years old	-The first phase – 120 patients with CHE applying with mometasone furoate fatty cream OD until the dermatitis cleared	- The first phase -> 50 of 106 patients need 3 weeks controlled their	-Clinical severity score

Table 3 (Cont.)

First Author	Year	Study Population	Method	Outcome	Measurement
		- 100Women	or for a maximum of 9 weeks (Cont.)	dermatitis -> 29 patients need 6 weeks (Cont.)	
Cont.		-20 Men	-The second phase – for maintenance phase divided to 3 groups, treatment for up to 36 weeks and follow up the results -Applying with mometasone furoate - Group A: on Sunday, Tuesday and Thursday - Group B: on Saturday and Sunday - Group C: no further corticosteroid treatment	-27 patients need 9 weeks - The maintenance phase →29 of 35 (83%) in group A →25 of 37 (68%) in group B → 9 of 34 (26%) in group C -Minimal side effects	

Table 3 (Cont.)

First Author	Year	Study Population	Method	Outcome	Measurement
H. Grandlund [60]	1997 Finland	n=41	Randomization either oral cyclosporine or Topical Betamethasone 17 ,21 dipropionate 6 weeks	The EDI score was decreased significantly in both groups	-The Eczema Disability Index(EDI)

6. Role of Occlusive Dressings in Hand Eczema

Occlusive dressings define skin area covering with a sticky dressing to enhance treatment effect. The first record uses an occlusive wound in 1615, it reported that closed wounds can be healed more quickly than open wounds[64]. Currently, there are many commercially products of occlusive dressings such as hydrocolloid, hydrogel, silicone, and films.

There are numerous studies about occlusive effects in atopic eczema. It is widely known that pathogenesis of hand eczema is similar to atopic eczema that both caused by barrier dysfunction. Wet wrap therapy (WWT) composes of topical steroids administered under a layer of wet bandages or garments. Several trials with wet wrap therapy (occlusive techniques) report favorable results in atopic dermatitis[65].

As mentioned above, the therapeutic efficacy of wet wrap therapy is beneficial. A study in South of Korea,2007 showed induced mechanism releasing of lamellar body and restoration of intercellular lipid lamellar structure, resulting in an increase of water content in corneum[66].

About hand dermatosis, there is a comparative study of a topical corticosteroid ointment against occluded solution with thin hydrocolloid dressing in Sweden,1996[26].

The result stated that topical corticosteroid ointment is occluded with thin hydrocolloid to reduce mean score of symptoms approximately 80% after 28 days of treatment. While there was a data from a study in India,2013, showed that topical corticosteroid without occlusion can reduce clinical score about 60%[62].

Table 4 Role of Occlusive Dressings in Hand Eczema Review of Literature

First Author	Year	Study Population	Method	Outcome	Measurement
D. Thaçi [67]	2003	n=13 -8 Females, 5 Males -20–57 years of age -Chronic Hand Dermatosis	-Open-label study - Applying topical pimecrolimus cream 1% twice daily to dorsal and palmar areas (affected and unaffected) of both hands -Evening applications (except day 8) are immediately followed by overnight occlusion (66 h)	- 12 patients completed the study - 85% (11 patients) improvement at day 22	Investigators' Global Assessment (IGA)

Table 4 (Cont.)

First Author	Year	Study Population	Method	Outcome	Measurement
H. Beitner [26]	1996	n=30 9 Men, 21 Women -Hand dermatosis -Mean age 51 years old	-Group A- 15 patients treated with Clobetasol propionate ointment with occlusion (Coloplast) -Group B-15 patients treated with Clobetasol propionate solution with occlusion -Applied twice a week for the first 2 weeks & once a week for the next 2 weeks	-24 patients completed study -After 28 days, mean score is reduced approximately by 80% -No statistic difference in clinical outcome	Clinical severity score
G Volden [25]	1992	n= 161 patients with chronic skin diseases including palmoplantar pustulosis	-Applying once a week with clobetasol propionate lotion left under the completely occlusive patch (Duoderm)	-Nearly 92% -completely resolved after 9 days to 4weeks - 8% -partial remission	-Physician Global Assessment (PGA)

7. History and Development of Transdermal Patches

Transdermal patch is an invention generated to penetrate drug through skin and diffuse to circulatory system. Human skin, the thickness of exposed layer is about 10 millimeters[68]. The history of transdermal delivery[69] has evolved over thousands of years. The large amount of describing and prescriptions drugs by P.Ebers[69] were appeared to be with the best pharmaceutical record from ancient times. In the past, transdermal patches have been treated with various skin conditions, including burns, wounds, blisters, and exudation. At the beginning of 20th century, the researchers discovered and improved quality of transdermal patches. After that, the study of Kramer,et al[70] stated *using rate-controlling membrane* to control transdermal delivery rate.

There are 3 pathways of drug penetration which are transcellular route, paracellular route, and transappendgeal route. The advantages of transdermal routes are documented including targeting delivery, lowering systemic exposure, lowering toxicity than oral medications, and providing steady plasma level[68].

Currently, variability in dosing and type of drugs have been generated for multi purposes. The study in India,2007, showed ethosomes bearing methotrexate (MTX) treating in psoriasis is evaluated and concluded that ethosomes are an efficient carrier for dermal and transdermal delivery of methotrexate[71]. Another study in South of Korea,2019, found transdermal delivery of minoxidil is carried out and efficiently delivered drug to hair follicles[72]. In atopic dermatitis, hyaluronic acid(HA) based transdermal delivery has been developed due to abundant of HA at epidermis of atopic dermatitis[73].

The enhancement of drug delivery through skin by transdermal patch is achieved in various skin disease. However, transdermal patch containing topical corticosteroids has never been documented, so this thesis will purposefully develop transdermal patch containing topical corticosteroid treating in chronic hand eczema.

Table 5 History and Development of Transdermal Patches

First Author	Year	Study Population	Method	Outcome	Measurement
Nien H.K. et. al. [73]	2020	-	Hyaluronic-acid mediates drug delivery system targeting for inflammatory skin disease		Skin
Jeong W.Y. et. al. [72]	2019	-	Transdermal delivery of Minoxidil used HA-PLGA nanoparticles for the treatments= in alopecia	Both of HA-PLGA/MXD NPs and HA-PLGA/Rho B NPs are successfully prepared to confirm that HA-PLGA NPs sufficiently delivered to cells without any	

Table 5 (Cont.)

First Author	Year	Study Population	Method	Outcome	Measurement
				significant cytotoxicity by cell viability, cellular uptake and skin permeation test	
Dubey V. et. al. [71]	2007	-	Dermal and transdermal delivery of an anti-psoriatic agent via ethanolic liposomes		

8. Hydrogel patch in drug delivery systems

Hydrogels are three-dimensional, polymeric networks consisting of crosslinked hydrophilic components[74]. The flexibility in mechanical properties of hydrogels is significantly influenced in drug delivery.

There was an evidence supporting the strength of hydrogel patch containing corticosteroid, an in vivo study of Baboota S. et al[75] in 2011 was showed that the hydrogel patches for the delivery of the corticosteroid betamethasone diproprionate, which normally has poor permeability through the skin, was found to inhibit inflammation by 72.11% compared with a 43.96% inhibition in a psoriasis model of rat hind paw edema.

Table 6 Study of the efficacy of hydrogel patch

First Author	Year	Study Population	Method	Outcome	Measurement
Park K. et. al.[34]	2013	15 Atopic dermatitis patients	applied the hydrogel patch over one lesion for 6-8 h daily and triamcinolone (TAC) 0.1% cream twice daily to another lesion.	After 2-week no treatment follow-up showed hydrogel patch had notable efficacy, and comparable to TAC 0.1% cream.	Clinical severity score
Park K. et. al. [34]	2013	15 Atopic dermatitis patients	applied the hydrogel patch over one lesion for 6-8 h daily and triamcinolone (TAC) 0.1% cream twice daily to another lesion.	After 2-week no treatment follow-up showed hydrogel patch had notable efficacy, and comparable to TAC 0.1% cream.	Clinical severity score

9. Outcome Measurement of Hand Eczema

Practically, severity of hand eczema can be measured in different methods by physician-rated, patient-rated, or burden disease indicator. In general, the severity score should be highly correlated with patient-related severity score. The ideal result of hand eczema assessment is the same for both physician-rated and patient rated severity score. However, it is less supported by outcome from the research in Netherlands, 2006, suggested that it is uncorrelated, so burden hand dermatosis has a greater impact than visible aspects of the disease[76].

Generally, there are no standard score system to evaluate. Then, numerous score systems have been used such as HECSI score, Dyshydrotic Eczema Area and Severity Index (DASI), Hand Eczema Area and Severity Score (HEAS), and Hand Eczema Extent Score (HEES) etc. It is important to carefully select the most suitable methodology applied for patients because there are many available methods. There was a published report in Germany,2010, reviewed different skin scores used to quantify hand eczema[77]. The three methods are composed of the Hand Eczema Severity Index (HECSI), the Osnabruck Hand Eczema Severity Index (OSHI), and Manuscore were recommended because they were reported as the interobserver reliability[78, 79]. In addition, the most suitable scoring system suggested is HECSI score because it portrays observers (repeatability) and interobserver reliability.

The study in Germany in 2013, revealed a comparison of four methods to assess severity of hand eczema (i.e. Hand Eczema Severity Index (HECSI), Physician Global Assessment (PGA), Clinical Photo Guide, and Dermatology Life Quality Index (DLQI))[80]. The strongest correlation is found between HECSI and the PGA, both performed by the physicians. However, a weak correlation is retrieved between DLQI and Clinical Photo guide, both performed by the patients. These findings agree with in agreement with a previous study[76]. Another supported reason for weaker correlations between DLQI and other methods could be that HECSI, PGA and Clinical Photo Guide are specifically designed for hand eczema, whereas the DLQI has been generated for the assessment of HR-QoL in all skin diseases.

Patients-Reported Outcomes Measured (PROMs) illustrates an important data to physician-assessed clinical outcome measures in dermatologic diseases such as atopic dermatitis (AD) and chronic hand eczema (CHE)[81]. For pruritus, it is no standard wording for assessment. A Pruritus Numeric Rating Scale (NRS) is used to providing the itching. A typical NRS is a scale from 0 to 5, or 0 to 10, with verbal anchors. The study in Germany,2014, assessed itching by verbal rating scale in 4 categories (absent to severe) and reported itching about 78.1% of chronic hand eczema patients[82].

Overall, this thesis will use HECSI and PGA to carefully assess severity of hand eczema.

Additional information of HECSI and PGA score

Hand Eczema Severity Index (HECSI) score is a tool to assess six clinical symptoms. HECSI score ranges from 0 to 360 points.

Grading of HECSI score is defined as[83]

- Score 0–11 Mild
- Score 12–27 Moderate
- Score ≥ 28 Severe

Clinical signs	Fingertips	Fingers (Except tips)	Palm of hands	Back of hands	Wrists
Erythema (E)					
Infiltration/Papulation(I)					
Vesicles (V)					
Fissures (F)					
Scaling (S)					
Oedema (O)					
SUM (E + I + V + F + S + O)					
Extent (Ex)					
Total HECSI score =	Sum * Ex +	Sum * Ex +	Sum * Ex +	Sum * Ex +	Sum * Ex +

Total HECSI score (min 0; max 360). For each location (total of both hands) the affected area was given a score from 0 to 4 (0, 0%; 1, 1–25%; 2, 26–50%; 3, 51–75% and 4, 76–100%) for the extent of clinical symptoms. Finally, the score given for the extent for each location was multiplied by the total sum of the intensity of each clinical feature (each contributing equally to the final score), and the total sum called the HECSI score was calculated, varying from 0 to a maximum severity score of 360 points

Figure 8 Hand Eczema Severity Index (HECSI) Score[78]

PGA score is based on a five-point intensity scale (clear, almost clear, mild, moderate, and severe)

Score	Category	Description
0	Clear	No signs of plaque psoriasis
1	Almost Clear	Just perceptible erythema and just perceptible scaling
2	Mild	Light pink erythema with minimal scaling with or without pustules
3	Moderate	Dull red, clearly distinguishable erythema with diffuse scaling, some thickening of the skin, with or without fissures, with or without pustule formation
4	Severe	Deep, dark red erythema with obvious and diffuse scaling and thickening as well as numerous fissures with or without pustule formation

Figure 9 Physician's Global Assessment Score[84]

Other outcome measurements are Dermatology Life Quality Index (DLQI) and patients' satisfaction. DLQI is a simple practical questionnaire technique which was first developed in 1993 by A.Y. Finlay and G.K. Khan at University Hospital of Wales[85]. Each answer was analyzed by identifying different aspect of life quality impairment. The number of different aspects identified in each answer ranged from 0 to 8. This DLQI questionnaires was obtained test-retest reliability and the result was high[85]. Moreover, this questionnaire has been used worldwide to assess patients with skin disease. Similar to Thailand, DLQI was translated to Thai version and applied in clinical practice.

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name:
Address: Diagnosis:
Score: ☐

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ✓ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes ☐ No ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot ☐ A little ☐ Not at all ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much ☐ A lot ☐ A little ☐ Not at all ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you.

Figure 1. The Dermatology Life Quality Index (DLQI) questionnaire.

Figure 10 Dermatological Life Quality Index (DLQI) Score (English version)[85]

DLQI Thai version

แบบสอบถามวัดคุณภาพชีวิตของผู้ป่วยโรคผิวหนัง

(ข้อมูลของท่านจะเป็นความลับ ไม่ถูกนำไปเปิดเผยเป็นรายบุคคลต่อผู้ใดทั้งสิ้น)

ชื่อ _____ H.N. ____/_____ DLQI Score: _____

เพศ ชาย หญิง อายุ _____ ปี อาชีพ_____

Study No. _____วันที่ ___ / _____ / _____ Diagnosis_____

จุดประสงค์ของแบบสอบถามนี้ เพื่อประเมินว่า ผื่นผิวหนังทำให้เกิดปัญหากับคุณมากน้อยเพียงใดในช่วงหนึ่งสัปดาห์ที่ผ่านมา? **กรุณาตอบคำถามโดยทำเครื่องหมาย ✔ ลงในช่องทางขวามือ (ขอความกรุณาตอบคำถามทุกข้อ)**		
1. ช่วงสัปดาห์ที่ผ่านมา คุณมีอาการคัน, เจ็บ, ปวด, หรือปวดเสียว ที่ผิวหนังมากน้อยเพียงใด	มาก ปานกลาง เล็กน้อย ไม่มีเลย	
2. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังทำให้คุณรู้สึกอับอาย, ขาดความมั่นใจ มากน้อยเพียงใด	มาก ปานกลาง เล็กน้อย ไม่มีเลย	
3. ในช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังทำให้คุณมีปัญหาในการออกจากบ้านไปจับจ่ายซื้อสินค้า, ดูแลบ้าน หรือดูแลสวน มากน้อยเพียงใด	มาก ปานกลาง เล็กน้อย ไม่มีเลย	ไม่มีความเกี่ยวข้อง
4. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังของคุณ มีผลกระทบต่อการเลือกเสื้อผ้าที่จะสวมใส่ มากน้อยเพียงใด	มาก ปานกลาง เล็กน้อย ไม่มีเลย	ไม่มีความเกี่ยวข้อง
5. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังของคุณ มีผลกระทบต่อการเข้าสังคม หรือต่อกิจกรรมในยามว่าง มากน้อยเพียงใด	มาก ปานกลาง เล็กน้อย ไม่มีเลย	ไม่มีความเกี่ยวข้อง
6. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังมีผลกระทบต่อการเล่นกีฬา การออกกำลังกายของคุณ มากน้อยเพียงใด	มาก ปานกลาง เล็กน้อย ไม่มีเลย	ไม่มีความเกี่ยวข้อง
7. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังมีผลทำให้คุณขาดงานหรือขาดเรียนหรือไม่	มี ไม่มี	ไม่มีความเกี่ยวข้อง
ถ้า "ไม่มี" ในช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังทำให้มีคุณมีปัญหาในการทำงาน หรือ การเรียน มากน้อยเพียงใด	ปานกลาง เล็กน้อย ไม่มีเลย	
8. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังของคุณ ได้สร้างปัญหาให้กับคู่ครอง หรือญาติหรือเพื่อนสนิท มากน้อยเพียงใด	มาก ปานกลาง เล็กน้อย ไม่มีเลย	ไม่มีความเกี่ยวข้อง
9. ช่วงสัปดาห์ที่ผ่านมา ผื่นผิวหนังทำให้คุณมีปัญหาในการมีเพศสัมพันธ์ มากน้อยเพียงใด	มาก ปานกลาง เล็กน้อย ไม่มีเลย	ไม่มีความเกี่ยวข้อง
10. ช่วงสัปดาห์ที่ผ่านมา การรักษาผื่นผิวหนังก่อให้เกิดปัญหาแก่คุณ มากน้อยเพียงใด เช่น ทำให้มีการเปรอะเปื้อนในบ้าน, การรักษาทำให้เสียเวลา เป็นต้น	มาก ปานกลาง เล็กน้อย ไม่มีเลย	ไม่มีความเกี่ยวข้อง

Figure 11 Dermatological Life Quality Index (DLQI) Score (Thai version)[86]

There are 10 questions asking patients about how much does skin disease impact patient's life. Maximum score is 30 and minimum score is 0. It can be calculated scores following this,

- 3 = very much
- 2 = a lot
- 1 = little
- 0 = not at all, no relevant, and no answer

Table 7 Interpretation of Dermatological Life Quality Index (DLQI) Score[87]

DLQI scores	Meaning
0-1	No effect at all on patient's life
2-5	Small effect on patient's life
6-10	Moderate effect on patient's life
11-20	Very large effect effects on patient's life
21-30	Extremely large effect on patient's life

Chapter 3
Research Methodology

Research Design

This research is an experimental, prospective, randomised, controlled, assessor-blinded in chronic hand eczema study.

Target Population

Thai adolescents or adults aged over 18 years old have been diagnosed as mild to moderate chronic hand eczema or have history of intermittent or persistent skin lesions such as eczematous or vesicles on both hands for more than 3 consecutive months or relapse more than twice per year with or without prior treatment at Skin SWU Center, Sukhumvit21, Bangkok, Thailand.

Sampling Method

Sampling method in this project uses the consecutive sampling. Project information is distributed online via Facebook page and Instagram, also showed in the university via a poster presentation. The patients have specific inclusion criteria, who meet exclusion criteria are excluded. A number of expected patients are 56.

Randomization, Allocation Concealment, and Blinding

The researcher groups the patients via the block randomization method, http://www.randomization.com. Random sampling allows the sampling error to be calculated and reduced selection bias. The treatment allocation is done by using a computer-generated block randomization with a block size of 4. Sets of blocks with random sequences of treatment are generated and then applied to each patient according to their subject ID.

Central randomization is applied for allocation concealment. After generating the random sequences via computer software program, the researcher codes both study groups into the letter “A” and “B”. The letter A means group of patients with transdermal patch containing betamethasone17 ,21dipropionate whereas the letter

B means group of patients with topical 0.05%betamethasone17 ,21dipropionate ointment. Next, the researcher prints out and puts each of sheets in envelop and seal it. The document must not be visible from outside. If the document inside can be read with a flash of light, an aluminum foil will be used to conceal it. All sealed envelopes are placed at the nurse of Skin SWU Center to send to all patients, and she must be unaware of the methods of this study. When the patients meet all inclusion criteria and enroll to this study, the nurse will give the envelops to the patients. Each patient will receive one envelop to inform the intervention group. The researcher cannot be expected to ensure what the next intervention group.

The accessor in this study is a trained dermatologist at Skin SWU Center to perform an evaluation of HECSI and PGA score of all patients every follow-up visits. However, they do not uninform the methods and participate other activities of this study.

Sample Size Calculation

This research sample size calculation will be based on the study of H. Beitner from 1996[26]; treatment of hand dermatosis: a comparative study of a topical glucocorticoid ointment versus solution occluded with a new thin hydrocolloid dressing. This clinical trial, 30 consecutive patients, 9 men and 21 women, who had an average aged of 51 years old. In this study, the percentage of mean score after treatment 28 days decreased from 100% to approximately 18%, so its effectiveness after occlusion was about 82%. For this trial, only the effectiveness after occlusion was carried out. However, the efficacy of topical corticosteroid treatment without occlusion was investigated by U. S. Agarwal and R. K. Besarwal in 2013[62]; topical clobetasol propionate 0.05% cream alone and in combination with azathioprine in patients with chronic hand eczema: An observer blinded randomized comparative trial. 91 participants who clinically diagnosed chronic hand eczema were attended. The result showed a decrease in mean clinical score as the percentage after treatment 28 days by topical clobetasol propionate 0.05% cream alone, with 60.24% (Mean score 10.4565). According to the results of both studies, there was a significant difference of their effectiveness after treatment with or without occlusion, with about 22%. Furthermore, the

published paper of H. Grandlund et al. in 1996[60]; Comparison of Cyclosporine and Topical Betamethasone 17,21-dipropionate in the Treatment of Severe Chronic Hand Eczema was considered about the result of decreasing in clinical scores by treated with topical Betamethasone17, 21-dipropionate alone, with 58% of baseline score (SD4, mean change 5.7).

Some of the data from these 3 published papers were taken for calculating the mean difference and the standard deviation for calculation of sample size. The mean difference was approximately 3.234 and the standard deviation between before and after treatment was about 4.

In this thesis, the number of patients was calculated by this formula in the figure below[88].

$$n_1 = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 \left[\sigma_1^2 + \frac{\sigma_2^2}{r}\right]}{\Delta^2}$$

$$r = \frac{n_2}{n_1}, \Delta = \mu_1 - \mu_2$$

Figure 12 The Formulation for Sample Size Calculation

With values as followed

- α = type 1 error = 0.05 (5%)
- β = type 2 error = 0.20 (Power = 80%)
- Z1-α/2 = 1.96 (from the Z score table)
- Z1-β = 0.84 (from the Z score table)
- r (ratio) = 1
- Δ = 5.700-2.466 = 3.234
- σ 2 = (4) 2 = 16

After the calculating the number of patients, the result was 25 patients per group, so there are 50 patients in this study. In addition, if this clinical has the dropout rate around 10%, the sample size will be approximately 56 patients.

Study Criteria

Inclusion criteria

1. Female or male patients aged over 18 years old.

2. Patients who have been diagnosed as mild to moderate chronic hand eczema or have history of intermittent or persistent skin lesions such as eczematous or vesicles on both hands for more than 3 consecutive months or relapse more than twice a year with or without prior treatment.

3. Patients who have been assessed HECSI score as 0-27 and defined as mild to moderate severity.

4. Patients who participate in the project voluntarily and sign the consent form.

5. Patients who are able to follow-up examination in the 2^{nd}, 4^{th}, and 8^{th} week.

Exclusion criteria

1. Patients who have current or active bacterial, fungal, or viral infection of hands.

2. Patients who allergic to component of ingredients in topical steroid ointment or patch using in this study as shown in Table 7 and 8.

3. Female patients who are pregnant, lactating or planning to become pregnant during the study period.

4. Patients who have history of treatment with topical corticosteroids or topical calcineurin inhibitors within 2 weeks before and during this study.

5.Patients who have history of treatment with systemic corticosteroids, immunosuppressant such as cyclosporin, azathioprine, mycophenolate mofetil, and phototherapy within 4 weeks before and during this study.

Discontinuation criteria

1. Patients who have adverse effects during this study.

- Infection (Bacterial, Viral, Fungal). If patients have lesions suspected of infection such as raised border, central clearing, and group of vesicles on erythematous base with painful, these lesions should be investigated for rule out the infection. For example, the lesions raised border and central clearing should be done with potassium hydroxide preparation (KOH) for rule out fungal infection.

- Anaphylaxis. It is acute onset illness which is defined as typical skin features (urticarial rash or erythema/ flushing, and/or angioedema) plus involvement of respiratory and/or cardiovascular and/or persistent severe gastrointestinal symptoms.

2. Patients who prefer to quit the study after participating.

3. Patients who are pregnant during the research.

4. Patients who have worsening clinical disease defined as an increase in HECSI score more than 75 percent of the patients' baseline value.

Table 8 Ingredients in 0.05%betamethasone17 ,21dipropionate ointment[89]

Ingredients in 0.05%betamethasone17 ,21dipropionate ointment
Betamethasone dipropionate
Propylene glycol monostearate
Propylene glycol
White wax
White petrolatum

Table 9 Ingredients in transdermal patch containing betamethasone17 ,21dipropionate

Ingredients in transdermal patch containing betamethasone17 ,21dipropionate
Bovine gelatin
Betamethasone17 ,21dipropionate
Sorbitol special
Methylparaben
Propylparaben
Water
Ethanol

Research Instruments

1. Transdermal patch containing betamethasone17 ,21dipropionate
2. 0.05%betamethasone17 ,21dipropionate ointment
3. Patient information sheet
4. Case report form (CRF) of participants consist of all sections shown below
   - General information inquiry form
   - Adverse drug events reporting
   - Medical records of outcome clinical score by the HECSI and the PGA score
   - Records of the amount used and remaining of topical ointments and transdermal patches
   - DLQI questionnaires
   - Patient's satisfaction
5. Informed consent form
6. Patient's logbook
7. Appointment card
8. Photographic light box

9. A high-resolution digital camera (Fujifilm X-100F) with Fujifilm Fujinon 23mm f/2 Lens

10. Precision balance

Preparation of Transdermal Patches

The transdermal patches are prepared by heating roller machine. The formula is presented in Table 5. Bovine gelatin is used as polymer carrier. Bovine gelatin[90] is a natural polymer. Due to the hydrophilic behavior of gelatin, cross-linking and additives are necessary to maintain the scaffold's structure and overall strength in vivo. In this article, we discuss various processing techniques to determine the optimal electrospinning, cross-linking, sintering, and mineralization parameters necessary to yield a porous, mechanically enhanced scaffold. Betamethasone17 ,21dipropionate in the concentration of 0.05-1% weight for weight (w/w) is incorporated into the polymeric transdermal patches.

1. Bovine gelatin is dissolved in sorbitol special, glycerin, and water.

2. After that, the solution is placed in 121°C autoclave for 15 minutes.

3. Preparation for betamethasone17,21dipropionate by dissolving it into the preservatives which are propylparaben and methylparaben and mixing them into 95% ethanol : sterile water (4:6).

4. The bovine gelation solution is stirred with a magnetic stirrer for 30 minutes.

5. Left the bovine gelatin solution at the room temperature until its temperature decreased to 40-50°C.

6. Mixing the bovine gelatin and the betamethasone17 ,21dipropionate solution and then, performing the gel sheet by heating roller machine, with heating boiler temperature of 60°C, heating roller of 15°C, and speed of 15 Hz.

Table 10 Patch Formula

INGREDIENTS (G)	WEIGHT % BY WEIGHT (G) (100 G)	
	Rx1	Free-Base
Bovine gelatin	10.5	10.5
Sorbitol special	1.4	1.4
Methylparaben	0.07	0.07
Propylparaben	0.014	0.014
Water	23.716	23.756
Betamethasone17 ,21dipropionate	0.04	-
Ethanol : Sterile water (6:4)	29.96	29.96

*G: Grams. Rx: Recipe

Study of Properties of Transdermal Patches

1. Study of Physical Properties of the Transdermal Patches

1.1 Uniformity of Weight

The transdermal patch is cut into 10 pieces of 1 cm × 1 cm square and weighed them to calculate the mean and standard deviation for the obtained value.

1.2 Uniformity of Thickness

The transdermal patch is cut into 1 cm × 1 cm squares amounted 10 sheets and measured the thickness of each patch using a Vernier Caliper. Then, calculate the mean and standard deviation for the obtained value.

2. Study of Mechanical Properties of the Patches

The transdermal patch is cut into 1 cm × 5 cm squares. Tensile strength and elongation at break are measured using Texture Analyzer (TA 500, Lloyd instrument, United Kingdom) equipped with a load cell of 50 Newtons at a speed of 5 mm/s until the patch is torn. The applied force is recorded. Tensile strength and elongation at break are calculated by the following equation:

$$\text{Tensile strength } (N/m^2) = \frac{F}{A}$$

By F = Force (Newtons)

A = Surface of patch (Square meter)

$$\text{Elongation } (\%) = \frac{Final\ lenght - Initial\ lenght}{Initial\ lenght} \times 100$$

3. Study of Dissolution

The dissolution is performed with Dissolution test apparatus 5 (Paddle over Disk). The dissolution medium is 300-500 ml of phosphate buffer pH 7.4 at 37 ± 0.5 °C, using paddle rotation speed of 50 rpm/min. The film is cut into circle of 2.5 cm diameter to be placed in the Disk assembly. Then, 5 ml of receiver is sampled for 30 min., 1, 2, 4, 6, 8, 10 and 12 hours, respectively. UV-Visible spectrophotometer (UV-1601 Shimadzu, Japan) or HPLC is required for measurement of drug concentration. The amount release is plotted against time.

4. Study of Skin Penetration

The drug permeability studies using Franz diffusion cells are tested through the skins of newborn piglets. The receiver medium is 15 ml of phosphate buffer pH 7.4 at 37 ± 0.5 °C. The transdermal patch is cut into a circle and placed in the donor of 1 cm diameter (n=3). Then, 5 ml of receiver is sampled from the receiver. 5 ml of new phosphate buffer pH 7.4 is added instantly. UV-Visible spectrophotometer (UV-1601 Shimadzu, Japan) or High Performance Liquid Chromatography (HPLC) is required for measurement of drug concentration. The flux of drug release is plotted against time.

*UV: Ultraviolet radiation

Research processes

Table 11 Research processes

The process of study	Screening	Baseline (Day1)	1st follow up (2nd week)	2nd follow up (4th week)	3rd follow up (8th week)
1.Collect patients following by inclusion and exclusion criteria	✓				
2.Providing an information about this research	✓				
3.KOH preparation and other investigations	✓				
4.Taking general history and physical examination	✓				
5.Patch testing	✓				
6.Inform the consent form	✓				
7.Randomization patients into two groups		✓			
8.Assessment PGA score in pre- and post-treatment by physician and patient		✓			✓

Table 11 (Cont.)

The process of study	Screening	Baseline (Day1)	1st follow up (Week 2)	2nd follow up (Week 4)	3rd follow up (Week 8)
9.Taking photography all visits		✓	✓	✓	✓
10. Assessment HECSI score by dermatologist all visits		✓	✓	✓	✓
11.Monitor and record any adverse effects			✓	✓	✓
12.Recording drug usage from patient's logbook			✓	✓	✓
13. Evaluation patient's quality of life in pre- and post-treatment		✓			✓
14.Evaluation patient's satisfaction of treatment					✓

* Potassium hydroxide preparation (KOH)

Data Collection Processes

Screening visit

1. After recruiting patients who reach inclusion criteria, the researcher informs about the study including objectives, study methods, potential benefits, and possible adverse effects.

2. All patients attend KOH preparation to rule out a fungal infection. Furthermore, some patients with painful vesicle lesions and acute onset of symptoms will be examined the Tzanck smear test to rule out a herpes infection.

3. Patients reaching all inclusion and exclusion criteria voluntarily participate are informed by the consent form.

4. Patient's history and physical examinations are performed by the researcher.

5. Patient's history is written in the case record form (CRF). The case record form is shown in the appendices.

6. For all female patients with reproductive age, history of menstruation, last menstrual period, history of pregnancy or lactation must be stated.

7. Patients who are suspected of allergic contact dermatitis based on clinical symptoms and no history of doing patch testing are performed a patch testing.

8. Patients who had history of patch testing in the past or who are unwilling to do a patch testing at Skin SWU Center will offered to perform the used test of betamethasone17 ,21dipropionate before starting the study.

Enrollment visit (Baseline, Day 1)

1. All patients are randomized into two groups by block randomization method via computer hardware in the private room. The process is completed only by this personal computer of the researcher and the data is further added password protection.

2. The researcher and the accessor work separately in different room.

3. The researcher takes pictures of participants' lesions before starting the invention with a high solution digital camera, Fujifilm X-100F Fujinon 23mm f/2 lens in photographic light box with two hands pictures and one hand pictures. All pictures are

taken both volar dorsal sides from the same camera setting under the same environments such as lighting conditions or color of background of the photographic light box. Coding and dating of photos are recorded in the study record form by the researcher.

4. The accessor does not participate any activities of this study and the assessment will be done in the private room.

5. At baseline, the accessor trained as physician at SWU Skin Center assesses the clinical severity of all patients as HECSI and PGA score. This intervention is an accessor-blinded study. The accessor does not know the study methods and patient's data.

6. All patients assess PGA score and quality of life by themselves.

7. In this visit, all patients receive a logbook and an appointment card to follow-up in the next visit.

8. The researcher provides information about how to record drug usage and related adverse effects in a logbook and how to apply their treatment.

9. For group of using transdermal patch containing betamethasone17 ,21dipropionate, they receive 60 transdermal patches about 18*12 centimeters. Transdermal patch covers lesions on hands for 8 hours a day in the evening. They can adjust size of transdermal patch to cover their lesions. In the next morning, if transdermal patch falls off before hitting 8 hours, they have to apply a new patch and continue to reach 8 hours. Recording compliance with transdermal patches states starting time until peeling off. After peeling of, patients can apply any emollients. If they have new lesions, they can apply more transdermal patch on new lesions. However, if new lesions tend to happen more, they should consider for patch testing.

10. For the next group of using topical betamethasone17, 21dipropionate ointment, each patient receives about 15 grams of ointment to apply on lesions twice a day, in the morning and evening. In this group, patients are also capable of using emollients any time.

11. Any possible side effects such as redness, burning, stinging, or scaling are introduced to the patients.

12. If patients have any problems during this study, they can contact directly to the researcher via mobile phone 24 hours.

Follow-up visits (Week 2, 4, and 8)

1. For all follow-up visits, after general history and physical examination completed, the researcher asks patients any adverse effects or problems and obtains data from their logbooks. Possible adverse effects are redness, burning, stinging, and scaling.

2. The researcher collects residual drugs from both group of patients. Manual residual transdermal patches counting of patients is done. Also, remaining drugs of topical betamethasone17 ,21dipropionate ointment are weighted by a precision balance. All results are recorded in the patients' drug use sheet.

3. All patients will clean their hands with mild cleanser before the assessment.

4. Lesions are recorded with a high-solution digital camera, Fujifilm X-100F in a photographic light box by the researcher. Setting of digital camera and photographic light book are the same as prior visit.

5. Assessing clinical severity of disease as HECSI score is done by the accessor in a private room.

6. The researcher prescribes more transdermal patches and topical ointments.

7. All patients also receive an appointment card for the next visit.

8. The last follow-up visit, week 8, PGA score are accessed by the accessor and patients. Moreover, all patients can evaluate their quality of life and satisfaction after the study.

Outcomes Measurement

Primary outcome

The primary outcome is efficacy of transdermal patches containing betamethasone17 ,21dipropionate in treatment of patients with chronic hand eczema.

The Hand Eczema Severity Index (HECSI) score

Measuring overall clinical assessments are done by the accessor who is a dermatologist from SWU Skin Center based on a physical examination in first visit and after week 2, 4, and 8 on both hands. It can be divided into 5 areas as follows:

Those 5 areas can be categorized according to the number of lesions shown below:

Score 0 = 0% (no lesion)

Score 1 = There is lesion between 1-25%.

Score 2 = There is lesion between 25-50%.

Score 3 = There is lesion between 50-75%.

Score 4 = There is lesion > 75%.

Besides, each area can be classified into 6 lesion symptom appearances which are:

Erythema

Induration/ Papulation

Vesicle

Fissuring

Scale

Edema

The severity of symptoms can be divided as follows:

Score 0 = No skin changes

Score 1 = Mild disease

Score 2 = Moderate disease

Score 3 = Severe disease

The score is calculated by multiplying number of lesions in each area of two hands by the total symptom score in that area. When the total score of both hands calculated, it is ranged between 0 and 360 points.

Grading of HECSI score is defined as ([76])

Score 0–11 Mild

Score 12–27 Moderate

Score ≥ 28 Severe

An improvement of disease is related to a decrease in score more than 50 percent of patient base score.

Table 12 Hand Eczema Severity Index (HECSI) Score

Symptom	Fingertip	Finger (except fingertip)	Palm	Backhand	Wrist
Erythema: E					
Induration/ Papulation: I					
Vesicle: V					
Fissuring: F					
Scale: S					
Edema: O					
Overall symptoms (E+I+V+F+S+O)					
Lesion quantity (score 0-4)					
Total HECSI scores (Symptom x Lesion)					

Secondary outcome

1. Physician Global Assessment (PGA)

1. All participants assess a development of the disease by changing score before to after procedure by themselves and physicians.

2. Assessment after procedure is performed in week 0 and 8th.

3. PGA grading system ranges from 0 (clear) to 4 (Severe).

Table 13 Physician Global Assessment (PGA) Score

Score	Category	Description
0	Clear	No signs of hand dermatitis
1	Almost Clear	Just perceptible erythema and just perceptible scaling
2	Mild	Light pink erythema with minimal scaling with or without pustules
3	Moderate	Dull red, clearly distinguishable erythema with diffuse scaling, some thickening of the skin, with or without fissures, with or without pustule formation
4	Severe	Deep, dark red erythema with obvious and diffuse scaling and thickening as well as numerous fissures with or without pustule formation

2. Adverse effects

Severity and duration of possible adverse effects related to treatment by transdermal patch containing betamethasone17 ,21dipropionate and 0.05%betamethasone17 ,21dipropionate ointment include erythema, burning, stinging, or scaling. It is assessed in every visit from patients' logbook.

3. Patients' compliance

The patients' compliance of treatment in both groups are obtained from their logbooks. Each group has different pattern of logbook following table below.

Table 14 Logbook form of patients with transdermal patches group

	Week.....		
	Complete applying a patch for 8 hours	Incomplete applying a patch (Please specify the period)	Adverse effects
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

Table 15 Logbook form of patients with topical ointment group

	Week.....		
	AM	PM	Adverse effects
	Put on topical ointment	Put on topical oinment	
Monday			
Tuesday			
Wednesday			
Thursday			
Friday			
Saturday			
Sunday			

Furthermore, all patients in both groups record frequency of their daily activities impacting to their disease.

Table 16 Daily Activities Impacting to Chronic Hand Eczema in Patient Logbook

Daily Activities	Frequency per Day
Washing hands with soap	
Washing hands with gel or alcohol spray	
Applying an emollient on hands	
Housework activities	
Wearing gloves during working time	

4. Patients' satisfaction

All patients are assessed satisfaction on week 8 of treatment using questionnaire on transdermal patch containing betamethasone17 ,21dipropionate and topical 0.05%betamethasone17 ,21dipropionate ointment.

Table 17 Patients' Satisfaction Form

Issue	Excellent (5)	Good (4)	Average (3)	Poor (2)	Very poor (1)
Patient satisfaction					

5. Quality of life of patient by Dermatology Life Quality Index (DLQI)

All patients answer DLQI questionnaires for evaluation before and after treatment. There are 10 questions about how skin disease impacts their life. Maximum score is 30 and minimum score is 0. Scores can be calculated by following

3 = very much

2 = a lot

1 = little

0 = not at all, no relevant, and no answer

Total scores of 10 questions are interpreted in table 17.

Table 18 Interpretation of Dermatological Life Quality Index (DLQI) Score (79)

DLQI scores	Meaning
0-1	No effect at all on patient life
2-5	Small effect on patient life
6-10	Moderate effect on patient life
11-20	Very large effect on patient life
21-30	Extremely large effect on patient life

Data Management

After completing the study, the researcher puts all data to Microsoft excel. The entry data interface is the same as a case record form to avoid manual data entry errors. Data are checked, proofread, and cleaned by proofreader to ensure good quality before performing analysis. This process is called “single data entry with entry validation” and benefit is a prevention of human error. Patient medical records including consent form, case record form (CRF), DLQI questionnaires, outcome clinical score report, and patients’ photos are strictly confidential and will be destroyed in 5 years. Statistical analysis are performed in the next step by STATA version 17 for Windows license.

Statistical Analysis

Descriptive statistics

There are 2 types of data including categorical and continuous data. First, data are occupation, gender, hobby, underlying disease, family history of atopic dermatitis, and history of prior treatment. It is reported in frequency and percentage. Other data are age, weight, height, disease duration, and frequency of relapse. It is reported in mean with standard deviation (SD) in normal distribution data. If data is non-normal distribution, it is reported in median and inter-quartile range.

Inferential statistics

1. Clinical efficacy of transdermal patch containing betamethasone17 ,21dipropionate compared to topical 0.05%betamethasone17 ,21dipropionate ointment in treatment of chronic hand eczema is measured by HECSI and PGA score which are continuous data. Therefore, mean values between two groups are compared using the linear mixed model.

2. Quality of life of patient treatment with transdermal patch containing betamethasone17 ,21dipropionate compared to topical 0.05%betamethasone17 ,21dipropionate ointment in treatment of chronic hand eczema is measured by data from DLQI questionnaires. The results are continuous data reported as the mean values. Consequently, the mean values between two groups are compared by using the student t-test. Then, Chi-square test is used to compare quality of life between two groups of patients.

3. Patient satisfaction with transdermal patch containing betamethasone17 ,21dipropionate compared to topical 0.05%betamethasone17 ,21dipropionate ointment in treatment of chronic hand eczema is measured by questionnaire (score 1-5: very bad - very good) stated in ordinal scale. It is reported as group data in number and percentage. Then, Chi-square test is used to compare satisfaction between two groups of patients.

4. Patient compliance with transdermal patch containing betamethasone17 ,21dipropionate in treatment of chronic hand eczema is measured by data from patient logbook as amount of time applying transdermal patch per day. The results are percentage of using transdermal patch containing betamethasone17 ,21dipropionate.

5. Patient compliance with topical 0.05%betamethasone17 ,21dipropionate ointment in treatment of chronic hand eczema is obtained from patient logbook data as a frequency of drug usage by calculating times over the period. The results are calculated from total frequency of drug prescribed and drug usage. Patient's compliance in this group is also reported in percentage of using

0.05%betamethasone17 ,21dipropionate. Chi-square test is used to compare compliance between two groups of patients.

6. Information on side effects associated with the use of transdermal patch containing 0.05%betamethasone17 ,21dipropionate is occurred as number and percentage of occurrence. Then, Chi-square test is used to compare adverse effects between two groups of patients.

7. The statistical significance is based on p-value criterion less than 0.05.

Ethics

Informed consent form and information sheet will be provided at the beginning of the study. The participants must be acquiescent to fulfill an inform consent by themselves. Inform consent form, information sheet about this project will be submitted to the ethics committee (EC) of Srinakharinwirot University for approval.

Research Timelines

1. Research topic, review of related literature, and hypothesis stimulation
2. Research committee, proposal defend, and ethic committee
3. Recruiting participants of online survey
4. Analysis of data
5. Presentation and submission for publication of research

Table 19 Research Timelines

Task	Months							
	May-Jun 2021	Jul-Sep 2021	Oct-Feb 2021-22	Mar-Apr 2022	May-Jun 2022	July-Aug 2022	Sep-Oct 2022	Nov-Dec 2022
1.Literature review	↔							
2.Research methods planning and developing a proposal draft	↔							
3.Proposal presentation and ethical consideration		↔	↔					
4.Validation of equipment		↔	↔					
5.Data collection and data check			↔	↔				
6.Data entry, data analysis					↔	↔		
7.Report writing and presentation							↔	↔
8.Submission and publication								↔

Research Budgets

Table 20 Research Budgets

In total of	Financial statement (Baht)
1.Fees for project personnel	
1.1 Research assistant (1person)	10,000.00
1.2 Research participants (200 bath/person/time)	44,800.00
2.Materials and Supplies	
1.1 Betamethasone17 ,21diporopinate	24,000.00
1.2 Bovine gelatin	9,980.00
1.3 Betamethasone17, 21dipropionate ointment (size 5 g, 95.00 baht)	15,960.00
1.4 Chemical substances using in the process of transdermal patch development and quality check	21,810.00
1.5 Patch testing	20,000.00
1.6 Photographic light box size 40*40 cm	950.00
1.6 Other supplies ex. stationeries	1,000.00
3.Document printing	1,500.00
Total	150,000.00

Chapter 4

Data analysis and Findings

This chapter comprises of two main sections; the results of property testing of the transdermal patch and clinical outcomes assessment compared with the topical corticosteroid.

In the first section, we evaluated the properties of transdermal patch for various parameters in physical, mechanical, adhesive, thermal, dissolution, and skin penetration property.

Next section, the general characteristics of the participants and the data analysis compared efficacy and safety between 2 groups were described.

To recap, the research objectives set up in chapter one are as follows:

1. To compare efficacy of transdermal patch versus topical steroid by assessment of HECSI and PGA score

2.To compare safety of transdermal patch versus topical steroid

3. To compare compliance by using transdermal patch versus topical steroid

4. To compare satisfaction by using transdermal patch versus topical steroid

5. To compare quality of life by using transdermal patch versus topical steroid

4.1 Results of property testing of transdermal patch

Study of Properties of Transdermal Patches

1. Study of Physical Properties of the Transdermal Patches

Uniformity of Weight and Thickness

Four types of patches were developed in this study by cutting into 10 pieces of 1 cm × 1 cm. It was weighed by an analytical balance 4 digits and measured thickness by a digital Vernier Caliper. The average weight and standard deviation were calculated as shown in the table 21 below.

Table 21 Results of weight variation test and thickness conducted on 4 types of transdermal patches (Mean ± S.D.)

Type of transdermal patch	Weight (g)	Thickness (mm)
Thin patch base	0.037 ± 0.005	0.26 ± 0.05
Thick patch base	0.081 ± 0.009	0.49 ± 0.07
Betamethasone17 ,21dipropionate patch (Thin patch)	0.056 ± 0.005	0.32 ± 0.04
Betamethasone17 ,21dipropionate patch (Thick patch)	0.070 ± 0.006	0.45 ± 0.05

Data presented as Mean ± S.D. for normally distributed.

S.D.: Standard Deviation, g: gram, mm: millemetre.

The table 21 illustrates results of weight and thickness variation test. The average weight and thickness of thin betamesone17 ,21dipropionate patch was 0.056 ± 0.005 g and 0.32 ± 0.04 mm respectively. In contrast to thick betamethasone17 ,21dipropionate patch, the average weight was 0.070 ± 0.006 g and thickness was 0.45 ± 0.05 mm.

However, the mean weight of both thick and thin patch was 0.063 ± 0.006 g. Also, the average of both thickness patches was 0.385 ± 0.047 mm.

According to the average weight and the size of steroid patch, the drug loaded patch of size 1×1 cm^2 was approximately 31.50 µg (micrograms).

Thus, the amount of betamethasone17 ,21dipropionate in patch of weight 100 g was about 0. 05 g which was equal to 0.05%betamethasone17 ,21dipropionate ointment.

2. Study of Mechanical Properties of the patches

The transdermal patches were cut into 1 cm × 5 cm. Tensile strength and elongation at break point were measured by using Texture Analyzer (TA 500, Lloyd instrument, United Kingdom) equipped with a load cell of 50 Newtons at a speed of 5 millimeters per second(mm/s) until the patch was torn. The applied force was recorded to dive a deeper analysis.

The average tensile strength of base was 0.916±0.221 Megapascal (Mpa) while the mean strength of betamethasone17 ,21dipropionate patch was 0.334±0.102 Mpa. Due to inverse relation between tensile strength and percentage of elongation, betamethasone17 ,21dipropionate patches were found more flexible than base patches, with 559.840 ± 192.140% and 430.947 ± 50.775% respectively.

3. Study of Dissolution

The dissolution is performed with Dissolution test apparatus 5 (Paddle over Disk). UV-Visible spectrophotometer (UV-1601 Shimadzu, Japan) or HPLC is required for measurement of drug concentration. The amount release is plotted against time as shown in Figure 13.

According to table 22, the drug was started to be detected by UV-Visible spectrophotometer after placing in the disk which was about 28.04%. Then, the average drug dissolution was approximately shown at 83.11% after 15 minutes and the highest average percentage of drug dissolution was about 95.19% after 60 minutes.

UV: Ultraviolet

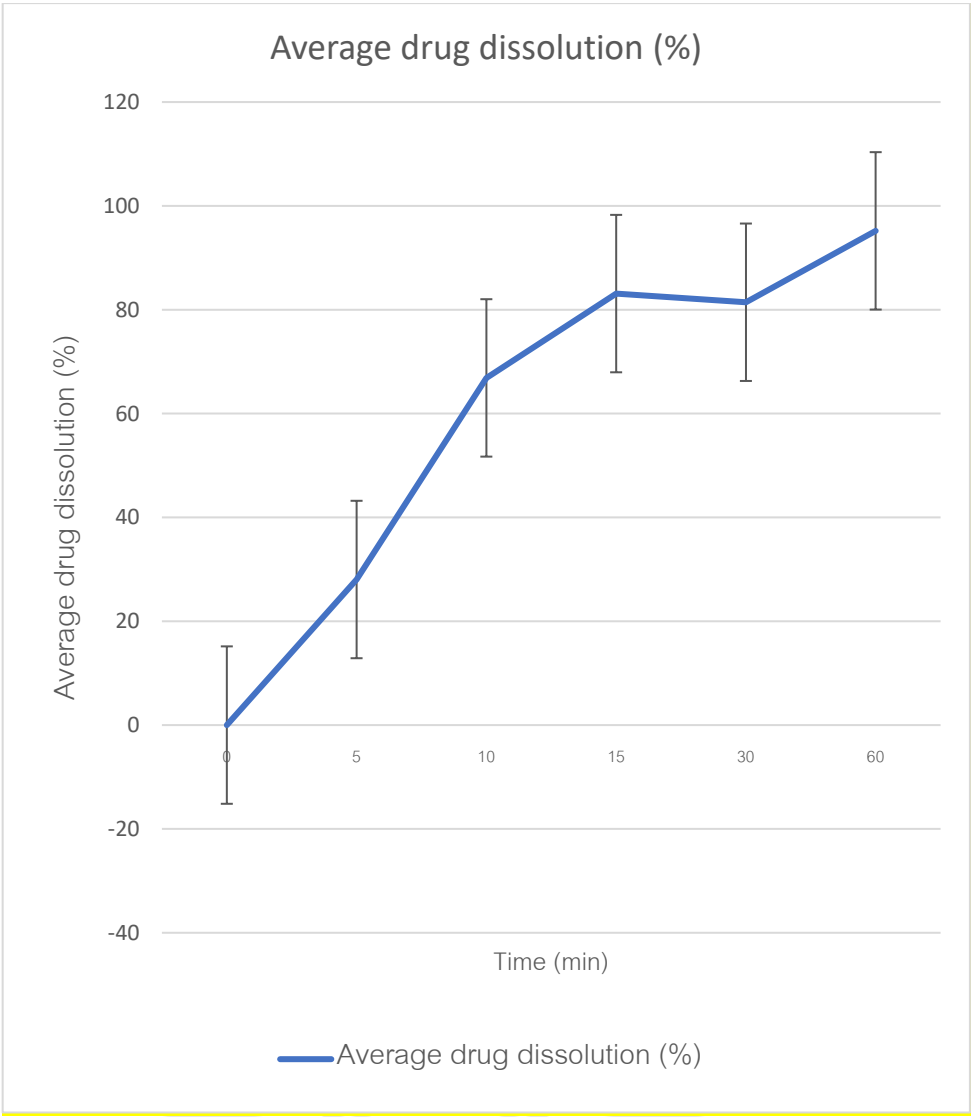
HPLC: high-pressure liquid chromatography

Table 22 Result of drug dissolution test (Mean%, S.D.)

Dissolution test		
Time (min)	Average drug dissolution (%)	S.D.
0	0	0
5	28.04	21.48
10	66.87	18.91
15	83.11	24.76
30	81.44	19.54
60	95.19	17.14

Data presented as Mean ± S.D. for normally distributed.

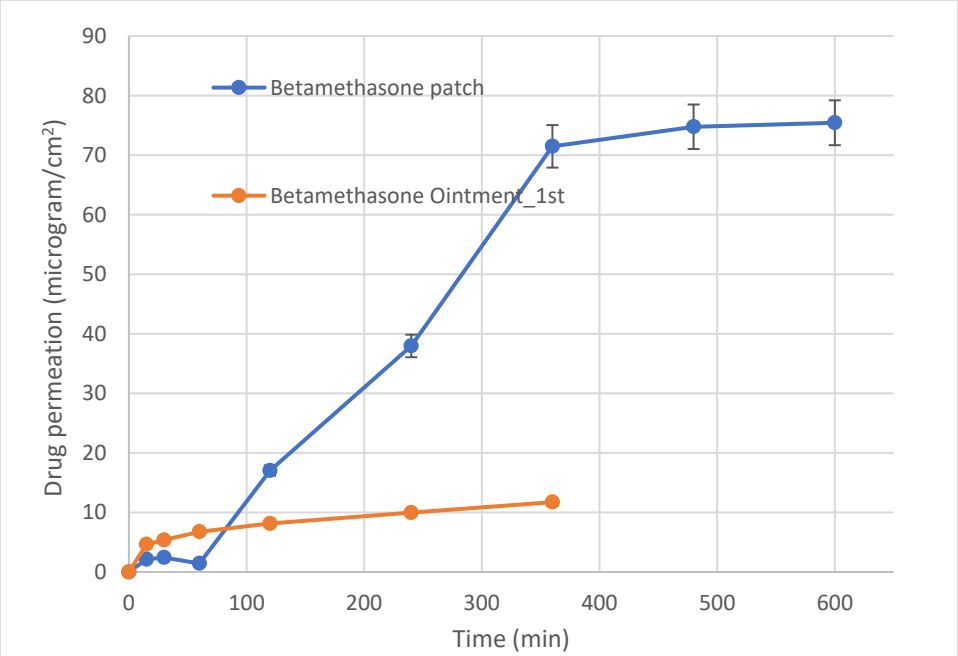
S.D.: Standard Deviation, min: minute



min: minute

Figure 13 The average drug dissolution correlation with time

4. Study of Skin Penetration



*min: minute

Figure 14 Result of average drug penetration through newborn peppy skin Comparison to topical drug

The drug permeability studies using Franz diffusion cells are tested through the skins of newborn piglets.

At the beginning, the average of drug penetration of betamethasone17 ,21dipropionate patch was slow. The line graph illustrated that transdermal patch was started release after 15 minutes and continuous released and the amount of drug was reached up nearly 75 µg/cm^2 at 480 minutes (8 hours) and steady constant until 600 minutes (10 hours). In contrast to drug penetration of betamethasone17 ,21dipropionate ointment, the line graph was steady constant 10 microgram/cm^2 which indicated that topical ointment had no sustained-release.

4.2 Clinical outcomes assessment

4.2.1 Demographic data of participants

After this study was approved by the ethics committee (EC) of Srinakharinwirot University on December 27th, 2021, the researcher started to begin the study by recruitment the patients who reach inclusion criteria. The data were collected from January 4th, 2022 to April 29th, 2022. Fifty-eight subjects were enrolled in this study. One of the patients had a positive-patch test with relevant history and another one had PGA score higher than 27 points. Then, a total of 56 participants were included and completed the protocol as shown in figure 15.

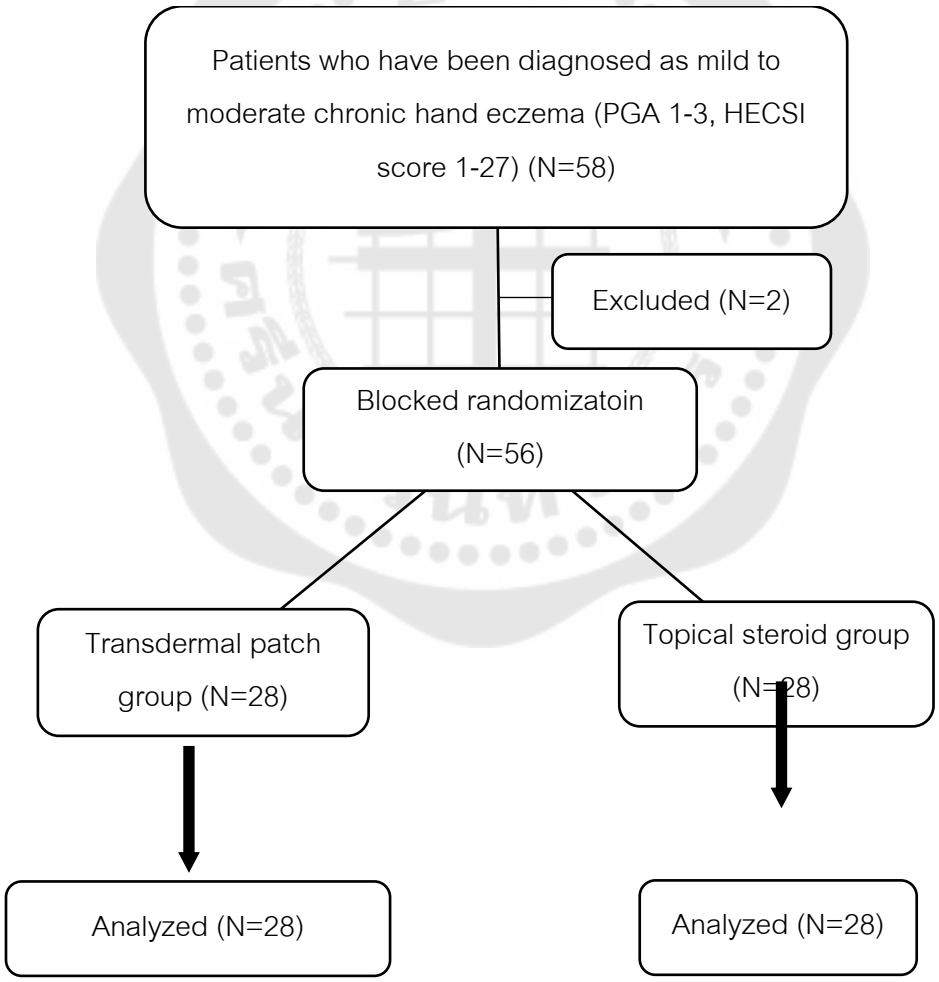


Figure 15 The algorithm for enrollment of the subjects

The age of the participants was a range from 21 to 60 years. The overall duration of disease was 6 months to 20 years. All participants were collected to each group by randomization and their general information such as age, gender, occupations, previous treatments etc. shown in Table 23.

Table 23 Demographic data of all participants in both groups

Characteristics	Transdermal patches (N=28)	Topical corticosteroids (N=28)	*P*-value
Gender, N (%)			0.131
- Male	10(35.71%)	5(17.86%)	
- Female	18(64.29%)	23(82.14%)	
Age (years), mean (SD)	36.93 ± 12.10	38.50 ± 12.29	0.825
Type of Hand eczema, N (%)			0.199
-Hyperkeratotic hand eczema	24 (85.71%)	25 (89.29%)	
-Pulpitis	4 (14.29%)	1 (3.57%)	
-Recurrent vesicular	0 (0.00%)	2 (7.14%)	
-Nummular hand eczema	0 (0.00%)	0 (0.00%)	
-Dry, fissured hand eczema	0 (0.00%)	0 (0.00%)	
Duration of Hand eczema (years), median (IQR)	2 (1, 3.5)	4.5 (1, 10)	0.178
Occupations, N (%)			0.119
-Health care worker	4 (14.29%)	4 (14.29%)	
-Housekeeper	10 (35.71%)	3 (10.71%)	
-Office worker	8 (28.57%)	15 (53.57%)	
-Others	6 (21.43%)	6 (21.43%)	

Table 23 (Cont.)

Characteristics	Transdermal patches (N=28)	Topical corticosteroids (N=28)	*P*-value
Hx of underlying disease, N (%)			0.752
-YES	6 (21.43%)	7 (25.00%)	
-NO	22 (78.57%)	21 (75.00%)	
-Allergic rhinitis	3 (10.71%)	3 (10.71%)	1.00
Previous treatment, N (%)			0.771
-YES	20 (71.43%)	19 (67.86%)	
-NO	8 (28.57%)	9 (32.14%)	
-Topical treatments	17 (60.71%)	17 (60.71%)	1.00
-Systemic treatments	0 (0.00%)	0 (0.00%)	1.00
Hx of doing prior patch test, N (%)			1.00
- NO	24 (85.71%)	23 (82.14%)	
- YES	4 (14.29%)	5 (17.86%)	
Hx of doing patch test in this study, N(%)			
NO	9 (32.1%)	7 (25%)	0.554
YES	19 (67.9%)	21 (75%)	
Positive patch test			
-Nickel sulfate	5 (17.86%)	1 (3.57%)	0.193
-Fragrance mix I	2 (7.14%)	3 (10.71%)	1.00
-MCI/MI	0 (0.00%)	4 (14.29%)	0.111

*MCI (Methylchloroisothiazolinone), MI (Methylisothiazolinone)

S.D.: Standard Deviation

N: Number

Data presented as Mean ± S.D. for normally distributed

IQR: Interquartile range

P-value significant at **P*-value < 0.05

Table 23 (Cont.)

Characteristics	Transdermal patches (N=28)	Topical corticosteroids (N=28)	*P*-value
Daily activities			
-Hand wash			
-Frequency per day, (mean±S.D.)	14.32 ± 10.09	11.50 ± 8.04	0.252
-Hand wash >20 times/day, N (%)	7 (25.00%)	3 (10.71%)	0.163
-People exposed with wet work by definition, N (%) AE			
-YES	14 (50.00%)	11 (39.29%)	0.42
-NO	14 (50.00%)	17 (60.71%)	

S.D.: Standard Deviation

N: Number

Data presented as Mean ± S.D. for normally distributed

IQR: Interquartile range

P-value significant at **P*-value < 0.05

There were 10 males (35.71%) and 18 (64.29%) females in transdermal patch group, and 5 males (17.86%) and 23 females (82.14%) in topical corticosteroids group with no statistically significant difference between two groups (*P*-value 0.131). The mean age of participants in transdermal groups was 36.93 ± 12.10 and 38.53 ± 12.29 year-old in transdermal and topical corticosteroids groups, respectively (*P*-value 0.825).

Hyperkeratotic hand eczema was the most common type in both groups, 24 (85.71%) cases in transdermal group and 25 (89.29%) cases in topical corticosteroid group. A housekeeper was the most common occupation in transdermal group (35.71%) whereas an office worker was the highest percentage in topical corticosteroid group (53.57%). The median disease duration were 2 years (IQR 1, 3.5) in transdermal group, and 4.5 years(IQR 1, 10) in topical corticosteroids group. Most participants had not any underlying disease. Approximately sixty percent of cases received topical treatment before. Most participants in this study have never done the patch testing before (85.70%) whereas 4 patients in each group have been done (14.30%). For wet-work activity that is defined as the activities where workers have to immerse their hands in liquids for >2 hours per shift, or wear waterproof (occlusive) gloves for a corresponding amount of time, or wash their hands >20 times per shift[91]. Participants in transdermal group wash their hands about 14.32 ± 10.09 times/day whereas participants in topical corticosteroid group wash their hands 11.50 ± 8.04 times/day. Moreover, participants who exposed with wet work in the former group were 14 (50.00%), and had more than the latter group which was 11 (39.29%). However, there was no statistically significant difference of all demographic data in both groups.

Table 24 Mean change of HECSI score

HECSI score (Mean ± S.D.)	Week of intervention				*P*-value (Between two groups)
	Week 0	Week 2	Week 4	Week 8	
Erythema					**0.317**
Transdermal patch group	2.96 ± 2.17	2.04 ± 1.48	0.93 ± 1.15	0.46 ± 0.79	
P-value	Reference	0.002*	<0.001*	<0.001*	
Topical corticosteroids group	4.21 ± 2.87	2 ± 1.72	1.14 ± 1.58	0.32 ± 0.67	
P-value	Reference	<0.001*	<0.001*	<0.001*	
Induration					**0.336**
Transdermal patch group	1.64 ± 1.37	1.04 ± 0.96	0.79 ± 0.99	0.36 ± 0.73	
P-value	Reference	0.004*	<0.001*	<0.001*	
Topical corticosteroids group	2.18 ± 1.76	1.29 ± 1.24	0.79 ± 1.32	0.47 ± 0.88	
P-value	Reference	0.001*	<0.001*	<0.001*	
Vesicle					**0.884**
Transdermal patch group	0.18 ± 0.55	0.04 ± 0.19	0.07 ± 0.38	0 ± 0	
P-value	Reference	0.046*	0.134	0.012*	
Topical corticosteroids group	0.18 ± 0.77	0.07 ± 0.38	0 ± 0	0 ± 0	
P-value	Reference	0.342	0.114	0.114	

Table 24 (Cont.)

HECSI score (Mean ± S.D.)	Week of intervention				*P*-value (Between two groups)
	Week 0	Week 2	Week 4	Week 8	
Fissuring					**0.449**
Transdermal patch group	4.86 ± 4.46	2.96 ± 3.68	1.64 ± 2.42	0.54 ± 0.96	
P-value	Reference	0.002*	<0.001*	<0.001*	
Topical corticosteroids group	5.32 ± 3.29	3.21 ± 2.48	2 ± 2.14	1.21 ± 1.71	
P-value	Reference	<0.001*	<0.001*	<0.001*	
Scale					**0.110**
Transdermal patch group	4.93 ± 3.56	3 ± 2.96	1.93 ± 2.19	0.5 ± 0.75	
P-value	Reference	<0.001*	<0.001*	<0.001*	
Topical corticosteroids group	6.57 ± 3.25	3.39 ± 2.39	2.25 ± 2.27	1.43 ± 1.95	
P-value	Reference	<0.001*	<0.001*	<0.001*	
Edema					**0.312**
Transdermal patch group	0.04 ± 0.19	0 ± 0	0 ± 0	0 ± 0	
P-value	Reference	0.15	0.15	0.15	
Topical corticosteroids group	0 ± 0	0 ± 0	0 ± 0	0 ± 0	
P-value	Reference	N/A	N/A	N/A	

Table 24 (Cont.)

HECSI score (Mean ± S.D.)	Week of intervention				*P*-value (Between two groups)
	Week 0	Week 2	Week 4	Week 8	
Total score					**0.106**
Transdermal patch group	14.61 ± 7.77	9.07 ± 5.87	5.36 ± 4.22	1.86 ± 2.38	
P-value	Reference	<0.001*	<0.001*	<0.001*	
Topical corticosteroids group	18.46 ± 7.36	9.96 ± 5.27	6.18 ± 4.88	3.43 ± 3.10	
P-value	Reference	<0.001*	<0.001*	<0.001*	

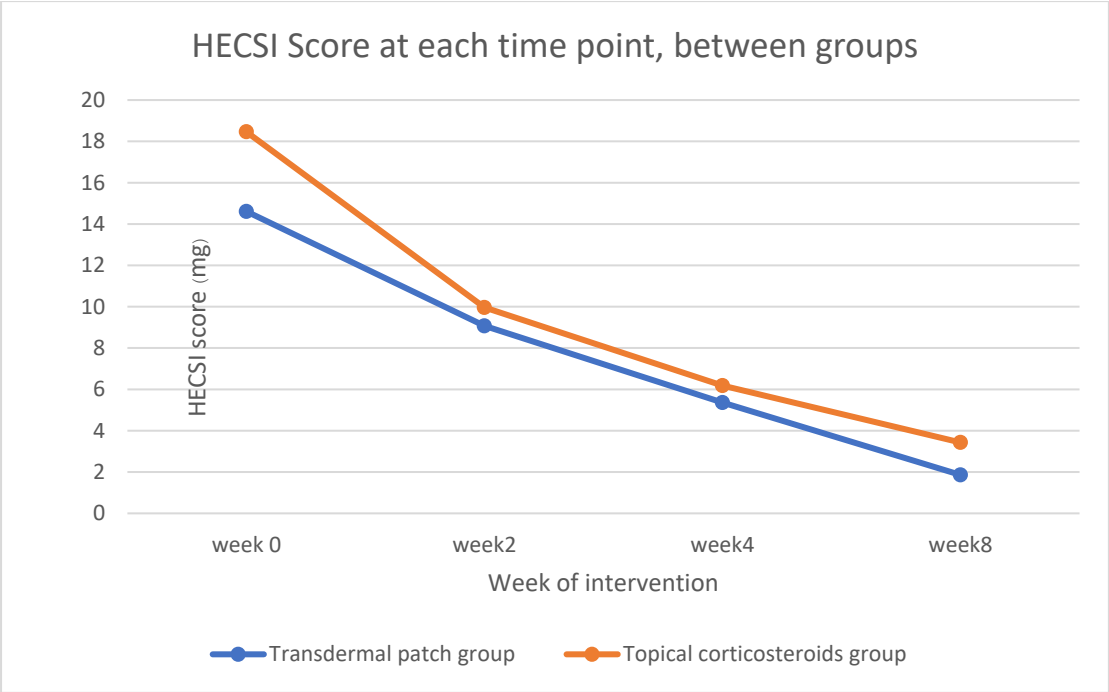


Figure 16 Line graphs of HECSI score at each time point comparing between two groups

According to Table 24 and Figure 16, there are 6 subcategories of the HECSI score which composes of erythema, induration, vesicle, fissuring, scale, and edema. During the study, all 6 subcategories of the HECSI score were no statistically significant difference between two groups (*P*-value 0.106). At the beginning, the mean HECSI score of participants in trandermal patches group was 14.61 ± 7.77 whereas the mean score of topical corticosteroids group was 18.46 ± 7.36 without statistically significant difference between two groups (*P*-value 0.057). Over the period of this study, the HECSI score of transdermal patch group was statistically significant reduced from 14.61 to 9.07 at week 2, 5.36 at week 4 and 1.86 at week 8 (*P*-value <0.001). For topical topical corticosteroid group, there was statistically significant reduced from 18.46 to 9.96 at week 2, 6.18 at week 4 and 3.43 at week 8 (*P*-value <0.001). In term of erythema, induration, fissuring, and scale, we found statistically significant difference at week 4 and 8 after treatment in both group. However, vesicle and edema did not change during the study period in both group.

Table 25 Comparison of the number of participants in both groups by PGA scores between week 0 and 8

Characteristics	PGA score (Clear, Almost clear)		PGA score (Mild, Moderate, Severe)	
Characteristics	Week 0	Week 8	Week 0	Week 8
Transdermal patches (N=28), N (%)	0 (0.00%)	24 (85.71%)	28 (100.00%)	4 (14.29%)
Topical corticosteroids (N=28), N (%)	0 (0.00%)	16 (57.14%)	28 (100.00%)	12 (42.86%)
P-value	1.000	0.018*	1.000	0.018*

Data presented as N (%)

P-value significant at **P*-value < 0.05

PGA: Physician Global Assessment, N: Number

For the PGA score, all participants were classified into two groups of the PGA score which was group 1(Clear and Almost clear) and group 2 (Mild, Moderate, and Severe) as shown in the Table 25. Begining of our study, no participants were classified into group 1. In contrast to week 8, 4 (14.29%) participants in transdermal patches group were assessed to group 2 whereas 12 (42.86%) participants in topical corticosteroids group were assessed to group 2. Comparison between these two groups at week 8, participants in transdermal group were classified into group 1 (Clear, Almost clear) more than participants in topical corticosteroid group with statistically significant difference (*P*-value 0.018). These data refer to participants in transdermal patch group had an improvement more than topical corticosteroid group. However, the mean PGA

score by physician in transdermal patches group was 2.93 ± 0.47 while the mean score in topical corticosteroids group was 3.04 ± 0.5, without statistically significant difference (*P*-value 0.448) at week 0. Furthermore, the mean score of PGA by patients at baseline in transdermal patches group and topical corticosteroids group were no statistically significant difference, 2.96 ± 0.64 and 3.07 ± 0.60 respectively (*P*-value 0.521). At the end of study, the PGA score was statistically significant decreased in both groups in similar rate as shown in Table 26.

As well as the DLQI score, there was a significant decrease after treatment in both groups. For transdermal group, there was a decrease of score from 10.93 ± 5.84 to 2.79 ± 3.57 with statistically significant difference (*P*-value <0.001*). Likewise, the mean score of topical corticosteroids group was significantly declined from 11.82 ± 4.74 to 2.29 ± 3.24 (*P*-value <0.001*). However, there was no statistically significant difference of mean score between two groups (*P*-value 0.31) as shown in Table27.

Table 26 Comparison of clinical outcomes scores of both groups between week 0 and 8

Characteristics	Weeks	Transdermal patches (N=28)	Topical corticosteroids (N=28)	*P*-value
PGA score (Mean ± S.D.) by physician	Week 0	2.93 ± 0.47	3.04 ± 0.58	0.448
	Week 8	0.86 ± 0.71	1.14 ± 0.93	0.394
	P-value	<0.001*	<0.001*	
PGA score (Mean ± S.D.) by patients	Week 0	2.96 ± 0.64	3.07 ± 0.60	0.521
	Week 8	0.79 ± 0.69	1.14 ± 1.15	0.338
	P-value	<0.001*	<0.001*	

Table 26 (Cont.)

Characteristics	Weeks	Transdermal patches (N=28)	Topical corticosteroids (N=28)	*P*-value
DLQI score (Mean ± S.D.)	Week 0	10.93 ± 5.84	11.82 ± 4.74	0.532
	Week 8	2.79 ± 3.57	2.29 ± 3.24	0.212
	P-value	<0.001*	<0.001*	

Data presented as (Mean ± S.D.)

P-value significant at **P*-value < 0.05

PGA: Physician Global Assessment, N: Number, DLQI: Dermatology Life Quality Index, S.D.: standard deviation

Table 27 Mean differences of other scores

Mean differences of each characteristic	Transdermal patches (N=28)	Topical corticosteroids (N=28)	*P*-value
PGA score (Mean ± S.D.) by physician	2.07 ± 0.60	1.89 ± 0.92	0.39
PGA score (Mean ± S.D.) by patients	2.18 ± 0.78	1.93 ± 1.18	0.34
HECSI score (Mean ± S.D.)	12.75 ± 7.12	15.04 ± 7.25	0.21
DLQI score (Mean ± S.D.)	8.14 ± 5.56	9.54 ± 4.65	0.31

Table 28 Other outcome scores at week 8

	All (N=56)		*P*-value
	Transdermal patch group (N=28)	Topical corticosteroids group (N=28)	
Patient Compliance (mean ± S.D.)	88.64 ± 11.87	80.77 ± 14.77	0.02*
Patient Satisfaction (mean ± S.D.)	3.89 ± 0.31	3.57 ± 0.84	0.049*
Adverse effects, N(%)			0.349
No	26 (92.86%)	24 (85.71%)	
Yes	2 (7.14%)	4 (14.29%)	
itching	1 (3.57%)	2 (7.14%)	
Dry skin	1 (3.57%)	2 (7.14%)	
Patient Preference, N (%)	21 (75%)	18 (64.29%)	0.383

In term of patient compliance during the study, the participants in each group were assigned to do a logbook themselves every day. The topical corticosteroid group must check their topical corticosteroid applying on their lesions in the morning and evening. For the transdermal group, they also must check in their logbook if applying transdermal patches once a day is done. Besides, there are additional tasks for them by recording duration of time that transdermal patches are put on their lesions. Patients in transdermal patches group was significant higher percentage of adherance to the treatment than in topical corticosteroids group, with 88.64 % (11.87) and 80.77% (14.77) respectively (*P*-value 0.02) as in table 28 and figure 17, Furthermore, the patient satisfaction in transdermal patches group was 3.89 (0.31%) , slightly higher than in

topical corticosteroids group was 3.57 (0.84%) with statistically significant difference (*P*-value 0.049).

For the adverse effects shown in Figure 18 and 19 below, there was a report of 2 (7.14%) participants in transdermal patches group and 4 (14.29%) participants in topical corticosteroids group which were itching and dry skin. However, all of 6 participants who reported adverse effects performed betamethasone17 ,21dipropionate patch testing and has no skin reaction before attending in this study. Overall, 21 (75%) participants preferred transdermal patches more than topical corticosteroids, n=18 (64.29%).

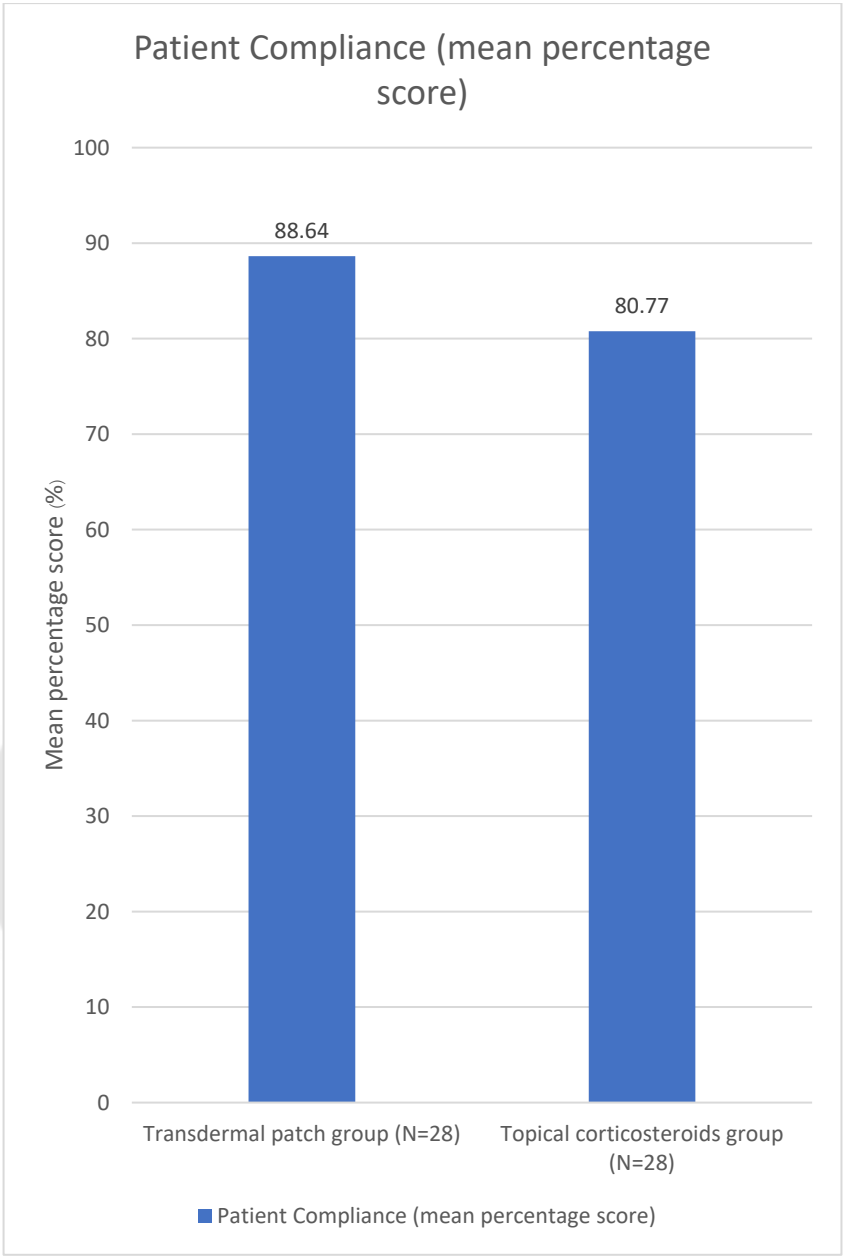


Figure 17 Compare to average percentage of patient compliance in both groups

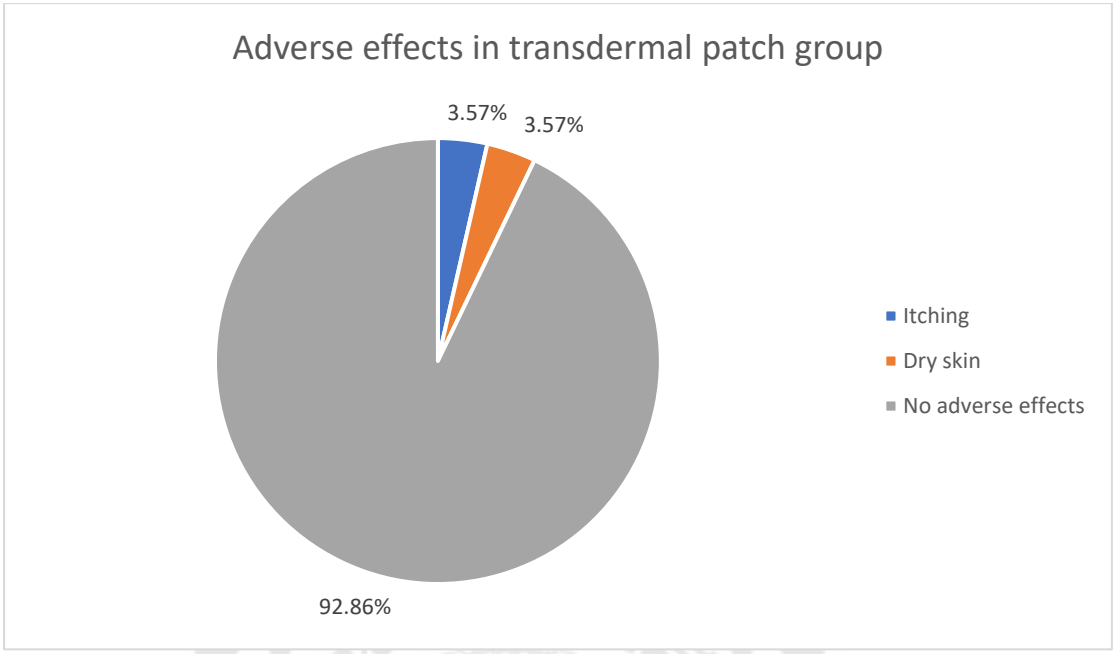


Figure 18 Adverse effects in transdermal patches group

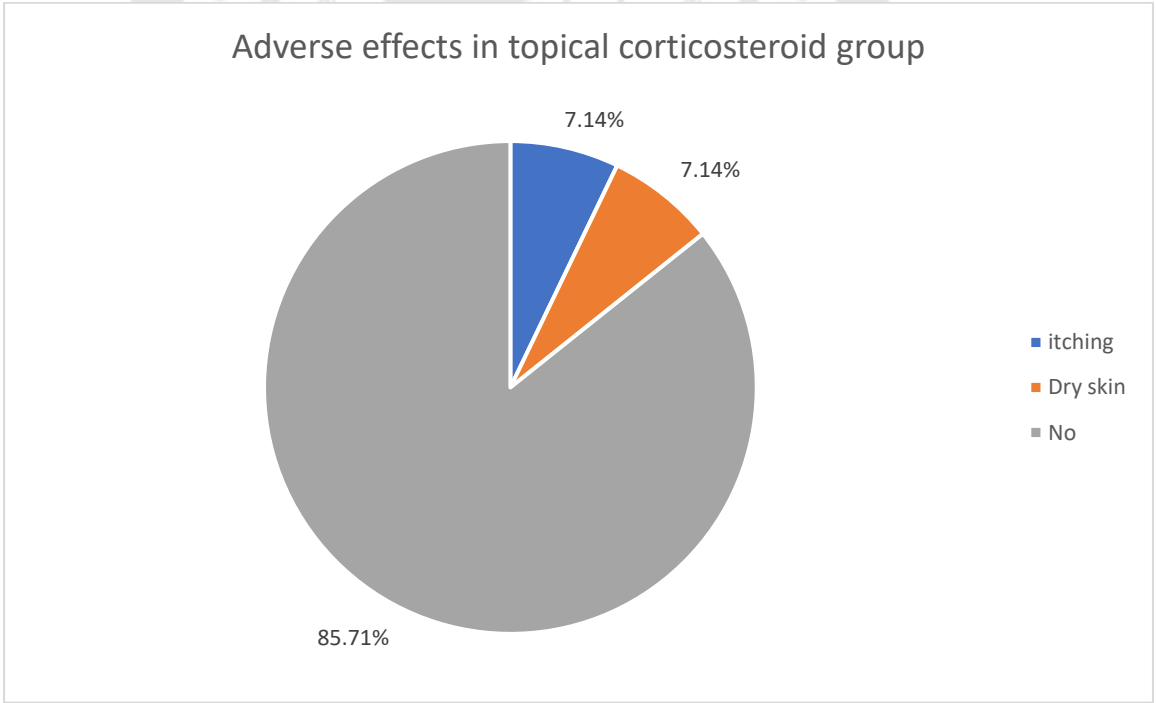


Figure 19 Adverse effects in topical corticosteroids group

Chapter 5

Summary, Implications and Recommendations

The study is a randomized-control trial in Thai chronic hand eczema patients who have not attended successful treatment for more than 3 months or their diseases have been relapsed twice or often per year. The target group is comprised of 58 patients in total aged between 18 to 60 years old. They were randomly categorized into two groups; betamethasone17 ,21dipropionate cream group and betamethasone17 ,21dipropionate transdermal patch group. The results were assessed by clinical outcomes with approximately 8 weeks at Skin SWU Center, Srinakharinwirot (SWU) University, Sukhumvit21, Bangkok, Thailand.

5.1 Summary of the study

5.1.1 Laboratory results of transdermal patches

After preparing and performing the formula of transdermal patches including betamethasone17 ,21dipropionate, the transparent light yellowish patches were generated. The patches were tested in physical, mechanical properties, dissolution, and permeation test. For physical properties, the mean weight was 0.063 mg and the average of thickness was 0.385 mm. The amount of betamethasone17 ,21dipropionate in the patch was approximately 0.05% which was close to 0.05%betamethasone17 ,21dipropionate ointment.

For mechanical properites, the tensile strength of betamethasone17 ,21dipropionate patches were more flexible than patches without betamethasone17 ,21dipropionate (Base patch) . Moreover, patches were performed Dissolution test by UV-Visible spectrophotometer for measurement of drug concentration. The highest average percentage of drug dissolution was about 95% after 60 minutes. From the drug permeabilities test, the patch was sustained-release over 6 hours.

5.1.2 The results from clinical assessment

According to our study, we found that both topical corticosteroid and transdermal patches can reduce the severity of hand eczema evaluated by HECSI score without any statistically significant difference. The HECSI score were statistically significant decreased in 2 weeks and gradually reduction of score was noted throughout study period. Four clinical signs including erythema, induration, fissuring, and scale were improved after both treatment modalities. Along with the PGA score and DLQI, it was reduced at the end of the study, but there was no statistically significant difference between both treatment groups.

Interestingly, participants treating with transdermal corticosteroid patches had better compliance and more satisfy than participants treating with topical corticosteroids. For an adverse effects, there was a report of 12 patients in topical corticosteroid group and 8 patients in transdermal group. The most adverse effect which was occurred in both groups was itching without statistically significant difference.

5.2 Discussion

Hand eczema is a common skin condition causing several negative effects on daily activities [(50)] from chronic course and high relapse rates [(1)]. Nowadays, the incidience related to hand eczema has an upward trend [(9)]. The most tendency towards the higher pooled prevalence of hand eczema is occupation frequent contacting dermatitis with approximately 70% [(10)]. Similarly in Thailand, the hand eczema associations and professions have analyzed that hand eczema is also related to certain occupations [(11)]. Besides, the COVID-19 pandemic has stimulated people having proper hand hygiene which is one of the main preventives against COVID-19 transmission. However, frequent handwashing may affect hand skin barrier and incite hand eczema. According to the European Society of Contact Dermatitis guideline treatment of hand eczema 2017 [(18)].

Topical corticosteroids is recommended to be used as a first-line treatment and high-potency steroids is suitable for the palms and soles due to the thick stratum corneum[(92)]. In this study, betamethasone17 ,21dipropionate was chosen because of its

efficacy which was significantly greater in clinical outcomes with clear adrenal suppression compared to clobetasol propionate[93]. Partition coefficient which describes how a solute is distributed between two immiscible solvents of betamethasone17 ,21dipropionate is higher than clobetasol propionate, with 3.6 and 3.3 respectively[94].

. Moreover, the study of Granlund H. et al 1997[60] showed that betamethasone17 ,21dipropionate reduced significantly of the total disease activity score and less occurred adverse effects than cyclosporine in severe chronic hand eczema at the end of treatment. Also, there was a report of betamethasone17 ,21dipropionate had successful treatment in refractory of chronic hand eczema[95]. However, it was difficult to control a disease due to a poor adherence to topical treatments[24].

Based on the knowledge background of pathophysiology of eczema, a disturbance of epidermal barrier is one of major factor resulting in dry skin as a consequence of a high transepidermal water loss. The solution is an enhancement of barrier function by providing occlusion will contribute increasing penetration of corticosteroids to improve skin disease[96].

There was a randomized controlled trial study showed that occlusive effect had significantly reduced the severity score of chronic skin disease[25]. Another study by Volden G et al in 1992[97], forty-eight patients with therapy-resistant chronic skin lesions of atopic dermatitis were treated with once a week with clobetasol propionate lotion left under Duoderm® , hydrocolloid occlusive patches. They concluded that clobetasol propionate and Duoderm® once a week had complete remission in atopic dermatitis patients with resistant lesions. Another study reported by Beitner H et al in 1996[26], it was a comparative study of a topical glucocorticoid ointment versus solution occluded with a new thin hydrocolloid dressing. Thirty consecutive patients with an acute outbreak of symptoms of hand eczema were included in the study and were followed for 12 weeks after treatment. The result indicated that both hydrocolloid dressing with topical corticosteroid illustrated the good clinical outcome. Due to an inconvenient to use because of two application of topical drug and occlusive dressing, we bring this

concept to generate incorporated drug in transdermal patch which have occlusive and sustained-release effect of drugs. A transdermal drug delivery system fitting for eczema is hydrogel which has desired physical properties[98]. For examples, it has high absorption capacity, high durability and stability, high biodegradability without formation of toxic species, low soluble content, and low price. As reported by Park KK et al in 2011[34], hydrogel patch is self-adhesive, convenient, hypoallergic, and elegant. Unlike plastic wraps, which often cause skin irritation and mechanical trauma when removed. Moreover. It contains approximately 50% of water, as opposed to hydrocolloid dressings, which compose of lower water content. In addition, hydrogel patch has been demonstrated in numerous practical applications, using for controlled drug release such as pioglitazone for wound healing, simvastatin for bone regeneration, and neuropeptide substance P for angiogenesis[99-101]. Moreover, the study of steroid-loaded hydrogel has recently published in 2021[35]. They demonstrated the benefit of steroid hydrogel patch for alleviation of psoriasis in mouse model.

In our study, we developed transdermal corticosteroid patch by heating roller machine. Our patch had light yellowish, transparent, and odorless gel sheet. There were more flexible compared to base gel without corticosteroid drug. It was dissolved about 95% in 60 minutes and slowly release a drug on the skin over an extended period, with approximately over 6 hours. This study is an experiment, prospective, assessor-blinded, randomized, and controlled study. Fifty- six participants with mild-moderate chronic hand eczema were enrolled. We found that both topical corticosteroid and transdermal patch similarly cause decreasing in severity of hand eczema over the study period without statistically significant difference. Overall, the reduction of HECSI were observed by approximately 80% at week 8 in both groups. At week 4, HECSI score was decreased by around 60% in transdermal patch group. Compared to previous study of Beitner H et al in 1996[26], they reported that the severity scores was decreased at 80% by week 4 in topical glucocorticoid ointment occluded with a hydrocolloid dressing group. The reason for superior outcome in previous study may be due to difference amount of steroid penetration. Simple occlusive dressings can increase 7 folds in

steroid penetration[52] compared with transdermal patch which is adhered to the skin for specific site and durations of wear and slow release for maintaining steady-state blood levels[69, 102]. So, the topical glucocorticoid with occlusive dressing group might be higher and faster penetration properties than transdermal steroid patch, but the burst release of topical steroids may cause of systemic toxicity[103]. To the best of our knowledge, this is the first study evaluation the efficacy of the hydrogel containing corticosteroid in human study, and we discovered the benefit of this patches to treatment of steroid responsive skin diseases similar outcome to topical corticosteroid.

The sustained release property of this patches might have a benefit than the topical corticosteroid with occlusion in term of safety. An inappropriate amount of drug permeation through skin may increase risk of systemic absorption, local and systemic complications[104]. For examples, atrophy, striae, purpura, hypopigmentation, bacterial infection, hypothalamic-pituitary-adrenal suppression, glaucoma, hyperglycemia, and hypertension etc[105]. From Beitner H et al 's study[26], there was 4(13.33%) participants who reported adverse effects from applying clobetasol propionate solution/ointment with thin hydrocolloid occlusive dressings. and N patients reported severe erythema, bacterial infections and one of them dropped out of the study. Comparison to our study, only 2(7.14%) participants in transdermal patch group had adverse effects which were mild, itching and dry skin and it seem to be less common than the topical treatment group. The high content of water of hydrogel patches and occlusive effect might relieve the itchy symptom. We did not find any infection, skin atrophy, hypopigmentation on the application area even we used the super potency steroids.

For the compliance, the transdermal patches showed better compliance than topical corticosteroid ointment as well as higher patient satisfaction. Patients were used corticosteroids patches only once daily at night without interfering patients' daily activities making it more adherence to the treatment than twice daily topical corticosteroids. The self-adhesive property of transdermal patches also makes it easy to use. On the contrary, ointments preparation tend to be greasy, difficult to remove, and

lack the ability to provide a cooling effect through surface evaporation which may affect patient satisfaction[33].

Table 29 Comparison of baseline characteristics in this study and previous study

	Beitner H et al [26]	Park KK et al[34]	Our study
Year of study	1996	2011	2021
Study methods	RCT*	RCT*, Pilot study	RCT*, accessor-blinded
Number of participants (N)	30	15	58
Mean age of participants	51	Not report	36.93 ± 12.10 to 38.50 ± 12.29
Hand eczema types	Not report	Atopic dermatitis	All types of hand eczema
Durations of study	12 weeks	6 weeks	8 weeks
Topical corticosteroids	Clobetasol propionate ointment	Triamcinolone 0.1% cream	Betamethasone17 ,21dipropionate ointment
Occlusion types	Hydrocolloid	Hydrogel	Hydrogel
Frequency of applying drugs	2/week	7/week	7/week
	Harry Beitner	Kelly K. Park	Our study
Duration of applying transdermal patch	Not report	6-8 hours a day	8 hours a day
Clinical severity scores	4 symptoms (itching, erythema, infiltration, scaling)	5 symptoms (erythema, induration, lichenification, pruritus, excoriation)	6 symptoms (erythema, infiltration, vesicle, fissure, scaling, edema)
Mean sum scores	Decreasing 80% by 4 weeks	Decreasing 60% of erythema by 4 weeks	Decreasing 63.31% by 4 weeks
	Beitner H et al[26]	Park KK et al[34]	Our study
PGA* by physician	Not report	Not report	Decreased in mean score from 2.93 to 2.07 by 8 weeks

Table 29 (Cont.)

	Beitner H et al [26]	Park KK et al[34]	Our study
PGA* by patient	Not report	Not report	Decreased in mean score from 2.96 to 2.18 by 8 weeks
DLQI* score	Not report	Not report	Decreased in mean score from 10.93 to 2.79 by 8 weeks
Patient compliance	Not report	Not report	Significant reduction in trasdermal patches group
Patient satisfaction	Not report	Not report	Significant reduction in trasdermal patches group
Side effects	-Erythema (1/30, 3.33%) -Bacterial infection (2/30, 6.67%)	0/15 ,(0%)	-Itching (1/28, 3.57%) -Dry skin (1/28, 3.57%)
Loss follow up	6/30, 20%	0/56, 0%	0/56, 0%

*RCT = Randomized controlled trial

*PGA = Physician Global Assessment

*DLQI = Dermatology Life Quality Index (DLQI)

Conclusion

In the present study, we developed a new preparation of topical corticosteroid for treatment of chronic hand eczema. Hydrogel transdermal patch containing 0.05%betamethasone17 ,21dipropionate showed the desired properties. The efficacy of transdermal patch containing 0.05%betamethasone17 ,21dipropionate was similar to topical 0.05%betamethasone17 ,21dipropionate ointment. Although there were no statistically significance difference in the efficacy, patients in the transdermal patch group had better compliance, patient's satisfaction and less side effect than in topical

corticosteroid group. We suggested that transdermal steroid patches can be used as an alternative treatment in chronic hand eczema who had poor compliance to topical medication. Furture study is need to improve some properties of this steroid containing patch for enhance the effectiveness.

Limitation of this study

- There were female participants more than male participants.
- There was a contamination and co-intervention of moisturizer because this study did not limit brands or types of moisturizers.
- According to the study, one physician was assigned to evaluate the clinical severity scores. Therefore, it might cause cognitive bias in the evaluation process.

Suggestions

- The sample size should be increased in future studies.
- More than one accessor can be assigned due to prevention of cognitive bias.
- Transdermal patches should be developed with wall adhesive properties.
- The period of study should be increased to follow a relapse.

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Appendix

แบบบันทึกข้อมูล (ฉบับภาษาไทย)

<u>ข้อมูลพื้นฐานทั่วไป</u>

วันเดือนปีเกิด(ตัวอย่าง 13/05/2536).....

เพศ ☐ ชาย ☐ หญิง

อายุ ……ปี

ที่อยู่ปัจจุบัน……

……

เบอร์โทรศัพท์บ้าน..... เบอร์โทรศัพท์มือถือ .....

น้ำหนัก.....กิโลกรัม

ส่วนสูง.....เซนติเมตร

ประวัติโรคประจำตัว ☐ ไม่มี ☐ มี ระบุ.....

ประวัติโรคคนในครอบครัว ☐ ไม่มี ☐ มี ระบุ.....

ยาที่กำลังใช้ในปัจจุบัน ☐ ไม่มี ☐ มี ระบุ.....

ระยะเวลาในการใช้

.....

อาหารเสริมที่รับประทาน ☐ ไม่มี ☐ มี ระบุ.....

ระยะเวลาที่รับประทาน

.....

ประวัติแพ้ยา ☐ ไม่มี ☐ มี ระบุ.....

(กรณีผู้ป่วยหญิง) ประวัติประจำเดือนครั้งสุดท้าย

.....

1.อาชีพและลักษณะงาน

☐ บุคลากรทางการแพทย์ ระบุ.....

☐ แม่บ้าน

☐ ช่างทำผม

☐ พนักงานทำความสะอาด

☐ อื่นๆ (โปรดระบุ) .....

2. งานอดิเรก.....

3. ประวัติผื่นอักเสบที่มือ. .....

-ระยะเวลาที่เป็นมาทั้งหมด .....

-ระยะเวลาโดยเฉลี่ยที่เป็นแต่ละครั้ง.....

4. ประวัติการทำpatch test

☐ ไม่เคย

☐ เคย ระบุ (วัน/เดือน/ปีพ.ศ.)ที่ทดสอบ.....

สถานที่ทดสอบ.....

ผลจากการทดสอบแพ้สาร.....

5. ประวัติการรักษาในอดีต

☐ ไม่เคย

☐ เคย ระบุวิธีการรักษา.....

6. ประวัติการสารที่มือ โดยใช้ผลิตภัณฑ์.....

- จำนวนครั้งต่อวัน.....

- วันเวลาที่ใช้ล่าสุด.....

7.กิจกรรมในชีวิตประจำวันที่ส่งผลต่อการเกิดผื่นอักเสบที่มือ

- งานบ้าน ☐ ทำ ระบุ.....จำนวนครั้ง.....ครั้งต่อวัน

☐ ไม่ทำ

- อื่นๆ ระบุ.....

8.จำนวนครั้งที่ล้างมือด้วยสบู่ (นอกจากเวลาที่อาบน้ำ)

- ครั้งต่อวัน.....

- โดยใช้.....ในการล้างมือ

9.จำนวนครั้งที่ล้างมือด้วยเจลหรือสเปรย์แอลกอฮอล์

- ครั้งต่อวัน.....

- โดยใช้แอลกอฮอล์ในรูปแบบ.....

10.ประวัติการทำงานที่เปียกชื้นเป็นเวลาต่อเนื่อง (Wet work).....ชั่วโมงต่อวัน

11. ประวัติการใส่ถุงมือต่อเนื่องเป็นเวลา..... ชั่วโมงต่อวัน

Case Record Form (English version)

General Information

Date of Birth (example 13/05/2536) .....

Sex ☐ Male ☐ Female Age ……

Address

……

Home Phone ..... Mobile Phone .....

Weight ..... kg Height ..... cm

Personal Medical Information

Have congenital disease? ☐ No ☐ Yes, please list……..

Have family history congenital disease? ☐ No ☐ Yes, please list.....

Have currently using medicine? ☐ No ☐ Yes, please list.....

Using duration .....

Have dietary supplements? ☐ No ☐ Yes, please list.....

Using duration .....

Have drug allergy ☐ No ☐ Yes, please list.....

Last menstrual history.....

Occupation Information Related to Disease

1. Occupation and job description

☐ Medical personnel, specify .....

☐ Housemaid/ Housewife

☐ Hairdresser

☐ Cleaner

☐ Others, specify .....

2. Hobby .....

3. Chronic hand eczema history .....

- Total duration .....
- Average duration per time .....

4. Have patch test history

☐ No

☐ Yes, specify test date .....

Test location .....

Result of patch test.....

5. Have past treatment history

☐ No

☐ Yes, specify treatment method .....

6. History using substance on hands, specify product .....

Numbers of using per day .....

Last using date .....

7. Daily activities that affect hand eczema

Housework activity ☐ Yes .... numbers per day

☐ No

Others, specify .....

8. Number of times washing hands with soap (not include taking shower)

Numbers per day.....

Product used .....

9. Number of times washing hands with gel or alcohol spray

Numbers per day.....

Using alcohol in the form of .....

10. Wet work history .....hours per day

11. Wearing gloves history ..... hours per day

ตัวอย่างรายละเอียดใน Logbook ของผู้ป่วย (ฉบับภาษาไทย)

สัปดาห์ที่			
	แปะแผ่นครบ 8 ชั่วโมง	แปะแผ่นไม่ครบ 8 ชั่วโมง (ระบุเวลารวมที่แปะแผ่น)	อาการผิดปกติ
วันจันทร์			
วันอังคาร			
วันพุธ			
วันพฤหัสบดี			
วันศุกร์			
วันเสาร์			
วันอาทิตย์			

สัปดาห์ที่			
	เช้า	เย็น	อาการผิดปกติ
	ใช้ผลิตภัณฑ์ยาทา	ใช้ผลิตภัณฑ์ยาทา	
วันจันทร์			
วันอังคาร			
วันพุธ			
วันพฤหัสบดี			
วันศุกร์			
วันเสาร์			
วันอาทิตย์			

กิจกรรมในชีวิตประจำวัน	ความถี่ในการทำแต่ละวัน
ล้างมือด้วยสบู่	
ล้างมือด้วยเจลหรือสเปรย์แอลกอฮอล์	
ทาครีมบำรุงที่มือ	
ทำงานบ้าน เช่น ล้างจาน, ซักผ้า, ถูบ้าน	
สวมถุงมือในการทำงาน	

VITA