International Journal of Pharmaceutics 523 (2017) 386–397

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

# Exploring the structure-permeation relationship of topical tricyclic antidepressants used for skin analgesia

Kuo-Sheng Liu[a], Tse-Hung Huang[b,c,d], Ibrahim A. Aljuffali[e], En-Li Chen[f], Jhi-Joung Wang[g,*], Jia-You Fang[f,h,i,j,**]

[a] Department of Pharmacy, Chia Nan University of Pharmacy and Science, Tainan, Taiwan
[b] Department of Traditional Chinese Medicine, Chang Gung Memorial Hospital, Keelung, Taiwan
[c] School of Traditional Chinese Medicine, Chang Gung University, Taoyuan, Taiwan
[d] School of Nursing, National Taipei University of Nursing and Health Sciences, Taipei, Taiwan
[e] Department of Pharmaceutics, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
[f] Pharmaceutics Laboratory, Graduate Institute of Natural Products, Chang Gung University, Kweishan, Taoyuan, Taiwan
[g] Department of Medical Research, Chi Mei Medical Center, Tainan, Taiwan
[h] Chinese Herbal Medicine Research Team, Healthy Aging Research Center, Chang Gung University, Kweishan, Taoyuan, Taiwan
[i] Department of Anesthesiology, Chang Gung Memorial Hospital, Kweishan, Taoyuan, Taiwan
[j] Research Center for Industry of Human Ecology and Research Center for Chinese Herbal Medicine, Chang Gung University of Science and Technology, Kweishan, Taoyuan, Taiwan

ARTICLE INFO

*Article history:*
Received 10 November 2016
Received in revised form 6 March 2017
Accepted 19 March 2017
Available online 23 March 2017

*Keywords:*
Tricyclic antidepressant
Propamine
Analgesia
Cutaneous absorption
Structure-permeation relationship

ABSTRACT

The purpose of this study was to evaluate the skin permeation of tricyclic antidepressants (TCAs) with propamine moiety to select candidates for the development of topical analgesics to treat cutaneous pain. We sought to establish the structure-permeation relationship (SPR) of topical TCAs. The lipophilicity, melting point, and aqueous solubility were determined to develop the physicochemical characterization. The TCA permeation into pig and nude mouse skins was estimated using Franz diffusion cell. TCAs and lidocaine were comparatively examined for cutaneous analgesia by pinprick assay. Cutaneous tolerance to TCAs was assessed using nude mouse skin. The skin deposition increased following the increase of lipophilicity after excluding the effect of solubility, with clomipramine exhibiting the highest skin retention. A contrary result was observed for TCA penetration into the receptor. Of the permeants tested, clomipramine demonstrated the best skin-targeting ability. Nortriptyline and clomipramine demonstrated selective uptake into the hair follicles, exhibiting a 2.5-fold higher follicular accumulation than desipramine. Replacement of nitrogen with carbon in the seven-member ring increased skin absorption. The tertiary amine TCAs demonstrated higher absorption than the secondary amine TCAs. The position of the double bond also affected skin transport. Topical clomipramine had a longer duration of analgesic action than lidocaine (240 min versus 60 min). Exploring the SPR revealed that clomipramine could be an analgesic candidate drug for future development.



## 1. Introduction

Topical drug administration can be an efficient method for skin targeting and cutaneous disease management. The actives must first be absorbed by the skin if the drugs are to provide therapeutic benefits. The drugs must diffuse across certain barriers, such as the stratum corneum (SC) and a tight junction, to achieve effective permeation. Various factors can influence this process, including the physicochemical characteristics of the drugs and the vehicles into which the drugs are loaded. An elucidation of how the physicochemical factors affect drug absorption is important for selecting and designing feasible drugs for topical application. The establishment of a structure-permeation relationship (SPR) attempts to link the delivery of the chemicals to their physicochemical properties and structures, thereby providing insights into the cutaneous absorption mechanisms (Riviere et al., 2014). The

* Corresponding author at: Pharmaceutics Laboratory, Graduate Institute of Natural Products, Chang Gung University, 259 Wen–Hwa 1st Road, Kweishan, Taoyuan 333, Taiwan.
** Corresponding author at: Department of Medical Research, Chi Mei Medical Center, 901 Chung Hwa Road, Yungkang, Tainan 710, Taiwan.
*E-mail addresses:* 400002@mail.chimei.org.tw (J.-J. Wang), fajy@mail.cgu.edu.tw (J.-Y. Fang).

http://dx.doi.org/10.1016/j.ijpharm.2017.03.048
0378-5173/

development of this relationship to predict the skin permeability of a series of drugs remains a challenge.

Numerous homologous series of tricyclic antidepressants (TCAs) are appropriate model permeants to organize SPR. TCAs are employed in the treatment of neuropathic skin pain. The mechanisms of TCA-related pain relief are the establishment of a blockade of the neuronal sodium channel and the *N*-methyl-D-aspartate receptor, activation of the μ- and δ-opioid receptors, and inhibition of norepinephrine reuptake (Kalso et al., 2013). Topically applied TCAs for analgesia exert peripheral effects approximating the administration region and reduce systemic adverse responses (Flores et al., 2012). TCAs can alleviate the pain associated with skin infection, malignant skin tumors, acute burns, postherpetic neuralgia, and radiation dermatitis (Jongen et al., 2014). Currently, only a few topical TCA options are commercially available. The clinical efficacy of the selected topical analgesics is often based on an empirical approach without wide studies on skin permeation (Peppin et al., 2015). The first objective of this study was to evaluate cutaneous absorption and the local anesthetic efficacy of a series of TCAs. We attempted to identify new candidates for peripheral pain treatment. Although some studies have been conducted for modeling SPR, the majority of the work focuses on the permeant transport across the skin (flux) but not on retention in the skin. Because the primary target of topical TCAs is the skin tissue, the second aim was to explore the relationship between cutaneous drug deposition and physicochemical properties. We endeavored to understand the mechanisms and pathways of TCA absorption as well as the permeant natures governing cutaneous delivery.

Most SPR databases employ heterogeneous permeants (Moss et al., 2002). The database involved in the homologous series is insufficient due to the limited physicochemical variety. As Fig. 1 illustrates, we chose the TCAs containing propamine moiety as the model permeants for investigating the SPR of these analogues. These structures are similar, although they do differ in some respects, including the presence of secondary amine (desipramine, protriptyline, and nortriptyline) or tertiary amine (imipramine and clomipramine), replacement of nitrogen (desipramine) with carbon (nortriptyline), different positions of the double bond (protriptyline versus nortriptyline), and the absence or presence of chlorine (imipramine versus clomipramine). The physicochemical properties, including the melting point, the partition coefficient (log *P*), the capacity factor (log *K'*), and the aqueous solubility, were determined. The cutaneous absorption was evaluated by Franz diffusion cell with pig and nude mouse skins as the barriers. The in vivo analgesic activity of the topically applied TCAs was examined using the pinprick test. Finally, the in vivo skin tolerance of the topical TCAs was analyzed based on the profiles of cutaneous physiology and histology. The data collected in this study allowed us to discriminate the contributions of different drug properties to cutaneous transport.

## 2. Materials and methods

### 2.1. Conversion of TCA salts to base forms

All propamine TCAs were purchased from Sigma-Aldrich (St. Louis, MO, USA). $NH_4OH$/water solution at pH 9 was added by drops into methanol containing TCA salt to precipitate the base form. The precipitate was filtered and washed with double-distilled water for $NH_4OH$ removal. The structures of the TCA base forms were validated by infrared spectrophotometry and nuclear magnetic resonance.

### 2.2. N-octanol/water partitioning (log P) and capacity factor (log K')

A methanolic solution (1 ml) of TCA base forms (0.5 mg) was prepared in a sample vial. Methanol was evaporated by a vacuum. *n*-octanol and double-distilled water, 1 ml of each, were added to the vial. After being shaken for 24 h at 37 °C, the *n*-octanol and water phases were divided by centrifugation at 10,000 × *g* for 10 min. The TCA concentration in *n*-octanol and water was quantified by high-performance liquid chromatography (HPLC). The partition coefficient was estimated as log *P* (log TCA concentration in *n*-octanol/TCA concentration in water). The stationary phase of HPLC was a 25-cm-long, 4-mm inner diameter

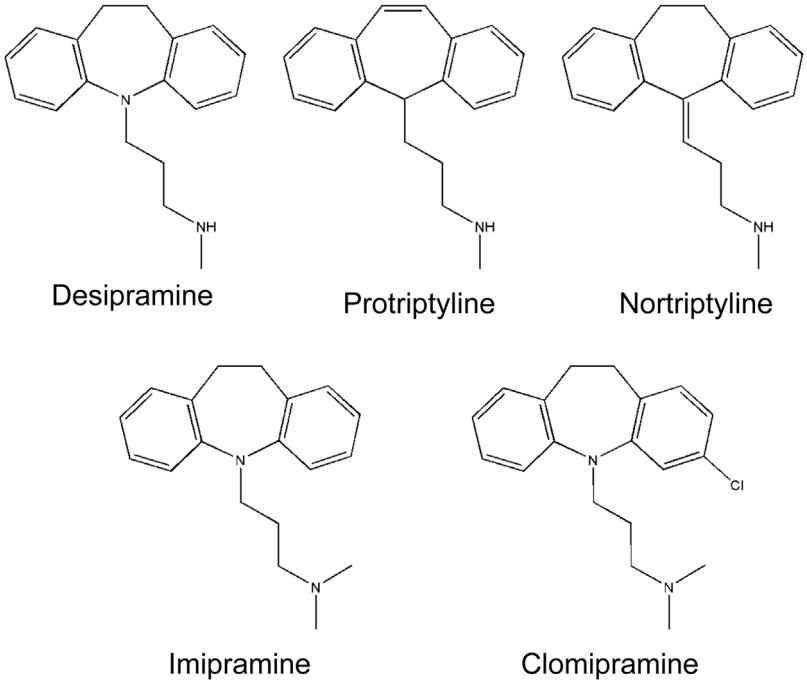


**Fig. 1.** The chemical structures of desipramine, protriptyline, nortriptyline, imipramine, and clomipramine.