Surfaces and Interfaces 52 (2024) 104903

Contents lists available at ScienceDirect

Surfaces and Interfaces

journal homepage: www.sciencedirect.com/journal/surfaces-and-interfaces

Dissolving microneedle integrated with benidipine loaded ethosomes for transdermal delivery

Khater AL-Japairai [a], Samah Hamed Almurisi [b], Nadiya Abdul-Halim [a,*], Syed Mahmood [c,*]

[a] Department of Pharmaceutical Engineering, Faculty of Chemical and Process Engineering Technology, Universiti Malaysia Pahang Al-Sultan Abdullah, Gambang 26300, Malaysia
[b] Department of Pharmaceutical Technology, School of Pharmacy, International Medical University, Kuala Lumpur 57000, Malaysia
[c] Department of Pharmaceutical Technology, Faculty of Pharmacy, Universiti Malaya, Kuala Lumpur 50603, Malaysia

ARTICLE INFO

Keywords:
Benidipine
Ethosomes
Dissolving microneedles
Transdermal
Bioavailability

ABSTRACT

Benidipine HCl (BEN) is a drug used for the treatment of hypertension. However, this drug suffers from low oral bioavailability. This study introduces a novel approach to address this issue by developing BEN-loaded ethosomes (BEN-E) that integrate into dissolving microneedles for transdermal delivery. The BEN-E was prepared using a rotary evaporation method and optimised using the Box-Behnken design. Following that, the optimised BEN-E formulation was integrated into dissolving microneedles (DMNs). The optimised lipid vesicles selected comprised lipoid S75 (339.66 mg), ethanol (34.51 %), and sonication time (70 s) and showed a vesicle size of 149.4 ± 3.81 nm, an EE% of 88.57 ± 0.38 %, and a transdermal flux of 19.12 ± 0.19 μg/cm^2/hr. On the other hand, the resulting BEN-E-DMNs exhibited sharp pyramidal microneedles, sufficient mechanical strength, good insertion capability, and fast dissolution in rat skin. In the *ex vivo* study, the permeation coefficient of BEN was significantly improved by BEN-E-DMNs compared with optimised BEN-E and BEN-DMNs. The pharmacokinetic studies showed that the BEN-E-DMNs had a C_{max} of about 0.698 ± 0.037 μg/mL and an AUC_{0-t} of about 15.821 ± 0.868 μg/hr/mL. Moreover, it improved the relative bioavailability of BEN by about 1.58 times compared to the orally marketed BEN tablet and about 2.95 times compared to the BEN-DMNs. In conclusion, the ethosomes combined with dissolving microneedles have shown high potential as carriers for the transdermal delivery of BEN.

1. Introduction

Transdermal drug delivery (TDD) can be described as the movement of drug molecules across the stratum corneum (outermost layer of the skin) into the systemic circulation [1]. TDD can avoid the gastrointestinal tract and eliminate the first-pass hepatic metabolism, which eventually enhances the bioavailability of the drug and reduces the side effects [2]. Benidipine hydrochloride (BEN) is highly prescribed by medical practitioners for the management of dual conditions like hypertension and angina pectoris. It belongs to the class of calcium channel blockers and is supplied as a tablet of 2–4 mg as a daily dose, gradually increasing to 8 mg according to need. The oral bioavailability of BEN has been reported to be as low as about 23–30 % due to extensive hepatic first-pass metabolism and a short biological half-life (0.97 to 1.7 h) [3]. The main side effects of BEN are palpitation, hot flushes, and headache, which are often seen in other calcium channel blockers [4]. Transdermal drug delivery is an alternative route that tends to be more efficient; it can avoid the gastrointestinal tract and eliminate the first-pass hepatic metabolism, which eventually reduces the dose and dosage frequency and eliminates the dose-related side effects [2,5].

Transdermal delivery of drugs is generally restricted by the skin's barrier function, which is the stratum corneum (SC). In general, a limited number of drugs can successfully permeate the stratum corneum in sufficient quantities to have a therapeutic effect. For drug molecules to viably permeate into the stratum corneum layer of the skin, they should possess several ideal features. These include a small molecular weight (i.e., less than 600 Da), a Log P value between 1 and 3, and a melting point of less than 200 °C [6]. To overcome this, several methods have been employed to improve transdermal drug absorption, and these include chemical permeation enhancement such as enzyme inhibition and lipid vesicles as well as physical permeation enhancement such as iontophoresis, electroporation, thermal ablation, ultrasound, and

* Corresponding authors at: Department of Pharmaceutical Technology, Faculty of Pharmacy, Universiti Malaya, Kuala Lumpur 50603, Malaysia.
E-mail addresses: nadiya@umpsa.edu.my (N. Abdul-Halim), syedmahmood@um.edu.my (S. Mahmood).

https://doi.org/10.1016/j.surfin.2024.104903
Received 30 May 2024; Received in revised form 21 July 2024; Accepted 1 August 2024
Available online 5 August 2024