In vitro study of a foamable microemulsion for improved topical delivery of diclofenac sodium*.

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ABSTRACT

Purpose: Topical microemulsions (ME) are a novel and advanced topical delivery system that can enhance drug solubility and permeability across the skin. Foams have excellent patient compliance due to their ease of administration and the convenience of application. This study investigated a foamable microemulsion as an alternative topical dosage form for diclofenac sodium (DS). ***Method:*** The physicochemical properties (optical clarity, percentage transmittance, homogeneity, consistency of formulation, globule size, zeta potential, pH, conductivity, viscosity, and morphology) of the microemulsion with and without DS were investigated. The foam quality and foam stability with and without DS were determined over 90 days. Franz diffusion cells were used to assess the in vitro drug release from a DS loaded foam and compared with a commercial topical product. ***Results:*** A foamable and 90 days stable DS loaded ME was successfully formulated by evaluating the transparency and translucency, globule size, zeta potential, and foam quality. The foam exhibited an increased rate and extent of drug release compared to the commercial product. ***Conclusion:*** The foamable DS loaded ME was stable for three months. The tested formulation has great potential to enhance the topical delivery of DS for pain management locally. Foamable ME is a promising alternative to the current topical formulation of DS.

INTRODUCTION

Topical administration can protect a drug substance from gastric enzymes, avoid hepatic first-pass metabolism, and improve an active substance delivered to the target site[1]. Diclofenac sodium (DS) is one of the most widely topically used nonsteroidal anti-inflammatory drugs (NSAIDs) in the treatment of musculoskeletal pain[2,3]. Because the commercially available strengths of 1 and 2 % often do not effectively reduce inflammatory pain, doctors began to prescribe 5%, 10%, 15%, or even higher doses to increase the therapeutic effect[4]. However, increasing the dose does not necessarily mean that more drug reaches the target area but instead raise the risk of side effects[5]. Microemulsion (ME) is a transparent and thermodynamically stable micro-dispersion drug delivery system composed of oil, water, surfactant, and cosurfactant[6]. The ME can potentially provide better therapeutic outcomes at lower doses than the prescribed high-dose preparations by enhancing both drug solubility and penetration of the drug substance across the stratum corneum[7]. Topical foams are less sticky, spread easier to reach difficult access skin areas, reduce the touching and rubbing, leave fewer residues, and minimize potential staining, compared to other common semi-solid dosage forms (cream, lotion, gel, ointment, and solution)[8-10]. Therefore, foams are suitable for highly inflamed, swollen, irritated, infected, and sensitive skin and show excellent patient compliance, acceptability, and preference[8,10]. A foamable ME combined the benefits of ME and foams.

OBJECTIVES

Assessed the physicochemical properties, morphology, stability, and in vitro drug release performance of a foamable microemulsion base in a propellent-free device as an alternative topical dosage form for the transdermal delivery of DS.

METHODS

The optical clarity, percentage transmittance, homogeneity, consistency of formulation, globule size, polydispersity index (PdI), zeta potential, apparent pH, conductivity, viscosity, morphology, and type of emulsion were assessed, respectively. The foam quality and the stability with and without DS were determined over 90 days. The in vitro drug release from a DS-loaded foam compared with a commercial topical product were evaluated using Franz diffusion cell.

RESULTS

Table 1. Physicochemical characteristics of the microemulsion and diclofenac sodium loaded microemulsion (Mean ± SD, n=3)

Properties	Microemulsion	Diclofenac Sodium Loaded Microemulsion
Refractive index	1.36 ± 0.47	1.36 ± 0.00
Transmittance (%)	99.26 ± 0.41	98.89 ± 0.67
Globule Size (nm)	47.64 ± 0.27	22.73 ± 0.15*
PdI	0.148± 0.000	0.210± 0.010*
Zeta Potential (mV)	-34.20 ± 0.10	-34.40 ± 2.26
pH	5.22 ± 0.00	7.64 ± 0.20*
pH (After five heating-cooling cycles)	5.23 ± 0.04	7.61 ± 0.04
Viscosity (cP)	6.76 ± 0.01	9.09 ± 0.24*
Conductivity (mS/cm)	0.002±0.000	0.869±0.000*
Hydrophilic-lipophilic balance	9.74	9.45
Saturation solubility of diclofenac sodium in microemulsion (mcg/mg)	-	163.20 ± 5.14

*P<0.05

Table 2. Particle size and foam quality of diclofenac sodium loaded microemulsion in foam dispensers at room temperature for 90 days. (Mean ± SD, n=3)

Time (days)	Particle size (nm)	Foam quality
0	21.51 ±1.19	Stable-fine foam with a couple of coarser bubbles
30	21.48 ± 1.14	Stable-fine foam with a couple of coarser bubbles
60	21.33± 0.07	Stable-fine foam with a couple of coarser bubbles
90	20.70 ± 0.56	Stable-fine foam with a couple of coarser bubbles

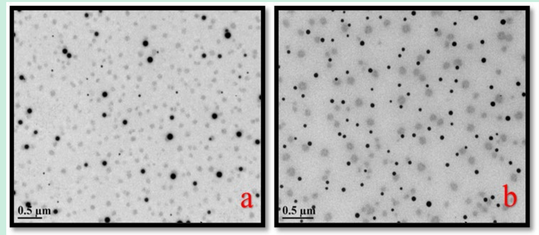

Figure1. Transmission electron microscopy images of **(a)** microemulsion and **(b)** diclofenac sodium loaded microemulsion droplets

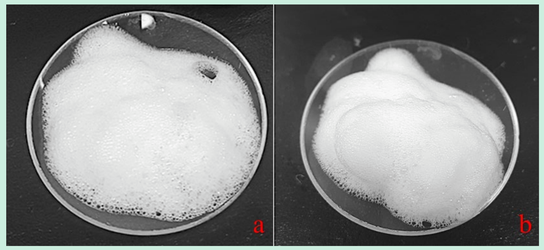

Figure 2. The appearance of **(a)** foamed microemulsion and **(b)** foamed diclofenac sodium loaded microemulsion

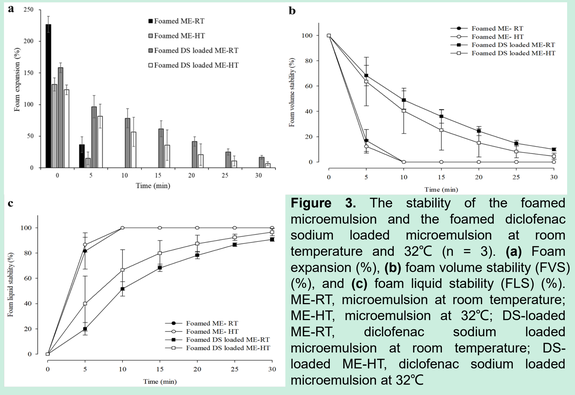

Figure 3. The stability of the foamed microemulsion and the foamed diclofenac sodium loaded microemulsion at room temperature and 32℃ (n = 3). **(a)** Foam expansion (%), **(b)** foam volume stability (FVS) (%), and **(c)** foam liquid stability (FLS) (%). ME-RT, microemulsion at room temperature; ME-HT, microemulsion at 32℃; DS-loaded ME-RT, diclofenac sodium loaded microemulsion at room temperature; DS-loaded ME-HT, diclofenac sodium loaded microemulsion at 32℃

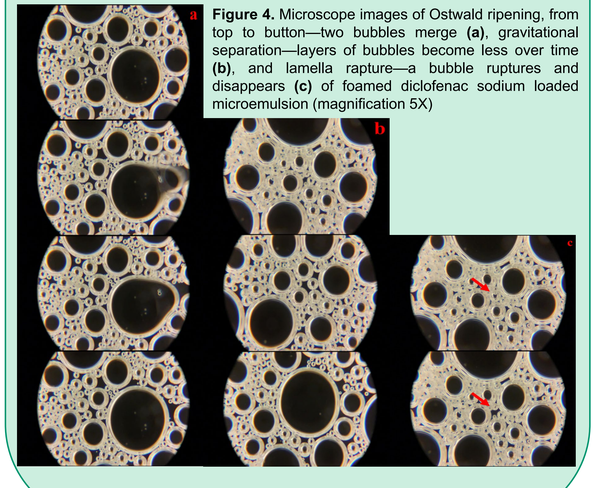

Figure 4. Microscope images of Ostwald ripening, from top to button—two bubbles merge **(a)**, gravitational separation—layers of bubbles become less over time **(b)**, and lamella rapture—a bubble ruptures and disappears **(c)** of foamed diclofenac sodium loaded microemulsion (magnification 5X)

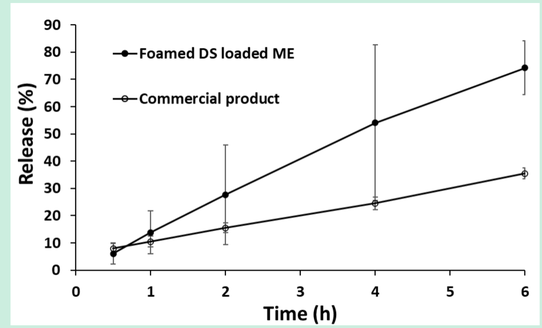

Figure 5. *In vitro* release profiles of diclofenac sodium from a foamed diclofenac sodium loaded microemulsion and a commercial product (Voltaren®). Foamed DS-loaded ME, foamed diclofenac sodium loaded microemulsion (n = 6)

CONCLUSION

- The DS-loaded foam showed better foam properties (globule size, PdI, and foam quality) compared to the blank ME base.
- The DS-loaded foam was stable for 90 days.
- The foam has an increased rate and extent of drug release compared to a commercial DS product.
- The foamable DS-loaded ME has a great potential to enhance topical and transdermal delivery of DS for pain management locally.
- The foamable ME is a promising topical and transdermal delivery system and a suitable alternative to the current topical formulation available on the market.

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* The original work was published as Hajjar B, Zuo JY, Park CH, et al. AAPS PharmSciTech. 2022; 23(4): 1-9.

ACKNOWLEDGEMENTS

This work was supported by Taibah University (Madinah, Saudi Arabia), Mitacs Accelerate (IT24899, Canada), and the Alberta Innovates Graduate Student Scholarship (Alberta, Canada).