The Topical Delivery of Benzoyl Peroxide Using Elegant Dynamic Hydrofluoroalkane Foams

YANJUN ZHAO,[1] MARC B. BROWN,[2,3] STUART A. JONES[1]

[1]Pharmaceutical Science Division, King's College London, 150 Stamford Street, London SE1 9NH, UK

[2]MedPharm Ltd, Unit 3/Chancellor Court, 50 Occam Road, Surrey Research Park, Guildford GU2 7YN, UK

[3]School of Pharmacy, University of Hertfordshire, College Lane Campus, Hatfield, Herts AL10 9AB, UK

Received 28 April 2009; revised 4 August 2009; accepted 7 August 2009

Published online 1 October 2009 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/jps.21933

ABSTRACT: Formulating benzoyl peroxide (BPO) in an effective topical product is challenging due to its poor water solubility and chemical instability, but delivering BPO using elegant foams is an attractive solution to this problem. The aim of this work was to investigate how nanoparticle properties influence BPO release and permeation when administrated using dynamic hydrofluoroalkane foams. Lipid (LN, ~50 nm) and polymeric (PN, ~350 nm) nanoparticles were produced and loaded into topical foams. Drug release and permeation was measured using ultrafiltration and Franz cells studies, respectively. No BPO release was detected when the nanoparticles were stored in the aqueous solvent, but upon administration to silicone membrane the pluronic surfactant-induced LN swelling and BPO delivery ($35.7 \pm 3.8\ \mu g\,cm^{-2}\,h^{-1}$). In the same situation the PN aggregated with a delivery rate of $2.5 \pm 0.2\ \mu g\,cm^{-2}\,h^{-1}$. Surprisingly the aqueous nanosuspensions delivered BPO at an equivalent rate to the foams despite the poor drug solubility in the dispersing medium presumably due to ultra-rapid BPO solubilization kinetics of the drug in water. The delivery of BPO from the foams (0.1% BPO) was superior compared to the commercial products (5% BPO), but further testing in human skin is required prior to clinical use. © 2009 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 99:1384–1398, 2010

Keywords: formulation vehicle; controlled delivery; nanoparticles; encapsulation; stability

INTRODUCTION

Acne is a very common skin disorder that typically affects 70–80% of the population at some time in their life.[1] The cause of acne is multifactorial and can involve excess seborrhea, proliferation of *Propionibacterium acnes*, inflammation and abnormal desquamation of the follicular epithelium.[2] A wide range of treatments are available for both inflammatory and noninflammatory acne lesions, but topical benzoyl peroxide (BPO) is the most popular therapy as it has both a keratolytic and a broad-spectrum anti-bacterial effect.[3] In several clinical trials BPO has demonstrated superiority over other topical antibiotics employed to treat acne and bacteria have been shown not to develop resistance to this agent.[2,3]

BPO is chemically unstable in numerous solvents. Decomposition of this therapeutic agent forms benzoic acid (BA) and other side-products via a rapid free-radical mechanism arising from the instability of the O–O bond in the BPO molecule.[4] As a consequence of this chemical instability and its poor aqueous solubility (1.6 μg/mL),[5] BPO is commonly formulated as a

Correspondence to: Stuart A. Jones (Telephone: 44-20-7848-4843; Fax: 44-20-7848 4800; E-mail: stuart.jones@kcl.ac.uk)

Journal of Pharmaceutical Sciences, Vol. 99, 1384–1398 (2010)

suspension in topical "over the counter" products. Although drug release from these topical suspensions is efficient, the extremely high concentrations of drug incorporated into the product (typically 2.5–10%, w/w) often leads to skin irritation.[6] The deleterious effects of BPO which are particularly prevalent during treatment initiation include erythema, dryness, scaling, burning, and stinging. As the degree of irritation is believed to relate to the amount of BPO applied to the skin,[6–8] the development of an alternative, more efficient formulation strategy for BPO delivery could be advantageous.

One method to reduce the amount of drug applied to the skin is to formulate BPO as a simple gel or solution. In order to do this, however, agents to improve the chemical stability of BPO are required and this has previously been shown to be difficult. Bartlett and Nozaki[9] combined BPO with oxidation inhibitors such as hydroquinone, *p*-*t*-butylcatechol, *m*-dinitrobenzene, and picric acid in attempt to minimize drug decomposition, but this approach failed to retain 100% of the agent in its native form. Majekodunmi et al.[10] investigated the effect of a range of stabilisers including butylated hydroxytoluene, butylated hydroxyanisole, eugenol, Tenox-2™, vitamin E and vitamin C, but none of these compounds could successfully stabilize BPO. An alternative method to reduce BPO irritation whilst retaining the chemical integrity of the agent upon storage is to encapsulate the active into a carrier. For example, Patel et al.[11] loaded BPO into liposomes and demonstrated a reduced local skin irritation. Furthermore, Wester et al.,[12] Embil and Nacht,[13] Jelvehgari et al.,[14] and Bikowski and Del Rosso[15] have all developed microspheres to deliver BPO with the aim of reducing topical irritancy. However, the problem associated with loading BPO into microparticles is that the surface area available for drug release is low and this leads to the poor drug release rate from microparticles.

Formulating BPO in a nanoparticle carrier may offer many of the potential advantages shown with other compounds including improved formulation aesthetics,[16] reduced skin irritation,[17,18] controlled release,[19] and follicular targeting.[20] There is a precedent for this type of delivery system as numerous types of nanoparticles including both polymeric and lipid nanoparticles have previously been applied topically.[20,21] However, like microparticles as they do not penetrate the outermost layer of the skin, the *stratum corneum*,[22,23] the rate of drug release from nanoparticles dictates the topical delivery efficiency. Due to a greater surface area, drug release from nanoparticles is more rapid compared to that from microparticles, but it is still very inefficient compared to a solution. To resolve this problem, a dynamic nanoparticle-containing foam system has been developed that breaks open nanoparticles upon delivery to enhance drug release rate. Previous work has shown that a dynamic foam can enhance the release of vitamin E acetate from lipid nanoparticles upon dose application,[24] but it is still not clear whether a similar strategy is suitable and effective for other agents such as BPO. In addition, the relationship between the type of nanoparticles and dynamic foam drug delivery efficiency has not been developed.

The aim of this work was to investigate how nanoparticle properties influenced BPO delivery efficiency when administrated using dynamic hydrofluoroalkane foams. To achieve this aim the objectives of the study were to determine the effectiveness of BPO encapsulation in two different types of nanoparticles, characterize these nanoparticles and to investigate the topical BPO delivery efficiency from these nanocarriers using dynamic foams. First, both lipid (LN) and polymeric (PN) nanoparticles were used to encapsulate BPO and the drug-loaded nanoparticles were formulated in foams. Second, nanosuspensions and foam formulations were characterized before dose application in terms of particle size, drug content uniformity, and drug release which was examined using centrifugal filtration method. Third, the formulations were characterized after dose application via monitoring the particle size and drug permeation performance from these formulations. Ultimately it was anticipated that the results from this study would help to elucidate the effects of the drug, the nanoparticles and the vehicle upon topical delivery in order to optimize the administration of this popular topical active agent.

MATERIALS AND METHODS

Materials

Pluronic L62D and heptafluoropropane were obtained from BASF (Mount Olive, NJ) and DuPont de Nemours Int'l SA (Geneva, Switzerland), respectively. The lipophilic Labrafac® WL 1349 (medium chain triglycerides) and Capryol® 90 (propylene glycol monocaprylate) were provided