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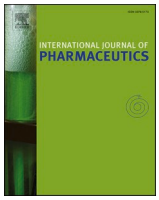

Enhancing topical delivery of ISRIB: Optimizing cream formulations with chemical enhancers and pH adjustment

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ABSTRACT

Chemical warfare agents, particularly vesicants like lewisite, pose a threat due to their ability to cause skin damage through accidental exposure or deliberate attacks. Lewisite rapidly penetrates the skin, causing inflammation and blistering. This study focuses on developing a cream formulation of a therapeutic agent, called integrated stress response inhibitor (ISRIB), to treat lewisite-induced injuries. Moreover, animal studies demonstrate a molecular target engagement (ISR) and significant efficacy of ISRIB against lewisite-induced cutaneous injury. The goal of this formulation is to enhance the delivery of ISRIB directly to affected skin areas using an oil-in-water cream emulsion system. We investigated various excipients, including oils, surfactants, emollients, and permeation enhancers, to optimize ISRIB's solubility and penetration through the skin. The result of this study indicated that the optimal formulation includes 30 % w/w of N-Methyl-2-pyrrolidone, dimethyl sulfoxide and Azone® at a pH of 5. 5. It delivered the highest amount of ISRIB into the skin, demonstrating highest skin absorption with no detectable systemic exposure. Additionally, characterization of the cream, including texture analysis, emulsion type, and content uniformity, confirmed its' suitability for topical application. These findings suggest that ISRIB cream formulation is a promising approach for the localized treatment of skin injuries caused by lewisite.

1. Introduction

Chemical warfare agents (CWA) pose a significant concern due to their potential to inflict extensive harm and disruption through accidental exposure or terrorist attacks. CWAs upon exposure encompass a wide range of toxic chemicals, among which vesicants are notable for their direct potent irritating and blistering effects on the skin and mucus membranes including eye and airway mucosa. Vesicants like mustard and arsenicals are of high concerns due to their simple synthesis methodologies, easy availability and severe toxic manifestations. Lewisite is a highly reactive arsenical-based CWA which manifests debilitating effects rapidly as compared to Sulphur mustard gas, which causes delayed but similar cutaneous blistering and inflammation (Dogaroiu, 2003; Vora et al., 2022a). Lewisite rapidly penetrates the skin due to its lipophilic properties, causing immediate inflammation, blisters, and intense burning pain within a few seconds. The initial effect is followed by severe erythema, characterized by the formation of vesicles and large fluid-filled blisters. Moreover, the impact of lewisite can be profoundly long-lasting, as a single accidental exposure can cause chronic and debilitating effects that may persist for years. These vesicants initially accumulate in the epidermis and hair follicles, leading to frequent occurrences of epidermal necrosis followed by edema and vascular thrombosis (Kshirsagar et al., 2023; Li et al., 2016a; Talabani et al., 2018). However, their systemic effects are also known (Araj et al., 2022; Li et al., 2016a). Therefore, we and others have developed multiple cutaneous and systemic models of injury of these chemicals (Roberts et al., 1988; Srivastava et al., 2020, 2024; Zafar et al., 2024; Zhylkibayev et al., 2023). Cutaneous exposure to even low doses of vesicant compounds for a brief period can activate reactive oxygen species (ROS) and trigger endoplasmic reticulum stress, which upregulates the unfolded protein response (UPR) signaling pathway. This upregulation leads to the accumulation of unfolded proteins and induces stress granule (SG) formation, which is considered fundamental to the molecular pathogenesis of skin, eye as well as systemic injury (Roberts et al., 1988; Li

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