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Original Article

Exploration of ethyl anthranilate-loaded monolithic matrix-type prophylactic polymeric patch

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ARTICLE INFO

Article history:
Received 30 March 2016
Received in revised form
31 October 2016
Accepted 7 November 2016
Available online 5 December 2016

Keywords:
Controlled release
Ethyl 2-aminobenzoate
Insect repellent
ICH guidelines
Polymeric patch

ABSTRACT

Compromised stability of pharmaceutical formulations loaded with volatiles is a serious problem associated with devices designed to deliver volatile compounds. The present study has been focused to evaluate the stability potential of matrix-type polymeric patches composed of volatile ethyl anthranilate for prophylaxis against vector-borne diseases. Ethyl anthranilate-loaded matrix-type polymeric patches were fabricated by solvent evaporation method on an impermeable backing membrane and attached to temporary release liners. Stability testing of the polymeric patches was performed as per the International Conference on Harmonization (ICH) guidelines for 6 months under accelerated conditions. In addition, the quantification of residual solvents was also performed as per the ICH guidelines. After conducting the stability studies for 6 months, the optimized patches showed the best possible results with respect to uniformity of drug content, physical appearance, and other analytical parameters. Furthermore, the amount of residual solvent was found well below the accepted limit. Thus, the present report outlined the analytical parameters to be evaluated to ensure the stability of a certain devices consisting of volatile compounds.

1. Introduction

Pharmaceutical formulations designed to deliver volatile compounds, such as insect repellents, herbicides, pesticides, essential oils, flavours, perfumes, and pheromones, are subjected to degradation because the volatiles are lost easily due to their inherent properties as well as due to the influence of different environmental factors, including heat and humidity. Thus, the stability potential of a very important

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http://dx.doi.org/10.1016/j.jfda.2016.11.002

pharmaceutical formulation is compromised, which is highly undesirable. With the advent of modern technology, both natural (e.g., ethyl cellulose, gelatin, dextran, etc.) and synthetic polymers (e.g., polyvinyl alcohol, polyvinyl chloride, etc.) have been widely used in different fields as biomaterials, controlled drug delivery, in protection of functional ingredients, etc. [1–3]. However, the end product designed with polymeric materials should remain relatively stable to storage conditions over a long period. Polymeric materials used for designing different devices not only enhance the physical–chemical stability but also the safety by entrapping the volatile compounds in their matrix, thereby releasing the volatiles at a desired controlled rate [4].

Stability testing is a significant prerequisite criterion that warrants the efficiency and safety of a particular pharmaceutical product to sustain its properties throughout its declared shelf life under predefined conditions [5–8]. Stability testing of pharmaceutical products is a complex set of procedures involving scientific expertise, considerable cost, and time in order to build in quality, efficacy, and safety in a drug formulation [6,9]. The chemical, physical, and microbiological aspects of stability are generally assessed by adhering to the International Conference on Harmonization (ICH) guidelines with two primary goals: (1) selection of an effective formulation and packaging material; and (2) estimation of shelf life and suitable storage conditions for the formulation [10]. A comprehensive development plan includes pharmaceutical analysis and stability studies that not only ensure the identity, potency, and purity of ingredients as well as those of the formulated products but also determine scientific and commercial success of a pharmaceutical product [11,12].

Ethyl anthranilate (EA, CAS. 87-25-2), chemically known as ethyl 2-aminobenzoate, is a new member in the realm of entomology and has drawn significant attention in repellent research in the recent years; it is considered as an improved alternative to DEET, chemically known as diethyltoluamide [13–16]. Insect repellent formulation containing EA has not been attempted till date in any form; therefore, there is a vast opportunity in the formulation development. However, because of the volatile nature of EA, fabrication of a controlled-release insect repellent formulation is difficult. Membrane-moderated matrix-type monolithic polymeric device or otherwise known as “polymeric patch” is a newer invention and has been a subject of scientific investigations recently. The polymeric patch is a versatile, solid-state, asymmetric (relatively small molecules of one or more active principles mixed with large polymer molecules), controlled-release diffusing system in which the active material is dispersed in a rate-controlling polymer matrix [17]. A polymeric patch is a promising and an attractive option to deliver volatile compounds in a controlled-release manner [17–20]. Its advantage over the traditional control measures is that it may be affixed to hat, collar, cuffs, shirt, belt, pant, boots, socks, and certainly may also be affixed to furniture, walls, or appliances too [21].

In the present study, EA-loaded polymeric patch has been developed in our laboratory for prophylaxis against different vector-borne diseases, and their stability potential was evaluated as per the ICH guidelines [10]. Further, in the present investigation, the residual solvents were quantified to assure the quality attributes of developed patches as per the ICH guidelines [22]. The study would be useful for the routine analysis of formulation containing EA not only in topical prophylactic polymeric patch formulation but also in other dosage forms.

Thus, the overall study put forward a one-step novel method to confirm the stability aspects of an emerging insect repellent prophylactic patch.

2. Methods and materials

2.1. Materials

The following chemicals were purchased from different chemical suppliers and used as received. EA, phthalate esters, acetonitrile, and water were purchased from Sigma-Aldrich (Sigma-Aldrich Chemical Co., St. Louis, MO, USA). Chloroform, dimethyl sulfoxide, ethyl cellulose, and polyvinylpyrrolidone K-30 were purchased from HiMedia (HiMedia Laboratories Pvt. Ltd, Maharashtra, India). A 3M double-coated polyethylene tape 9766 was received from 3M (3M, St. Paul, USA) as a gift sample. All reagents and solvents used were of analytical grade.

2.2. Methods

2.2.1. Preparation of matrix-type polymeric patch

Matrix-type polymeric patch was prepared by dry casting solvent evaporation method with slight modifications, as per the method described by Chattopadhyay et al [23,24]. Briefly, varied ratio of ethyl cellulose and polyvinylpyrrolidone K-30 was dissolved in a solvent of chloroform and water (96:4). After stirring for a certain period of time, EA and phthalate ester, which was used as a plasticizer, were added to the resultant mixture with continuous stirring at room temperature until a homogeneous mixture was obtained. This mixture was degassed and subsequently moulded into a ring in a customized mould with defined surface area and thickness over a horizontal surface of suitable backing membrane, followed by solvent evaporation at ambient temperature for next the 48 hours. The rate of evaporation was controlled by inverting a funnel. The formed polymeric patches were separated and attached to a temporary release liner and finally stored in desiccators under vacuum until analysis.

2.2.2. Accelerated stability-testing studies

The best optimized matrix-type polymeric patches were subjected to accelerated stability testing for 6 months as per the ICH guidelines at $40 \pm 2^{\circ}C$ and relative humidity of $75 \pm 5\%$ [10]. The samples were placed inside a stability chamber (Thermolab Scientific Equipments Pvt. Ltd, Maharashtra, India) in a sealed aluminum pouch and collected at different time intervals (0, 15, 30, 60, 90, 180 days) for physical appearance, surface morphology, EA content uniformity, etc. At Day 0 and after Day 180, fourier transform infrared spectroscopy (FTIR), scanning electron microscopy with energy dispersive X-ray spectroscopy (SEM-EDX), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and X-ray powder diffraction (XRD) studies were performed to confirm the stability of the matrix-type polymeric patches (Table 1).