Available online at www.sciencedirect.com

ScienceDirect

International Journal of Pharmaceutics 355 (2008) 126–130

INTERNATIONAL JOURNAL OF PHARMACEUTICS

www.elsevier.com/locate/ijpharm

Method for the development of topical medicinal aerosols using liquified hydrocarbon gas

F. Caballero *, M. Foradada, M. Miñarro, P. Pérez-Lozano,
E. García-Montoya, J.R. Ticó, J.M. Suñé-Negre

Unit of Pharmaceutical Technology, Pharmacy and Pharmaceutical Technology Department, School of Pharmacy,
University of Barcelona, Avda Joan XXIII s/n, 08028 Barcelona, Spain

Received 19 October 2007; accepted 29 November 2007
Available online 4 December 2007

Abstract

Low chain liquid hydrocarbons (LH) at room temperature and atmospheric pressure can be used to simulate the effect of gas hydrocarbons (GH) in aerosol systems without the need of using pressured flasks. Samples of different tetracycline formulations were tested with LH and GH in order to study their behaviour and physicochemical stability in the system. The results showed a similar behaviour between samples when LH or GH were used, suggesting the use of LH to simulate the effect of GH introduction in the system, as a useful predictive method for the development of pressured aerosol formulations without using pressured containers in early steps of the process, such as pre-formulation studies.

Keywords: Aerosol; Propellant; Pre-formulation; Tetracycline; Liquefied gas; Veterinary drug

1. Introduction

Aerosols using liquefied gas as a propellant are dosage forms used in the current therapeutic scenario as inhaled therapy, topical therapy, or also in cosmetics. In the veterinary field, aerosols are widely used as topical therapy for the dosage of antibiotics such as tetracyclines, using in the same composition, ingredients with very different polarity, making difficult to find the proper system to ensure the homogeneity of the formulation inside the container, and therefore a right expel of the content and performance of the device.

One of the problems in formulating aerosols is the lack of previous knowledge about the behaviour of the composition once the propellant will be added. Changes of polarity in the media may produce the unstability of the solution and the immediate or delayed precipitation of some of the ingredients in the aerosol system. Actually, solubility of drugs and surfactants in the propellant is one of the physical properties that is routinely determined as a first step in the rational formulation design (Vervaet and Byron, 1999; Gupta and Myrdal, 2005) and methods for determination of drug solubility in aerosol propellants, have been reported (Dalby et al., 1991; Gupta and Myrdal, 2004). However, some other requirements have to be considered, such as the previous knowledge about a proper mixture between the concentrate and the propellant to render one single phase that leads to a proper aerosol formation (Le Hir, 1995) or appropriate re-dispersion when the formulation is a suspension (Vervaet and Byron, 1999).

Usually in the development of aerosols, special pressure resistant transparent glass flasks are used in order to see the behaviour of the aerosol system once the propellant is added, and carry out an appropriate follow up of it in the subsequent study period. Special facilities are needed to handle the gas and to incorporate it into the flasks, on the other hand, for a safe handling the flasks have to be well protected against breakings and potential glass particles projection.

The aim of this work is to explore the possibility of using a method in the pre-formulation phase of the development of an aerosol to be formulated with a GH as propellant, in order to foresee the future behaviour once the propellant is added, without using a pressurised gas and special containers or facilities in such pre-formulation phase.

---

* Corresponding author. Tel.: +34 973 353 806; fax: +34 973 353 806.
E-mail address: fcaballero@ars-vitae.com (F. Caballero).

0378-5173/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2007.11.053

Table 1
Composition of the samples

Ingredients	Composition (%, w/w)				
	A	B	C	D	E
Active ingredient	3.3	3.3	3.3	3.3	3.3
Alcoholic solvent	88.5	60.5	40.2	81.6	85.2
Non aqueous solvent	0.0	10.0	52.0	4.5	4.5
Filming agent	3.0	3.0	3.0	6.0	6.0
Co-solvent	0.0	1.0	2.0	2.3	0.0
Tensioactive	0.0	2.0	2.0	2.3	1.0
Colouring agent	0.20	0.20	0.20	0.02	0.02
Water	5.0	20.0	0.0	0.0	0.0

2. Materials and methods

2.1. Materials

n-Pentane (PANREAC, Barcelona, Spain), *n*-hexane (PANREAC, Barcelona, Spain); Propel-45, propellant commercial isobutane and propane (75:25) mixture (REPSOL, Tarragona, Spain), polyvinylpyrrolidone C-15 (ISP TECHNOLOGIES, INC., Wayne, USA). Patent blue (E-131), ethyl alcohol, isopropyl alcohol, propyleneglycol, polysorbate, macrogol and tetracycline (FRAGON, Terrassa, Spain).

2.2. Concentrate preparation

Five concentrates for aerosol prepared under different formulation strategy were selected from previous experiments in order to evaluate their behaviour after adding the GH propellant or low chain LH at room temperature and atmospheric pressure.

Composition of concentrates consisted in a tetracycline solution or suspension with the following excipients: a main solvent or solvents mixture, a co-solvent, a tensioactive, a water-soluble colouring agent and a film agent. Compositions are displayed in Table 1.

A variation on the formulation A was also prepared without the active ingredient (A1), and another variation consisted in the formulation A without the active ingredient and with the colouring agent 10 folds diluted (A2) in order to see in these formulations the behaviour of the colouring agent without interferences of the active ingredient.

All the proposed formulations were selected only for experimental purposes on the basis of an acceptable behaviour in concentrate form in terms of physicochemical stability, and no commercial or therapeutic behaviour was considered for the choice.

2.3. Sample preparation

The different compositions were filled into 100 ml glass flasks adding the corresponding hydrocarbon *n*-pentane, *n*-hexane, and Propel-45® (propane and iso-butane propellant mixture), respectively at an amount of 1 ml for each ml of concentrate, and a final volume of 74 ml per flask. Parallel compositions have been filled into aluminium flasks closed with standard expulsion valves in order to know the formulation behaviour and aerosol system functionality in the final form (Fig. 1).

2.4. Sample evaluation

Resulting samples were shaken 30 s and observed about the following characteristics: (1) miscibility between phases (concentrate and hydrocarbon) was evaluated considering as mixed phases if appeared as one single phase after shaking; (2) lasting of mixed phases measured as time when phases remained as one single phase after shaking; (3) changes in the solution evaluated as presence of turbidity or precipitates into the solution.

Samples were left at room temperature for 7 days, daily visually checking any changes in the solution. After 7 days, a re-evaluation was carried out, including spraying tests using the aluminium flask samples with and without previous shaking. During spraying, plugging, continuity of delivery, aspect of aerosol, size of delivered particles, homogeneity of sprayed product, and sprayed cone diameter were considered.

3. Results

3.1. Miscibility between phases

On formulations (B and C) of polar component an immediate separation of phases was observed after adding the hydrocarbon. When samples were shaken a dispersion of the hydrocarbon phase into the concentrate could be observed.

Solutions A, A1 and A2 appeared as a single phase, where gas and solvents of concentrate were perfectly mixed.

Formulations in suspension form appeared in two phases, a liquid phase corresponding with the mixture of concentrate and hydrocarbon, and the other one corresponding with the solid phase of suspension. After shaking, the dispersion of the solid phase was produced rendering a homogeneous system as normally occurs with suspensions.

3.2. Lasting of mixed phases after shaking

Formulations B and C that appeared as separate phases after adding the hydrocarbon, showed a very short lasting (<1 min) and immediate separation occurred, when one phase was dispersed into the other after shaking.

The other preparations that appeared as hydrocarbon solvents single phase after adding the hydrocarbon remained with this behaviour. On the suspension formulation, the hydrocarbon addition is contributing to a better behaviour of the suspension with respect to the concentrate, in terms of re-suspension ability, flocculation and caking absence.

Regarding to the different hydrocarbons in the B and C formulations, the separation of the phases is quickly produced with liquefied GH than LH *n*-pentane and *n*-hexane. Between *n*-pentane and *n*-hexane is the *n*-pentane preparation which displays a quicker separation. This fact occurs against what could be expected having in mind the polarity of the different hydrocarbons, and with the wrong supposition that as more non-polar,