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

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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.

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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,

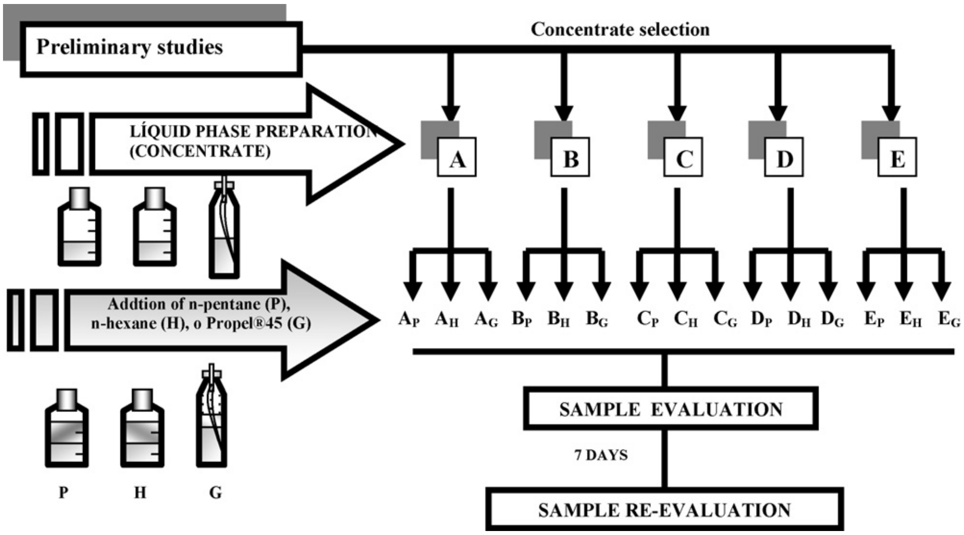

Fig. 1. Experimental design.

quickest the separation because of a less affinity with the phase where is dispersed.

It is observed therefore, a relationship between the aliphatic chain length and miscibility of the phase dispersion, in an inverse proportion. It has to be considered, that the formulations containing the liquefied gas are pressured forms, and pressure into the flask will be higher than the pressure into the flasks containing the liquid hydrocarbons. This fact can influence the phase separation behaviour, and could explain a quicker separation.

Formulations where main solvent is an alcohol, a good miscibility is displayed, since formulations appears as one single solvent and hydrocarbon phase. The behaviour is very similar in the immediate evaluation and no differences can be appreciated between formulations with liquefied gas and formulations with liquid hydrocarbon. On these formulations (A, A1, A2, D and E), a permanent mixture of the phases has been considered.

3.3. Changes in the solution (turbidity or precipitate appearance)

Precipitate apparition is observed on A, A1, A2 and B formulations. In A formulation, precipitate appears immediately after adding the hydrocarbon. In B formulation, precipitate appears in a gradual manner, probably caused by hydrolysis reactions due to the high water content. A similar behaviour is observed in the previous concentrate without adding the hydrocarbon. This formulation was chosen, although the precipitate formation into the initial solution because the possibility of improving this behaviour after adding the hydrocarbon due to a solubility improvement and stabilizing effect.

In the solutions containing colouring agent (A1 and A2), no separation between phases is observed, and flask content in all cases, gas or liquid hydrocarbon, is forming an undifferentiating phase with the concentrate.

Into the more concentrate solution of colouring agent (A1), an immediate precipitation is observed as dark particles corresponding to the same colouring agent that cannot be maintained in solution. Into the diluted solution, particle appearance not occurred until a period of 24–48 h when begin the process increasing and being more apparent in the following days. These results are attained in all the cases GH or LH. This phenomena is known as Ostwald Rippening (Noakes, 2002).

Ostwald Rippening phenomena was not observed within the studied period in the other formulations where the colouring agent is stabilised by means of appropriate excipients.

Preparations C and D no alterations was appreciated and a proper behaviour was displayed considering stability of phases and of ingredients including the colouring agent. On these preparations, a phase separation was observed due to the formulation strategy, but was not corresponding to the separation of hydrocarbon and solvent phase that remained perfectly mixed. The separate phase is corresponding to the solid phase of suspension dispersed in the liquid single phase (solvent + hydrocarbon).

In the C, D and E formulations, precipitate appearance were not observed, in this case, when hydrocarbons are added, there are no important changes on the polarity of the media, because of the nature of the concentrate, similar in terms of polarity to the hydrocarbon. In the C formulation, there is no miscibility between concentrate and hydrocarbon phase, leaving unaltered the concentrate phase.

3.4. Daily checking (precipitate formation or phase separation)

No changes were observed in the daily control of any samples. In the formulation A2, a slight turbidity appears from 24 h that is totally evident at 48 h with greater particle formation.

3.5. Re-evaluation at 7 days

No significant changes were observed with respect to the initial evaluation except of the diluted colouring solution (A2). Re-suspension of D and E formulations is correct and no caking formation can be appreciated in both gas and liquid hydrocarbon preparations.

Table 2
Seven days sample evaluation without shaking

	A	B	C	D	E
Spraying	+	−	−	+	+
Performance	+	−	−	−	−
Appearance	−	−	+	−	−

Table 3
Seven days sample evaluation after shaking

	A	B	C	D	E
Spraying	+	−	−	+	+
Performance	+	−	−	+	+
Appearance	−	−	+	+	+

Behaviour is practically identical between formulations where gas and liquid hydrocarbon were added.

3.6. Spraying test without shaking

Formulation A shows an acceptable spraying, homogeneous, with fine drops. The sprayed solution is practically uncoloured displaying absence of colouring agent and active ingredient, that as can be observed in the glass flask are precipitated on the bottom. Formulations B, C, D and E have a defective behaviour with an unhomogeneous spraying, with no fine particle formation. Expulsion cone is closed and obstruction can appear in formulations D and E. Formulations A1 and A2 have a similar behaviour than formulation A (Table 2).

3.7. Spraying test after shaking

Behaviour of formulations A, A1, and A2 are practically than without shaking. Formulation B has a better behaviour at a first moment, but immediately defective expulsion (non homogeneous and great particles) is attained. Formulation C displayed also a defective behaviour similar to the one observed without shaking. Formulations D and E displayed a correct spraying behaviour without interruptions due to obstruction, and homogeneous expel of the product (Table 3).

4. Discussion

Hydrocarbon incorporation into the formulation as an excipient in order to carry out the expulsion of the product, produce a polarity change resulting in solubility alterations of the more polar ingredients of the concentrate solution. On the assayed formulations is coinciding with the colouring agent and part of the active depending on the excipients that in some cases may act as a stabilizing.

Affectation of polar compounds is mainly produced when a perfect mixture is formed between solvent and hydrocarbon, and even when no liquid phases separation is appreciated. In this case, the initial characteristics of the previous concentrate are changed, concerning to the solubilization ability of different ingredients dissolved. Changes can be clearly observed in the preparations without active ingredient. These preparations serve as a model to evidence the effect of polarity change produced into the formulation when hydrocarbon is added.

The colouring agent is a chemical entity of hydrosoluble nature, totally immiscible in non-polar solvents, and therefore cannot be dissolved in the hydrocarbon. The colouring agent used is freely soluble in water and less soluble in alcohols, rendering, however, stable solutions into hydroalcohol mixtures with low water content. The colouring solution, totally stable, experimented changes in the media polarity when hydrocarbon was incorporated. In a first period, no changes are appreciated in the solution, with homogeneous one phase aspect. Some minutes later, precipitation started and was constituted by the colouring agent that cannot be maintained soluble in the new media polarity at the initial concentration. This fact occurs in the same manner with all the formulations and with independence of the gas or liquid nature of hydrocarbon, suggesting the correspondence in the physicochemical behaviour when propellant is added.

Preparation containing the diluted solution of colouring, has a similar behaviour, although precipitate formation, does not appears until 24–48 h, this delay may be caused because of polarity is still sufficient to support the dissolution in the new mixture and precipitation process is slow.

This is a fact to be pointed out in formulations prepared as suspension form, because some part of the solid can be dissolved, in the concentrate. Hydrocarbon incorporation may lead to the consequent polarity change and in the same way that in the case of colouring agent, resulting in the precipitation of previously solved part, rendering particle formation of uncontrolled diameter that could contribute to plugging the expulsion valve or suspension deflocculation with caking appearance phenomena.

Formulations where because of nature of concentrate (B and C), a mixture with hydrocarbon was not achieved, each phase maintained their own physicochemical behaviour. In this case, the initial stability of previous concentrate was also maintained, because there were not or there were minimum changes in the polarity of concentrate due to the lack of mixture between phases. This fact could be clearly appreciated in formulation C. The inconvenience of this system is that depending on the mixed amount of hydrocarbon with the concentrate, the expulsion of the product will not be adequate and in any case an appropriate shaking would be necessary to ensure it. Often this system where no mixture between phases is achieved is used in pressured foam formulations.

The behaviour of all preparations formulated as suspension is similar and hydrocarbon incorporation improves re-suspension and flocculation characteristics with respect to the initial concentrate. Precipitate formation is not observed in any of the samples, probably by the effect of co-solvents and tensioactive incorporated. Formation of two phases show a correct mixture between the concentrate solvent an hydrocarbon, corresponding in this case the other observed phase to the solid phase or dispersed into the initial suspension. This perfect mixture gas-solvent explains the appropriate behaviour in terms of expulsion of the product rendering a continuous, homogeneous and fine aerosol in these formulations, with the obvious need of shaking the container before the use in order to avoid plugging the valve and have a homogeneous product.

One of the items to be pointed out considering the separation of phases is the different behaviour depending on the length of hydrocarbon aliphatic chain. As longer the chain, the higher lasting of dispersed phases. This fact occurs against what could be expected, as longer the chain, higher liposolubility as the partition coefficient values K_{ow} shows and therefore less ability to be integrated into the more polar phase, however, the duration of the hydrocarbon phase dispersed into the concentrate phase is directly proportional to the length of aliphatic chain. In addition, it should be considered that in the case of preparations containing liquefied gas, a higher pressure exists into the containers than those containing liquid hydrocarbon, contributing to a quicker separation between phases, nevertheless this is not the only element contributing to this separation, also have to be considered the length of the hydrocarbon, having into account the observed behaviour in samples containing *n*-hexane and *n*-pentane, contributing probably to be maintained dispersed into he concentrate phase.

From the obtained results, a very similar behaviour can be expected in the main of the evaluated parameters using GH (propel-45®) and LH at room temperature and atmospheric pressure pentane and hexane, that let us to make a previous prediction about what will occur in the definitive product once the propellant will be added without using the gas propellant in such developmental phase. Differences between properties of liquid and gas short chain hydrocarbons cannot be observed into the different studied systems in terms of compatibility with the rest of formulation, alteration of the solubility characteristics and phases integration.

The use of LH at room temperature and atmospheric pressure to simulate the effect of a liquefied GH as propellant into the formulation is an appropriate method to know the compatibility of the formulation with the propellant gas and foresee the results in terms of physicochemical stability and overall behaviour of the formulation. The use of hydrocarbons such *n*-pentane or *n*-hexane in the pre-formulation phase is useful to avoid in such phase handling gas propellants, as well as, the risks associated and special equipment or facilities. Use of special containers for pressurised formulations can be avoided also in that phase.

The use of liquid short aliphatic chain hydrocarbons as *n*-pentane or *n*-hexane or mixtures, is as simple and useful system for development of pressurised formulations, since such hydrocarbons acts simulating the effect of gas propellant into the formulation. Ostwald Ripening phenomena can be also observed using this method, this phenomena occurs when partially soluble compounds are used and some of their crystals can grow falling down to the bottom of the flask after some period of not shaking (Noakes, 2002).

Short chain hydrocarbons in the development of an aerosol based on tetracycline provide information about compatibility of concentrate and the hydrocarbon that can be extrapolated to the behaviour of the formulation when definitive propellant (Propel-45®) be added. Although theoretical extrapolations to chemical stability could be done using this method, further work with different experimental design should be carried out to demonstrate it. The incorporation of water to improve solubility of active ingredient and colouring agent in the concentrate is not appropriate because radical changes of media polarity occurs when propellant is added leading to a precipitation of such ingredients. These changes can be also observed when *n*-pentane or *n*-hexane is added.

Results suggest that as liquid hydrocarbons used have a longer chain than propellant Propel-45®, and lower polarity, is likely to obtain a more restrictive and therefore conservative vision of the real behaviour with the propellant. Formulations that work well with liquid hydrocarbons will also work well with propellant, however, is possible that some formulation presented as a defective considering the results on liquid hydrocarbons could work well after with propellant. Finally, it is clear that the aerosol system has a better performance when liquefied gas and concentrate are mixed in a single phase. This fact can lead to the potential advantage when used in inhaled therapies, of generating finer aerosol sprays involving a grater extent of lung deposition, although other factors will influence in the respirable fraction of an aerosolised drug, such size of primary droplets tat can be modulated by the orifice of the actuator, or propellant evaporation that can be impaired by the determinate excipients (Warren and Farr, 1995).

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