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ScienceDirect
International Journal of Pharmaceutics 340 (2007) 84–91
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Liquid spray formulations of xibornol by using self-microemulsifying drug delivery systems

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Received 15 November 2006; received in revised form 30 January 2007; accepted 19 March 2007
Available online 30 March 2007

Abstract

Xibornol is a lipophilic drug mainly used in Italy and Spain in spray dosage forms for the local treatment of infection and inflammation of the throat. Its poor water solubility makes difficult the development of aqueous formulations of the drug, thus giving rise to a limited number of stable and pharmaceutically accepted preparations. In fact, xibornol is actually marketed only as spray aqueous suspension. The aim of this work was to evaluate the possibility of developing a stable liquid formulation of the drug intended for oral spray administration using a self-microemulsifying drug delivery system (SMEDDS). These systems are able to adequately improve the drug solubility, allowing the introduction of relatively high concentration of drugs in the form of solution. Labrafil M1944, Labrafil M2125 and Labrafac CC were screened as oil phases, Labrasol and Labrafac PG as surfactants and Transcutol as co-surfactant. Pseudo-ternary phase diagrams were constructed, by titration with the aqueous phase of different oil phases and surfactant/co-surfactant mixtures in order to identify the self-microemulsification region and the optimal micro-emulsion composition. Then, complete pharmaceutical formulations were prepared and evaluated for stability and viscosity properties. The final selected formulations, containing Labrafil M1944, Transcutol, Labrafac PG and a hydrophilic co-solvent (propylene glycol or PEG 200) allowed complete solubilization of the required xibornol concentration (3%, w/v) and showed physical good stability up to 2 months at 25 and 4 °C, suitable viscosity and organoleptic properties.

Keywords: Xibornol; Liquid spray formulation; Self-microemulsifying delivery systems; Pseudo-ternary diagrams; Viscosity

1. Introduction

Xibornol [6-(isoborn-2-yl)-3,4 xylenol] is a highly lipophilic and poorly soluble drug used as spray mouthwash for the local treatment of infection and inflammation of the throat and in the dental care, due to both its bacteriostatic activity, mainly against Gram positive micro-organisms and its antiviral properties (Fabbri et al., 1988; Scaglione et al., 1988).

The drug concentration required for the therapeutic activity is 3% (w/v). Its poor water solubility makes difficult to set up drug formulations based on aqueous solvents, so xibornol is at present commercially available only as spray aqueous suspension (http://www.biam2.org).

Among the most common approaches aimed to improve the oral bioavailability of poorly water soluble compounds, lipid-based formulations such as drug incorporation into oils (Burcham et al., 1997), emulsions (Myers and Stella, 1992) and in particular self-microemulsifying formulations (Gursoy and Benita, 2004; Ghosh and Murthy, 2006) are known to be successful.

However, in the present case, the use of oil solvents to obtain solutions of the drug is not recommended because of the topical oral use of such formulations, that could give rise to problems of unpleasantness or irritancy.

Thus, the formulation approach of self-microemulsifying drug delivery systems (SMEDDS) was considered. Self-emulsifying and self-microemulsifying drug delivery systems have recently received increasing attention in the development of oral dosage forms with improved solubility and bioavailability of lipophilic drugs, particularly in virtue of the successful results obtained by using such a strategy with compounds such as cyclosporin A, lipid-soluble vitamins and the HIV protease inhibitors (Pouton, 2000; Ho et al., 1996; Gursoy et al., 2003;

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doi:10.1016/j.ijpharm.2007.03.021

Gao et al., 2003; El-Laithy, 2003; Kang et al., 2004; Grove et al., 2006).

SMEDDS are isotropic and thermodynamically stable solutions consisting of an oil, surfactant, co-surfactant and drug mixtures which spontaneously form oil-in-water micro-emulsions when mixed with water under gentle stirring. The advantages of these systems include not only improved drug solubilization, but also enhanced release and absorption properties, due to the already dissolved form of the drug in the formulation and the resulting small droplets size, providing a large interfacial surface area (Farah et al., 1994; Craig et al., 1995; Gershanik and Benita, 2000).

However, SMEDDS have to be carefully formulated on a case-by-case basis according to the characteristics of the drug compound. In fact, both the amount and hydrophobicity of the solubilized drug, the nature, combination, mixing ratio and amount of each of the oil, surfactant and co-surfactant used greatly affect the self-emulsification process (Pouton, 1985; Wakerly et al., 1986, 1987; Warisnoicharoen et al., 2000; Rhee et al., 2001). Several authors have demonstrated that only specific excipient combinations can give rise to efficient self-emulsification formulations (Charman et al., 1992; Chanana and Sheth, 1995; Kimura et al., 1994). Therefore, when designing a SMEDDS, a very thoughtful selection of both type and amount of excipients is necessary in order to define the optimal combination of the components that will create stable, fluid and reproducible micro-emulsion systems.

In the present work we evaluate the possibility of developing and optimizing a new oral liquid spray formulation of xibornol as a valid alternative to the current aqueous suspension formulations by using the self-emulsifying micro-emulsion approach in order to adequately improve the drug solubility. Both long and medium chain triglyceride oils with different degrees of saturation were mainly used as oily-phase of SMEDDS, whereas non-ionic compounds with a relatively high hydrophilic-lipophilic balance (HLB) are the most widely recommended as surfactants (Gursoy and Benita, 2004). On this basis, Labrafil M1944, Labrafil M2125 and Labrafac CC were screened as possible oil phases, and Labrasol (HLB 14) and Labrafac PG (HLB 10) as surfactants, whereas Transcutol was used as co-surfactant.

2. Materials and methods

2.1. Materials

The following materials were kindly donated by Gattefossé (Milan, Italy): Labrafil M1944 (Oleoyl macrogol-6 glycerides), Labrafil M2125 (Linoleoyl macrogol-6 glycerides) and Labrafac CC (Medium chain triglycerides), used as oily-phases, Labrasol (Caprylocaproyl macrogol-8 glycerides) and Labrafac PG (Propylene Glycol caprylate/caprate) used as surfactants and Transcutol (Diethylene glycol monoethyl ether) as co-surfactant. Propylene glycol and PEG 200, used as hydrophilic solvents were from Sigma (St. Louis, MO, USA). Xibornol and the additional other excipients required by formulations (chlorobutanol as preservative, sodium saccharinated and ammonium glycyrrhizinated as sweeteners, essence of mint as aromatizer) were supplied by Euphar Group (Piacenza, Italy). Water obtained from a Millipore water purification system was used.

2.2. Phase diagrams

Pseudo-ternary phase diagrams were constructed by progressive titration of the component mixtures, both in the absence and presence of the drug. Initially the mixture of Surfactant/CoSurfactant (S/CoS) was used at a 4:1 (v/v) ratio and the oily-phase was added to such mixture in different amounts: 3, 10, 20, 30, 40, 50, 60, 70% (v/v) (Rhee et al., 2001; Khoo et al., 1998; Kim et al., 2000). Each mixture was then titrated by adding water up to clouding. The experiments were repeated at different S/CoS (v/v) ratios (3:1, 1:1, 1:2, 1:3, 1:10). The same procedure was followed for construction of pseudo-ternary phase diagrams where PEG 200 or propylene glycol was used as aqueous phase.

2.3. Preparation of xibornol micro-emulsions

A first series of SMEDDS was prepared by using Labrafil M1944 or Labrafil M2125 or Labrafac CC as oil phase, Labrasol as surfactant and Transcutol as co-surfactant. The hydrophilic components (0.2%, w/v chlorobutanol, 0.1%, w/v sodium saccharinated and 0.05%, w/v ammonium glycyrrhizinated) and the drug (3%, w/v) were solubilized in Transcutol, and afterwards the surfactant was added. The resulting mixture was then added to the oil phase (where the mint essence had been previously added) under vigorous stirring to obtain clear transparent micro-emulsions. Then, a second series of micro-emulsions was prepared by using Labrafil M1944, chosen as oil phase, and varying the surfactant/co-surfactant ratio, and the Transcutol and Labrasol content. Finally, a last series of micro-emulsions was set up by replacing Labrasol with Labrafac PG as surfactant and introducing PEG 200 or propylene glycol as hydrophilic co-solvent.

2.4. Rheological studies

Rheological studies were performed using a rotational viscometer Rheomat 108 from Contraves (rotor N1, 30 mm diameter, 0.010–1.100 Pa s viscosity range). The temperature was controlled and kept constant at two different values (27.5 and 12 °C). The sample volume was 80 mL. Experiments were performed in triplicate with shear rate in the 0–20 s^{-1} range. The apparent viscosity was determined at shear rate of 20 s^{-1}. Viscosity measurements were carried out on fresh micro-emulsions and after 2 month's storage.

2.5. Stability studies

Each micro-emulsion formulation was kept at 4 and 25 °C up to 2 months. Transmittance measurements at 550 nm were carried out to monitor micro-emulsion limpidity during stability studies using a Shimadzu UV-1601 spectrophotometer. Visual inspection of samples was also employed to verify the transparency under light and the isotropy between crossed polarized

filters and to rule out any phase separation process and/or precipitation of xibornol during storage. The chemical stability of the formulations in terms of drug degradation was assessed by GLC.

2.6. Small angle X-ray scattering (SAXS) analysis

SAXS experiments were performed on the SAXSess small and wide angle X-ray scattering system (Anton Paar GmbH, Austria). The X-ray generator PW3830 (PANalytical S.r.l., Italy) was operated at 40 kV and 50 mA with a sealed tube Cu anode (Kα radiation, 0.154 nm). The SAXSess system was equipped with a thermostated sample holder and an image plate detector (Cyclone Reader). A Göbel mirror was used as monochromator and focusing optics, to separate the Kα radiation from the Kβ radiation and from the hard X-rays.

2.7. In vivo studies

In vivo tests were performed with the written consent from the volunteers. Selected formulations were administered to 10 healthy human volunteers to verify their acceptability and the absence of undesirable collateral effects due to the formulation components. Possible irritation, taste and patient compliance were also evaluated.

3. Results and discussion

Pseudo-ternary phase diagrams were constructed, as described in Section 2, by titration with water of mixtures of each of the selected oils with different surfactant/co-surfactant ratios, in order to find the optimal component concentration range to obtain transparent and stable O/W micro-emulsions. The shaded areas in the pseudo-ternary phase-diagrams shown in Fig. 1A represent the existence field of stable, clear and transparent O/W micro-emulsions containing Labrafil M1944 as oil and with the Labrasol:Transcutol mixing ratio fixed, respectively, at 4:1, 3:1, 1:1 and 1:2 (v/v). Independent of the surfactant/co-surfactant ratio, the addition of great volumes of aqueous phase did not allow the obtainment of clear systems, as shown by the very limited micro-emulsion existence field extended in the surfactant-rich part of the phase diagram, except for the lowest oil concentrations. In this latter case, a region of infinite dilution can be observed. Probably, when the co-surfactant is present at low concentrations, the surfactant is not able to sufficiently reduce the water/oil interfacial tension and to form a barrier to coalescence. The incorporation of xibornol into the system did not clearly alter the regions of the phase-diagrams (Fig. 1B) except in the presence of the highest concentration of co-surfactant, where the area of SMEDDS became more extended. This finding could be attributed to the solvent capacity of Transcutol towards the drug, thus allowing the incorporation of a higher amount of water without turbidity transition. As expected, the pseudo-ternary diagrams obtained for Labrafil M2125 as oil phase, were comparable to those described for Labrafil M1944, due to the similar composition of these oil phases. A very similar behaviour was also observed in the presence of Labrafac CC as oil phase, particularly at high surfactant/co-surfactant ratios, whereas, with decreasing the surfactant/co-surfactant ratio, the shaded area tended to become slightly larger.

Based on these results, a preliminary series of complete formulations was then prepared as described in Table 1, by using appropriate amounts of oil, Labrasol and Transcutol.

Upon visual inspection, all these formulations appeared perfectly clear, transparent, homogeneous and stable, both under stirring and at rest. Their isotropy between crossed polarized filters was also verified.

Due to the intended use of such formulations as oral mouthwashes from a suitable spray-can supply system, the rheological behaviour of the samples was also studied. The flow curves showed a non-linear relationship between shear stress (τ) and shear rate (D) indicating a non-Newtonian flow, which can be classified as of dilatant type, as can be seen in Fig. 2A for formulation I. The same behaviour was observed for the other samples. Moreover, the thixotropy degree of all the examined formulations was found to be negligible, as demonstrated by the almost complete overlapping of the up and down ramps obtained in the shear stress versus shear rate cycle, without appreciable hysteresis areas (Fig. 2B).

When a linear correlation between shear stress and shear rate cannot be found, the viscosity can be termed "apparent viscosity" and it is dependent on shear rate, temperature and time (Atkinson, 2005). The flow behaviour can be described by the Ostwald-de-Waele equation:

$$\tau = k \times D^n$$

where k is a constant parameter related to the viscosity (consistency index) and the exponent n is the flow behaviour index. If the exponent $n = 1$ the equation is reduced to the expression for a Newtonian fluid and the constant k is equal to the viscosity; $n < 1$ indicates a pseudoplastic fluid, whereas $n > 1$ represents a dilatant fluid. Values of n and r^2 (regression coefficient) obtained for formulations I, II and III are reported in Table 2. In all cases n values were greater than the unity, thus confirming their dilatant, shear thickening, flow behaviour, as emerged by their rheograms.

Sometimes a dilatant behaviour can give rise to problems during the manufacturing process of formulations due to a tendency to thickening of the system with increasing shear stress. In fact, unfortunately, with these formulations an excessive slowing-down in the spray can-filling phase was observed, due to their high viscosity. So these formulations had to be discarded.

In order to overcome such a drawback, a new series of formulations containing a lower percentage of Labrasol (the most viscous component of the formulation) was then set up. Labrafil M1944 was selected as oil phase for these new systems, as it seemed to be the most suitable from both the economic point of view and the absence of toxicity. The Labrasol content was decreased in respect to its concentration in the previously examined micro-emulsions and replaced by corresponding amounts of Transcutol, in such a way that the Labrasol:Transcutol ratios in the new systems were 1:1, 1:2, 1:3 and 1:10 (v/v) (SMEDDS IV, V, VI and VII), respectively.

These systems were characterized in terms of viscosity and stability. The higher fluidity of these SMEDDS made it possible

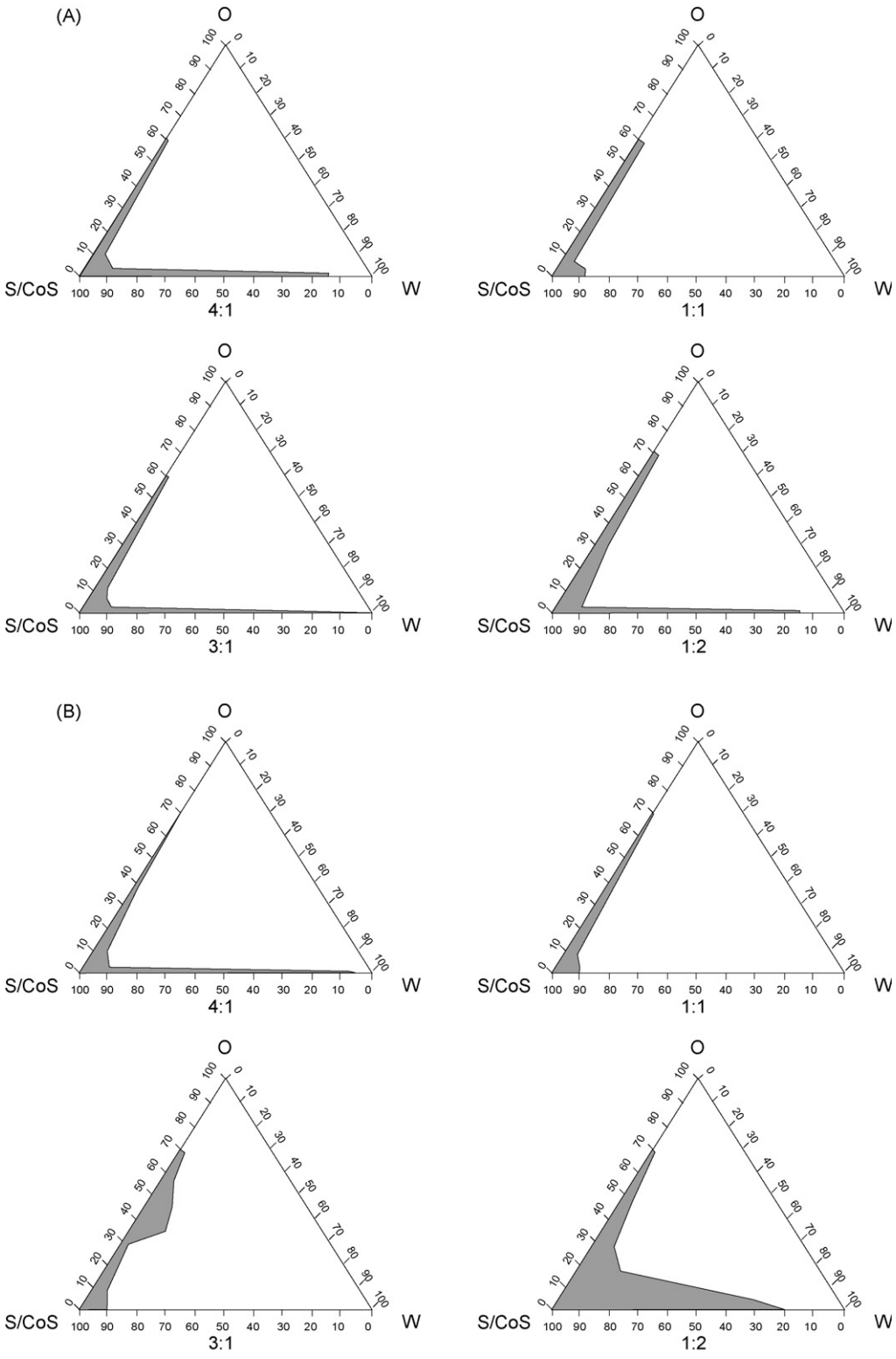

Fig. 1. Pseudo-ternary phase diagrams of micro-emulsion composed of Labrafil M1944 (oil), surfactant (Labrasol), co-surfactant (Transcutol) and water, in the absence (A) and presence (B) of xibornol, at different S/CoS ratios.

to determine the viscosity only at the highest shear rate value and thus did not allow construction of flow curves. Table 3 shows the apparent viscosity values obtained from SMEDDS IV and V at a shear rate of 20 s^{-1} at two different temperatures and the transmittance percentages for freshly prepared samples and after 2 month's storage at 25 and 4 °C, respectively. Values obtained from SMEDDS I are also reported for comparison purposes. The viscosity measurements confirmed the improved fluidity of SMEDDS IV and V compared to SMEDDS I, due to the increased hydrophilic nature of the formulations as a

Table 1
Composition of a preliminary series of complete formulations

Components		SMEDDS I (%, w/v)	SMEDDS II (%, w/v)	SMEDDS III (%, w/v)
Lipophilic phase	Labrafil M 1944	19.33		
	Labrafil M 2125	–	19.33	
	Labrafac CC	–	–	19.33
Surfactant	Labrasol	57.97	57.97	57.97
CoSurfactant	Transcutol	19.33	19.33	19.33
Drug	Xibornol	3.00	3.00	3.00
Excipients	Chlorobutanol	0.20	0.20	0.20
	Sodium saccharinate	0.10	0.10	0.10
	Ammonium glycyrrhizzinate	0.05	0.05	0.05
	Mint essence	0.02	0.02	0.02

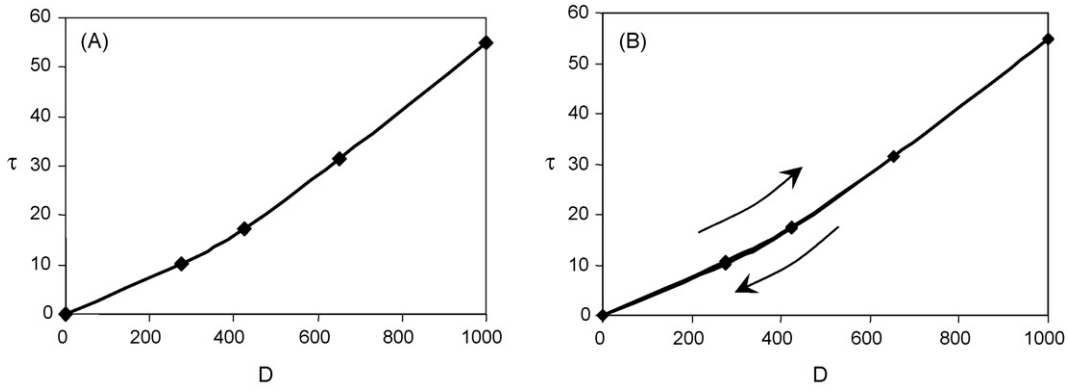

Fig. 2. Rheological behaviour of micro-emulsions in the flow curve up ramp (A) and up and down ramps (B).

Table 2
Flow behaviour parameters for micro-emulsions I, II and III

	n	r^2
SMEDDS I	1.30	0.9986
SMEDDS II	1.36	0.9945
SMEDDS III	1.21	0.9986

consequence of the higher co-surfactant content. Moreover, the almost constant values of the transmittance percentages, as well the absence of phase separation or precipitation phenomena in the samples during storage also at lower temperature indicated the physical stability of these systems. The chemical stability of the formulations in terms of drug degradation was assessed by GLC analysis. The GLC chromatograms recorded for the samples kept at 25 and 4 °C for 2 months resulted almost the superimposition of that obtained from the corresponding freshly prepared samples, thus allowing to rule out the occurrence of any degradation process of the drug (data not shown).

The new formulations were then passed to the production of the dosage forms, and they were successful with regards to both spray can-filling phase and spray performance, without giving any problems of clogging of spray nozzles or of blockage of the supply system. Finally, the dosage forms obtained were administered to 10 healthy human volunteers to assess their actual acceptability and tolerability. Unfortunately, some of the volunteers complained about some light sensation of unpleasantness in the throat, and therefore, also these series of formulations were ultimately discarded. Subsequent studies allowed identification of Labrasol as the component mainly responsible for the appearance of this undesired effect, making it necessary its elimination from the formulations.

Therefore, a new series of micro-emulsions was prepared where Labrasol was totally replaced by Labrafac PG, chosen

Table 3
Viscosity values obtained for micro-emulsions I, IV and V at two different temperatures and transmittance measurements of samples freshly prepared and after 2 months storage at 25 and 4 °C

	η (Pa s) $T = 27.5$ °C	η (Pa s) $T = 12$ °C	T % (550 nm) freshly prepared	T % (550 nm) 2 months storage 25 °C	T % (550 nm) 2 months storage 4 °C
SMEDDS I	0.020	0.042	99.6	99.2	99.0
SMEDDS IV	0.012	0.015	99.7	99.1	98.8
SMEDDS V	0.013	0.016	99.5	99.5	99.1

in virtue of both its lipophilic and surfactant properties. However, due to the higher hydrophobic nature of Labrafac PG with respect to Labrasol, these new formulations needed the addition of a hydrophilic co-solvent such as propylene glycol or PEG 200 to solubilize ammonium glycirrhizzinate. Moreover, these organic solvents can also act as co-surfactants.

In order to select the most proper ratios between the different components, pseudo-ternary diagrams were elaborated before making-up the complete formulations by progressive titration of the surfactant/cosurfactant and oil mixtures with both kinds of hydrophilic phase, i.e. propylene glycol and PEG 200, respectively. Fig. 3A shows pseudo-ternary diagrams obtained from titration with propylene glycol of oil–surfactant–cosurfactant mixtures at each examined surfactant/cosurfactant ratio, whereas only those obtained at the most representative surfactant/cosurfactant ratios are reported in the case of PEG 200 (Fig. 3B). Irrespective of the hydrophilic phase used, by increasing the Transcutol content, the existence field of the micro-emulsion became larger, allowing the dilution with great volumes of aqueous phase. Obviously, the mixtures of surfactant/co-surfactant are more efficient than the single surfactant in reducing the interfacial tension between oily and aqueous phases, and the greater the co-surfactant content, the greater the self-microemulsifying ability of the system. However, the last two complete formulations were prepared using a limited Transcutol content (not more than 50%, v/v), in order to reduce any possible risk of local irritation effect after administration.

The composition of the last complete xibornol formulations (SMEDDS VIII and IX) is reported in Table 4. Viscosity and transmittance measurements were performed to characterize

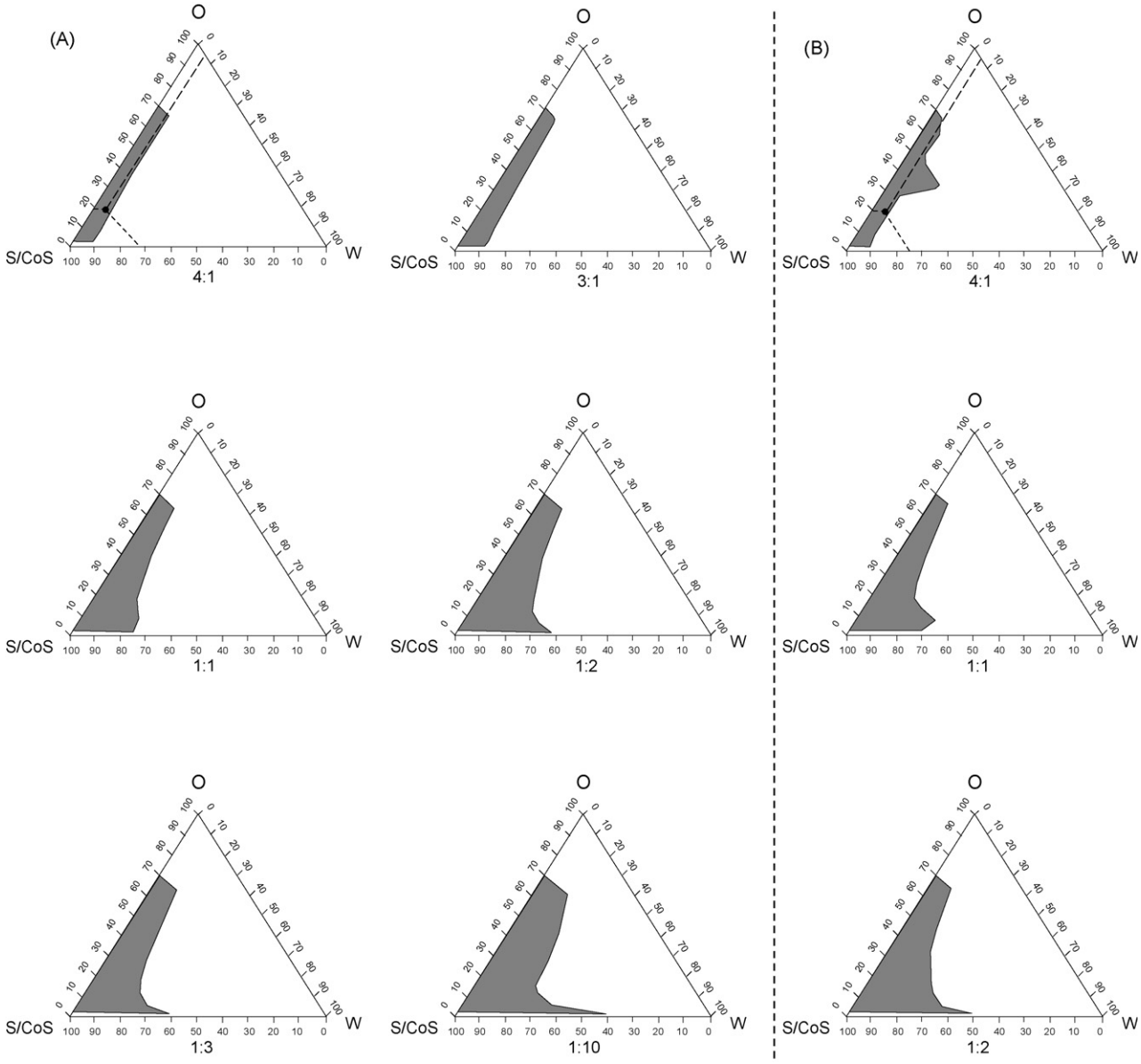

Fig. 3. Pseudo-ternary diagrams of micro-emulsion composed of Labrafil M1944 (oil), surfactant (Labrafac P.G.), co-surfactant (Transcutol) and propylene glycol (A) or PEG 200 (B) at different S/CoS ratios.

Table 4
Composition of the last series of micro-emulsions

Components	SMEDDS VIII (%, w/v)	SMEDDS IX (%, w/v)
Labrafil M1944	19.33	19.33
Labrafac P.G.	36.15	23.30
Transcutol	36.15	49.00
Propylene glycol	5.00	–
PEG 200	–	5.00
Xibornol	3.00	3.00
Chlorobutanol	0.20	0.20
Sodium saccharinate	0.10	0.10
Ammonium glycyrrhizzinate	0.05	0.05
Mint essence	0.02	0.02

these preparations. The viscosity values of the final formulations were found to be very low, equal to 0.012 and 0.015 Pa s at 27.5 and 12 °C, respectively for SMEDDS VIII, values very similar to those of previous formulations SMEDDS IV and V (See Table 3), thus confirming the good fluidity of this system. The same behaviour was revealed by SMEDDS IX.

These formulations maintained their original characteristics of transparency and clarity after 2 month's storage, both at 4 °C and at room temperature, as confirmed by the high values of transmittance percentages that were found to never be less than 95%, without showing any precipitation or phase separation phenomena.

The physicochemical stability of the final selected formulations was also assessed by SAXS analysis. Fig. 4 shows the SAXS curves obtained for the formulation VIII in the absence (grey curve) and in the presence of the drug. It is evident that the two curves were perfectly superimposable and that there was no contrast between the two examined samples in the small angle region. This finding indicated that the introduction of the drug in the micro-emulsion did not lead to any changes in the internal structure of the dispersed system, further confirming the stability of the developed formulation.

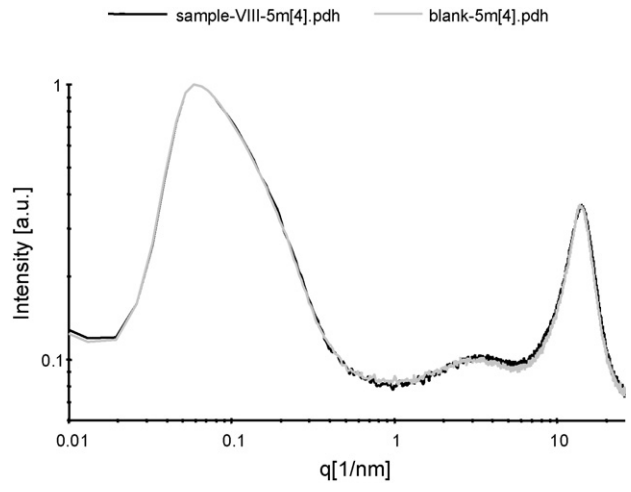

Fig. 4. SAXS curves obtained for the formulation VIII in the absence (grey curve) and presence of xibornol.

Finally, when administered to 10 healthy human volunteers, these formulations were found to be well accepted for both their sweet smell and taste, and lack of any collateral effects.

4. Conclusions

The self-microemulsifying approach was found to be effective to formulate stable and pharmaceutically acceptable liquid spray formulations of xibornol. In fact, it was possible to introduce in these systems an adequate concentration of the drug for therapeutic effects in the form of solution, thus making it possible to develop a valid alternative to the current aqueous suspension formulations.

Moreover, this study also highlighted the importance of carefully selecting specific pharmaceutical excipient combinations and their most appropriate concentrations in the development of an effective self-microemulsifying drug delivery system.

Acknowledgements

The authors would like to thank Dr. Peter Mario Worsch (Anton Paar GmbH, Graz, Austria) for kindly performing SAXS analysis.

Vincenzo Di Marzio (PANalytical S.r.l., Milan, Italy) is also gratefully acknowledged for his availability and helpful technical assistance.

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