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Solvent and surfactant induced interactions in drug dispersions

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ABSTRACT

The interaction between Salbutamol base and Salbutamol sulphate drug particles with a number of non-aqueous and mixed liquids is investigated. The non-aqueous liquids extend form hydrocarbon to halo-hydrocarbon liquids, including propellant liquids previously used in Metered Dose Inhalers. The properties are correlated using two commonly used solvent scales, the Hamaker constant and Solubility parameter scales. The focus is laid on evaluating their relationship to the effective surface charge (ζ-potential), the particle size and their capability to predict the solubility of the drugs. The influence of a standard surfactant, oleic acid on the chosen properties is another topic of key interest. The stability of the dispersions was successfully predicted by the Coulomb interaction model of Morris.

1. Introduction

The weak Lewis acidity of halogenated hydrocarbons and weak Lewis basicity of aromatic hydrocarbons has been investigated by Fowkes and co-worker [1,2]. He found that an acidic solute adsorbs on a basic solid provided that the solvent is less acidic. If the basicity of the liquid is greater than that of the solid it preferentially solvates the acidic solute and prevent adsorption. The opposite also holds true, a basic solute adsorbs on an acidic solid provided that the solvent is less basic. A basic probe may also be preferentially solvated by an acidic solvent. The latter case results in a reduced adsorption of the solute onto the surface sites of the solid [3]. For non-aqueous dispersions the solvation interaction is obviously of fundamental interest.

Halogenated hydrocarbons are unique in that they are predominantly acidic and they are necessary to establish the acid–base balance suggested by Fowkes. Moreover, a large amount of data has been accumulated about their dispersion properties due to their use as propellant liquids in Metered Dose Inhalers (MDI). Previously chlorofluorocarbons (CFCs) have been extensively used but due to their detrimental influence on the ozone layer [4] alternative propellant liquids, such as hydrofluoroalkanes (HFAs) have been extensively investigated [5]. Due to their importance a large number of characterization techniques have been tested [6,7].

In binary systems the interaction between drug powders and liquids are determinative for the stability of the dispersion. Dispersion stability, on the other hand, is a pre-requisite for a controlled dosage of drugs [4–9]. However, if the interaction is too favorable, a dissolution of the drug particles may result [10,11]. In many cases this is an unwanted phenomenon, but in other cases the dissolution may be used to enable a controlled recrystallization, e.g. into a particular particle shape with desired properties. Surfactants are commonly used to adjust the interaction of particles with the solvent and thereby the dissolution of drug particles [10–12].

The aim of this investigation is not to continue the research on Metered Dose Inhalers, but to identify whether a common solvent scale could be found which would relate the interaction between liquid and particles to charging and particle stability in non-aqueous dispersions. A great number of molecular properties have been suggested to determine the interaction between particles in different solvents [3,13]. In this paper we have selected two parameters, the Hamaker constant [14,15] and the Solubility parameter [16–18]. The Hamaker constant is the key parameter when establishing the attractive (dispersive, van der Waals) energy and the Solubility parameter express the capacity of organic sol-

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Table 1
Hamaker constant (A_H, ref. [14]) and Solubility parameter (δ, refs. [16,17]), including their dispersive (d) and polar (p) components of the substances investigated. Zepto-Joule is introduced (zJ = 10^{-21} J) to comply with the numeric value of electron volt (1 eV = 1.6021×10^{-19} J = 160.21 zJ) used in spectroscopy and physics. The frequency, $\nu_e \approx 3 \times 10^{15}$/s were assumed to apply for all liquids.

Subst.	Brand	A_H	A_H^d	A_H^p	δ_{tot}	δ^d	δ^p
		zJ	zJ	zJ	$(MPa)^{1/2}$	$(MPa)^{1/2}$	$(MPa)^{1/2}$
n-C_5H_{12}	Merck, pa	39.3	39.1	0.26	14.5	14.5	0
c-C_6H_{12}	Merck, pa	53.1	52.7	0.35	16.8	16.8	0.2
C_6H_6	Merck, pa	71.0	70.5	0.46	18.6	18.4	2.0
CCl_2H_2	Merck, pa	54.8	52.9	1.94	20.3	18.2	8.8
CCl_3H	Merck, pa	59.0	57.7	1.31	19.0	17.8	6.5
CCl_4	Merck, pa	61.4	60.9	0.44	17.8	17.8	0.6
$C_2Cl_2H_4$	Merck, pa	58.9	56.9	2.07	20.9	19.0	8.5
CCl_3F	ICI	42.8	42.3	0.46	15.4	15.3	2.1
CCl_2F_2	ICI	26.6	26.2	0.40	12.5	12.3	2.0
$C_2F_4H_2$	DuPont	ca. 14			ca. 20		
OA	Sigma, Xp				ca. 15.6		
Salb.A	Leiras, base	ca. 57			ca. 18.9		
Salb.C	Leiras-HSO_4				ca. 25.6		

vents to solvate solutes and polymers. Likewise, it expresses the ability of liquids to dissolve organic powders.

The influence of the FDA approved surfactant oleic acid [8–10,12] on the interactions in a number of liquids is also reported. Both pure and mixed liquids are investigated. One example is given, where the charging and change in particle size is related to the adsorption onto the particles [7,12]. It has previously been found that the DLVO model being successful in predicting the stability in dilute aqueous electrolyte dispersions [19] cannot be applied on particles in a low dielectric medium. However, a simple model based on Coulomb interaction [20] was found to be surprisingly successful.

In our previous studies [8,9,12,21] non-aqueous systems have been characterized by measuring the electrophoretic mobility (ζ-potential) and the particle size in different non-aqueous solvents. In this report the interaction between Salbutamol base (Sb) and Salbutamol sulphate (Ss) drug particles and a number of non-aqueous and mixed solvent systems are investigated. Salbutamol base owes its basicity to an amine group in the side chain, Salbutamol sulphate is an ammonium salt.

2. Experimental

2.1. Materials

The solvents used may be subdivided into hydrocarbons, halogenated hydrocarbons, propellant liquids and mixed solvents. They are presented in Table 1 with key properties pertinent for this investigation.

In the order presented the substances are: n-Pentane (Merck, KGaA, pa quality), Cyclohexane (Merck, KGaA, pa quality), Benzene (Merck, KGaA, pa quality), Dichloromethane (Merck, KGaA, pa quality), Chloroform (Merck, KGaA, pa quality), Carbon tetrachloride (Merck, KGaA, pa quality), Dichloroethane (Merck, KGaA, pa quality), CFC 11 (Trichloromonofluoromethane, Frigen and Arcton Fluorocarbons, ICI), CFC 12 (Dichlorodifluoromethane, Frigen and Arcton Fluorocarbons, ICI), HFC 134a (1,1,1,2-Terafluoroethane, Du Pont), was used in the experiments. The micronized drugs were: Salbutamol base powder (Leiras Ltd., Lot: 914098) with a particle size of 1.9 μm (Malvern 2600c) and a specific surface area of 8.8 m^2/g (BET, nitrogen adsorption). Salbutamol sulphate (Leiras Ltd., Lot: 924263) with a particle size of 2.7 μm and a specific surface area of 7.0 m^2/g. The powders were stored in a desiccator at room temperature (23 °C). The moisture content as determined by the Karl-Fisher method was less than 0.01%. Consequently water could not be detected in the DRIFT spectrum taken from the powder. The only model surfactant concerned in this study was oleic acid (cis-9-octadecenoic acid, Sigma, extra pure) which was stored in a refrigerator in dark.

2.2. Methods

A fixed amount of powder (0.16 wt%, but 1.0 wt% for adsorption experiments) and surfactant (0–4 mmol/dm^3) was weighed into a glass container to which the solvent was added. In the case of propellant blends the high-boiling propellant $C_2F_4H_2$ (HFC 134a) or CCl_2F_2 (CFC12) was introduced through an aerosol valve on a balance in order to get the correct CCl_2F_2/CCl_3F or $C_2F_4H_2$/C_5H_{12} blend. The aerosol containers were specially manufactured for this purpose and fitted with Bespak nonmetered aerosol valves. All the sample tubes were very carefully dried in order to avoid the presence of water. In the previous investigations this procedure was found to be very accurate. In total some 14–34 ml dispersion were produced, depending on the density of the liquids. The mixing was followed by sonication in an ultrasonic bath for 1 min. The suspensions were further shaken by hand and left to stabilize at room temperature (23 °C) for two days before measurements.

2.3. Characterization

The effective surface charge of the drug particles were measured with the Malvern Zetasizer IIc instrument equipped with the pc26 non-aqueous cell arrangement. The cell had been modified for the propellant liquids as described previously [8,9]. With this specially designed cell one obtains an optimal reproducibility with respect to both cell location and alignment. The optimization of this procedure has been discussed in earlier reports [8,9]. In this work a voltage of 10 V was used producing sufficient field strength of 100 V/cm. The measurement time was 30 s and at least 15 measurements were averaged. The zeta potentials were calculated from the electrophoretic mobilities using the Huckel equation [19].

The particle size distribution was measured with a laser diffraction technique. A Malvern Instruments 2600c system was used. Again, the measuring cell was modified in order to withstand the enhanced pressure of the propellant liquids [8,9]. With these techniques particle sizes between 0.2 and 1880 μm could be detected.

The dissolution of the drug particles was determined by a colorimetric method developed by Lowry and Tinsley [12,22] using a Schimadzu UV–Vis 240 spectrometer. The amount was read from a calibration curve related to the Lambert–Beers law. The equilibrium concentration was determined with HPLC liquid chromatography with a Jasco HPLC unit equipped with a UV-detector. The concentration of free oleic acid in the propellant blend was determined with a Varian 3400 Gas Chromatograph. The dispersions were fil-