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Volatile fluorinated nanoemulsions: A chemical route to controlled delivery of inhalation Anesthesia

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ABSTRACT

Novel dispersions of the volatile inhalation anesthetic sevoflurane have been formulated that can provide controlled, sustainable release of anesthetic over clinically useful timescales. The emulsions can be simply formed with manual shaking, reproducibly yielding droplets of the order of 250 nm diameter, i.e. within the nanoemulsion range. Using a custom flow-rig, release of anesthetic gas from the emulsion has been evaluated, and clinically useful levels achieved through appropriate stirring of the formulation. Stirring can also be used to temporarily increase or decrease the amount of anesthetic released. Once consideration of the unusual nature of the fluorinated systems (phase separation by sedimentation rather than creaming), and the highly perturbed environment of their evaluation (under stirring and flow of gas), the observed behavior regarding sevoflurane evaporation can be reasonably well explained by existing theoretical models. Links between anesthetic release and emulsion structure have been defined, providing the basis for future development.

1. Introduction

Nonionic partially fluorinated surfactants have been used to stabilize emulsions and microemulsions of fluorinated oils in water, e.g. for formation of blood substitutes [1–4] or as templating media for the preparation of porous materials [5–9]. For volatile emulsions previous fundamental studies have shown that oil evaporation depends both on the type of stabilizer used and on the solubility of the oil in the continuous water phase [10–12]: evaporation rates of water soluble oils approach that of the bulk oil, but evaporation of very low solubility oils is significantly hindered, an effect magnified by the use of a polymeric (as opposed to low molecular weight surfactant) stabilizer [10–12]. Other groups have focused on relationships between phase structures and the evaporation pathway, primarily for fragrance emulsions [13–15]. Here we utilize a volatile anesthetic as the evaporating component of an oil-in-water (o/w) emulsion. This is used to evaluate the feasibility of using a colloid science based approach to inhalation delivery of an anesthetic (as opposed to intravenous delivery [16]).

Currently, safe and accurate anesthesia delivery is reliant on large, complex and expensive machines operated by very specialized, highly trained personnel. All of these factors limit their use outside of modern clinical settings, and a simpler, safer and cheaper delivery system could provide an alternative means of anesthesia delivery. This is particularly relevant for challenging situations including pre-hospital medicine, in-the-field anesthesia, warfare anesthesia and in the challenging conditions often encountered in developing countries. Ethically, the delivery of anesthesia and analgesia are mandatory for surgical procedures worldwide, but in developing countries access to safe anesthesia can be limited due to a shortage of trained staff, and compromised by failure of complex equipment, leading to reduced access to healthcare.

The aim of the work is therefore to provide proof of concept for a dispersion based anesthetic delivery device. Anesthetic is released in vapor form from a formulation, and picked up by a carrier flowing through the device and to the patient (Fig. 1). Specific targets are to demonstrate (i) release of clinically safe and useful concentrations of anesthetic (0.5–4 vol.% in the carrier gas stream). This is evaluated over a 60 min timescale at fixed gas flows of 1 L min^{-1} and 4 L min^{-1}, chosen to exemplify typical clinically used flow rates; (ii) to obtain higher release (up to 8 vol.%) for shorter periods to create a release profile suitable for both induction and maintenance of anesthesia, and (iii) to provide a means of adjusting anesthetic release in a controllable and responsive

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manner, without changing the carrier-gas flow used. This controlled variability is essential for the potential clinical use of the device and formulation.

2. Materials and methods

2.1. Materials

Sevoflurane (99.98%, Abbot, UK) and Zonyl FSN-100 (technical grade, ABCR, Germany) were both used as received. Industrial nitrogen gas (BOC, UK) was used as the carrier gas throughout. Water was reagent-grade produced by a RiOs 5 purification system (Millipore, USA).

2.2. Methods

2.2.1. Sample preparation

All formulations were prepared on ~150 mL scale in 500 mL DURAN laboratory bottle with a screw cap and equilibrated at 20 °C prior to testing. Formulation compositions are given in Table 1. Emulsions were prepared by vigorously shaking (by hand) a known volume of the anesthetic with a pre-prepared aqueous surfactant solution, for a fixed time of 60 s. Method validation experiments were performed using different shaking times, and independent preparation by different personnel to ensure robustness of the preparation procedure. This simple method of dispersion greatly simplifies the formulation stability requirements, as the emulsion itself is formed at point of use.

2.2.2. Characterization

Ternary phase diagrams were constructed by visual inspection. The continuous phase of the emulsion was determined by a standard drop-test method (an added drop of the continuous phase will disperse freely into the bulk; a drop of the dispersed phase will separate at the top or bottom of the sample, depending on density difference). Emulsion droplets were characterized by light-microscope imaging using an Olympus BX50 system microscope (Olympus, UK) fitted with JVC TK-C1380 color video camera (JVC, Japan) and analyzed using Image J software (Fiji, USA). Additional measurements were obtained from dynamic light scattering analysis using a Brookhaven ZetaPlus (Brookhaven Instruments Ltd., USA). For light scattering measurements the emulsions were diluted by a factor of 20–50 depending on the emulsion concentration.

Table 1
Formulation composition and oil droplet sizes for different performance sevoflurane containing emulsions.

Carrier gas flow rate/L min^{-1}	Release level/ vol%	Surfactant[a] concentration/ wt.% (aq)	vol% anesthetic in formulation	Average droplet diameter/ nm
1	4[b]	18	31	209 (±2)
1	3	10	19	259 (±0.6)
1	2	7	13	261 (±4)
1	1	4	6	239 (±5)
1	0.5	8	6	188 (±4)
4	4	25	44	256 (±5)
4	3	22	36	206 (±2)
4	2	17	29	384 (±5)
4	0.5	7	13	188 (±4)

[a] Zonyl FSN-100.
[b] 4 vol% equates to 2× maximum alveolar concentration (MAC). One MAC is the alveolar concentration of a volatile anesthetic that produces no movement in 50% of spontaneously-breathing patients during skin incision.

2.2.3. Release testing

The controlled release of anesthetic agents from the formulations was evaluated using the experimental flow-rig shown in Fig. 1. The upper module consists of a 250 mL cylindrical plastic container (which holds the formulation and a magnetic stirrer bar) attached to a custom built Teflon fitting which has an inlet port for entrance of the free carrier gas and an outlet port for the exit of the anesthetic-loaded carrier gas. The module was placed on a standard magnetic stirrer (Heidolph MR 3002, Germany) for controlled stirring. Nitrogen gas was passed through the flow module at a controlled flow rate, typically 1 L min^{-1} and 4 L min^{-1}. In lab experiments nitrogen was used as the carrier gas for convenience, although control experiments using air and air/O_2 mixtures showed that the performance was independent of gas composition. The concentration of the anesthetic agent in the outlet stream was measured with a standard anesthetic monitor (Capnomac Ultima, Datex Instrumentarium Inc., Helsinki, Finland). The formulation

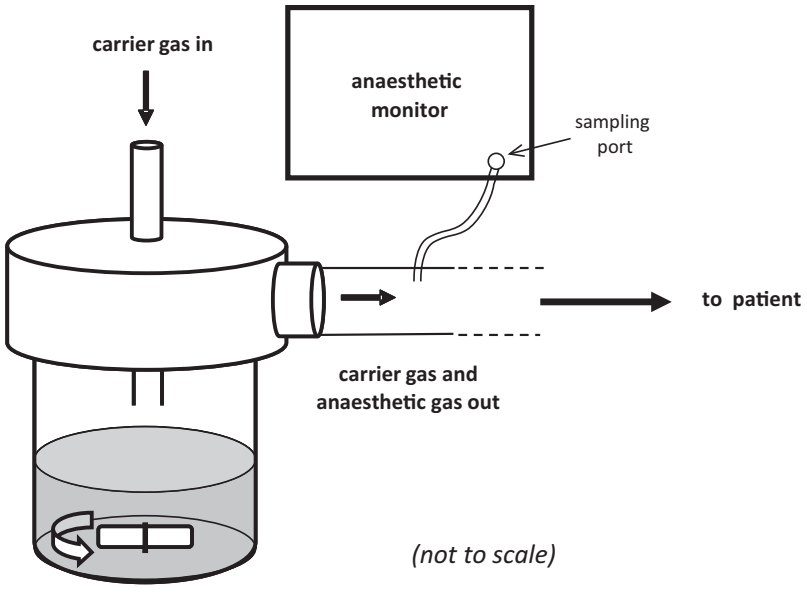

Fig. 1. Schematic of test flow-rig. SA = 60 cm^2. Typical stirring rates 100–800 rpm. Typical formulation volume 120 cm^3.