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Laboratory evaluation of a novel anaesthesia delivery device

A. Paul,[1] J. N. Clark,[2] I. E. Salama,[3] B. J. Jenkins,[4] N. Goodwin,[5] A. R. Wilkes,[4] P. F. Mahoney[6] and J. E. Hall[7]

1 Senior Lecturer in Physical Chemistry, 3 Post-Doctoral Research Assistant, School of Chemistry, Cardiff University, Cardiff, UK
2 Technician, 4 Senior Lecturer, 7 Professor, Department of Anaesthetics, Intensive Care and Pain Medicine, School of Medicine, Cardiff University, Cardiff, UK
5 Consultant, Department of Anaesthetics, Cardiff and Vale UHB, University Hospital of Wales, Cardiff, UK
6 Defence Professor of Anaesthesia, Academic Department of Military Anaesthesia and Critical Care (ADMACC), Royal Centre for Defence Medicine, Birmingham, UK

Summary

Here, we describe proof of concept of a novel method for delivering volatile anaesthetics, where the liquid anaesthetic (sevoflurane or isoflurane) is formulated into an emulsion that is contained in a compact, lightweight device through which carrier gas flows. Release of anaesthetic is achieved by stirring of the formulation, allowing controlled and responsive release of anaesthetic at a variety of fixed flow rates between 0.5 $l.min^{-1}$ and 5 $l.min^{-1}$, with ventilated, non-ventilated and draw-over breathing systems. Anaesthetic release was evaluated using target anaesthetic concentrations ranging from 0.5% v/v to 8% v/v to mimic those typically required for induction and maintenance of anaesthesia, and lower concentrations suitable for sedation. Under all conditions, output could be maintained within 0.1% v/v of the intended setting, and the device could deliver a controlled level of anaesthetic for at least 60 min, with compensation for different ambient temperatures (10–30 °C) and carrier gas flow rates. This device offers a simple, inexpensive method of delivering safe concentrations of volatile anaesthetics for a wide range of applications.

Introduction

There are two basic types of vaporisers: plenum and draw-over [1]. The plenum vaporiser has a high resistance to gas flow and is placed 'out of circuit', typically on the back-bar of an anaesthetic machine. In contrast, draw-over vaporisers are placed in the breathing system. They have a lower resistance to gas flow, making them suitable for use with spontaneously breathing patients. Other methods of vapourising volatile anaesthetic agents include using an injector system, for example, in the Flow-i anaesthetic machine (Maquet Cardiovascular LLC, Wayne, NJ, USA), or the DIVA cassette used by the Zeus anaesthesia machine (Drager, Lübeck, Germany). Alternatively, the liquid anaesthetic can be vapourised close to the patient, as in the Ana-ConDa device [2].

Vaporisers classically used by anaesthetists are not without clinical problems. During the 1988–1996 period, 16 incidents were reported in the United Kingdom to the Medical Devices Agency (MDA), where leaky

vaporiser back-bar connections led to patient awareness during surgery [3]. Adverse incidents associated with anaesthetic vaporisers were also reported to the Manufacturer and User Facility Device Experience Database (MAUDE) operated by the US Food and Drug Administration [4]; eight separate reports involving vaporisers were logged in the nine months from 1 January to 30 September, 2013. In addition, some of the equipment required to deliver volatile anaesthetics to patients is extremely expensive and complex.

These issues led this group to consider alternative methods of delivery for volatile agents, seeking a compact, portable and simple-to-use delivery device that would have the potential to broaden access to safe anaesthesia in challenging situations such as field anaesthesia and the developing world. Hence, a simple solution with low-power requirement and the potential to be battery-driven was required. It was hypothesised that formulating the anaesthetic as an oil-in-water emulsion would reduce the rate of evaporation by restricting transport of anaesthetic to the surface of the liquid [5]. This could reduce the concentration of anaesthetic vapour in the headspace of a chamber containing the emulsion. Hence, the formulation would provide a mechanism for controlled release of anaesthetic into a carrier gas stream, forming the basis of a device for delivery of volatile anaesthetics.

Such a device may also have a number of novel features that could make administration of anaesthetics safer. There are inherent limitations in the concentration of vapour that can be delivered from a specifically formulated emulsion. Also, if agitation of the emulsion resulted in the production of predictable vapour concentration, this would for the first time introduce the potential for simple feedback control mechanisms of vapour concentration. Replacing the 'traditional' design of large metal heat-sink and control of gas flow with a simple, light and potentially disposable device would introduce new opportunities for portability and cost reduction.

Here, we describe a novel device containing an emulsion of the volatile anaesthetic agent. The device is intended to be connected to the fresh gas flow inlet of a circle, Bain or Magill breathing system. Drug delivery is designed to be controlled by stirring rate. However, for experimental completeness, performance was tested at a range of flow rates. For this proof of concept study, the performance of a single formulation was tested over a range of temperatures from 10 °C to 30 °C and gas flows of 0.5 to 5 l.min^{-1}, with target anaesthetic release concentrations of between 0.5 and 8% v/v. It was decided to examine the delivery of both sevoflurane and isoflurane, as these are two of the most commonly used volatile agents, and have boiling points that are easily managed within the proposed drug delivery system. For this reason, we avoided testing desflurane due to its low boiling point.

Methods

Research Ethics Committee approval was not required for this laboratory-based study.

Reagent-grade water was produced by a RiOs 5 purification system (Millipore, Billerica, MA, USA). The fluorinated surfactant Zonyl FSN-100 (technical grade, ABCR, Karlsruhe, Germany) was used as received. Zonyl FSN-100 is a commercial non-ionic surfactant of the perfluoroalkylpolyoxyethylene type with an average chemical structure of $F(CF_2CF_2)_{3-8}CH_2CH_2O(CH_2CH_2O)_{10-15}H$ [6, 7]. Two anaesthetic agents, sevoflurane (99.98% purity; Abbott, Maidenhead, UK) and isoflurane (99.9% purity; Nicholas Piramal, London, UK) were used as received.

Formulations of sevoflurane and isoflurane were prepared by vigorously shaking (by hand) a known volume of the anaesthetic with a pre-prepared aqueous surfactant solution for a fixed time of 60 s. Formulation compositions were 50 ml sevoflurane with 90 ml of aqueous Zonyl FSN-100 solution (20 w/w %), and 30 ml isoflurane with 110 ml of an aqueous Zonyl FSN-100 solution (30 w/w %). All formulations were prepared in a 500ml DURAN laboratory bottle with a screw cap, and were thermally equilibrated at 20 °C before testing.

The prepared emulsions were characterised by light microscope imaging using an Olympus BX50 system microscope (Olympus, London, UK), fitted with JVC TK-C1380 colour video camera (JVC, Yokohama, Japan) and analysed using Image J software (Fiji, available at http://fiji.sc/Fiji). Additional measurements were obtained from dynamic light-scattering measurements using a Brookhaven ZetaPlus analyser (Brookhaven Instruments Ltd., Holtsville, NY, USA). For light-scattering measurements, the emulsions were

diluted by a factor of 20–50 depending on the emulsion concentration. Gas chromatography–mass spectometry (GC–MS) analyses were carried out on a Waters GCT Premier instrument (Waters Corporation, Milford, MA, USA) to determine both the amount of anaesthetic gas in the gas space above the formulation and whether any of the excipients were identifiable in this gas phase.

The controlled release of anaesthetic agents from the formulations was tested and delivered using the experimental setup shown in Fig. 1a. The anaesthetic delivery device is comprised of two main parts. The first part is the cartridge, which contains the formulation and is where evaporation of the anaesthetic agent occurs. The cartridge comprises a 250-ml cylindrical plastic chamber plugged into a Teflon fitting (the flow module) with standard 22-mm inlet and outlet connectors (Fig. 1a). The second part is a magnetic stirrer which controls the stirring rate of the formulation through a magnetic bar placed inside the chamber. A demonstrator device is shown in Fig. 1b; however, for this proof of concept work a commercial stirrer was used (MR 3002; Heidolph UK, Saffron Walden, UK) in tandem with the cartridge. Changing the rate of stirring alters the rate of evaporation of the anaesthetic and hence the concentration of anaesthetic delivered from the device.

The flow required will range from 150 ml.min^{-1} (basal oxygen consumption in a closed circuit system) to a minimum of 4 l.min^{-1} when used with a semiclosed breathing system such as the Bain or Magill. As flow of gas through the chamber changes, the concentration of the volatile anaesthetic will also vary. However, as the anaesthetic delivery device is intended to be placed between the fresh gas source and the breathing system, flow through the device will remain constant once set by the user. Initial testing was, therefore, performed at a fixed flow rate of 1 l.min^{-1}, with further testing at both higher (4 l.min^{-1}) and lower (0.5 l.min^{-1}) flows.

Concentration of the anaesthetic agent in the outlet flow was measured with an anaesthetic monitor (Capnomac Ultima; Datex Instrumentarium Inc., Heslinki, Finland), calibrated according to the manufacturer's instructions immediately before the start of the study. The Capnomac records the anaesthetic gas concentration (in volume percent) every 10 s, to a
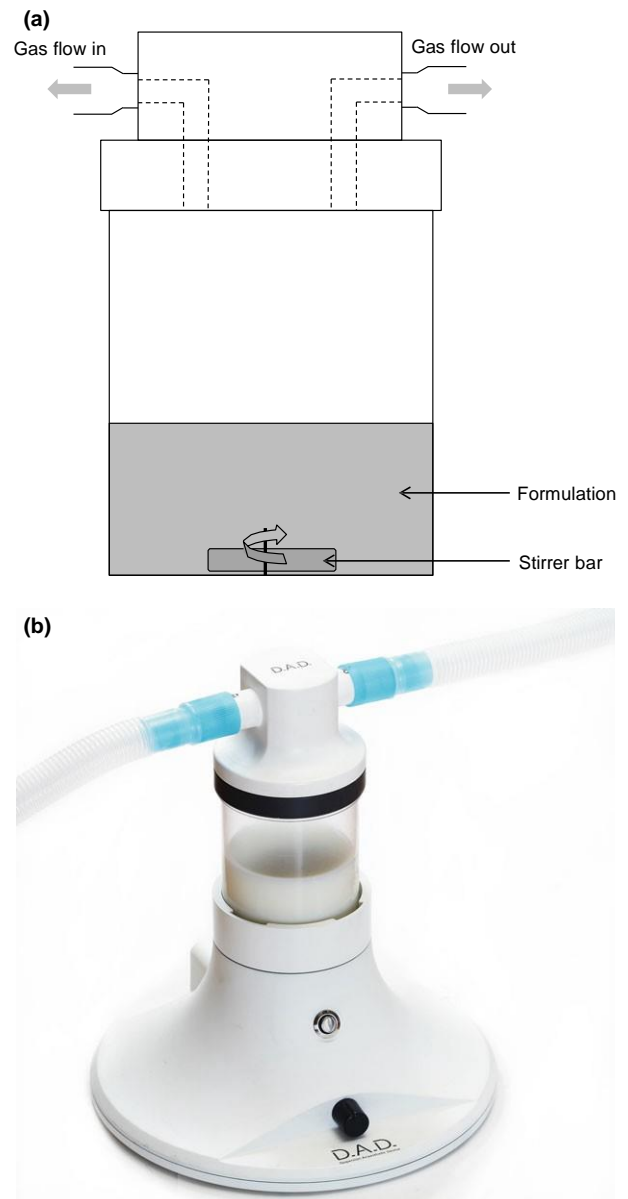

Figure 1 The anaesthetic delivery device. (a) Schematic representation of the device (not to scale). (b) Photograph of the demonstrator device. The inlet connector is connected to the gas supply and the outlet connector is connected to an anaesthetic monitor.

precision of 0.01%. A serial port connection to a PC was used to record data for subsequent analysis.

The stirring rate of the magnet was varied to determine its effect on the output of the anaesthetic delivery device. The stirring rate was then used to deliver particular different concentrations of sevoflurane at room temperature (20 °C). Stirring was also used to compensate for changes in sevoflurane release caused

by working at (i) different ambient temperatures, and (ii) different gas flows.

The concentration of the volatile anaesthetic released from the emulsion was measured over a temperature range from 10 °C to 30 °C to allow for variations in ambient temperatures. For temperatures other than room temperature (20 °C), the temperature of the flow module was controlled using a double-walled glass water jacket connected to a circulating water bath. Changes in the temperature of the emulsion during evaporation were monitored using a digital thermometer (KM 3013; Kane-May Ltd., Welwyn Garden City, UK) with a thermocouple placed inside the emulsion. Repeat experiments were performed to ensure reproducibility of the formulation and device output. In all cases, the levels of anaesthetic released were able to be reproduced to within $\pm0.2\%$ v/v. Example data are given in the results section.

In order to demonstrate the possibility of using the device with volatile anaesthetics other than sevoflurane, an emulsion was also formulated with isoflurane. This was tested at 1 l.min^{-1} carrier gas flow with stirring rate adjusted to maintain target concentrations of 1.2 and 2.3% v/v, which corresponds to approximately 1 and 2 minimum alveolar concentration (MAC), respectively, in the carrier gas.

Breathing system test rigs were set up as shown in Fig. 2, using Mapleson A (Fig. 2a), circle (Fig. 2b) and draw-over (Fig. 2c) systems for spontaneous breathing and a co-axial Mapleson D system for positive pressure ventilation (Fig. 2d). An artificial lung (Vent Aid TTL Model 1600 Training Test Lung; Michigan Instruments, Grand Rapids, MI, USA) was used to test the anaesthetic breathing systems in all configurations.

Results

Characterisation of the formulation by microscopy confirmed the presence of discrete droplets (Fig. S1), typically 5 1m or less in diameter; that is, a dispersion or 'nano-emulsion' structure. The formulation was optimised to ensure that no separation of the neat anaesthetic occurred over a timescale significantly greater than the experiment (> 12 h). It is also worth noting that a single formulation was used to obtain release at the full range of gas flows and target concentrations studied. This represents an improvement on

formulations identified previously, where different formulations were used for individual target concentrations [8].

If dried carrier gas is used during anaesthetic release, some evaporation of water occurs (< 5% over 90 min), but this has no effect on formulation stability, and substantial dilution of the evaporated water into the carrier gas ensured that no water droplets were formed in the breathing circuit tubing. Where the carrier gas was pre-humidified by bubbling through a water trap, no measureable loss of water from the formulation was observed during release testing.

At a fixed gas flow rate and constant stirring rate, the level of anaesthetic release from a given formulation drops gradually over time as the amount of sevoflurane remaining in the formulation decreases (Fig. S2), consistent with the proposed evaporation mechanism [8]. By altering stirring rate, the output of the anaesthetic delivery device can be made to vary in a responsive and predictable manner (Fig. 3). It was, therefore, possible to deliver clinically relevant target concentrations of sevoflurane (Fig. 4a–c), which could be maintained for at least 90 min by periodically adjusting the stirring rate to compensate for the drift observed otherwise. Hence, a target value could be maintained with minimal variation (well within the required regulatory tolerance) of the measured concentrations. These data could be reproduced at the different flow rates: 1 l.min^{-1} (Fig. 4a); 4 l.min^{-1} (Fig. 4b); and 0.5 l.min^{-1} (Fig. 4c) tested in this preliminary study. The consequences of stirring failure were also studied (Fig. S3).

Despite the relatively simple method of emulsion preparation, the results obtained were reproducible to within regulatory tolerance. Example data to demonstrate this are shown in Fig. S4. Good reproducibility was also obtained on recycling the emulsion by 'topping-up' the anaesthetic content (Fig. S5), although regulatory requirements would prohibit this approach in practice. Headspace analysis by GC–MS was carried out to confirm that only sevoflurane was released from the formulation. No surfactant was detected in the volatile phase to the detection limit of the instrument used (Fig. S6).

For a given formulation, the time for which the release is maintained is dependent primarily on the amount of formulation and, therefore, anaesthetic
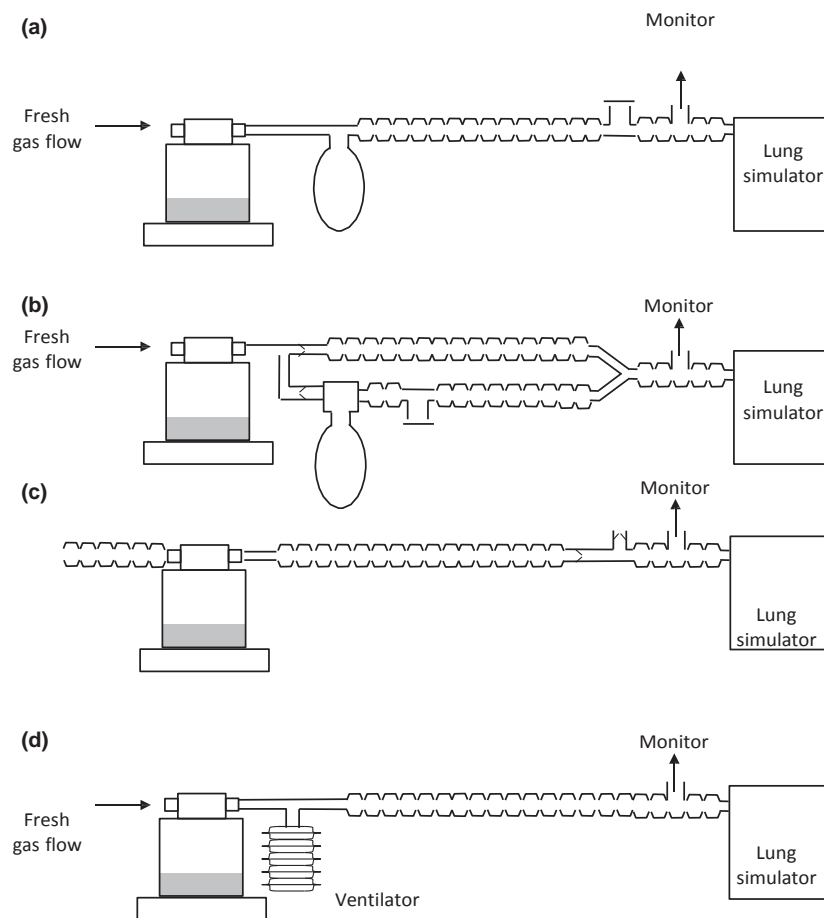
Figure 2 Test rigs used. For spontaneous breathing, Mapleson A (a), circle (b) and draw-over (c); for ventilation, co-axial Mapleson D (d).

present. At higher flow rates and higher target anaesthetic concentration, for example, 4% v/v and 2% v/v at 4 l.min^{-1} (Fig. 4b), the time for which a given volume of formulation will deliver the desired output is shorter than at lower flows and/or concentrations (data acquisition has been halted at a maximum of 90 min). Where longer timescales are required, the cartridge-based design of the device means that a fresh anaesthetic cartridge can be easily installed.

Controlled anaesthetic release could also be obtained using emulsified isoflurane, indicating that the formulation-based mechanism of vapour release translates to other volatile anaesthetics (Fig. 5).

As shown in Fig. 6a, for a given stirring rate, the ambient temperature has an effect on the output of the delivery device, with a higher measured anaesthetic concentration observed at higher ambient temperatures

(as expected). However, these effects were easily counterbalanced by adjusting the stirring rate to obtain the target output independent of the ambient temperature.

The effect of carrier gas flow rate at constant stirring rate was also investigated (Fig. 6b). As anticipated, as flow rate increases, dilution of the evaporating anaesthetic causes a drop in the measured sevoflurane concentration. However, by adjusting the stirring rate the measured concentration can be restored to the target level.

When the device was tested using an equivalent volume of neat anaesthetic, the observed release levels were $9 \pm 1\%$ v/v and $7 \pm 1\%$ v/v at 1 l.min^{-1} and 4 l.min^{-1} gas flows, respectively (Fig. S7a), indicating the importance of the emulsion in retarding anaesthetic evaporation to clinically useful levels.

For neat anaesthetic liquid, significant evaporation-induced cooling occurs (Fig. S7b). For the formulation, however, the liquid temperature remains broadly constant during sevoflurane evaporation (Fig. S7b), changing by only approximately $2\ ^{\circ}$C over 60 min. This is due to the high specific heat capacity of the aqueous continuous phase of the emulsion.
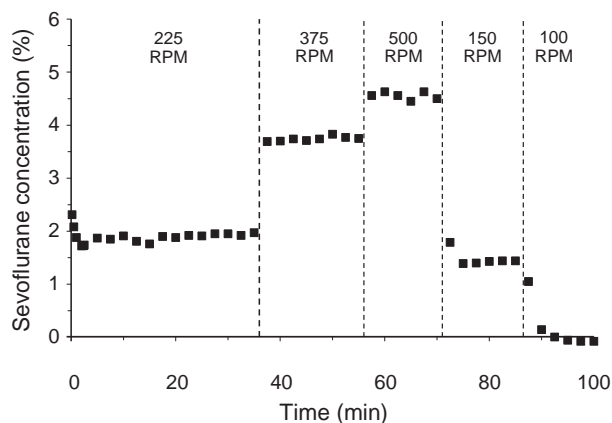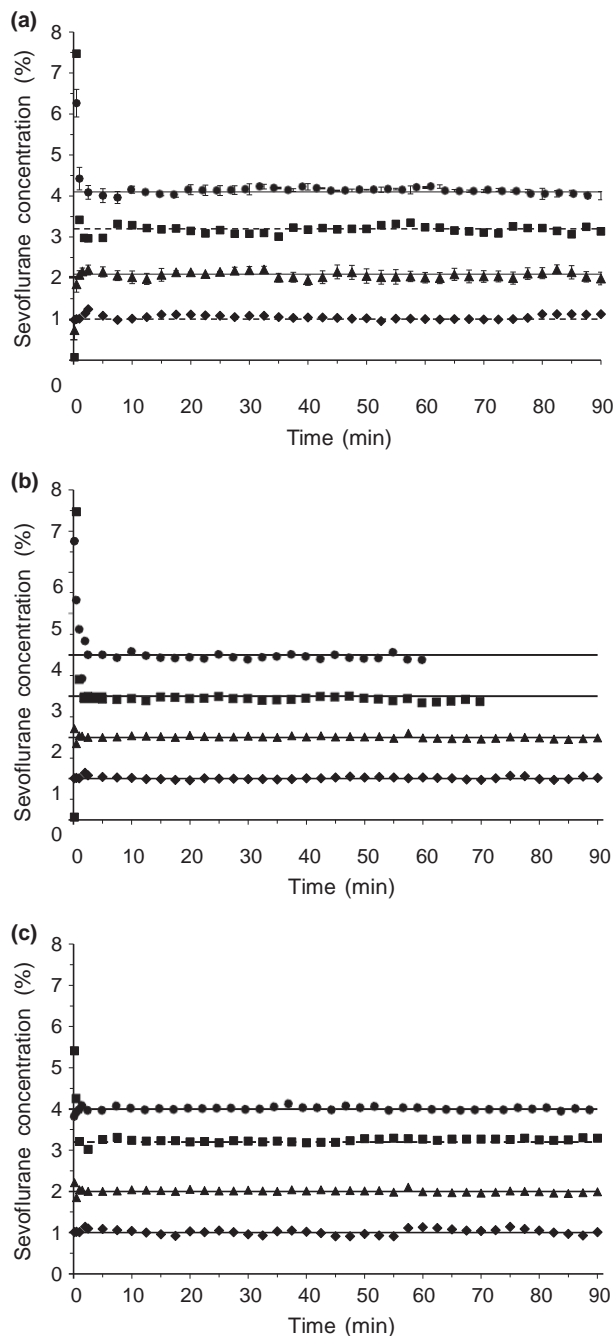
Figure 3 Sevoflurane output concentrations of the anaesthetic delivery device at various stirring rates with an input flow of 1 l.min^{-1} nitrogen at 20 °C.

The dispersion device was also tested with a range of clinically-used breathing circuits, using a ventilator and/or lung simulator to mimic spontaneously breathing or ventilated patients. These data show that vapour levels required for inhalation induction, as well as maintenance of anaesthesia, could theoretically be obtained with this device, and that this could be achieved in the same manner (flow and anaesthetic concentration profile) as with conventional vaporiser-based systems (Figs. 7 and 8). Figures 7a and b show data using a Magill (Mapleson A) breathing circuit with flows set to mimic a spontaneously breathing patient (500 ml end-tidal volume, 15 breaths.min^{-1}, inspired:expired ratio 1:2), illustrating that high anaesthetic concentrations of sevoflurane can be achieved and maintained (up to 8% v/v); the target timescale of 10 min (Fig. 7a), and a target maintenance value of 2% v/v as maintained over an extended time period (Fig. 7b). Figure 8 shows maintenance data using a co-axial Mapleson D system, indicating that the formulation and device would be

suitable for a mechanically ventilated patient. Figures 9a–c illustrate function at low fresh gas flow rates (1 l.min^{-1}) used with circle breathing systems for mechanically ventilated (Figs. 9a and b) and spontaneously breathing (Fig. 9c) patient models, with induction (Fig. 9a) and maintenance (Figs. 9b and c) targets maintained. Figure 9d shows the equilibration of the breathing system, showing that at a constant 1 l.min^{-1} rate, the target 2% v/v sevoflurane is reached within

10 min.

Figure 4 Output sevoflurane concentrations of the anaesthetic delivery device for target sevoflurane concentrations of 1.0% v/v (circles), 2.1% v/v (squares), 3.2% v/v (triangles) and 4.0% v/v (diamonds), with an input flow of nitrogen at 20 °C with gas flows of (a) 1 l.min^{-1} (b) 4 l.min^{-1} and (c) 0.5 l.min^{-1}. Variation from the target output was generally less than 0.1% v/v.

Finally, Figs. 10a and b demonstrate that low target concentrations suitable for volatile sedation can be obtained with the formulation. Target values of 0.5%
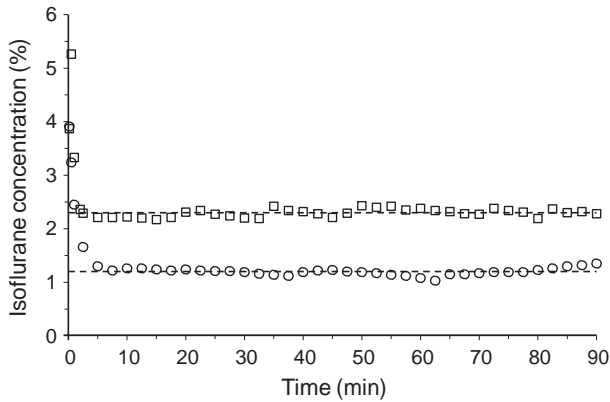
Figure 5 Output isoflurane concentrations of the anaesthetic delivery device for target isoflurane concentrations of 1.2% v/v (circles) and 2.3% v/v (squares), with an input flow of nitrogen of 1 l.min^{-1} at 20 °C. Variation from the target output was generally less than 0.1% v/v.

v/v, 1% v/v and 1.5% v/v sevoflurane were achieved and maintained using a Magill breathing circuit (Fig. 10a), and in draw-over mode (Fig. 10b).

Discussion

Concentrations of sevoflurane and isoflurane over a range of MAC values (up to 4 MAC) could be delivered from a single-emulsion formulation of the volatile anaesthetic, with the level of release at flows of 0.5–4 l.min^{-1} and over a temperature range of 10–30 °C, controlled by varying the rate at which the formulation

is stirred. Any formulation would be subject to full regulatory approval before clinical testing, and the formulation presented is used to demonstrate proof of concept for the dispersion. Other emulsion formulations containing alternative stabilisers can also be used to the same effect, as described in the published patent [9].

Delivered anaesthetic concentrations are consistent, predictable and reproducible yet controllable, and as such, the device can provide an accurate solution for delivering volatile anaesthetics. The power requirements for the stirring are low, so the device could be either battery- or mains-powered.

We have demonstrated that the device is suitable for use with circle, semi-closed, such as the Bain and
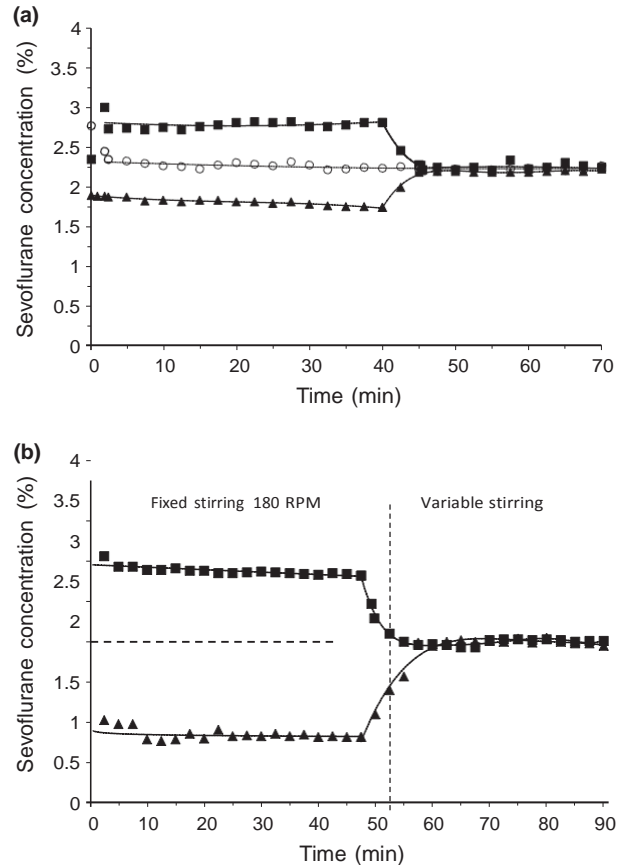

Figure 6 Sevoflurane output concentrations of the anaesthetic delivery device (a) at temperatures of 10 °C (triangles), 20 °C (circles) and 30 °C (squares) and fixed flow of 1 l.min^{-1} and (b) at fixed temperature of 20 °C and flow rates of 0.5 l.min^{-} and 4 l.min^{-} (triangles) ^{1} (squares). The stirring rate was fixed Magill, or draw-over breathing systems. With all these breathing systems, vapour can be delivered reliably

until about 41 min and 46 min, respectively, after which stirring rate was altered to provide the same output at all three temperatures/both flows.

over a wide range of gas flows and concentrations in a lighter and more portable device. This portability suggests potential for delivery of anaesthesia in the field, pre-hospital care or the developing world, where access to complex equipment such as anaesthetic machines may be limited and portability is a major advantage. Frequently, draw-over vaporisers such as the Oxford Miniature Vaporizer and the Diamedica Draw-Over Vaporizer [10] are used in these situations. However, the flow through this type of vaporiser, and hence the concentration of the anaesthetic delivered, varies widely throughout the respiratory cycle, and limits precision of the vaporiser. This new device can deliver predictable concentrations of vapour with a wide

Figure 8 Sevoflurane output of the anaesthetic delivery device at 20 °C with a Bain (Mapleson D) breathing circuit mimicking a patients whose lungs are mechanically ventilated (fresh gas flow 5 l.min^{-1} oxygen, end-

tidal volume 500 ml, 15 breaths.min^{-1}, inhaled:exhaled phase time ratio 1:2) target sevoflurane concentration 2% v/v for 60 min. Data shown are an average over three runs. Error bars indicate SD.
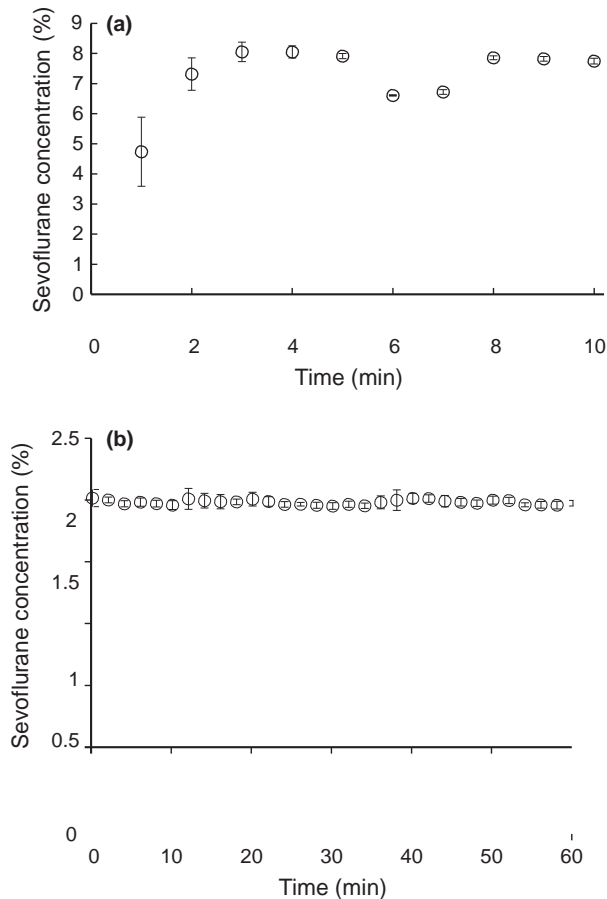

Figure 7 Sevoflurane output of the anaesthetic delivery device at 20 °C with a Magill (Mapleson A) breathing circuit mimicking a spontaneously breathing patient (end-tidal volume 500 ml, 15 breaths.min^{-1}, inhaled: exhaled phase time ratio 1:2 (a) fresh gas flow 6 l.min^{-1} oxygen, target sevoflurane concentration 8% v/v for 10 min; (b) fresh gas flow 5 l.min^{-1} nitrogen, target value 2% v/v for 60 min. Data shown are an average over three runs. Error bars indicate SD.

variety of gas flows, using either pressurised gas or inspiratory effort to generate these flows, and is, therefore, as flexible and at least as accurate as the Diamedica and the Oxford Minature draw-over vaporisers when used in similar situations.

In lower concentrations, anaesthetic vapours such as sevoflurane may be usefully used for sedation [11]. The new device is able to deliver such concentrations, which raises the possibility of using this technology to develop dedicated sedation devices that may be used in all the situations where draw-over vaporisers can be used. The emulsion formulation could be adjusted to limit the output concentration, making sedation, but
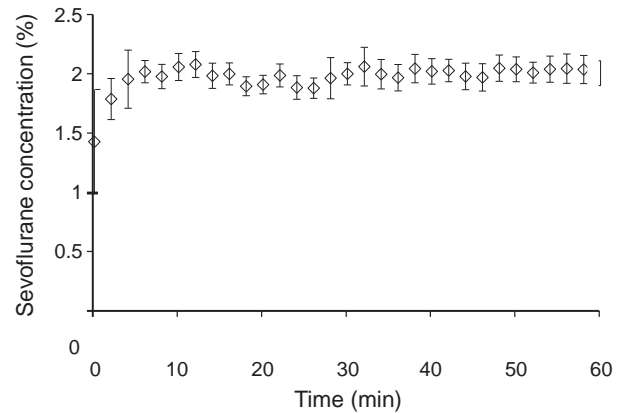
not anaesthesia, possible. Potentially, such a device could be safe for use by non-anaesthetists, and expands the potential market for anaesthetic vapours

outside operating theatres if gas scavenging can be appropriately managed in these areas.

The method of using stirring rate to alter delivered anaesthetic concentration also offers the possibility of using a feedback mechanism for delivery of anaesthetic vapour. Anaesthetic concentration may be measured and the stirring rate adjusted in a single device to produce stable concentrations in a wide range of ambient temperatures. Unlike vaporisers that use pure sevoflurane, the emulsion formulation limits the amount of anaesthetic vapour that can be delivered to the patient in the event of equipment failure, adding an extra element of patient safety.

It seems unlikely that the new device would replace conventional vapourisers for intra-operative use in the short term because of the long-term investment of manufacturers in the workstation model that is built around conventional anaesthetic machines and plenum vapourisers. These require the high-pressure gas source delivered by the anaesthetic machine, and the lack of portability of the whole system limits the potential use of anaesthetic vapours for anaesthesia and sedation outside operating theatres. However, the portability of the new device, the limitations in attainable vapour concentration that can be imposed by tailoring the emulsion formulation and the potential to include a feedback loop to control anaesthetic concentration offers potential for
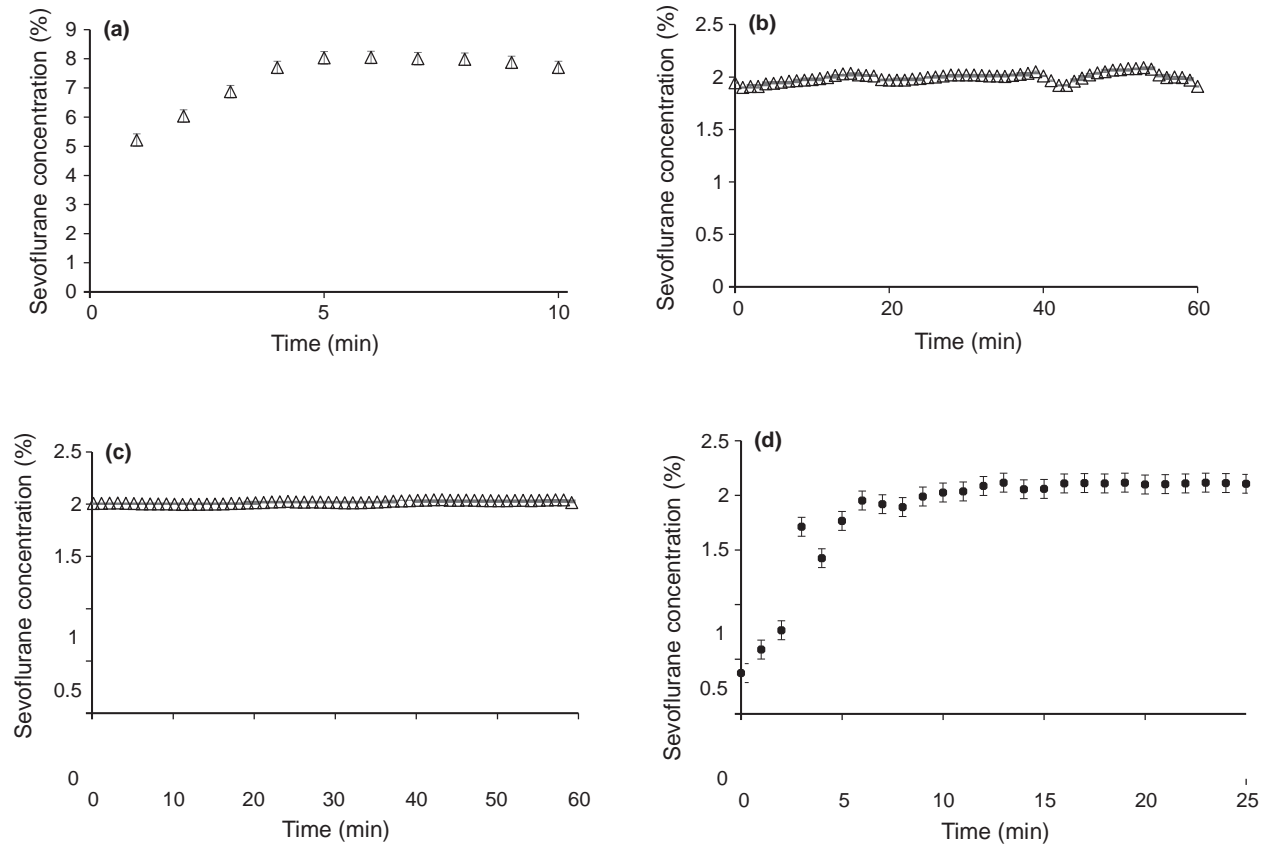
Figure 9 Sevoflurane output of the anaesthetic delivery device at 20 °C with a circle breathing circuit at fresh gas flow 1 l.min^{-1} oxygen (a), mimicking mechanically ventilated patient (end-tidal volume 500 ml, 15 breaths. min^{-1}, inhaled:exhaled phase time ratio 1:2) (b), mimicking spontaneously breathing patient (end-tidal volume 600 ml, 12 breaths.min^{-1}, inhaled:exhaled phase time ratio 1:2) (c). Target sevoflurane concentration 8% v/v for 10 min (a). Target sevoflurane concentration 2% v/v for 60 min (b and c). Also shown, sevoflurane concentration equilibration on start-up (d). Data shown are an average over three runs. Error bars indicate SD.
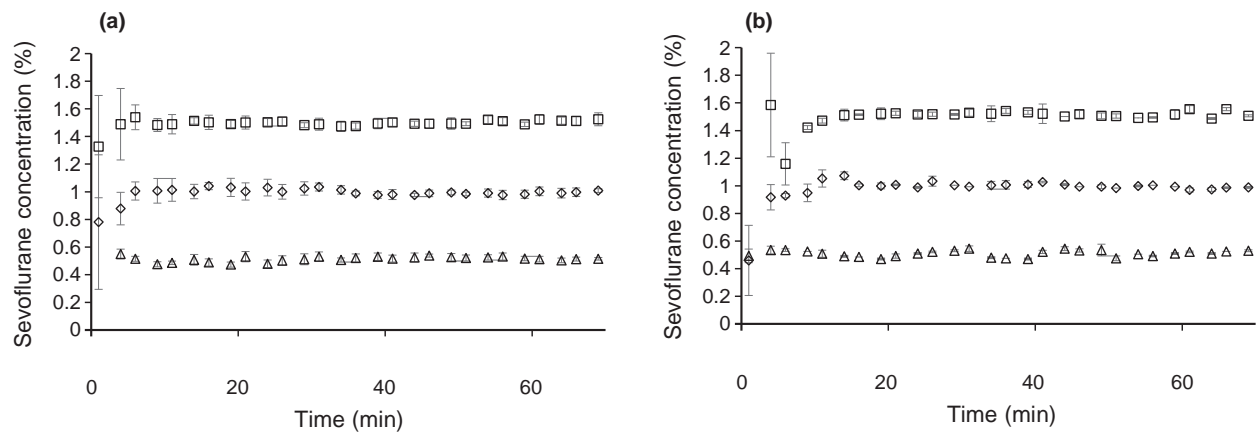

Figure 10 Sevoflurane output of the anaesthetic delivery device at 20 °C, target output 0.5%, 1.0% and 1.5% v/v sevoflurane. Mimicking spontaneously breathing patients: fresh gas flow 6 l.min^{-1} oxygen, end-tidal volume 500 ml, 12 breaths.min^{-1}, inhaled: exhaled phase time ratio 1:2 with Magill breathing circuit (a), and used in draw-over mode (b). Data shown are an average over three runs. Error bars indicate SD.

safe use of a vapouriser to provide anaesthesia or sedation in contexts that are currently impracticable.

As with all anaesthesia methods, and in accordance with recommendations of the Association of Anaesthetists of Great Britain and Ireland (AAGBI) that the concentration of volatile anaesthetic agents is routinely monitored from induction through maintenance and into recovery [12], the routine use of an

appropriate analyser would be required with this device in order to confirm that the correct concentration of anaesthetic is delivered.

The device was designed with the aim of providing anaesthesia to a 'standard' patient for up to 1 h, although in practice it was possible to extend this to 90 min. If used with paediatric patients, the concentration of anaesthetic required would be greater, but this would be compensated for by the lower flow of fresh gas. It is envisaged that the final design for the device will include a cartridge system containing the emulsion, so that for surgery requiring anaesthesia for longer than 90 min, the cartridge containing the anaesthetic can be replaced easily in only a few seconds. Different formulations could be used to provide anaesthesia or to limit the available vapour concentration to safely provide lower sedative concentrations.

In conclusion, a novel method for delivering volatile anaesthetic agents to patients from an emulsion contained in a delivery device is described. In combination with appropriate monitoring, the device is suitable for use using either a circle or semi-closed breathing system, over a range of flows and temperatures. The flexibility to provide low, constant concentrations of anaesthetic suggests that the formulation is also suitable for delivery of volatile sedation. Once fully developed, this device may have a place in situations, where access to complex anaesthetic equipment is difficult or impractical. The next stage will be to demonstrate that the unique emulsion formulation does not produce any unexpected effects on lung tissue, which is required before we can conduct clinical trials and apply for CE marking.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Light-microscopy images of formulation droplets for the sevoflurane (a) and isoflurane (b) formulations.

Figure S2. Concentration drift without stirring control.

Figure S3. Result of stirring failure.

Figure S4. Reproducibility/Recyclability.

Figure S5. Recyclability study.

Figure S6. Confirmation that only anaesthetic is released into the carrier gas stream.

Figure S7. Importance of the emulsion in moderating anaesthetic release.