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The Effect on Syringe Performance of Fluid Storage and Repeated Use: Implications for Syringe Pumps

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ABSTRACT: Syringe stiction has been reported to cause syringe pump malfunction, hence the effect on syringe performance of syringe use and the formulations used in the syringe were investigated. The force required for syringe plunger motion (at 2.5 mm min^{-1}), when filled with soybean oil emulsion (SBOE) and with water, and the extraction of silicone oil from syringes by these fluids, were measured for Primo®, Talus and Terumo® 10 mL, and Terumo 50 mL syringes. The breakloose, average extrusion and maximum force required to maintain plunger motion increased after storage of SBOE for 7 days in all syringes tested ($p < 0.05$). The storage of water increased the breakloose force of all syringes, but only increased the maximum force of Talus syringes, and both the average extrusion and maximum forces of Terumo 10 mL syringes. The mechanism for this is most likely swelling of the elastomer of the piston due to sorption of fluid. The force was found to increase logarithmically with repeated syringe use. Electrothermal atomization atomic absorption spectroscopy was used to measure the silicone oil content of syringe extractions. Three extractions were performed: repeated flushing, vigorous washing, and storage for 7 days with occasional agitation. Up to 69.4% of the silicone oil present in the syringes was extracted with both water and SBOE when they were stored or washed. In contrast to water, SBOE also extracted the lubricant when the syringe was filled and flushed immediately. If syringes are refilled, stored filled before use, or used over a prolonged period, particularly with a SBOE formulation, syringe stiction may occur during infusion with a syringe pump.

Introduction

Syringe pumps have become popular for intravenous drug infusion in intensive care, coronary care, and neonatal units because of the need for accurate infusion rates while administering minimal volumes. Drugs commonly given by syringe pumps are those for short-term and prolonged anesthesia and sedation including hypnotics such as midazolam and propofol, opioid analgesics, neuromuscular blocking agents such as atracurium and vecuronium, and those for hemodynamic support such as dopamine and epinephrine. These drugs are presented as aqueous solutions except propofol, which, due to low solubility in water, is formulated in a 10% soybean oil emulsion (1). Diazepam is also available formulated in a 15% soybean oil emulsion (2) and may be infused by syringe pump. The emulsion may be infused by syringe pump for parenteral nutrition of neonates (3, 4).

In medical practice syringe pumps are used with commercially available disposable syringes that have been primarily designed for manual use. There have been reports of syringe pump malfunction due to so called syringe "stiction," sticking of the piston during movement down the barrel (5, 6). Stiction occurs when the syringe pump fails to overcome the friction between the syringe piston and barrel, causing uneven, jerky movements and hence fluctuating flow rates. The resultant boluses and periods of no flow have been associated with hemodynamic fluctuations during dopamine infusion in neonates (7). Stiction may also activate pump occlusion or run-away alarms and was the reason for the recent recall of more than a million syringes (8).

Commercial syringes are generally made of polypropylene with an elastomer piston on the end of the syringe plunger. The barrel is lubricated with silicone oil to reduce the coefficient of friction of the piston, while maintaining a seal to prevent solution leakage past the piston (9). Plunger movement is determined principally by the type and amount of lubricant, the interference or squeeze between the piston and barrel, and the amount of compression set (deformation) a constrained piston takes during sterilization and subsequent storage (10). Water washes have been shown to flush a proportion of the silicone lubricant from syringes (11) which may contribute to the reported syringe stiction problem, but the effect of soybean oil emulsion has not been documented. Syringe performance may also be influenced by the way the syringe is used. Syringes may be used after being filled and stored in a refrigerator for periods up to seven days (up to a month if frozen) particularly for

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patients at home, depending on drug stability, microbial quality assurance, convention and supply practicalities at the institution (12, 13). Syringes may also be used multiple times. For example, one may be used to draw up the solvent, inject it into the vial for reconstitution of the powder, draw the drug solution out of the vial once dissolved, and then to inject the drug solution into the patient or infusion device.

The aim of this study was to investigate the effect on syringe performance of syringe use, and the influence of water and of soybean oil emulsion when used in the syringe. In order to achieve this, the force required for syringe plunger motion and the extraction of silicone oil from syringes were evaluated.

Materials and Methods

Syringes

The following syringe brands and sizes were chosen for evaluation: Terumo® 10 mL (Terumo Australia Pty Ltd, Melbourne, Australia, B: 2F205), Terumo 50 mL (B: 2B626), Talus 10 mL (Livingston, Sydney, Australia, B: 23E for extrusion rates and extraction, and B: 18E for storage and repeated use) and Primo® 10 mL (Asik, Rodby, Denmark, B: 0191019691A18 for syringe plunger motion and B: 200289 for silicone oil extraction). Primo brand is known as Pharmaplast®, Once®, Steriseal® and Ersta® in other countries.

Primo syringes have a unique plunger piston consisting of a thin ring made of silicone elastomer (Fig. 1) designed to minimize contact with the barrel and contents in the syringe. The pistons of Talus, Terumo 10 mL and Terumo 50 mL syringes consisted of bromobutyl rubber, Santoprene® rubber (Monsanto Polymer Products Co., Akron OH), and an unspecified rubber respectively.

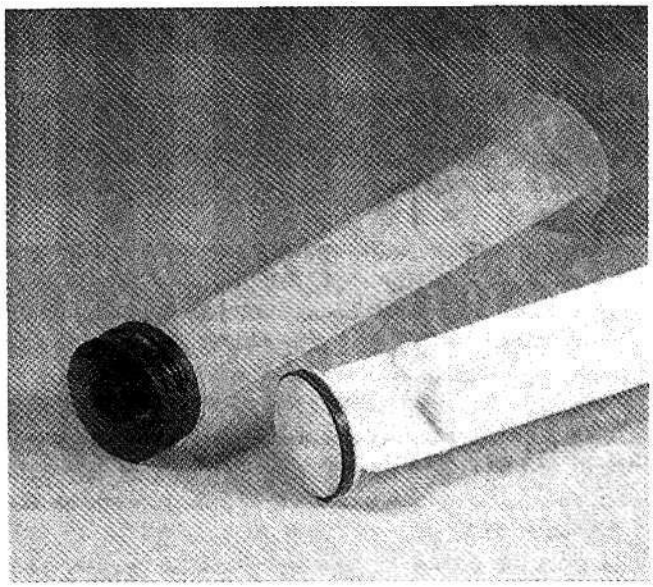

Figure 1—Photograph of the plunger and piston of a conventional syringe (left) and a Primo® brand syringe (right) illustrating the difference in piston design. The piston of the Primo® brand is ring shaped and fits around, rather than over the top of the plunger, to reduce the contact area with the contents of the syringe.

Approximate quantities of silicone oil (polydimethylsiloxane) claimed to be sprayed into the syringes by the manufacturers (personal communication) are Terumo 50 mL—12 mg, Terumo 10 mL—6 mg, Talus 3.5 mg and Primo 2.7 mg. Oil of viscosity 12,500 $mm^2\ s^{-1}$ was used for the Terumo and Primo brands and 350 $mm^2\ s^{-1}$ for Talus brand.

Force Required for Syringe Plunger Motion

The force required to initiate and maintain syringe plunger motion was measured with an adaptation of the methods specified by the Australian Standard (14) and Parenteral Drug Association (10). Syringes were tested at three speeds using two types of apparatus. The speed recommended by the Australian Standard is 50 mm min^{-1} and the others are factors of approximately 20–30 times slower (as practical according to the equipment settings). Nominal speeds were 50, 2.5 and 0.08 mm min^{-1}.

With the apparatus used for testing at 50 mm min^{-1} the syringe was stationary and the force gauge (Accuforce Cadet 0-90 N, resolution 0.1 N, Ametek, Largo FL, U.S.A.) was driven down onto the syringe plunger button. In contrast, with the apparatus used for the 2.5 and 0.08 mm min^{-1} speeds, the force gauge was stationary and the syringe plunger button was driven up against the force gauge. The net effect of both apparatus was the same, the syringe plunger was driven down the barrel at a controlled speed with the force required to do so being continuously measured and recorded. When checked in triplicate with a stopwatch the actual speeds were found to be 47.22 (CV ± 1.38%), 2.53 (CV ± 0.01%) and 0.079 (CV ± 0.04%) mm min^{-1}. The force gauge was calibrated regularly with weights and the error was found to be ±0.2 N in the range used. However, temperature fluctuations during the prolonged runs at the slowest speed, caused drift of zero resulting in errors up to ±1.0 N with the 0.08 mm min^{-1} results.

At least three new syringes were used for each test. When the syringe was filled with liquid, the plunger was drawn a minimal distance past the graduated capacity line, sufficient only to expel the air. With a new, dry syringe the plunger was first fully inserted. The piston seal was then aligned with the nominal capacity line, except for Talus brand which was tested from the graduated capacity line of 12 mL. The syringe was positioned vertically in the apparatus with the nozzle downwards and supported only by the flange. The plunger was straightened in the barrel so that the major axes of the plunger, barrel and force gauge were parallel to prevent lateral forces or rocking of the piston during operation. A fluid collection vessel was positioned under the syringe when required, so that the fluid height did not reach the syringe nozzle during operation.

Data from the force gauge were available and recorded every 0.6 s by an IBM compatible PC on specifically written software. A typical data print-out is shown in Figure 2. Information derived from these data

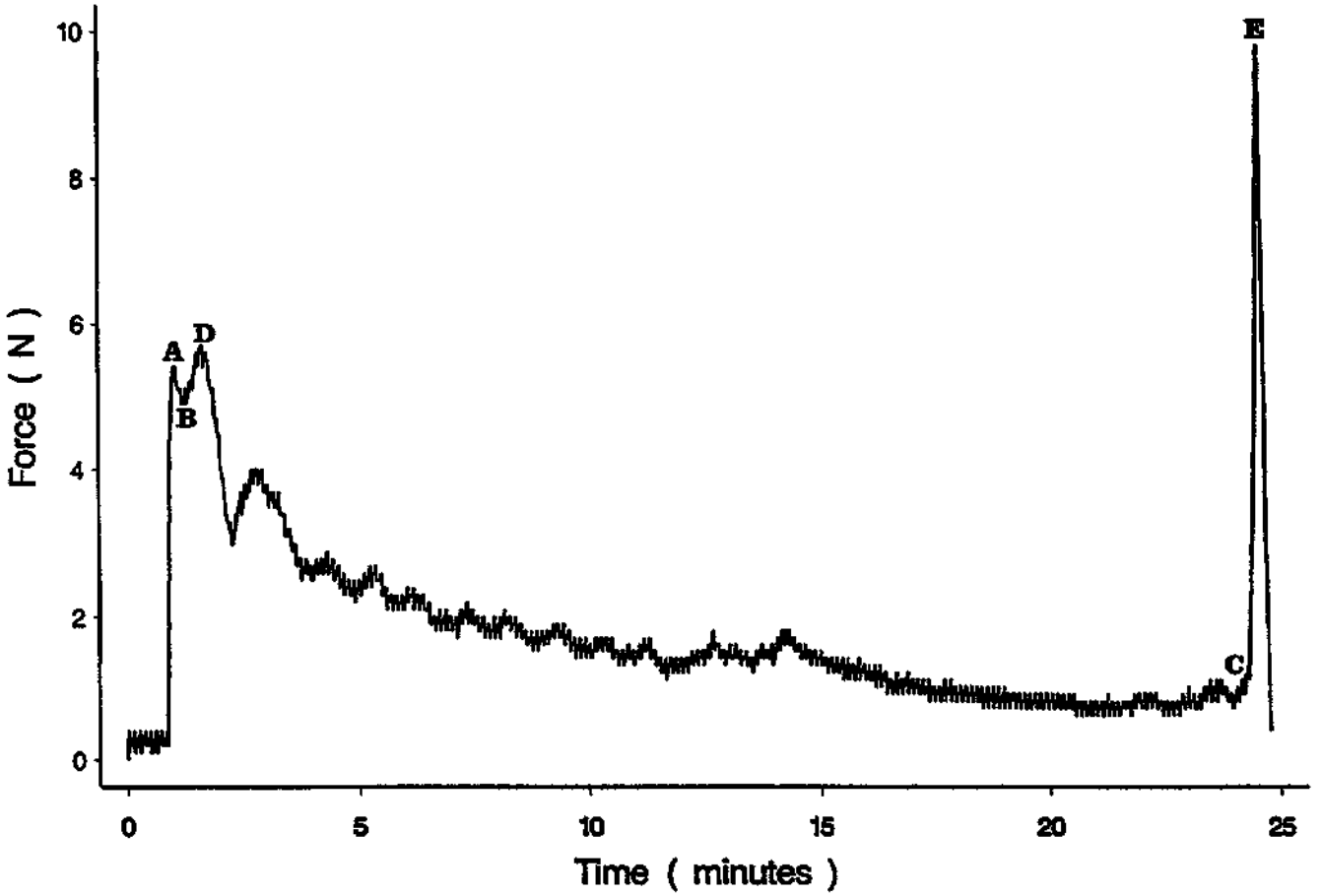

Figure 2—Example of a data printout from a Talus syringe at an extrusion rate of 2.5 mm min^{-1}, illustrating (A) breakloose force, (B) start of average extrusion force, (C) end of average extrusion force, (D) maximum force and (E) piston compressed against end of barrel.

included the breakloose force, average extrusion force, and maximum force. The breakloose force is defined as the force required to commence movement of the plunger, and the extrusion force as that required to maintain plunger movement (9, 10). The average extrusion force excludes the breakloose force and the sharp increase in force at the end when the piston is compressed against the end of the barrel. An average was taken of all readings recorded between these exclusions. The maximum force is simply the highest force recorded during the experiment.

To establish the effect of extrusion rate, Talus syringes were tested at each rate, when used unfilled (i.e., dry), and when filled and used immediately with both milli-Q water and 10% w/v soybean oil emulsion (Intralipid®, KabiVitrum AB, Stockholm, Sweden). All other experiments were subsequently performed at 2.5 mm min^{-1}. The linear least-squares regression method was used to curve fit the data.

The force required to maintain plunger motion after storage filled with water and with soybean oil emulsion was compared with the force when filled and used immediately. Talus syringes were tested after storage filled for one, seven and 91 days prior to use, but Primo and Terumo syringes were tested only after storage for seven days. Differences were evaluated by analysis of variance, and Fisher's protected least significant difference test for multiple comparisons was used to ascertain the origins of any significant ($p < 0.05$) differences.

The effect of repeated use of syringes was investigated by re-using each syringe 12 times when unfilled and also immediately after filling. Talus brand was also tested after storage filled for 91 days prior to repeated use. The linear least-squares regression method was used to curve fit the data.

Silicone Oil Extraction from Syringes

Silicone oil extracted from syringes was measured as silicon using electrothermal atomization atomic absorption spectrometry. It was considered the most appropriate method to achieve the low detection limits required by this study, with minimal sample handling to avoid contamination. Other techniques, notably inductively coupled plasma, have silica components that are likely to produce relatively high background levels when measuring low concentrations of silicon. The silicone oil concentration was calculated on the basis that silicon is 37.91% of the molecular weight of silicone oil of viscosity 12,500 $mm^2 s^{-1}$ (9).

A Varian SpectrAA 40 Zeeman atomic absorption spectrometer equipped with an auto sampler and controlled by an Epson PCAX2 computer was used to quantify silicon concentrations. A pyrolytic coated graphite tube was used for all measurements. The silicon hollow cathode lamp was operated at a current of 10 mA. Absorbance was measured at 215.6 nm with a slit width of 0.2 nm. All absorbances were measured in peak

height. The furnace was operated in ten steps at temperature settings from 85 to 2900°C.

To avoid potential silicon contamination from the environment all syringe manipulations were carried out in a class 10 horizontal laminar air flow cabinet. All equipment was rinsed thoroughly with milli-Q water and allowed to dry under the laminar flow cabinet. Non-lubricated plastic equipment was used for water and soybean oil emulsion to avoid silicon contamination from glassware, but glassware was used with carbon tetrachloride solutions. Care was taken to avoid the use of glassware to store samples and reagents; plasticware was used, and the graphite tube was given a number of "tube cleans" to remove contaminating silicon from the workings of the furnace and establish a suitable base line.

Calibration curves were produced automatically by dilution of a 0.1 mcg mL^{-1} silicon standard solution to 15×10^{-6} L, with 5×10^{-6} L of palladium modifier plus 5 or 10×10^{-6} L of standard solution and 5 or 10×10^{-6} L of blank solution. The standard solution was prepared from a 1 mg mL^{-1} silicon bulk solution (Alpha Resources Inc., Stevensville, U.S.A.). The palladium modifier was used to improve sensitivity and also to facilitate a high ashing temperature (700°C) for the removal of interfering matrix species prior to atomization. The modifier was a 500 mg mL^{-1} palladium solution in 1% v/v hydrochloric acid, that was prepared from palladium metal (Johnson-Matthey, Royston, England) and deionised water was used as the blank. Samples of soybean oil emulsion were spiked with the silicon calibration solution to examine the effect of that matrix on the atomization of silicon (compared to the aqueous medium). It was revealed that there was no significant enhancement or suppression of silicon atomization by the soybean oil emulsion matrix under these conditions. The silicon concentration measured in the fluids before use with the syringes was 182 mcg L^{-1} (SD ± 10) for the soybean oil emulsion and 2 mcg L^{-1} (SD ± 0) for water, and the limit of detection was 2 mcg L^{-1}. Any drift due to degradation of the graphite tube was compensated for by recalibration after every ten samples. Containers with airtight lids were used, and immediately prior to sampling for analysis the sample container was vigorously shaken to disperse the silicone oil.

Three different extractions were performed (three syringes of each brand and size were used) with the soybean oil emulsion (B: 77934-51) and water:

1. Flushing—syringes were filled and emptied repeatedly with each successive flush being expelled into a separate container. Ten flushes were performed but not all were analyzed to rationalize the number of measurements required.
2. Storage with occasional agitation—syringes were filled, stored for seven days, inverted 180° three times for five out of the seven days, and then emptied. For both of the above, the syringes were filled to the nominal volume mark (care was taken not to draw back past this mark to avoid extracting "extra" silicone lubricant from beyond the mark) and inverted 180° three times.
3. Washing—syringes were washed by shaking vigorously (piston aligned with nominal volume mark) with five separate quantities of 1 mL, and the washings were pooled for analysis.

In an effort to extract all the silicone oil present, an adaptation of a method for extraction from elastomeric closures was used (6). Because of the higher concentrations, flame atomic absorption spectrometry was used to determine the silicone oil concentration. Three syringes of each brand and size were washed five times with 1 mL of carbon tetrachloride (AnalaR, BDH Chemicals Ltd, Poole, England) and the washings pooled. The carbon tetrachloride was evaporated and the residue dissolved in methyl iso butyl ketone (MIBK, AR Ajax Chemicals, Auburn, Australia). A Varian 475 flame atomic absorption spectrometer with a nitrous oxide/acetylene flame was used. The silicon hollow cathode lamp was operated at a current of 10 mA with a slit width of 0.2 nm. A stock solution of silicone oil 20 mg mL^{-1} (12,500 $mm^2 s^{-1}$ Dow Corning 200 Silicone Fluid, Dow Corning, Midland MI, U.S.A.) in MIBK was used to prepare calibration solutions of 0, 5 and 10 mg mL^{-1}. The efficiency of silicone oil extraction with carbon tetrachloride washings was validated by washing 3 syringes to which 3.5 mg of silicone oil had been added. Two mL of a 1.75 mg mL^{-1} solution in hexane (AR Ajax Chemicals, Auburn, Australia) were instilled and the hexane evaporated using a vacuum rotary evaporator with a stream of hot air applied to the syringe.

Results and Discussion

The effect of extrusion rate upon the force required to maintain the plunger motion of Talus syringes, when used unfilled, and filled and used immediately with soybean oil emulsion and with water, is shown in Figure 3. The logarithmic and linear curves of best fit to the mean data gave similar results, but the logarithmic curve is shown for clarity of data presentation. The average extrusion force increased as the extrusion rate decreased with soybean oil emulsion (r^2 0.898), as did the maximum force with water (r^2 0.593), but both forces decreased as the extrusion rate decreased when used unfilled (r^2 0.948 and 0.643). The coefficient of determination was less than 0.2 for the average extrusion force with water and the maximum force with soybean oil emulsion. Since there was no clear relationship with extrusion rate, 2.5 mm min^{-1} was chosen for all subsequent experiments because it provided a manageable and convenient time interval (20 minutes compared with 10.4 hours for the 10 mL size at 0.08 mm min^{-1}).

The effect of the duration of fluid storage in Talus brand syringes prior to use is shown in Figure 4. With water, the average extrusion force was significantly greater after storage filled for one, seven and 91 days when compared to filled and used immediately (0 days), but there was no difference between the storage periods (i.e., one and seven days, one and 91 days, seven and 91

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