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The evaluation of the force to expel oily injection vehicles from syringes

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Measurement of the force needed to expel oily injection vehicles from all-glass syringes through hypodermic needles has shown that the force required to maintain various rates of expulsion is in agreement with a modified form of the Poiseuille equation. The flow from disposable plastic syringes with rubber plunger tips fits this equation only if a correction is made to take account of the resistance to movement of the plunger (which is effectively zero for all-glass syringes). This resistance or binding force was shown to be increased by exposure to vegetable oils, and its magnitude was inversely dependent on vehicle viscosity. This increase was caused by swelling of the rubber plunger tips due to uptake of the oily vehicles by the rubber. No such increase in binding force was observed with a viscous aqueous vehicle.

In the formulation of parenteral products it may be desirable to use oily vehicles to modify the rate of drug release or to improve stability (Groves 1973). These vehicles are often sufficiently viscous to be difficult to expel through a hypodermic needle (Hem et al 1974–5). Disposable syringes of the type fitted with rubber plunger tips are widely used and with most oily vehicles the effort required to move the plunger may increase, sometimes to the point where the plunger jams in the barrel. No systematic evaluation of the factors involved in this problem has been reported but Huber (1972) and Levin (1974) have evaluated the difficulty in expelling a limited number of products from syringes.

We set out to describe and quantify the parameters affecting the force needed to expel oily vehicles from syringes since this information, together with a knowledge of vehicle properties, should permit a more rational approach to the selection of a vehicle for injection.

One commonly used type of disposable syringe was used because of the variability between the varieties in use and the effects of oily vehicles on their plungers.

MATERIALS AND METHODS

Vehicles

The oily vehicles used were: ethyl oleate B.P., fractionated coconut oil B.P.C. 1968, sesame oil B.P., ethyl oleate sesame oil mixture 50/50 w/w, fractionated coconut oil/sesame oil mixture 50/50 w/w, ethyl oleate/fractionated coconut oil mixture 50/50 w/w. A glycerol B.P./water mixture 50/50 w/w was also used.

Syringes and needles

These were: all-glass 10 ml centre-nozzle syringes; disposable polypropylene 10 ml centre-nozzle syringes with rubber plunger tips (Plastipak, Becton-Dickinson U.K. Ltd., Middlesex); disposable hypodermic needles of 16, 18, 20 and 21 gauge (Yale, Becton-Dickinson) of nominal length 38·1 mm (1·5 in.) and nominal internal diameters 1·19, 0·84, 0·58 and 0·50 mm respectively.

Viscosity of vehicles

The viscosities of the vehicles were determined at room temperature (20 °C) using a Haake Rotovisko (Gebruder Haake GmbH, Berlin, F.D.R.) fitted with a bob and cup. All vehicles were Newtonian and the viscosities are shown in Table 1.

Force required to expel vehicles from syringes

Syringes were filled with an appropriate vehicle fitted with a needle and supported in a vertical position. The syringes were emptied at various rates

Table 1. Typical values of binding force (f) for disposable syringes after 5 min contact with vehicle (rate of expulsion $0{\cdot}26 \times 10^{-6}\ m^3\ s^{-1}$).

Vehicle	Mean binding force, f (N)	Viscosities (Pa s)
None	2·0	—
Sesame oil	5·7	0·056
Sesame/coconut 50/50 w/w	7·9	0·039
Fractionated coconut oil	9·6	0·025
Ethyl oleate/sesame 50/50 w/w	10·2	0·016
Ethyl oleate/coconut 50/50 w/w	10·5	0·013
Ethyl oleate	20·9	0·006
Glycerol/water 50/50 w/w	2·6	0·006

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by pressing down the plunger with the moving cross-head of a universal testing machine (Instron 1122, Instron Ltd., High Wycombe, Bucks). The force applied to the plunger was monitored with a load cell. With disposable syringes an unsteady force was recorded and the area under the force-time curve was integrated and divided by the time to obtain the average force. This procedure was used for empty syringes both before and after exposure to vehicle and was repeated at least three times for each condition examined on each syringe.

Examination of plunger tips

The rubber plunger tips of disposable syringes were weighed (± 1 mg) and the diameter measured ($\pm 0{\cdot}05$ mm) using an enlarged projected image (Baty Shadowgraph, Baty Ltd., Burgess Hill, Sussex). The syringe was reassembled, filled with a vehicle, left for various periods, dismantled and the plunger cleaned, weighed and measured. The increases in weight and diameter were noted.

THEORY

The force applied to a syringe plunger during expulsion of a liquid via a hypodermic needle would be expected to be dissipated in three ways: (1) overcoming the resistance to movement of the syringe plunger in the barrel (with all-glass syringes this is negligible); (2) forcing the vehicle through the needle; (3) imparting kinetic energy to the liquid. The streamline flow of a newtonian fluid though a narrow tube, such as a hypodermic needle, may be described by a form of the Poiseuille equation modified to allow for kinetic energy losses:

$$P = P_{KE} + Q\,\frac{128\eta L}{D^4}$$

where P (Pa) is pressure, P_{KE} (Pa) is a kinetic energy correction ($=16\rho Q^2/\pi^2 D^4$), Q ($m^3\ s^{-1}$) is flow rate, L(m) is needle length, η (Pa s) is viscosity, D(m) is needle diameter and ρ (kg m^{-3}) is density (Sherman 1970). However, due to the complex shape of a syringe and needle hub, deviations from this relationship might be anticipated.

In the present study the force applied to the syringe plunger F(N), was measured directly and this force is related to pressure P(Pa) on the liquid as follows: $F/A = P$, where A (m^2) is the cross-sectional area of the syringe plunger.

RESULTS AND DISCUSSION

Glass syringes

With the range of vehicles and needle sizes used, plots of force applied to the plunger vs rate of expulsion were straight lines though or very close to the origin in qualitative agreement with the Poiseuille equation (correlation coefficients $>0{\cdot}99$). A quantitative agreement could not be exactly confirmed because the needles had a bevelled end (British Standard 5081 1976) preventing precise definition of the length. However, the effective length calculated from the data lay between the lengths to the base and to the tip of the bevel. The application of the modified Poiseuille equation to expulsion from a syringe is thus justified.

Disposable syringes

Fig. 1 shows that the relationship between mean expulsion force (F) and rate of expulsion (Q) for a 50% w/w glycerol solution ejected from disposable

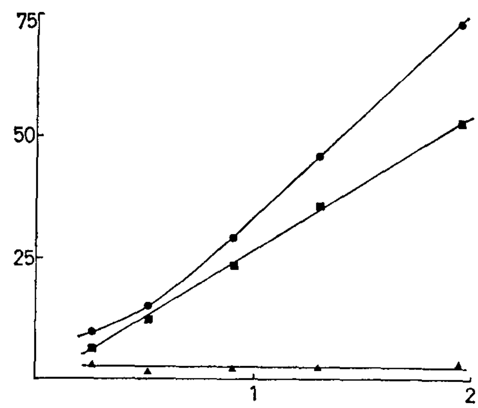

FIG. 1. Expulsion of 50/50 w/w glycerol–water from disposable syringes through 21 gauge needles. Ordinate: total force, F ●; binding force, f ▲; resultant force, $F-(f+F_{KE})$, ■ (N). Abscissa: flow rate ($m^3\ s^{-1} \times 10^6$).

syringes through a 21 gauge needle is non-linear at low expulsion rates. The plungers of empty disposable syringes, unlike those of glass syringes, exhibited a measurable resistance to movement of the plunger or binding force (f). The rate of plunger movement had little effect on binding force. For unused syringes, the mean value of this force was 2·0N (Table 1). After contact with 50/50 w/w glycerol–water, this was slightly increased to 2·6N possibly because the vehicle affected frictional resistance.

When the total force (F) required to expel the aqueous glycerol was corrected for binding (f) and kinetic energy losses ($F_{KE} = P_{KE}A$) determined for each expulsion rate, the resultant force ($R = F - (f + F_{KE})$) was linearly related to the rate of expulsion, as predicted by the Poiseuille equation (Fig. 1, correlation coefficient 0·99).

When disposable syringes were exposed to oily vehicles, the binding forces (ranging from 5·7N for sesame oil to 20·9N for ethyl oleate) were very much greater than after exposure to the aqueous glycerol vehicle (2·6N). The rate of increase in f was variable, being very rapid for the low viscosity oils and slower for those of higher viscosity, and for this reason the contact time between vehicle and syringe was standardized at 5 min (Table 1). The data for ethyl oleate in Fig. 2 exemplify the relationship between applied force and expulsion rate obtained with the

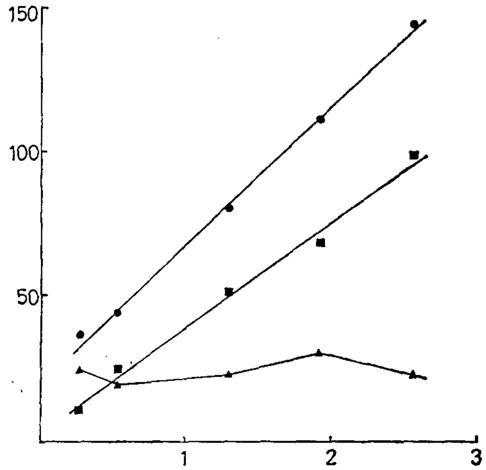

FIG. 2. Expulsion of ethyl oleate from disposable syringes through 21 gauge needles. Ordinate: force (N). Key as Fig. 1. Abscissa: flow rate (m^3 s^{-1} $\times$ 10^6).

oily vehicles and shows that, as with the aqueous glycerol vehicle, the resultant force (R) is linearly related to the rate of expulsion (correlation coefficient 0·99). However, the magnitude of the binding force was significantly higher than that with the aqueous glycerol vehicle (Fig. 1).

Similar linear relationships between resultant force and rate of expulsion were found for all oily vehicles examined. The least square slopes of these plots are linearly related to vehicle viscosity (Fig. 3, correlation coefficient 0·99). As predicted by the Poiseuille equation, this shows that the more viscous vehicles are more difficult to expel if binding is eliminated. However, binding is inversely proportional to vehicle viscosity at an expulsion rate of 0·26 $\times$ 10^{-6} m^3 s^{-1} (Fig. 4, correlation coefficient 0·97) and thus the less viscous vehicles exhibit greater binding forces. A linear relationship is also observed at 0·53 $\times$ 10^{-6} m^3 s^{-1}. However, the slopes of the least-square lines for the two expulsion rates do not coincide. These are the only two expulsion

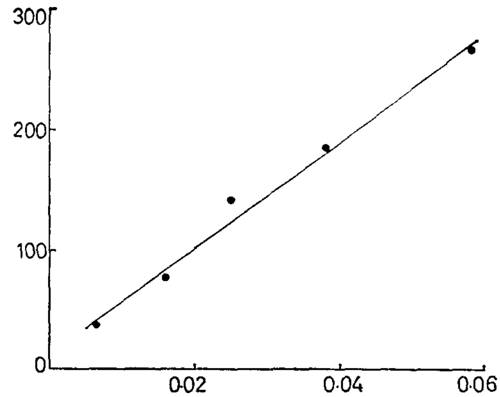

FIG. 3. Relationship between slope of resultant force/expulsion rate plots and vehicle viscosity. Ordinate: Force/flow rate (N m^{-3} s $\times$ 10^{-6}). Abscissa: viscosity (Pa s).

rates at which a significant number of different vehicles was examined. If the data for all expulsion rates are plotted as in Fig. 4 there is considerable scatter, but the general rise in binding force with reciprocal viscosity remains clear.

Investigation of the binding force

To explain the increase in binding force after contact with oily vehicles, and the inverse dependence on vehicle viscosity, the effect of vehicles on the syringe components was investigated. No physical changes, either macroscopic or microscopic in the syringe barrel were observed, even after prolonged immersion. The rubber plunger tips, however, increased in weight with duration of exposure to the oily vehicles, and these increases were inversely related to vehicle

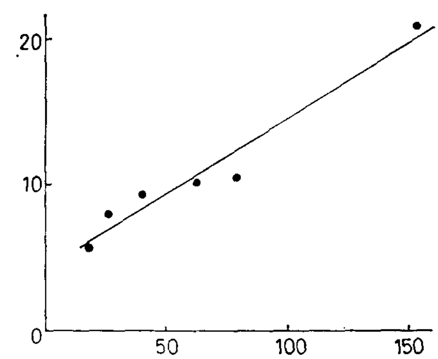

FIG. 4. Relationship between binding force and reciprocal viscosity at a flow rate of 0·26 $\times$ 10^{-6} m^3 s^{-1} for oily vehicles. Ordinate: binding force, f (N). Abscissa: 1/viscosity (1/Pa s). The oils and viscosities are as in Table 1.

viscosity (Fig. 5, correlation coefficient 0·99). A similar relationship was found with plunger tip diameter. This would suggest that the increase in binding force (f) was caused by dimensional changes in the plunger tip due to uptake of oil by the rubber. It is known that rubber will take up vegetable oils and diffusion of the oil into the rubber matrix causes the rubber to swell (Hopkins 1965; Le Bras 1957).

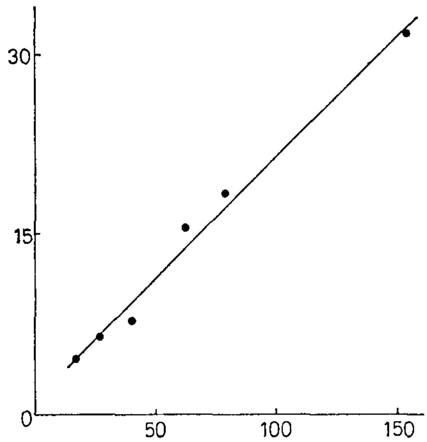

FIG. 5. Relationship between increase in plunger weight at 2 h and reciprocal viscosity for oily vehicles. Ordinate: weight increase (mg). Abscissa: 1/viscosity (1/Pa s).

Both the weight increases and the binding force varied from syringe to syringe. This was probably due to variations in the amount of silicone lubricant (immiscible with vegetable oils), applied by the manufacturer to the rubber plunger tips, which provides a barrier between vehicle and rubber. Such variation was visually obvious with the syringe chosen and other makes of disposable syringe, and has been reported by Miller et al (1969). The increases in plunger weight and diameter, like the binding force, (f), were inversely proportional to vehicle viscosity demonstrating that such physical measurements are predictive of the force needed to expel oily vehicles from this type of disposable syringe.

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