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The availability of nitroglycerin from parenteral solutions

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The availability of nitroglycerin from solutions infused from Viaflex plastic infusion bags or glass infusion bottles through Buretrol plastic giving sets has been examined. Each of the individual components of the infusion bag/giving set system (i.e. infusion bag, burette and infusion tubing) sorbed nitroglycerin to a significant extent. It was found that the extent and rate of nitroglycerin disappearance from solutions stored in each of the components were in the rank order: tubing > burette > infusion bag. The disappearance kinetics of nitroglycerin from solutions stored in each component was more accurately described by a 'diffusion' model than by the 'two compartment kinetic' model reported previously. The dimensions of the components and the volume of solution used were determinants of the rate and extent of nitroglycerin disappearance. In simulated infusions of nitroglycerin through plastic infusion bag (or glass bottle)/giving set system the flow rate of solution through the plastic infusion tubing affected the concentration of nitroglycerin in the effluent and the extent of sorption by the components of the infusion delivery system. The loss of nitroglycerin in these studies could be accounted for solely by the sorption of nitroglycerin by the plastic components of the infusion bag/giving set system.

When drugs are administered by continuous intravenous infusion, knowledge of the rate of drug delivery to the patient is essential. Studies have shown that the availability of insulin (Weber et al 1977), vitamin A (Moorhatch & Chiou 1974a) and diazepam (Parker et al 1979) may be reduced by sorption of the drug by the plastic container during storage. Several communications have reported the interaction of nitroglycerin prepared for intravenous administration with plastic infusion bags, glass infusion bottles (Sturek et al 1978; Ludwig & Ueda 1978; McNiff et al 1979) and plastic giving sets (Cossum et al 1978). Cossum et al (1978) reported that this interaction between nitroglycerin and the plastic giving set resulted in an apparent increase in the dose of nitroglycerin required to achieve a desirable haemodynamic effect in the treatment of myocardial infarction.

According to Roberts et al (1979), the extent to which solutes are lost from plastic containers during storage is dependent on various physicochemical factors such as solute concentration and solution volume. Roberts et al (1979) also suggested that interactions between drugs and plastic containers may be due to sorption of drug by the plastic and/or permeation of the drug into the environment. For nitroglycerin solutions stored in plastic infusion bags, no apparent permeation of nitroglycerin into the environment occurs (McNiff et al 1979), nitroglycerin disappearance from solutions being described by a reversible first order sorption process (Sturek et al 1978). Only some of the physicochemical determinants of nitroglycerin disappearance from solutions during storage or infusion in plastic infusion bag/giving set systems have been reported. It has been suggested by Fung (1978) and McNiff et al (1979) that some discrepancies have appeared in the published papers on the stability of intravenous nitroglycerin solutions.

In the present study, the determinants of nitroglycerin availability from solutions infused from Viaflex plastic infusion bags or glass infusion bottles through Buretrol plastic giving sets have been examined. These determinants included the contribution of each of the individual components in the infusion system to the loss of nitroglycerin during infusion, the infusion rate, the nitroglycerin concentration and the volume of solution in the infusion bag and burette.

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MATERIALS AND METHODS

Materials

Stock solutions of nitroglycerin (5%) in ethanol were obtained from the Department of Manufacturing Industry, Melbourne. Plastic infusion bags (Viaflex, 500 ml) containing either 5% dextrose or 0·9% sodium chloride in water and plastic giving sets (Buretrol) were provided by Travenol Industries,

Melbourne. The main resin and dimensions of the Viaflex infusion bag and Buretrol (burette plus infusion tubing) are given in Table 1. All stock solutions were prepared in glass distilled water unless otherwise specified.

Table 1. Derived kinetic constants for the sorption of nitroglycerin by infusion bags, burettes and tubing, and the nature of the container used.

Parameter*	Bag	Burette	Tubing
Composition (main resin)	polyvinyl chloride	cellulose propionate	polyvinyl chloride
V (ml)	500	150	7·9
A (cm^2)	360	150	148
W_p (g)	25	11	8·1
F_∞	0·405	0·100	0·070
α	0·681	0·111	0·075
K	29·4	122·7	12·9

* V = volume of solution, A = surface area of plastic in contact with volume V, W_p = weight of plastic component, and F_∞, α and K are defined in the text.

Analysis

Aqueous solutions of nitroglycerin were assayed by a slight modification of the kinetic assay of Yap et al (1975). In the present kinetic assay, a blank solution consisting of 1 ml of sample and 2 ml of water was used for reference.

Storage in infusion bags, burettes and tubing

To infusion bags containing 500 ml (unless otherwise stated) of water, 0·9% NaCl (saline) or dextrose solution, a known volume of ethanolic nitroglycerin was added to give a final concentration of 0·01 to 0·1%. For most of these studies, the concentration used was 0·02%. After mixing of the nitroglycerin in the bag by quick shaking, samples (1–5 ml) were withdrawn at regular intervals and stored in glass bottles with metal screw caps until analysed. During the storage experiments, the bags were kept upright to expose the maximum surface area of the bag to the environment.

The burettes were separated from the giving sets and their outlets closed with metal screw clamps. Solutions of nitroglycerin (150 ml unless specified otherwise) were added to the burettes and the disappearance of nitroglycerin monitored by analysing aliquots of the solution at specified times.

The disappearance of nitroglycerin from solutions stored in the plastic infusion tubing from the Buretrol giving sets was studied using lengths of tubing filled with nitroglycerin solution. Both ends of each piece of tubing were closed by means of screw clamps. At specified times the concentration of nitroglycerin in the solution was analysed.

Simulated infusions

The infusion of nitroglycerin to patients was simulated in the laboratory. The solutions of nitroglycerin (0·02% in saline) were prepared in both plastic infusion bags and glass infusion bottles either immediately or 24 h before the infusion. A bag or bottle containing nitroglycerin was then attached to a giving set consisting of either tubing alone or burette plus tubing and the solution allowed to flow through at a constant rate. The effluent from the giving set was then collected at specified times for analysis.

All storage studies and simulated infusions were carried out at least in duplicate at ambient temperature (20–24 °C).

RESULTS AND DISCUSSION

Disappearance kinetics of nitroglycerin from the infusion bag, burette and tubing during storage

The fraction of nitroglycerin remaining in solution after various times of storage in plastic infusion bags, plastic burettes and lengths of infusion tubing are shown in Fig. 1. Significant nitroglycerin disappearance is observed for each of the three components of the plastic infusion bag/giving set system. The most rapid and extensive disappearance was found for solutions of nitroglycerin stored in lengths of plastic infusion tubing where after approximately 5 h about 8% of the original nitroglycerin concentration remained in solution (Fig. 1).

During the storage of nitroglycerin solutions in infusion bags burettes and lengths of tubing, the nitroglycerin concentration declined initially and then became constant (Fig. 1). Nitroglycerin is therefore probably lost from solution by sorption into each of the plastic components. If permeation of nitroglycerin into the environment were significant, the disappearance of nitroglycerin from solution would be characterized by a biexponential disappearance profile (Roberts et al 1979). McNiff et al (1979) have shown that all of the nitroglycerin lost during storage of solutions in plastic infusion bags could be recovered by desorption into methanol. Although loss of nitroglycerin to the environment during the storage of nitroglycerin tablets has been reported (Pikal et al 1977), it is probable that the negligible permeation of nitroglycerin into the atmosphere apparent in the present study (Fig. 1) results from the high affinity of the plastic components of the infusion bag/giving set system for

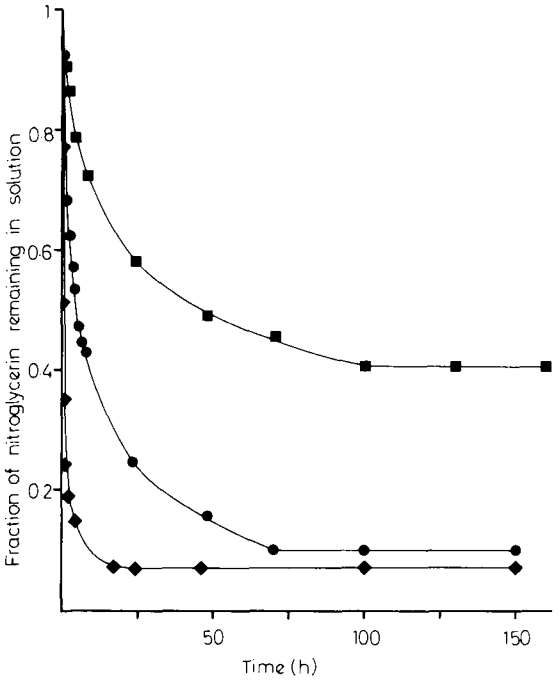

FIG. 1. Disappearance of nitroglycerin from solutions (0·02% nitroglycerin in water) stored in infusion bags (■) burettes (●) and plastic tubing (◆) for various times.

nitroglycerin (and therefore a low nitroglycerin vapour pressure in the plastic environment).

The disappearance kinetics of solutes from solutions stored in plastic containers has been described by a two compartment kinetic model (Sturek et al 1978; Roberts et al 1979) and by a diffusion model (Richardson et al 1977). According to the 'closed two compartment kinetic' model used by Sturek et al (1978) to describe the sorption of nitroglycerin from solutions stored in plastic infusion bags, the fraction of nitroglycerin remaining in solution (F_t) at various times (t) is given by the equation

$$\ln\left(\frac{F_t - F_\infty}{1 - F_\infty}\right) = -kt \qquad .. \quad (1)$$

where F_∞ is the fraction of nitroglycerin remaining in solution, and k is the first order rate constant for disappearance. When $\ln[(F_t - F_\infty)/(1 - F_\infty)]$ was plotted against time for the data obtained in the present work for nitroglycerin disappearance from solutions stored in infusion bags, burettes and lengths of tubing, the resulting regression lines did not pass through the origin in accordance with equation (1). The regression lines predict that the fractions of nitroglycerin remaining in solutions stored in infusion bags, burettes and infusion tubing at zero time are 0·78, 0·74 and 0·64, respectively. Furthermore, as shown in Fig. 2 for the infusion bag, the individual data were not randomly distributed about the regression lines. The present data were better described by a diffusion model in which the fraction of nitroglycerin remaining in solution (F_t) at various times (t) is given by equation (2)

$$\frac{F_t - F_\infty}{1 - F_\infty} = \sum_{n=1}^{\infty} \frac{2\alpha(1+\alpha)}{1 + \alpha + \alpha^2 q_n^2} \exp(-q_n^2 Dt/l^2) \qquad (2)$$

where α equals $F_\infty/(1 - F_\infty)$, q_ns are the non-zero positive roots of $\tan q = -\alpha q$, and D is the diffusion coefficient of solute in plastic of thickness l. Equation (2) was derived from equations given by Crank (1948) and Carman & Haul (1954) to describe the sorption of solutes from a 'stirred solution of limited volume by a plane sheet'. In the present context, it is assumed that (1) the concentration of nitroglycerin sorbed by the plastic is proportional to the free concentration of nitroglycerin, (2) diffusion of nitroglycerin in the matrix of the plastic is the rate determining step in the sorption process, (3) the properties of the plastic and the diffusion coefficient of nitroglycerin in the plastic remain unaltered during the sorption process, (4) the concentration of nitroglycerin in the aqueous solution at any time is independent of position, and (5) sorption of nitroglycerin by the plastic is restricted to the area in contact with solution. Fig. 2 shows that for the infusion bag data, equation (2) more accurately describes the disappearance kinetics of nitroglycerin during storage than equation (1). Similar plots were found for the burette and tubing (an alternative expression for equation (2) (Crank 1948) is used for small times with the burette and tubing as equation (2) converges slowly at these times). Thus, the disappearance of nitroglycerin from solutions stored in plastic infusion bags, burettes and lengths of tubing appears to be determined primarily by the diffusivity of nitroglycerin in the plastic ('diffusion' model) rather than by transfer of nitroglycerin across the solution-plastic interface ('compartment kinetic') model.

From the final fractional uptake ($1/\alpha$) of nitroglycerin by the plastic, an apparent distribution coefficient (K) of nitroglycerin between the plastic and solution can be estimated:

$$K = \frac{\rho V}{W_p \alpha} = \frac{(1 - F_\infty)\rho V}{F_\infty W_p} \qquad .. \quad (3)$$

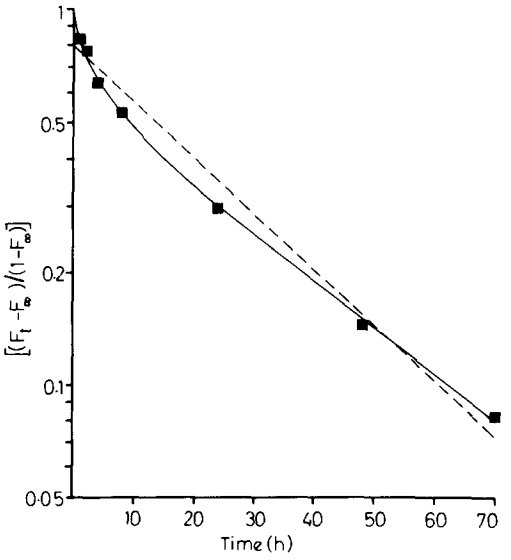

FIG. 2. Relation between 'closed two compartment kinetic' model (– –) and 'diffusion' model (——) plots of fraction of nitroglycerin remaining to be sorbed by plastic $[(F_t - F_\infty)/(1 - F_\infty)]$ versus time (t) and experimental data (■) for solutions of nitroglycerin stored in plastic infusion bags. (F_t is the fraction of nitroglycerin remaining in solution at time t and F_∞ is the equilibrium fraction of nitroglycerin remaining in solution. For the 'closed two compartment kinetic' model regression line is $ln\,[(F_t - F_\infty)/(1 - F_\infty)] = -0{\cdot}034t - 0{\cdot}22$; values of $\alpha = 0{\cdot}681$, $D/l^2 = 0{\cdot}0062\ h^{-1}$ have been substituted in equation (2) for the 'diffusion' model line.)

where V is the volume of solution of density ρ in contact with a given weight (W_p) of plastic and F_∞ is the equilibrium fraction of nitroglycerin remaining in solution. The apparent partition coefficients obtained for nitroglycerin in the present work (Table 1) suggest that the order of decreasing affinity of the components for nitroglycerin are burette > infusion bag > tubing (Table 1). Pikal et al (1977) have shown that the sorption of nitroglycerin by plastics is a function of the nature of the polymer and its density. They reported that the order of decreasing affinity of nitroglycerin for plastics was vinyls ≫ low density polyethylene > ionomers > high density polyethylene. The present results would suggest that the affinity of nitroglycerin for cellulose propionate (i.e. burette) is greater than that for polyvinylchloride (i.e. infusion bag and tubing). Cossum et al (1978) reported that the rate and extent of disappearance of nitroglycerin from high density polyethylene tubing during infusion was much less than for the infusion tubing used in this study, consistent with the rank order of nitroglycerin affinity for plastics proposed by Pikal et al (1977). The interaction of drugs with polyvinyl chloride is also a function of the type and concentration of plasticizer (Bray & Meakin 1977). Although it has been suggested by Moorhatch & Chiou (1974b) that di-2-ethylhexyl phthalate or a similar plasticizer is present in Viaflex bags, the exact composition of the bags and the plastic infusion tubing was not available to us. It was therefore not possible to relate differences in the nitroglycerin partition coefficients for the infusion bag and infusion tubing (Table 1) to differences in the composition of these components.

Whereas the apparent partition coefficient (K) can be estimated accurately, the diffusion coefficient (D) of nitroglycerin in the plastic obtained by solving equation (2) is less reliable as it is a function of several variables as specified in equation (2) and depends on model assumptions being fulfilled. For instance, the assumption (4) that the concentration of nitroglycerin in aqueous solution at any time is independent of position may not necessarily be met for solutions of nitroglycerin stored in lengths of infusion tubing. For the tubing, the uptake of nitroglycerin by the plastic is both rapid and extensive (Fig. 1) so that the concentrations of nitroglycerin in the solution adjacent to the plastic may be significantly lower than elsewhere. However, the faster sorption rate of nitroglycerin by the tubing compared with the burette and the infusion bag (Fig. 1) is consistent with its greater final fractional uptake in accordance with equation (2).

Volume

Fig. 3 shows the effect of solution volume on the fraction of nitroglycerin remaining in solutions stored in infusion bags and burettes for various times. For the infusion bags, the fraction of nitroglycerin remaining in solution decreases more rapidly with time for the smaller volumes (Fig. 3a). The disappearance rate of nitroglycerin from solution is therefore related to the surface area of plastic with which a given volume of solution is in contact. This surface area of plastic to volume of solution ratio increases as the volume of solution in the bag is decreased (e.g. during nitroglycerin infusion) due to the 'collapsing' of the bag. Thus, the concentration of nitroglycerin in the smaller volumes decreases to a greater extent with time than that for the larger volumes. Polack et al (1970) and Roberts et al (1979) have also shown that the disappearance of solutes from plastic containers during storage is a function of the surface area of plastic per unit volume of solution.

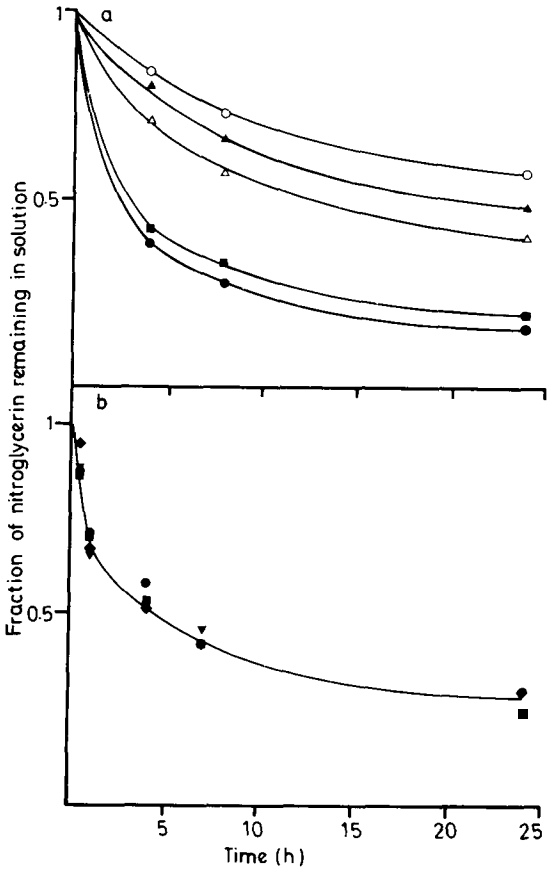

FIG. 3. Effect of volume of nitroglycerin solutions (0·02% nitroglycerin in water) stored in plastic infusion bags (a) and burettes (b) on the fraction of nitroglycerin remaining in solution at various times. ▼ 10 ml; ● 50 ml; ■ 100 ml; ◆ 150 ml; △ 200 ml; ▲ 300 ml; ○ 500 ml.

For all volumes of solution stored in the burette, the surface area of plastic per unit volume of solution is constant when the contribution of the base of the burette (a high density plastic) to the total surface area is neglected. Consequently, the fraction of nitroglycerin remaining in aqueous solutions stored in the burettes for various times appears to be independent of the volume of solution in the burette (Fig. 3b).

Concentration and other variables

Fig. 4 shows representative plots of fraction of nitroglycerin remaining in aqueous solutions stored in plastic infusion bags versus time for initial nitroglycerin concentrations of 0·01 and 0·05%. For these and other concentrations of nitroglycerin employed

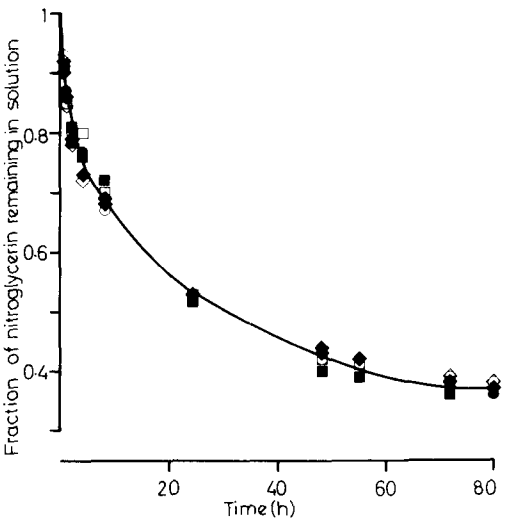

FIG. 4. Fraction of nitroglycerin remaining in solution for original nitroglycerin concentrations of 0·01% (open symbols) and 0·05% (closed symbols) following storage in plastic infusion bags at various times (h). ○● water; □■ dextrose (5%) in water; ◇◆ saline.

(range 0·01–0·1%), plots of fraction of nitroglycerin remaining in solution versus time appeared to be superimposable i.e. the fraction of nitroglycerin sorbed from solution by the infusion bag is independent of the concentration of nitroglycerin used. The fractions of vitamin A and methohexital sorbed from solutions by Viaflex plastic infusion bags also appear to be independent of concentration, whereas for warfarin, the fraction sorbed decreases with increasing warfarin concentrations (Moorhatch & Chiou 1974a). In a recent publication, Parker et al (1979) have reported that the percentage loss of diazepam from infusion bags was a function of concentration. Their results could also be explained in part by differences in the surface area of plastic per unit volume of solution for the two concentrations used.

It has been suggested by Fung (1978) and McNiff et al (1979) that some discrepancies have appeared in the literature concerning the stability of nitroglycerin solutions for intravenous use. In the present work, the loss of nitroglycerin from aqueous solutions stored in glass containers (with metal screw caps) over 96 h was minimal (<5%), consistent with the observations of McNiff et al (1979). Other studies (Sturek et al 1978; Ludwig & Ueda 1978) had showed some loss of nitroglycerin stored in glass containers. In the study of Ludwig & Ueda (1978), loss probably

arises from interaction of nitroglycerin with the rubber/plastic components (e.g. bung, administration set) of the bottles as described. The lack of effect of normal saline and 5% dextrose on the disappearance rate of nitroglycerin from aqueous solutions stored in plastic infusion bags (Fig. 4) is consistent with the previous report of Sturek et al (1978). Sturek et al (1978) and Ludwig & Ueda (1978) also found that the stability of aqueous nitroglycerin solutions was not affected by light.

Simulated infusions of nitroglycerin through plastic infusion tubing

When solutions of nitroglycerin were infused through plastic infusion tubing (from the Buretrol giving sets) from glass infusion bottles, the concentration of nitroglycerin in the effluent diminished immediately after beginning the infusion and then gradually increased for longer times (Fig. 5a). Consistent with the reversible first order sorption of nitroglycerin by the tubing (Fig. 1), the concentration of nitroglycerin in the effluent diminishes initially until an appreciable accumulation of nitroglycerin in the tubing becomes apparent. The extent and rate of nitroglycerin sorption by the tubing then begins to diminish, resulting in an increased concentration of nitroglycerin in the effluent. For longer times, the sorption of nitroglycerin by the infusion tubing will continue until an equilibrium is reached and the concentration of nitroglycerin in effluent will then equal the prevailing concentration of nitroglycerin in the glass infusion bottle.

Fig. 5a also shows that the concentration of nitroglycerin appearing in the effluent from the tubing in the infusion system is a function of infusion rate. Lowest concentrations of nitroglycerin in the effluent are observed for the slowest flow rates where the contact time of a given volume of solution with plastic is greatest. The times for the minimum concentrations of nitroglycerin in the effluent reflect the time required for the solution in the tubing at the beginning of the infusion to pass through the tubing. Subsequent solution entering the tubing from the glass infusion bottle will have a higher concentration of nitroglycerin in its effluent due to significant sorption of nitroglycerin by the tubing from the initial solution. Since the tubing contains approximately 8 ml of solution, times of about 10, 15 and 35 min would be anticipated for flow rates of 0·75, 0·52 and 0·23 ml min^{-1} respectively. The observed times for minimum concentrations of nitroglycerin in the effluent (Fig. 5a) are of similar magnitude to these values for corresponding flow rates. For all

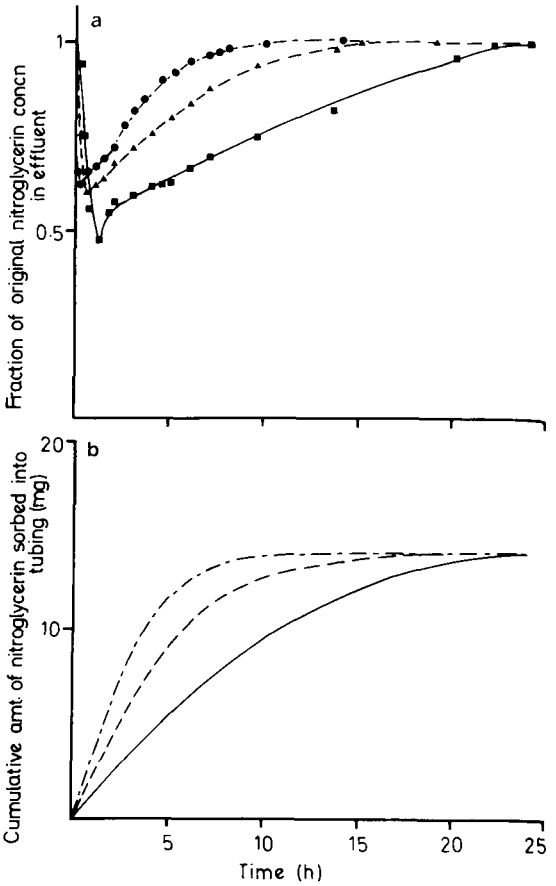

FIG. 5(a). Fraction of original nitroglycerin concentration in the effluent (ordinate) at various times (h) for solutions (0·02% nitroglycerin) infused from a glass infusion bottle through plastic infusion tubing at constant rates. — · — · 0·75 ml min^{-1}; — — 0·52 ml min^{-1}; —— 0·23 ml min^{-1}. In FIG. 5(b) the cumulative amount of nitroglycerin sorbed into the tubing (mg) for these flow rates is plotted as a function of time (h).

flow rates, the concentration of nitroglycerin in the effluent eventually returns to the original concentration of nitroglycerin in the infusion bottle (Fig. 5a). Loss of nitroglycerin during these infusions therefore arises solely from sorption by the plastic tubing. If decomposition, adsorption to the glass infusion bottle or loss to the external (atmosphere) environment had occurred, the concentration of nitroglycerin in the effluent for long times (i.e. steady-state) would not approach the original nitroglycerin concentration in the glass infusion bottles.

Using the data in Fig. 5a, the cumulative amount of nitroglycerin sorbed by the plastic infusion tubing was estimated and plotted as a function of time (Fig. 5b). Since the sorption of nitroglycerin by the

plastic is a concentration dependent process, greatest rates of sorption are found at the faster flow rates where the concentrations of nitroglycerin in solution throughout the entire length of tubing are higher than for the lower flow rates. Consistent with an equilibrium sorption process, the total cumulative amount of nitroglycerin sorbed by the plastic infusion tubing is independent of flow rate (Fig. 5b).

Since the sorption of nitroglycerin by the plastic infusion tubing is an equilibrium process, accurate delivery of known amounts of nitroglycerin to the patient could theoretically be achieved by pretreating the tubing before an infusion. For instance, the tubing could be flushed with solution from the attached glass infusion bottle at a rapid rate until the nitroglycerin concentration in the effluent approached the original nitroglycerin concentration in the bottle. It can be calculated from the data in Fig. 5 that approximately 350 to 400 ml of solution containing nitroglycerin should be flushed through the tubing over several hours to adequately pretreat the tubing before an infusion of nitroglycerin.

Simulated infusions of nitroglycerin through plastic infusion bag/giving set systems

Fig. 6 shows the effect of adding the plastic infusion bag (Viaflex) and burette (Buretrol) to the infusion tubing on the concentration of nitroglycerin appearing in the effluent of the tubing (Fig. 6a) and the corresponding amount sorbed by the plastic components (Fig. 6b) for various times of infusion. During the initial stages of infusion, the concentration of nitroglycerin in the effluent diminishes primarily as a result of sorption by the infusion tubing. At longer times, sorption of nitroglycerin by the infusion bag becomes more significant (Fig. 6), consistent with the slower process of sorption by the burette and infusion bag compared with the infusion tubing (Fig. 1). Thus, within the time course of these experiments, a final equilibrium was never reached so that the apparent steady-state concentration of nitroglycerin in the effluent is less than the original nitroglycerin concentration in the plastic infusion bag/glass infusion bottle as a result of sorption into the infusion bag and burette. Obviously, if a solution is prepared in the infusion bag 24 h in advance, the concentration of nitroglycerin in the effluent from the giving set will be diminished to an extent corresponding to sorption by the plastic infusion bag over 24 h (Fig. 6).

Cossum et al (1978) showed that the concentrations of nitroglycerin appearing in the effluent of solutions infused through plastic giving sets from glass infusion bottles were a function of flow rate. The lower 'apparent steady-state' concentration of nitroglycerin in the effluent for the slower flow rates observed in that work can be attributed to a combination of sorption of nitroglycerin by the burette (with long contact time of a given solution) and the slower rate of sorption of nitroglycerin by the tubing at these flow rates (Fig. 5). The present work further demonstrates the complexity of the nitroglycerin interaction with the plastic infusion bag/giving set system. Since prediction of the concentra-

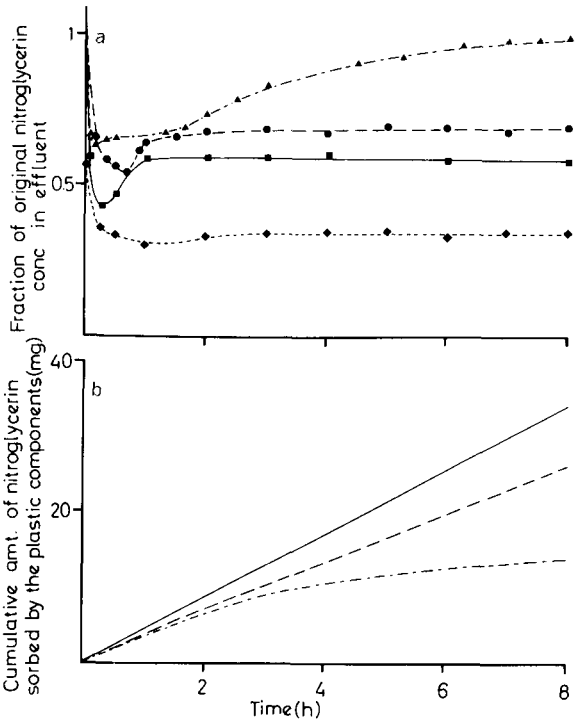

FIG. 6(a). Simulated infusions of nitroglycerin from various plastic infusion bags (or glass infusion bottles)/giving set systems. All nitroglycerin solutions (0·02%) were infused through the infusion tubing at a constant rate of 0·75 ml min^{-1}. — - — glass infusion bottle plus infusion tubing; — — glass infusion bottle plus Buretrol giving set (i.e. burette plus infusion tubing); —— Viaflex plastic infusion bag plus Buretrol giving set; - - - - Viaflex plastic infusion bag Buretrol giving set where nitroglycerin solution prepared in infusion bag 24 h before infusion. In FIG. 6(b) the cumulative amount of nitroglycerin sorbed (mg) by the plastic components in the infusion bag(bottle)/giving set system is plotted against time (h) for the first three infusion systems (the last infusion system (- - - -) is not included in Fig. 6 (b) because more than 40 mg of nitroglycerin is sorbed by the infusion bag before the infusion).

tions of nitroglycerin in the effluent of infusions is complicated, the alternative method of nitroglycerin infusion via a short piece of high density polyethylene tubing with a syringe pump as recommended by Cossum et al (1978) is to be preferred to the conventional plastic infusion bag/giving set system.

Conclusion

The present study has examined the kinetics of nitroglycerin interaction with plastic infusion bags and giving sets. It is likely that other drugs also interact with plastic infusion bags and giving sets leading to a reduced clinical effectiveness of the drug. There is therefore a need to understand the extent, rate and nature of the interaction of drugs given by intravenous infusion with their delivery systems. This type of study is important in the packaging of pharmaceuticals in plastic containers in general. For instance, Richardson et al (1977) and Blackburn et al (1978) have shown that the concentration of preservatives in some commercially available ophthalmic preparations may be less than that stated on the label. Although for most drugs, the interaction between drugs and the plastic container/delivery system is unlikely, the possibility of such an interaction (and its implications with respect to drug therapy of a given patient) cannot be overlooked.

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