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RESEARCH ARTICLE

A Study of the Interaction of Selected Drugs and Plastic Syringes

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ABSTRACT: It is common hospital pharmacy practice to preload syringes with selected drugs and store them ready for use. Because the several components of syringes, (such as barrels, gasket seals, etc.) may vary among manufacturers, there exists the possibility that syringe components of differing provenance might interact e.g., by sorption, with stored drugs to differing degrees. To examine possible interactions, three brands of commercially available syringes were compared to determine what influence, if any, short term storage of injectable solutions might exert on the solutions or the syringes. Four drugs; dexamethasone sodium phosphate, diazepam, diatrizoate meglumine and nitroglycerin USP were individually loaded into 3 mL syringes and stored at temperatures between −20°C and +25°C for periods from 6 hours to 30 days. The syringes were examined for any gross changes. Drug solutions were analyzed after storage to determine the presence of organic leachates from the syringes and any change from original drug concentration values. No syringes showed gross physical changes after storage with drug solution nor were any drug solutions found to contain leachates on gas chromatographic-mass spectroscopic analysis. Drug concentrations were seen to change following storage, the greatest changes occurring with the highly lipophilic drugs dexamethasone and diazepam. In most instances loss of drug concentration was most rapid at room temperature. Although there were clear differences among the three brands of syringe, no overall pattern emerged which might allow the selection or rejection of one syringe over another for the extemporaneous preloading of the drugs examined.

Background

Hospital services frequently have need for a range of drug solutions in quickly available injectable dosage forms. Certain drugs, for example, narcotics or aminoglycosides, for which there is frequent need, are available packaged in syringes as sterile unit doses by their manufacturers. Other less frequently used or less stable drugs, such as some antibiotics or amines are transferred or reconstituted to syringes from single or multiple dose containers by hospital personnel at the time of use. In instances in which drugs are not available prepackaged in syringes in the sizes or doses wanted, hospital pharmacies meet the need by aseptically preloading sterile drug solutions into sterile syringes and storing the resultant unit dose form for short periods at room, refrigerator or freezer temperatures.

Because the several components of syringes, e.g., plastic barrels, seals, vary among manufacturers there exists the possibility that syringe components might interact with stored drugs to differing degrees.

To examine the possible interactions of drugs and syringe component materials, three brands of commercially available syringes were compared to determine what influence, if any, short term storage of injectable solutions might exert on the solutions or the syringes. The drugs examined included dexamethasone sodium phosphate, diazepam, diatrizoate meglumine and nitroglycerin USP. The selected drug solutions were loaded into 3 mL plastic syringes sealed with commercially available syringe caps and stored in the dark at temperatures between −20 and +25 °C for periods ranging from 6 hours to 30 days. The syringes were examined for gross physical changes; drug solutions were analyzed to determine the presence of organic leachates from the syringes and for changes in drug concentration.

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Experimental Section

Materials

Three brands of 3 mL plastic syringe, each from a single manufacturer's lot, were utilized in the study: Becton-Dickinson lot No. 9D233, Sherwood Monoject lot No. 221873 and Terumo lot LE248MIX1. Four drugs, each from a single lot, were employed: dexamethasone sodium phosphate injection, USP, 4 mg/mL, (Quad Pharmaceuticals lot No. 405H51), diazepam injection, USP, 5 mg/mL (Warner Chilcott Labs lot No. 053D7) diatrizoate meglumine/diatrizoate sodium (Squibb Diagnostics) lot No. 9A47196) and nitroglycerin injection USP (Dupont Pharmaceuticals Tridil brand lot No. 8CA202). Syringe seals (Sherwood Medical Corp. Tip Cap brand, lot No. 67965) were used to close each syringe after filling.

All samples were coded and blinded and this information was not available to the analysts.

Sample Preparation

Syringes from each brand/lot were randomly divided into four groups of 18, numbered and assembled into four sets of 54, each set containing an equal number of syringes of each brand/lot. At appropriate times three syringes of each brand/lot were loaded with approximately 2.5 mL of one drug solution, capped, weighed to the nearest 10 mg, and exposed to thermal stress for one of the time at temperature periods listed below:

temperature °C	time in days
−20	30
−20	1
4	7
4	1
25	1
25	0.25

At the end of a time period at temperature the weight of each syringe and contents was checked to determine whether any appreciable loss had occurred. The two samples which changed weight by more than 5 mg were removed from the study. From all drug solution/syringe combinations which were unchanged in weight after storage, an aliquot of drug solution was taken for assay of drug content and the remainder was transferred and sealed into clean dry 2 mL prescored glass ampuls (Fisher Scientific Company No. 01-215B) for determination of leachants. In the instance nitroglycerin, in which it was not practical to conduct the assay for drug content immediately after a storage at temperature period, the contents of all syringes and an aliquot from a previously unbroached vial of drug to serve as control were promptly transferred to and sealed in clean dry 2 mL prescored glass ampuls for storage overnight at 4°C until the assay could be performed.

General Description of Assays for Leachants: Hexane extractions were performed on all samples and examined by gas chromatography/mass spectroscopy (GC/MS) for specific compounds previously identified as additives and reaction products of some of the syringe plunger gaskets (diethylhexyl phthalate (DEHP), acridine, hydrazine).

Specific Assay for Volatile Extractables: A 1.5 mL aliquot of the sample drug solution which had been in contact with a test syringe was added to a clean, dry test tube along with 1.0 mL hexane and 0.5 mL saline. The tube was vortexted for 30 seconds and the upper organic layer was aspirated into GC sample vials and crimped closed. One microliter samples were injected on-column and evaluated isothermally at 280° with a gas chromatograph (Hewlett Packard 5890) and mass selective detector (Hewlett Packard 5970) in the mass range between 50 and 600 atomic mass units (amu).

Extracts of blanks (drugs that were not stored in syringes), as well as blanks with 10 ng of carbon-13-labeled and unlabeled DEHP added, were prepared and analyzed. In addition, scans for specific ions which are characteristic of particular compounds were performed. For example, 149 amu is characteristic of phthalates extracted from the elastomeric silicone seal component of some syringes, while 169 amu and 194 amu are characteristic of hydrazine and acridine degradation products of some rubber seals.

General Description of Assays for Drug Concentration: For the assay of dexamethasone sodium phosphate, diatrizoate and diazepam, aliquots of the same commercial formulation as used in the study were drawn from the original container and accurately diluted with distilled water or aqueous methanol, as appropriate, to provide concentrations with absorbance maxima in the range between 1 and 2 absorbance units (A.U.) in the ultraviolet region between 230 and 350 nm. For nitroglycerin, the solution was utilized in a diazotization reaction providing a chromophoric product which, suitably diluted, provided coupled product concentrations with absorbances at about 455 nm in the range near 1.00 A.U. These dilutions were scanned to determine the wavelength of maximum absorbance for each drug.

New samples were accurately diluted to provide triplicate dilutions from which a standard curve for each drug at its wavelength of maximum absorbance was prepared and the corresponding regression equation generated. Standard curves and regression equations were based either on measured absorbances or on ratios of areas under elution curves. In the instance of diazepam, a constant amount of tolualdehyde was added to each of the dilutions to serve as internal standard in the high performance liquid chromatographic assay. For all drugs the average of triplicate determinations were employed to generate standard curves. Standard curve regression equations are presented below. The wavelengths of maximum absorbance and the standard dilutions used in assays of the four drugs are shown below:

Assay Wavelengths and Dilutions Employed in Assays

Drug	Wavelength (nm)	Dilution
dexamethasone sodium phosphate	242	1:200
diatriazoate meglumine	244	1:20000
diazepam	254	1:10
nitroglycerin	455	1:100

Specific Assays

Dexamethasone sodium phosphate injection:

The absorbance of an accurate distilled water dilution of 0.5 mL of sample to 100 mL was measured at 242 nm against a water blank. The remaining percent of original concentration was calculated using the regression equation:

$$\text{percent remaining} = 0.0045(A) + 1.447$$

where A is the absorbance measured at 242 nm; $r = 0.998$.

Diatrizoate meglumine injection: The absorbance of 0.005% (V/V) solution in distilled water was measured at 244 nm against a water blank and the remaining percent of original concentration was calculated using

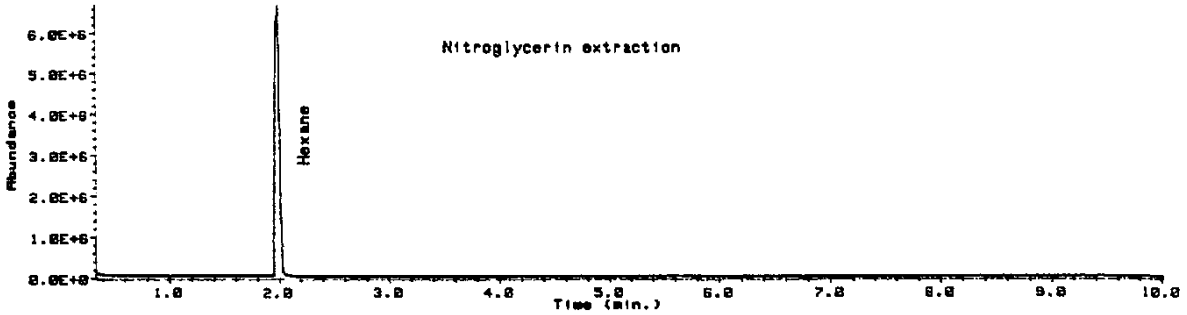

Figure 1—Gas chromatogram from hexane extract of nitroglycerin solution stored in a test syringe showing single peak for hexane extractant eluting at about 2.0 minutes.

the regression equation:

$$\text{percent remaining} = 0.0113(A) - 0.016$$

where A is the absorbance measured at 244 nm; $r = 0.999$.

Diazepam injection: A solution containing 20% tolualdehyde and 0.005% diazepam was passed over an octadecylsilyl (6 × 200 mm, 5 micron) HPLC column. The absorbances at 254 nm of diazepam and tolualdehyde were measured and integrated. The percent of original concentration was calculated using the regression equation:

$$\text{percent remaining} = 12.886(PAR) + 0754$$

where PAR is diazepam to tolualdehyde peak area ratio.

Nitroglycerin injection: In an automated analysis system 0.23 mL of sample was hydrolyzed with 0.42 mL of 1% strontium hydroxide solution. This solution was diluted to 2.5 mL with distilled water and diazotized by mixing successively with 0.73 mL of 3% procaine hydrochloride solution, 0.73 mL of 2N hydrochloric acid and 0.73 mL of 0.1% naphthalenediamine solution. The

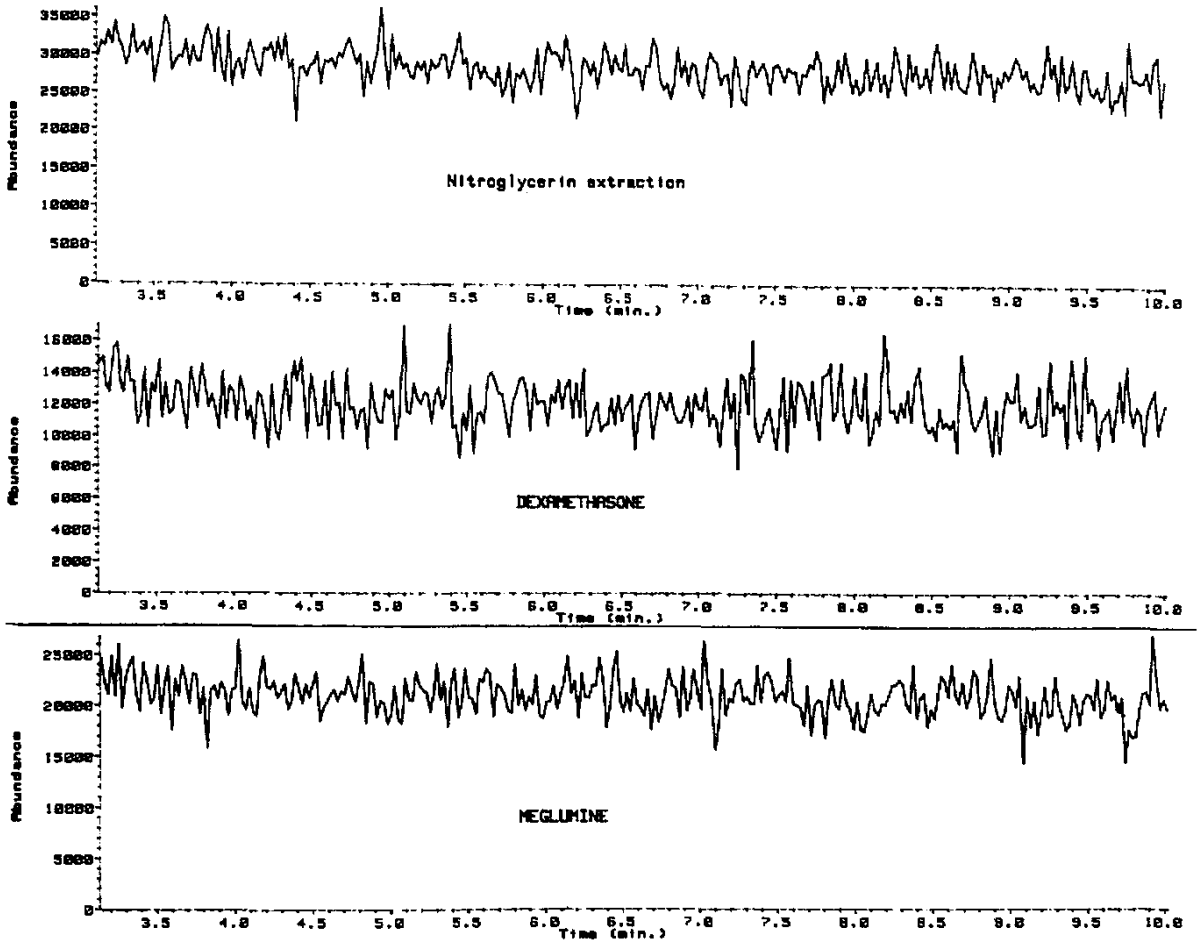

Figure 2—Mass spectrograms of hexane extracts from (A) nitroglycerin, (B) dexamethasone and (C) diatrizoate meglumine solutions stored in test syringes showing background noise but no characteristic peaks.

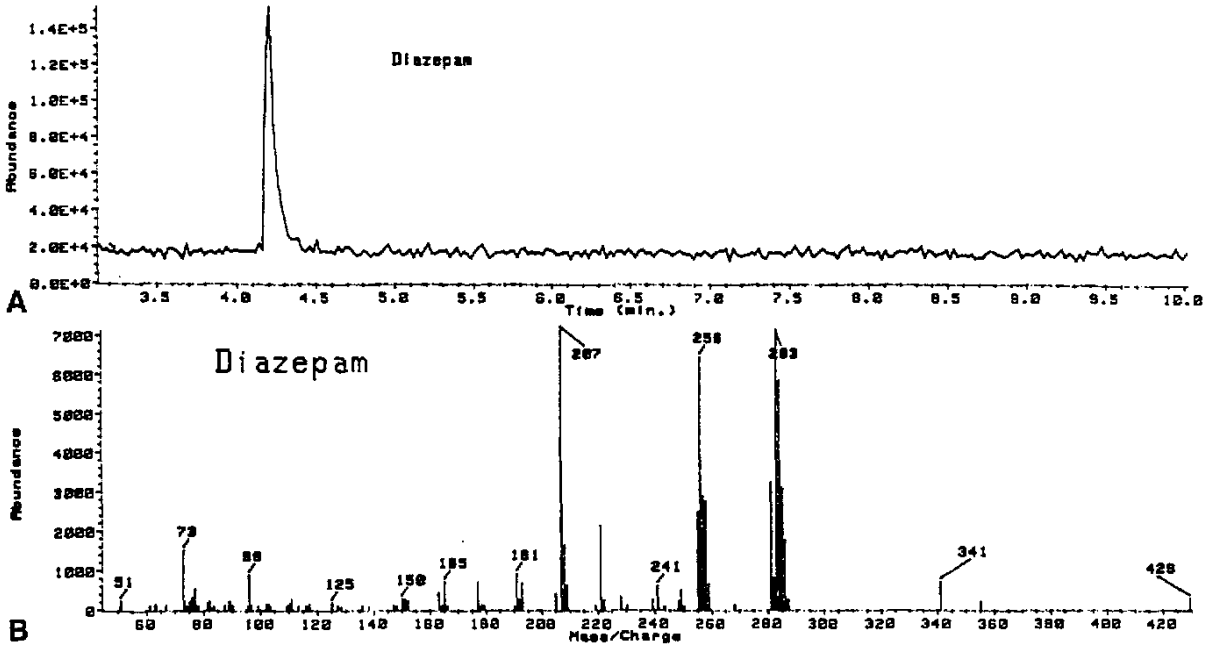

Figure 3—(A) Gas chromatogram from hexane extract of diazepam solution stored in a test syringe and (B) corresponding mass spectrogram of the diazapam peak eluting at about 4.4 minutes.

absorbance of the resulting diazotizotion product was measured at 455 nm and the remaining percent of original concentration was calculated with the regression equation:

$$\text{percent remaining} = A_U/A_R$$

where A is the absorbance measured at 455 nm and subscripts U and R refer to the unknown and reference samples, respectively.

Results

Gas Chromatographic/Mass Spectrometric Study

Chromatography of the nitroglycerin, diatrizoate meglumine and dexamethasone samples resulted in chromatograms similar to those shown in Figures 1 and 2. (Note the abundance axis in each figure.) The jagged line is background noise and shows the detector at the limits of sensitivity with no compound present. The

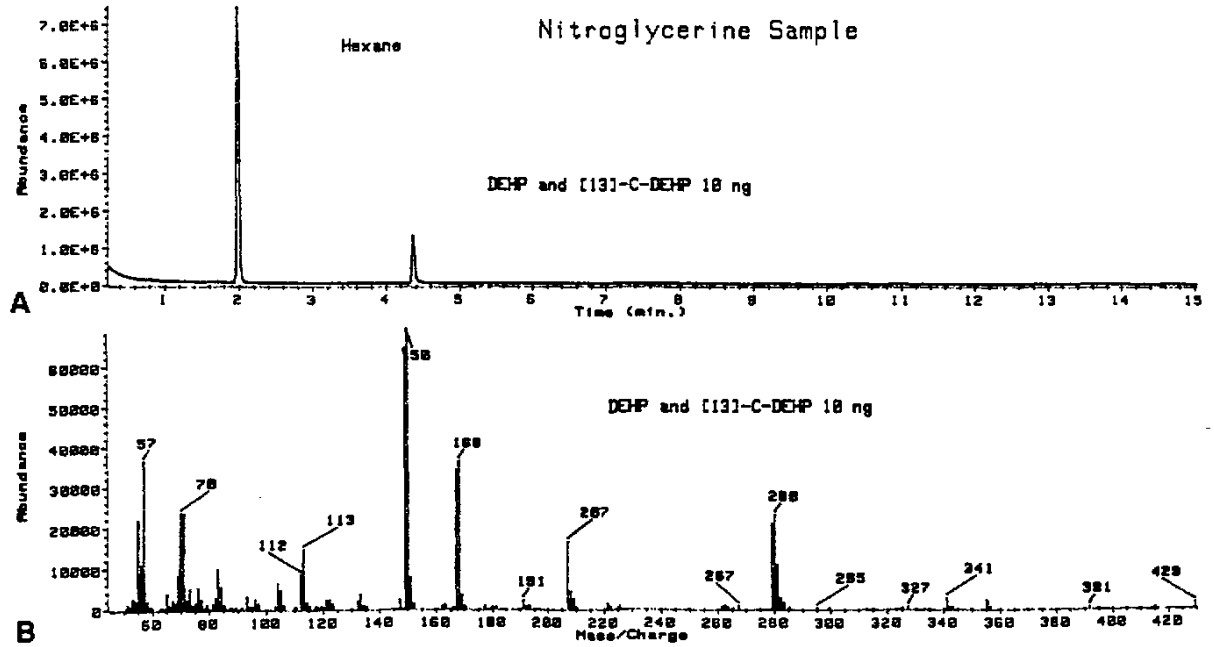

Figure 4—(A) Gas chromatogram from diethylhexyl phthalate spiked hexane extract of nitroglycerin solution stored in a test syringe and (B) mass spectrogram obtained from the diethyl hexyl phthalate peak at about 4.4 minutes.

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