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Stability of methotrexate injection in prefilled, plastic disposable syringes

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Summary

The stability of methotrexate (MTX) injection in 4 commercially available brands of sealed plastic disposable syringe has been investigated. MTX injection at a concentration of 50 mg/ml or less, stored in sealed Monoject (Sherwood Medical) or Plastipak (Becton Dickinson), plastic disposable syringes in the absence of light at a temperature not exceeding 25 °C was found to be stable (less than 10% degradation) for a period of up to 8 months. A possible alteration in the permeability of the syringe material to water vapour on prolonged storage in contact with MTX solution precluded storage in Sabre (Gillette) or Steriseal (N.I. Ltd.) syringes for more than 70 days at 25 °C. Sealed plastic disposable syringes are, therefore, a suitable secondary packaging system for the storage of MTX injection for periods of up to 8 months.

Introduction

The last 20–25 years have seen a considerable increase in the number and the usage of drugs developed for the treatment of neoplastic disease. The toxicity of these drugs has led to concern over their possible toxicity to medical personnel who prepare and administer the drugs and care for the patients during treatment. Centralised preparation of individual patient doses in controlled working areas in pharmacy departments does alleviate some of the manipulative and toxicity problems. However, the move toward the care of the cancer patient in the community and the need to provide inpatient doses at weekends requires comprehensive studies into the stability and compatibility of cytotoxics in secondary packaging systems over extended periods of time.

Secondary packaging systems in current use include polyethylene (PE) or polyvinylchloride (PVC) infusion containers, polypropylene (PP) or styrene acrylonitrile (SAN) syringes and glass syringes.

Drug stability in intravenous (i.v.) infusions has been widely studied and poses 3 main problems: the compatibility and stability of the drug in the infusion solution; the compatibility of the drug with the infusion container and the integrity of the container on prolonged storage under the predetermined storage conditions.

Unlike i.v. infusions, the stability and compatibility of drugs in sealed plastic disposable syringes has not been extensively investigated; see for ex-

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ample Bradford et al. (1984), Kirk et al. (1984) and Lee (1985); yet i.v. "stat" doses are given routinely in oncology outpatient clinics and home-care patients fitted with a syringe pump require supplies of prefilled syringes.

Plastic syringes currently licensed for use in the UK consist of a PP or SAN barrel and a rubber or silicone rubber piston and comply with B.S. 5081 (1976). Both PP and SAN have excellent tensile properties and are reported to be resistant to strong acids and alkalis. (Merck Index, X edn., 1983; Crompton, 1979). They are transparent to UV light in the range 300–400 nm (Cooper, 1974) but the addition of UV absorbers greatly reduces the potential for drug and polymer degradation by photolysis.

Absorption of several drugs by PP syringes has been shown to be negligible (Lee, 1985). However, certain agents (insulin, diazepam, secretin) are absorbed onto the surface of PP containers (Lee, 1985; Allwood, 1983). There are no reports on sorption to SAN containers. Leaching of additives from these polymers can occur under appropriate conditions although both are virtually inert with respect to water-extractable material at room temperature (personal communications, Sherwood Medical Ltd., 1984 and Gillette U.K. Ltd., 1984).

Rubber, from which the piston is manufactured, is a *cis*-polyisoprene polymer obtained from natural or synthetic sources. It is used extensively in pharmaceutical packaging for container closures because of its flexibility, resilience and thermal stability. However, its complex chemical nature can lead to compatibility problems when aqueous drug solutions are stored in contact with it (Ross, 1975; Petersen et al., 1981; Slater et al., 1983).

The integrity of plastic syringes poses the greatest problem as they are not true "sealed" systems. Thus, the seal between the piston and barrel, and the nozzle and closure must prevent microbial contamination of the contents and loss of syringe contents due to permeation and leakage. Mitrano et al. (1986) established that the potential for contaminating the syringe contents is negligible when the syringe is used only once, as with a syringe pump.

Methotrexate (MTX), a folic acid antagonist, is used in the treatment of a wide range of neoplastic conditions including leukaemias and solid tumours. The commercially available drug is formulated either as a freeze-dried powder for reconstitution with water for injections BP or as an aqueous isotonic liquid, stabilised at pH 8.3 (Methotrexate, Lederle; Emtexate, Nordic), and is packed in rubber-capped glass vials. Thus, further manipulation of the injection is required prior to administration, which could lead to instability.

Long-term stability data on MTX in secondary packaging systems are lacking. Until recently, the maximum recommended shelf-life of MTX injection in standard infusion solutions was 24 h. However, Karlsen et al. (1983) found no significant change in the concentration of MTX, 50 mg in 100 ml of glucose 5% after storage in a Viaflex (Travenol) minibag over a 30-day period at a temperature of $-20\,^{\circ}C$ and subsequent thawing using microwave radiation. In addition, Travenol Laboratories have marketed a range of cytotoxics packed in Viaflex minibags and recommend a shelf-life of 105 days for MTX injection 12.5 mg/ml at a storage temperature of $4\,^{\circ}C$. The only published report on the stability of MTX injection in plastic syringes looks at its stability and compatibility in combination with hydrocortisone sodium succinate and cytarabine. At a concentration of 1 mg/ml, MTX was stable for up to 24 h at room temperature (Cheung et al., 1984).

The obvious lack of information on the extended storage stability and compatibility of MTX injection in secondary packaging systems initiated this study of the effect of temperature, light and storage in contact with syringe materials, on the stability of MTX injection, 50 mg/ml, in 4 commercially available brands of plastic disposable syringe over periods of up to 8 months.

Materials and Methods

Chemicals and reagents

MTX STD (90.3% by HPLC); methopterin (93% by HPLC); 4-amino-4-deoxy-*N*-methylpteroic acid; *p*-aminobenzoylglutamic acid; 2-amino-4-hydroxypteridine-6-carboxylic acid; MTX, powder for injection, 500 mg vials, all used without further treatment, were supplied by Lederle Laboratories

Ltd. Aminopterin and *p*-aminosalicylic acid, sodium salt, used without further treatment, were supplied by Sigma Chemicals. Sodium acetate, anhydrous (Analar); sodium chloride (Analar); sodium hydroxide (Analar); acenaphthene (GPR) were supplied by BDH Chemicals Ltd. Water for injections BP was supplied by Antigen International Ltd. Acetonitrile, supplied by Rathburn Chemicals, and methanol and acetic acid, supplied by BDH Chemicals Ltd. were chromatographic grade.

An acetate buffer solution, pH 2.8, was prepared according to the method specified in the BP 1980, Appendix A51. All buffer solutions were filtered through a 0.45 μm membrane filter, type SM41, supplied by Sartorius, before use and stored at room temperature in the absence of light for up to 1 month. "Blank" solution, for use as an experimental control, was prepared freshly, as required, by adjusting the pH of a 0.49% w/v solution of sodium chloride to 8.3, using 0.1 N sodium hydroxide solution.

Equipment

High-performance liquid chromatography was carried out on an instrument composed of an Applied Chromatography Systems Ltd., model 300 pump; a Rheodyne injection valve with a 10 μl loop; an Applied Chromatography Systems Ltd., LC 750 monitor, model 750/11 operated at 254 nm and 280 nm by means of filter cassettes and a Venture Servoscribe Is, RE 541.20 potentiometric recorder. A 6 cm $\times$ 2.5 mm i.d. steel preinjection column packed with Whatman Pre-column Gel (37–53 μm particle size) was linked in series with a Waters Associates Nova-pak C_{18}, 15cm $\times$ 3.9 mm i.d. steel analytical column.

Temperature studies were carried out in thermostatically controlled incubators (Griffin incubators, Serial No. 784085 and 4211271172, and a laboratory incubator, Millipore Corp.). The variation in temperature within the incubators, at the temperatures studied, was found to be less than or equal to $\pm$ 1° C.

Photolytic degradation studies were carried out in a Fisons, Fi-Totron 600-H growth cabinet. The growth chamber is lined with a reflective material and the shelving was covered with aluminium foil. Illumination was by means of 12 EMI 40 W, warm-white fluorescent tubes, 150 cm long and 4 Osram Extralite, 40 W tungsten bulbs, located above a glass plate in the roof of the chamber. The samples were randomly positioned in a predesignated area over which the intensity of light did not vary by more than 1000 lux, with an average light intensity value of 21200 lux, at a distance of 33 cm from the glass plate (as determined using a Megatron Type EA22 luxmeter). Temperature and humidity were thermostatically controlled and maintained at 25° C and 25% throughout.

Four, commercially available, brands of plastic disposable syringe were used. All had luer-slip fittings and a nominal 2 ml capacity.

Manufacturer	Type	Barrel	Piston
Sherwood Medical Industries Ltd.	Monoject	PP	Rubber
Becton Dickinson UK Ltd.	Plastipak	PP	Rubber
Needle Industries Ltd.	Steriseal	PP	Silicone Rubber
Gillette UK Ltd.	Sabre	SAN	Rubber

The syringes were sealed with Vygon, female luer-lock obturator, Code 888.06 blind hubs (Vygon UK Ltd.). These are manufactured from acylon styrene (personal communication, Vygon UK Ltd., 1986).

Development of an HPLC assay for MTX

HPLC equipment was as detailed previously. All analyses were carried out at ambient temperature. A number of mobile phase solutions were prepared utilising acetate buffer (pH 2.8) in combination with acetonitrile and/or methanol. After equilibration of the system with each mobile phase, 10 μl (one loopful) of a standard mixture of MTX, its major degradation compounds and PAS were injected onto the column and the degree of separation was observed.

Preparation of samples and standards for degradation studies

MTX for injection, 500 mg, was reconstituted with 10 ml of water for injection to produce a solution containing approximately 50 mg of MTX per ml. Two 100 μl samples were immediately removed and each diluted to 50 ml with 0.035

mg/ml PAS solution. These were assayed by HPLC to determine the initial concentration of the solution. Two ml of solution was then filled into one of each brand of syringe and sealed with a "blind" hub; 0.4 ml of solution was sealed in each of 5 clear glass ampoules which were used as controls.

"Blank" solution was filled into 4 syringes as described above. Two ml of this solution were also sealed in a clear glass ampoule. This solution was analysed, undiluted, at time zero, using the chosen HPLC method.

Thermal and photolytic studies

Samples and blanks, prepared as described, were sampled at appropriate time intervals and inspected for any changes in appearance. Approximately 0.2 ml of solution from each syringe and the contents of one ampoule were removed for analysis. The syringes were re-sealed and the samples returned to the incubator or light box.

In the photolytic degradation studies, samples and blanks were prepared in duplicate. One set of each was wrapped in aluminium foil to be used as controls. These were sampled and inspected as for the samples exposed to light. All samples were analysed for intact MTX and degradation products by HPLC.

Determination of the water permeability of the sealed plastic syringes

Two ml of water for injections was filled into 2 of each brand of syringe and sealed with a "blind" hub. Each syringe was accurately weighed to ± 0.0001 g. The 8 syringes were then wrapped in aluminium foil and the weight of each syringe was determined at each sampling time during the degradation studies.

Results and Discussion

Development of an HPLC assay for MTX

Four criteria were established for the development of an HPLC assay for MTX: that it should be rapid and easy to operate; easily adaptable to use in most laboratories; able to detect a wide range of degradation products and impurities using standard techniques and stability indicating and quantitative for MTX. The many assays cited in the literature fulfilled some but not all of these criteria which led to the development of an HPLC assay method unique to this work.

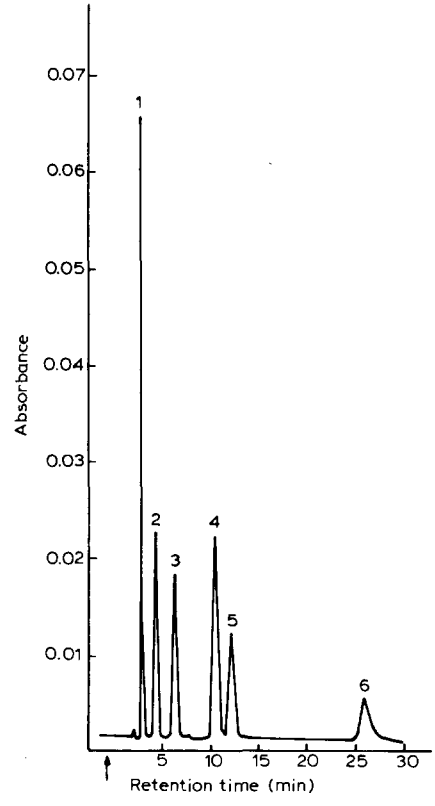

Fig. 1. HPLC chromatogram for the separation of MTX standard mixture with acetate buffer (pH 2.8) as eluate at a flow rate of 0.5 ml/min. AHPCA and PABGA (1), PAS (2), aminopterin (3), MTX (4), Methopterin (5), DAMPA (6).

Separation of the components of the mixture was not obtained with an organic component in the mobile phase. In all cases, total elution time was less than 5 min at a flow rate of 0.5 ml/min. However, using acetate buffer (pH 2.8) alone, 6 peak separation was obtained. A typical chromatogram is shown in Fig. 1. Peak identity was determined by single peak analysis of the degradation compounds and comparison of the retention times with those of the mixture. Unfortunately, the two photolytic degradation compounds (PABGA and AHPCA) could not be resolved in the system. As methopterin (thermal degradation

TABLE 1

Quantitative HPLC assay for MTX and its major degradation compounds

Mobile Phase	Acetate buffer (pH 2.8)
Column	Nova-pak C_{18}, 15 cm × 3.9 mm i.d.
Flow rate	0.5 ml/min
Detection	280 nm, 0.1–0.5 AUFS
Temperature	Ambient
Standard solutions	MTX 0.1 mg/ml in distilled water, pH > 8 aminopterin, methopterin, 4-amino-4-deoxy-*N*-methylpteroic acid (DAMPA), *p*-aminobenzoylglutamic acid (PABGA) and 2-amino-4-hydroxypteridine-6-carboxylic acid (AHPCA), 0.5 mg/ml in distilled water, pH > 8
Sample solutions	Nominal 0.1 mg/ml calculated as MTX
Injection volume	10 µl
Internal standard conc.	*p*-aminosalicylic acid (PAS) 0.035 mg/ml
Chart speed	5 cm/min

product) was likely to be the most important degradation product in the assessment of the stability of MTX injection in plastic disposable syringes, it was decided that qualitative analysis of the photolytic degradation products was sufficient provided all other components could be quantitatively analysed. Column resolution (R_s) for the other components in the system was greater than $R_s = 0.8$ (which is generally considered to be the lowest practical value for quantitative analysis).

Thus, a suitable stability indicating assay was developed which allowed the quantitative analysis of MTX and its major thermal degradation products and the qualitative analysis of its major photolytic degradation products. The assay was simple and rapid, utilising standard equipment and detection techniques. Details are given in Table 1.

Thermal degradation of MTX

The degradation of MTX stored in clear glass ampoules followed apparent zero order kinetics. An Arrhenius plot of the log of the observed rate constant as a function of the reciprocal of absolute temperature was linear with a slope value of −4.97 K and intercept of 22.5 (Fig. 2). Methopterin was identified as the major degradation product, its concentration increasing with time. Storage of the MTX injection in ampoules for longer than 20 days at 75 °C resulted in the formation of an orange precipitate. Its yield was insufficient to allow identification although, from chromatographic data, it was suspected that the precipitate could be methopterin.

MTX degradation in plastic syringes initially appeared to be much more complex and highly syringe-type dependent, yet the elution pattern for degradation peaks was identical to that for MTX in glass ampoules, with methopterin again being the major degradation product.

The investigation of the water permeability of the syringes indicated that all were permeable to water vapour and that evaporation exhibited zero order kinetics. Water permeability rate constants are given in Table 2. However, it was apparent that under normal storage conditions of 25 °C and 4 °C, the water loss from all brands of syringe should be negligible. A sealed Sabre syringe filled with 2 ml of water would only lose about 10% of its initial weight after one year's storage at 25 °C. This loss would be less with the other brands of syringe and considerably reduced if the syringes were stored at 4 °C. All subsequent MTX con-

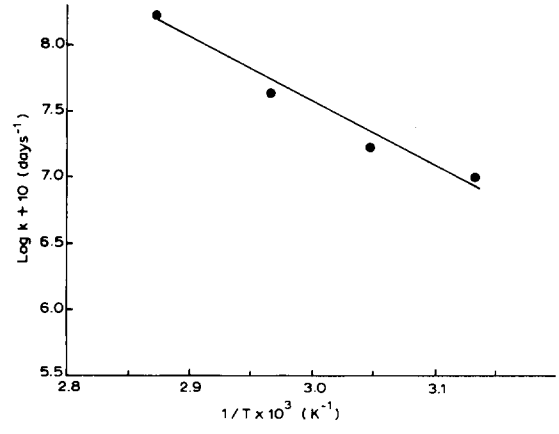

Fig. 2. Arrhenius plot of the logarithm of the observed zero-order rate constants against the reciprocal of absolute temperature for the thermal degradation of methotrexate injection 50 mg/ml, stored in clear glass ampoules.

TABLE 2

Water permeability rate constants for the 4 brands of syringe studied at 25 °C and 4 °C

Syringe type	Water permeability rate constants (ml/day)	
	25 °C	4 °C
Gillette	-3.16×10^{-4}	-6.61×10^{-5}
Steriseal	-1.32×10^{-4}	-2.14×10^{-5}
Monoject	-3.55×10^{-5}	-2.95×10^{-6}
Becton Dickinson	-5.01×10^{-5}	-5.62×10^{-6}

centrations were corrected for water loss. In both Sabre and Steriseal syringes, storage at elevated temperature appeared to result in an increase in MTX concentration with time (even after "water loss" correction) although degradation product formation was evident from the HPLC analyses. The change in MTX concentration of the 50 mg/ml injection, stored in sealed Sabre syringes under conditions of elevated temperature is illustrated in Fig. 3. Storage in Monoject and Plastipak syringes gave a very similar pattern. At 25 °C, 46 °C and 55 °C, there was considerable variability in the date but the change in MTX concentration did not deviate greatly from unity over the study period. Conversely, at 64 °C and 75 °C there was definite evidence of MTX loss with degradation again exhibiting apparent zero

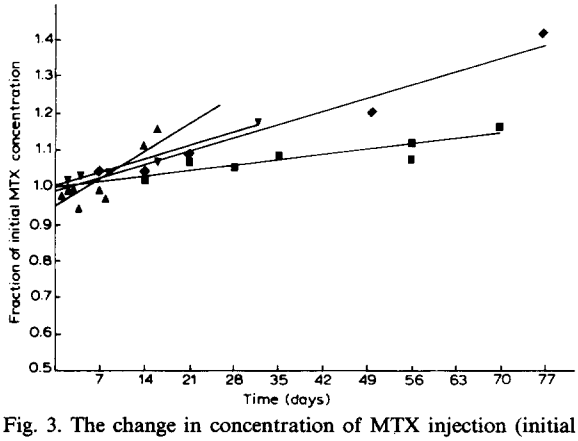

Fig. 3. The change in concentration of MTX injection (initial concentration 50 mg/ml) stored in sealed Sabre syringes at elevated temperatures. 46 °C, (■); 55 °C, (◆); 64 °C, (▼); 75 °C, (▲).

TABLE 3

Thermal degradation rate constants for MTX injection 50 mg/ml stored in Monoject and Becton Dickinson syringes

Syringe type	Thermal degradation rate constants (mg ml^{-1} day^{-1})	
	25 °C	4 °C
Monoject	-9.12×10^{-6}	-2.57×10^{-7}
Becton Dickinson	-7.94×10^{-6}	-1.82×10^{-7}

order kinetics. Arrhenius plots of the data allowed calculation of the predicted degradation rate constants for storage at 25 °C and 4 °C. These values are given in Table 3.

Closer investigation of the syringe experiments seemed to suggest that the rate of water loss from the sample syringes was much higher than from the "weight loss" syringes for identical storage conditions. This was confirmed by comparison of the predicted weight loss from a Sabre syringe containing MTX injection 50 mg/ml stored at 25 °C for 8 months with the actual weight loss (observed volume evaporated) over this period. From the weight loss data, an 8% decrease in volume would be predicted over an 8 month period yet the observed value was approximately 25% (0.5 ml). The initial and final concentration values for the storage of MTX injection in the 4 brands of plastic syringe over an 8 month period are given in Table 4. Adjustment of the MTX concentration for drug stored in Sabre syringes according to the observed weight loss rather than

TABLE 4

Initital and final concentration data for the storage of MTX injection in the 4 brands of plastic disposable syringe over 8 months

Syringe type	Initial concentration (mg/ml)	Final concentration (mg/ml) *
Gillette	0.108	0.127
Steriseal	0.108	0.115
Monoject	0.108	0.109
Becton Dickinson	0.108	0.110

* Concentration adjusted according to predicted evaporation rate from the syringes.

the predicted weight loss value gave a concentration of 0.1096 mg/ml which was close to the initial MTX concentration of 0.108 mg/ml. The differences between the predicted and observed evaporation rate from sealed plastic syringes seemed to suggest an alteration in the permeability of the plastic material to water vapour on prolonged storage in contact with the alkaline injection vehicle. The effect was most pronounced with SAN syringes. Both PP and SAN are reported to be resistant to acids and alkalis (Merck Index, X edn., 1983; Crompton, 1979). However, as plastic syringes are designed for immediate use it is unlikely that the long-term effects of storage in contact with dilute alkalis has been considered. In fact, the manufacturers of Monoject syringes only carry out compatibility studies over a 5 h period (Sherwood Medical, personal communication, 1984).

Photolytic degradation of MTX

All samples exposed to light exhibited a decrease in MTX concentration over a period of 70 days but there was no clear evidence of a mathematical relationship between the data points. Samples stored in the absence of light at 25 °C did not show any evidence of MTX degradation.

No change in MTX concentration was detected over the first 28 days storage in plastic syringes as assessed by comparison with samples stored in the dark. Thereafter, a decrease in intact MTX concentration was detected, the effect being most pronounced with Monoject and Plastipak syringes.

On the chromatograms, degradation peaks were detected in the samples at 0.01 AUFS as early as 7 days following exposure to light. A total of 7 peaks were separated in the system although the major peaks corresponded with PABGA and AHPCA as expected.

Chatterji and Gallelli (1978) found that the photolytic degradation of MTX injection 25 mg/ml, initial pH 8.3 (unbuffered), stored in 2 ml clear glass ampoules at room temperature in a light box, exhibited an initial lag period followed by zero order loss of MTX with time. Their observed lag period was 70 h with a subsequent loss of 1.1 mg/h $\times 10^{-4}$. This trend was noted in the current study for the MTX injection stored in plastic syringes, although the lag period was considerably longer than that reported by Chatterji and Gallelli (1978). The lag period associated with samples stored in Plastipak and Monoject syringes was in the order of 28 days. On closer inspection of the results, this period was around 35 days for Steriseal syringes and 42 days for Sabre syringes. Plastic syringes contain light-absorbing agents and as only absorbed light is photochemically active, the prolonged lag period could be predicted for solutions stored in plastic syringes.

The complete absence of photolytic degradation compounds in samples stored in the dark suggested that all MTX solutions stored for periods of more than a few hours in the primary or secondary packaging system should be protected from light.

Extraction from the syringes

Using this HPLC assay for MTX, "blank" solution stored in contact with the syringes showed evidence of extracted material, the extent of extraction increasing with increasing temperature. Extracted material was least evident for solution stored in Steriseal syringes, which have a silicone rubber piston, suggesting that the source of the extracted products was probably the rubber piston and not the syringe barrel. No attempt was made to identify the extracted products.

Conclusions

The stability of MTX injection stored in sealed prefilled plastic syringes has been found to be influenced not only by thermal and photolytic effects but also by the permeability of the syringes to water vapour. The rate of water loss from the syringes varied considerably, both with respect to the composition of the barrel and also between differing brands made of apparently similar material. Syringes fabricated from SAN (Sabre, Gillette) were considerably more permeable to water vapour than were the syringes made of PP (Steriseal, NI Ltd.; Monoject, Sherwood Medical; Plastipak, Becton Dickinson). Of the PP syringes, the Steriseal brand lost water at a higher rate than

either Monoject or Plastipak, possibly due to slight differences in the crystallinity of the polymer or differences in the thickness of the barrel wall. However, at normal storage temperatures of 25 °C and 4 °C, the rate of water loss from all brands of syringe was negligible with a predicted weight loss of about 10% for water stored in 2 ml Sabre syringes over a one year period at 25 °C. Contrary to this was the almost 25% fluid loss from Sabre syringes containing MTX injection and "blank" solution over an 8 month period at 25 °C. Steriseal syringes stored under identical conditions exhibited a 5% fluid loss over the same period. Thus, it was concluded that although both SAN and PP are reported to be resistant to acids and alkalis, long-term storage in contact with such solutions may alter the structure of the polymer sufficiently to allow more rapid permeation of water vapour through the plastics matrix.

The thermal degradation of MTX was characterised by the hydrolysis of MTX to methopterin, its major thermal degradation compound. Degradation exhibited apparent zero order kinetics. The formation of thermal degradation products appeared to be unaffected by container type or rate of evaporation from the syringes.

The photolytic degradation of MTX in plastic syringes was influenced less by the permeability of the syringes at 25 °C and more by the light-absorbing properties of the plastics. SAN appeared to afford the greatest light protection whilst PP was a less effective absorber of UV/visible radiation. All the syringes protected the solution from photolytic degradation to a greater extent than did glass. The physical manifestation of MTX photolysis was the formation of a yellow precipitate. Storage of the injection in the absence of light prevented photolytic degradation.

MTX injection at a concentration of 50 mg/ml or less, stored in sealed Monoject (Sherwood Medical) or Plastipak (Becton Dickinson), plastic disposable syringes in the absence of light at a temperature not exceeding 25 °C is stable (less than 10% degradation) for a period of up to 8 months. Based on these studies, storage in Sabre (Gillette) and Steriseal (NI Ltd.) syringes should not exceed 70 days.

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