STABILITY OF ANTIBIOTICS IN PERITONEAL DIALYSIS FLUIDS

by

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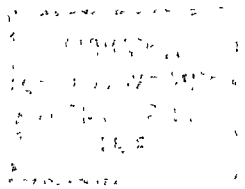

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This thesis contains no material which has been accepted for the award of any other higher degree or graduate diploma in any tertiary institution.

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SUMMARY

Literature review

A literature review of the stability of antibiotics in peritoneal dialysis fluids was conducted. The information obtained was collated and presented in a format which would serve as a useful working reference for hospital pharmacists. It was found that the stability of antibiotics in peritoneal dialysis fluids had received little attention in the literature. The review highlighted the lack of information on the stability and compatibility of many of the antibiotics and antibiotic combinations commonly used for the treatment of peritonitis. Despite increasing interest in intraperitoneal antifungal chemotherapy, there was no information on the stability of antifungal agents in peritoneal dialysis fluids.

Stability studies

A study of the stability of the antifungal agent, miconazole, in peritoneal dialysis fluid was conducted. Greater than 10% loss of the initial miconazole concentration occurred within 4 hours when this drug was added to peritoneal dialysis fluid and stored in polyvinyl chloride (PVC) bags at 20°C. Similar admixtures were stable for at least 3 days when stored in glass ampoules under the same conditions. These findings indicated that the loss of miconazole observed in PVC bags was due primarily to an interaction with the container, rather than chemical decomposition in solution. Approximately 28% of the miconazole lost from the solution was recovered from the plastic by methanolic extraction, representing sorption of miconazole by the PVC container. In the clinical situation, the rapid loss of miconazole from peritoneal dialysis fluid stored in PVC bags, would demand that such admixtures be prepared immediately prior to administration.

A study of the stability of both components of the antibacterial combination, co-trimoxazole, in peritoneal dialysis fluid was conducted. Greater than 10% loss of the initial trimethoprim concentration occurred within 3 days when admixtures of co-trimoxazole in peritoneal dialysis fluid were stored in PVC bags at 20°C. The concentration of trimethoprim in similar admixtures stored in glass ampoules under the same conditions, remained virtually unchanged for 9 days. This suggested that the loss of trimethoprim observed in admixtures stored in PVC bags, may have been due to an interaction with the container.

Greater than 10% loss of the initial sulphamethoxazole concentration occurred within 2 days in admixtures stored in PVC bags. Similar losses occurred in admixtures stored in glass ampoules, suggesting that the mechanism of this loss was primarily chemical decomposition in solution. Further evidence for this proposition, was the time dependent increase in concentration of an unknown decomposition product in admixtures stored in both plastic and glass containers. It was suspected that this compound was a derivative of sulphamethoxazole, however it was demonstrated that it was not sulphanilic acid or 5-methyl-3-isoxazolamine, which have previously been identified as decomposition products of sulphamethoxazole under acid conditions.

This study found that the shelf-life of admixtures of co-trimoxazole in peritoneal dialysis fluid stored in PVC bags at 20°C, was limited by the stability of the sulphamethoxazole component. The data conservatively indicated a shelf-life of approximately 12 hours, since greater than 10% loss of the initial sulphamethoxazole concentration had occurred in this time in one of the admixtures examined.

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CONTENTS

CHAPTER 1

STABILITY OF ANTIBIOTICS IN PERITONEAL DIALYSIS FLUIDS

1.1 Introduction

1.1.1 An overview of peritoneal dialysis

In 1923, Ganter reported an improvement in the condition of a uremic guinea pig after the intermittent infusion and removal of saline solution from the peritoneal cavity. He noted that after an intraperitoneal (i.p.) dwell time of one hour, the urea-nitrogen concentration in the fluid approximated that in the blood. Ganter also reported an improvement in the condition of a uremic woman after the instillation of 1.5 L of saline solution into the peritoneal cavity, and that the i.p. infusion of 3 L of saline solution in a patient with diabetic coma produced a reversal of the unconscious state. Following these observations, Ganter proposed that the peritoneal membrane allowed the passage of toxic substances from the blood into the peritoneal cavity (1).

During the period from 1923 to 1948, 101 patients were reported as having received some form of peritoneal dialysis. Of the 63 patients who suffered reversible renal disease, 32 were treated successfully with this dialysis technique. During this pioneering period of peritoneal dialysis, three complications accounted for the majority of deaths: (i) pulmonary oedema, (ii) uremia, and (iii) peritonitis. At this time peritoneal dialysis was largely confined to animal experimentation and the treatment of acute renal failure in humans. It was also used successfully for the treatment of hypercalcaemia and various poisonings. The high incidence of peritonitis, and the failure to develop a successful peritoneal access device, lead to the abandonment of attempts to establish long term peritoneal dialysis (1, 2).

In 1963, Boen commenced treatment of a patient using peritoneal dialysis in which the dialysis fluid was introduced into the peritoneal cavity using a repeated puncture technique. Effective control of the uremic state was obtained using an intermittent dialysis regime consisting of three or four dialysis sessions per week, each session lasting approximately 10 hours and using approximately 40 L of fluid. This regime became known as intermittent peritoneal dialysis. Using the repeated puncture technique, Boen's patient was maintained on intermittent peritoneal dialysis for three years prior to a successful kidney transplant, and the feasibility of long term peritoneal dialysis for the management of end-stage renal disease was therefore established. Tenckhoff, Boen's co-worker, confirmed the success of this procedure by maintaining a patient on intermittent peritoneal dialysis for three and a half years in a home setting. In 1966, Lasker et al also reported success with the repeated puncture technique in 5 patients (1, 3).

Peritoneal access devices

Although the repeated puncture technique was associated with a low risk of infection and enabled the feasibility of long term peritoneal dialysis to be established, the procedure was both unpleasant for the patient and demanding on staff, who would have to carry out the procedure at least three times weekly for each patient. Attention was once again turned to the development of a long term peritoneal access device. In 1968, Tenckhoff designed a silicone rubber catheter with two dacron cuffs which were intended to anchor the catheter to the abdominal wall, and to close the sinus tract around the catheter, thereby preventing bacterial intrusion. This catheter gained widespread acceptance and was the most important factor in promoting long term peritoneal dialysis in other centres (1). Many other catheter designs have evolved. A modified version of Tenckhoff's double cuff catheter, with a catheter adapter made of titanium and a luer lock configuration between the adapter and the plastic extension tubing, is in widespread use today (4).

Peritoneal dialysis fluid and automated dialysis

During the first years of peritoneal dialysis, either normal saline or 5% glucose solutions were used as dialysis fluids. Problems associated with pulmonary oedema and acidosis lead to the development of more appropriate dialysis fluid formulations and stricter fluid balance control. Water was found to be absorbed when hypotonic solutions were instilled into the peritoneal cavity, whereas hypertonic solutions produced ultrafiltration (water excretion). The osmolarity of dialysis fluids was varied by altering the glucose concentration and in this way the patient's fluid balance could be controlled. Magnesium and calcium were included in dialysis fluid formulations to maintain adequate serum levels. Bicarbonate was added to correct acidosis, however problems associated with sterilisation and storage (caramelisation of glucose and calcium carbonate precipitation), meant that the fluid had to be mixed immediately prior to administration. This ultimately lead to the replacement of bicarbonate with either acetate or lactate. Potassium was added when necessary to correct hypokalaemia (1, 5).

The development of a safe and practical source of dialysis fluid was a necessary step in ensuring a future for long term peritoneal dialysis. Prior to 1959, clinicians prepared the dialysis fluid by adding concentrated solutions of electrolytes and glucose to bottles of sterile distilled water. In 1959, commercial dialysis fluid became available. When Boen first attempted long term peritoneal dialysis in 1962, he decided to eliminate the bottle change as a source of infection. One intermittent peritoneal dialysis session using 40 L of dialysis fluid ordinarily involved 40 bottle exchanges. Boen developed a closed sterile system in which dialysis fluid was manufactured and sterilised in 40 L carboys. Timers and clamps were incorporated to control fluid inflow, dwell time and fluid outflow, and so the first automated peritoneal dialysis machine was created. Because of the special equipment required for Boen's "fluid factory", installation was only really suited to hospitals, however in this setting it proved to be extremely successful, with most hospitals in the United States of America still using this system during the early

1980's (1, 3).

The difficulty of transporting large volumes of fluid prevented the widespread application of peritoneal dialysis to the home setting. Tenckhoff's first attempt to manufacture sterile dialysis fluid in the home employed a miniature autoclave in which water was sterilised before being combined with a concentrated dialysis fluid using an automated proportioning device. More widespread application in the home was achieved in 1972, when reverse osmosis replaced the autoclave as a means of water sterilisation. The reverse osmosis dialysis machine established automated peritoneal dialysis in the home setting and increased the number of patients treated in this situation with peritoneal dialysis (1-3).

Continuous ambulatory peritoneal dialysis

In 1976, Popovich, Moncrief and co-workers described a novel portable peritoneal dialysis technique which they called "equilibrium dialysis" (6). A 2 L volume of dialysis fluid was gravity infused into the peritoneal cavity and allowed to equilibrate for approximately 5 hours. An empty container was then connected to the catheter, and the dialysis fluid effluent was drained out of the peritoneal cavity by placing the container below the level of the abdomen. A 2 L volume of fresh fluid was immediately infused again and the cycle repeated. Five exchanges were performed every day. Equilibrium dialysis meant that the peritoneal membrane was continually in contact with dialysis fluid and, apart from the exchange procedure, the patient was able to conduct normal activities. Additional experience with this technique was reported by Moncrief et al and Popovich et al in 1978, and it was given the name "continuous ambulatory peritoneal dialysis (CAPD)" (7, 8).

Recurrent infection was a major problem in these first CAPD patients, with an incidence of peritonitis of approximately one episode every ten patient weeks. In the same year,

Robson and Oreopoulos were able to halve the number of connections associated with this technique by using peritoneal dialysis fluid supplied in flexible plastic containers. After infusion, the empty bag remained connected to the catheter, was carried on the body, and was used subsequently to receive the peritoneal dialysis effluent. In this way the incidence of peritonitis was reduced to approximately one episode every 7.1 patient months (9).

Other peritoneal dialysis regimes

Several variations of the original concept of equilibrium dialysis have evolved. Continuous cyclic peritoneal dialysis (CCPD) was introduced in 1980 with the aim of providing automated dialysis at night and ambulatory dialysis during the day (10). An automated cycler machine delivers multiple overnight exchanges and an additional exchange in the morning. The dialysis fluid then remains in the peritoneal cavity for a prolonged dwell during the day. The advantages of this regime include the freedom from exchanges during the day, the restriction of the exchange venue to the home, and the reduction in the number of connections and disconnections. During CCPD, the direction of flow of dialysis fluid immediately after connection is always out of the peritoneal cavity, and this is considered to be an advantage in reducing the risk of touch contamination entering the peritoneal cavity. This feature can also be incorporated into CAPD following the development of various connection tubing designs (11). A reduction in the incidence of peritonitis was one of the major objectives of the development of CCPD, and although this has been demonstrated in some centres, the peritoneal dialysis regime with the least risk of complications remains controversial (12, 13).

Peritoneal dialysis population

The use of peritoneal dialysis increased slowly despite significant advances in the development of long term peritoneal dialysis in the 1970's, for example the introduction

of automated at home dialysis. Following the introduction of CAPD, however, an enormous increase in the peritoneal dialysis population occurred. The European Dialysis and Transplant Association reported a four-fold increase in the number of peritoneal dialysis patients between 1977 and 1979, with 38% of peritoneal dialysis patients in 1979 using CAPD (2). In the United States of America, the National Dialysis Registry data in 1974 showed only 72 patients being treated with peritoneal dialysis, which represented 1.4% of the total dialysis population. The number of peritoneal dialysis patients increased to approximately 4 000 in 1980, 10 200 in 1983, and 15 300 in 1987, which represented 7.7%, 14.2% and 15.6% of the total dialysis population respectively. In 1980, 61% of peritoneal dialysis patients were using CAPD and by 1987 this had increased to 85% (2, 14).

In October 1988 there were 2 598 dialysis dependent patients in Australia of whom 68% were receiving haemodialysis and 32% were receiving peritoneal dialysis. In 1980, peritoneal dialysis patients represented 15% of the total dialysis population. This increased steadily to 30% in 1984, but has not shown any appreciable change since. In 1988, peritoneal dialysis was the most common form of dialysis in young patients; 85% of children (<10 years), and 50% of the teenage group (10-19 years), were receiving peritoneal dialysis. Peritoneal dialysis was also used frequently in the elderly (70-89 years), (49%). CAPD accounted for 95% of all peritoneal dialysis patients in Australia, with the remainder receiving intermittent peritoneal dialysis. 32% of all dialysis dependent patients were using hospital based facilities for dialysis, 16% were using satellite based facilities, and 52% were dialysing at home. A majority of home dialysis patients (56%) were on CAPD (15).

1.1.2 Continuous ambulatory peritoneal dialysis (CAPD)

1.1.2.1 Advantages of CAPD

CAPD is an alternative to haemodialysis for the treatment of patients with end-stage renal disease. The main advantages offered by this dialysis method are greater patient mobility and independence (because there is no reliance on a machine), elimination of the need for a routine vascular access, and the availability of at home dialysis. A recent survey of renal units in Australia showed that the most common reason for selecting CAPD over other dialysis methods was the desirability of at home dialysis (16).

CAPD does not compromise the dialytic efficiency possible with haemodialysis, and in fact offers several advantages over intermittent dialysis methods.

Steady state blood chemistries

The blood chemistries of patients on CAPD achieve steady state after a few weeks of treatment because there is constant removal of water and waste products from the body. In contrast, intermittent dialysis techniques such as haemodialysis and intermittent peritoneal dialysis are associated with large fluctuations in blood concentrations of waste products. These fluctuations can produce clinical symptoms. A disequilibrium syndrome, characterised by headache, nausea, CNS disturbances and rapid decline in blood pressure, results from the rapid removal of water and solutes during haemodialysis (17).

Haemodynamic control

CAPD avoids the large fluctuations in fluid volume and blood pressure which are often associated with intermittent dialysis techniques. Because there is continuous removal of water, excellent control of blood pressure and fluid balance can be achieved, enabling a

more liberal fluid intake than is tolerated with haemodialysis. The removal of excess salt and water, and therefore the control of hypertension and oedema, can be achieved by using dialysis fluid of high osmolarity or by increasing the frequency of exchanges. Conversely, intravascular volume can be increased by using dialysis fluid of low osmolarity or by prolonging the i.p. dwell time (18). It is often possible to withdraw antihypertensive medication in CAPD patients (19). In addition, CAPD patients generally show a rise in haematocrit, not normally seen with other dialysis methods (20, 21).

Dietary restrictions

Although moderate dietary restrictions are imposed on the CAPD patient, these are less rigid than those associated with intermittent dialysis techniques, especially with respect to salt and water intake. A restricted carbohydrate diet is necessary due to the appreciable glucose absorption from the dialysis fluid, whereas a high protein diet is necessary to compensate for protein losses to the dialysis fluid. Restriction of dietary potassium is seldom necessary (18).

Children

CAPD is an attractive alternative to haemodialysis in the paediatric population. The features which favour the use of CAPD in the younger age group include: (i) freedom from repeated needle punctures and other difficulties associated with maintaining a vascular access, (ii) reduced dietary restrictions, and (iii) ambulatory home based dialysis (22). Data on the age distribution of dialysis dependent patients in Australia suggests that CAPD has become the treatment of choice for children with end-stage renal disease (15). This has also been the experience in the United States of America (23).

Diabetics

Diabetic nephropathy is a significant cause of renal disease in dialysis dependent patients and CAPD has become the preferred method of dialysis in diabetics (15). Firstly, peripheral vascular disease and the difficulties associated with maintaining a vascular access limit the application of haemodialysis in diabetic patients. Secondly, CAPD achieves better blood glucose control than other dialysis methods. Insulin is routinely administered intraperitoneally via the dialysis fluid, and this has been shown to produce better glucose control than subcutaneous administration. The diabetic patient is taught to add insulin to the dialysis fluid bag, or to inject the insulin into the connecting tubing immediately before infusion of the dialysis fluid (24, 25).

1.1.2.2 Problems associated with CAPD

CAPD imposes an appreciable technical burden on the patient. The technique involves multiple connections and disconnections which are time consuming and are associated with a risk of infection. Intensive patient training in aseptic technique, care of the chronic indwelling catheter and control of fluid balance is required. CAPD patients must possess the capability and motivation to accept the responsibility of self dialysis. Many authors have emphasised the importance of patient selection and psycho-social factors in influencing the success of CAPD (18, 26, 27). Although CAPD makes home dialysis possible for many patients, a successful CAPD program requires a large commitment by specialised staff for both training and support services. It also requires adequate hospital back-up facilities, including haemodialysis, in the event of complications (28).

Protein loss

Protein loss in the dialysis fluid is considerable and can be compensated for by adherence to a high protein diet. Dietary education is important to promote the ingestion of high quality protein with least reliance on milk and milk products which, in large

amounts, can produce hyperphosphataemia. Malnutrition and wasting are common problems in patients with end-stage renal disease but are perhaps more prevalent in peritoneal dialysis patients. Malnutrition can develop through increased protein loss during dialysis and/or decreased appetite, both of which occur during episodes of peritonitis (18, 29).

Glucose absorption

The quantity of glucose absorbed from the dialysis fluid contributes significantly to the carbohydrate and energy intake of the CAPD patient. It is suggested that this glucose absorption is responsible for the frequency of obesity and hypertriglyceridaemia in CAPD patients (29, 30). Cardiovascular disease is the main cause of death in dialysis dependent patients, but it is unclear how obesity and hypertriglyceridaemia affect the long term prognosis of CAPD patients (15, 29). Much attention has been directed towards the development of an alternative osmotic agent. Many agents have been investigated, including fructose, sorbitol, xylitol, amino acids, gelatin, glycerol, dextrans and glucose polymers, but none have proven to be as effective as glucose in producing ultrafiltration, and at the same time devoid of side-effects (30).

Intra-abdominal pressure

Increased intra-abdominal pressure due to the continuous presence of dialysis fluid in the abdominal cavity, can give rise to several complications. The most common of these is the development of abdominal hernias. Raised intra-abdominal pressure can also aggravate or lead to the development of haemorrhoids and lower back pain. Internal and external dialysis fluid leaks can occur and, less commonly, cardiopulmonary function may be compromised (29).

Long term membrane viability

Unlike haemodialysis, CAPD is dependent on a living membrane which has characteristics that vary between individuals and circumstances. Some patients have been treated for more than five years on CAPD without any apparent deterioration in dialysing capacity, while others have shown progressive loss of ultrafiltration and gross impairment after less than two years. Patients in whom impairment of dialysing capacity has occurred may have developed extensive i.p. adhesions and/or fibrosis or, in rare instances, go on to develop sclerosing peritonitis, a severe complication associated with a high morbidity (31).

The long term viability of the peritoneal membrane, and the factors which influence this, are uncertain. Possible causes of decreased dialysing capacity include low dialysis fluid pH, excessive use of hypertonic dialysis fluids, chemical irritation (for example dialysis fluids containing acetate, i.p. administered drugs or antiseptics), irritation due to particulate matter in the dialysis fluid, administration of beta blockers, irritation caused by the catheter, and peritonitis (31-34).

Peritonitis

Recurrent peritonitis continues to be the primary complication of CAPD and is the major impediment to prolonged success with this dialysis technique. This has been illustrated by a recent survey of CAPD patients in Australia which found that 64% of patients transferring from CAPD to another form of dialysis, did so because of peritonitis (16). Other reasons for transfer included infections along the catheter tract (tunnel infections), and skin exit-site infections, giving a total of 73% of transfers due to infectious complications. It is also possible that infection played a role in some other reasons given for transferring to an alternative form of dialysis, for example "unable to manage self-care" and "inadequate dialysis".

An analysis of CAPD technique survival in Australia shows that the probability of uninterrupted peritoneal dialysis in patients commencing CAPD during the period from 1985 to 1988 inclusive, was 65% one year after commencement, and 47% at two years. In this analysis, transfer to an alternative form of dialysis (for a period greater than one month), and death were regarded as technique failures. Increasing age was associated with a significant reduction in technique survival, whereas diabetes did not confer any adverse effect. Of interest is the relationship between technique survival and the year in which CAPD was commenced, which shows that there has been very little change in one year technique survival between 1981 (61%) and 1987 (64%). The incidence of peritonitis in CAPD patients in Australia is unknown, however during the twelve month period to October 1988, peritonitis was directly responsible for thirteen deaths in dialysis dependent patients (15, 16).

A greater appreciation of the extent of the peritonitis problem can be gained from the Report of the National CAPD Registry of the United States of America (13). Patients commencing CAPD during the period from 1981 to 1988, and receiving end-stage renal disease therapy for the first time, experienced an overall peritonitis rate of 1.3 episodes per patient year. Despite the introduction of newer connection devices, improvement in patient training and reports of decreased rates of peritonitis by individual centres, the incidence of peritonitis, when related to the year in which CAPD was commenced, has not changed since 1981 (1.3 episodes per patient year). For patients new to CAPD, the probability of experiencing at least one episode of peritonitis is 40% at the end of 6 months of therapy, 60% at one year, and 80% at two years. Long term single centre studies in other countries have reported similar figures (35).

Peritonitis is usually characterised by a cloudy dialysis fluid effluent (with an elevated white blood cell count); low grade fever, mild abdominal pain and changes in peritoneal membrane permeability. Approximately two-thirds of peritonitis episodes are caused by

gram-positive organisms originating from the skin (13, 36-38). *Staphylococcus epidermidis*, previously recognised as an important pathogen in infections associated with vascular catheters (39), is the most common infecting organism. Approximately 20% of peritonitis episodes are caused by gram-negative organisms, including *E.coli* and *Pseudomonas spp*, and a small number are caused by non-bacterial pathogens including fungi and algae (40-42). The bio-type and phage-type of organisms cultured from the skin, nose and hands of CAPD patients, when compared to the bacteria isolated from the peritoneal effluent of these patients during peritonitis episodes, shows that CAPD patients are at a much greater risk from their own flora than from their external environment (38).

Many centres have reported that a majority of peritonitis episodes have occurred in a minority of their patient population (18, 38, 43). The factors which predispose a patient to recurrent episodes of peritonitis are unknown. Non-adherence to aseptic technique is often implicated as the cause of a peritonitis episode, and the number of connect/disconnect procedures is considered to be related to the risk of infection. However, the failure of changes which have occurred in patient selection, patient training, connection devices (for example UV sterilisation chambers, sterile welding devices), and delivery systems (for example in-line filters), to produce a significant and consistent improvement in the incidence of peritonitis, indicates that there are multiple risk factors involved (13, 15, 43, 44). Changes which occur in the peritoneal defence mechanisms of the CAPD patient are poorly understood but may be of great importance (45-47). Bacterial and fungal colonisation of the catheter have been frequently observed (48, 49), and adherent bacteria have been shown to have greater resistance to the action of antibiotics (50, 51). Ash has suggested that the type of catheter employed and the method of catheter placement are related to the incidence of peritonitis (52). Some authors have commented that the role of material defects, for example cracks in the connection equipment leading to dialysate leaks, may have been

understated in recurrent peritonitis (18, 53). Two other factors which indicate that the cause of peritonitis is far more complex than can be singularly attributed to contamination during the exchange procedure, are the well recognised but obscure phenomena of sterile peritonitis and eosinophilic peritonitis in which no causative organisms can be isolated. These episodes have been reported to occur in approximately 15% of cases (13), and they are often assumed to be associated with chemical irritants, for example components of the dialysis fluid, plasticisers leached from the dialysis fluid container, or i.p. administered drugs (54-56). Others have claimed that this anomaly is due to inadequate microbiological culture techniques (37).

1.1.2.3 Treatment of peritonitis

The treatment of peritonitis must be initiated on empiric grounds before culture and sensitivity results are known. Initial antibiotic therapy should cover a broad spectrum of organisms, both gram-positive and gram-negative, and should be dependent on the sensitivity pattern of *Staphylococcus epidermidis* in each centre (57, 58). When a microbiological diagnosis is available the antibiotic therapy can then be rationalised.

Antibiotics are most frequently administered by direct addition to the dialysis fluid. This i.p. route of administration has several advantages over other parenteral routes of administration:

(i) It is a convenient route of administration because it employs a pre-existing access and eliminates the need to obtain a vascular access.

(ii) Intraperitoneal administration achieves high local drug concentrations and has a greater potential to eradicate organisms which may persist in stagnant residual pools of dialysate within the peritoneal cavity.

(iii) Therapeutic blood levels of most antibiotics are achievable by i.p. administration alone. Penetration of antibiotics from the peritoneal cavity to serum is usually rapid and

extensive, eliminating the need for intravenous (i.v.) loading doses. Seldom, however, is penetration from serum to the peritoneal cavity as effective (59, 60).

(iv) The i.p. administration of antibiotics enables uncomplicated episodes of peritonitis to be managed at home or on an out-patient basis. Individual centres have demonstrated their preference for out-patient management (61, 62), and the majority of renal units in Australia do not routinely admit patients for the treatment of peritonitis (16).

1.1.3 Stability of antibiotics in peritoneal dialysis fluids

Questions are often directed to hospital pharmacists concerning the stability and compatibility of drugs for i.p. administration. An overwhelming majority of patients undergoing peritoneal dialysis in Australia are on CAPD and use proprietary "ready to use" dialysis fluids which contain between 0.5% and 4.5% glucose. Antibiotics for i.p. administration are added directly to the dialysis fluid prior to its instillation into the peritoneal cavity. Peritonitis episodes in CAPD patients are routinely managed on an at home or out-patient basis and, in these settings, it is important to know the viability of the drug in pre-loaded bags. For example, is it possible to dispense a weekend supply of pre-loaded bags to a patient? Is it appropriate for a patient to pre-load a day's supply of dialysis fluid at one sitting? Of considerable interest to pharmacists is the use of drug combinations for the treatment of CAPD peritonitis. Initial empiric therapy is directed to broad-spectrum cover and frequently involves a combination of a penicillin or cephalosporin with an aminoglycoside. In many centres, heparin is routinely added to the dialysis fluid during episodes of peritonitis; it prevents the formation of fibrin filaments and is believed to be important in preventing the development of i.p. adhesions (5). The insulin requirement of diabetics generally increases during episodes of peritonitis and this group of patients will continue adding insulin to their dialysis fluid. The fluid is usually warmed to approximately 37°C prior to use in order to prevent discomfort when instilled into the peritoneal cavity. These practices have the potential to

create a number of pharmaceutical problems.

Knowledge of drug stability in concentrated dialysis fluids is also important for a minority of patients undergoing intermittent peritoneal dialysis. Concentrated dialysis fluids contain 30% or 50% glucose and are intended for use with dialysis machines containing automated proportioning systems. The machine which lead to the widespread application of intermittent peritoneal dialysis to the home setting during the 1970's, uses reverse osmosis to convert a tap water supply into sterile, apyrogenic water, and an automated proportioning system for using the water so produced to accurately dilute the concentrated dialysis fluid. The dialysis fluid delivered to the peritoneal cavity generally contains between 0.5% and 4.5% glucose, however drugs intended for i.p. administration are added to the concentrated fluid prior to its passage through the automated proportioning system. Drugs added at the beginning of the dialysis session will be in contact with the concentrate for up to 10 hours, and will be heated to 37°C during this time.

Great interest has been generated in the pharmacokinetics of drugs in peritoneal dialysis patients. Knowledge of the stability of a drug in dialysis fluid is also necessary in this context in order to accurately quantitate the processes of drug absorption and clearance after i.p. administration (59).

Pharmacists seeking information on the stability and compatibility of drugs in peritoneal dialysis fluids encounter a number of problems:

(i) Few studies have investigated the stability of drugs in peritoneal dialysis fluids

(ii) Ready retrieval of the published data is seldom possible due to the scatter of information over a wide range of sources

(iii) The application of the information is limited when differences exist between the study parameters and the clinical setting (for example composition of the dialysis fluid),

or when study parameters (for example storage temperature) have not been stated

(iv) Two or more studies may provide conflicting information

Because of these problems, pharmacists advising on i.p. drug administration frequently refer to the readily accessible information on drug stability and compatibility in i.v. infusion fluids. The application of this information to i.p. drug administration is questionable, primarily because of the differences in composition between the commonly used i.v. infusion fluids and peritoneal dialysis fluids. Infusion fluids used for i.v. drug administration are isotonic and are generally either solutions of glucose, sodium chloride, glucose and sodium chloride combined, or electrolyte solutions containing sodium, potassium, calcium, chloride and lactate ions (for example Hartmann's solution). Peritoneal dialysis fluids usually contain glucose and sodium chloride in combination with other electrolytes (calcium, magnesium and lactate), and are hypertonic. Differences also exist between the drug concentrations normally administered intravenously and those concentrations administered intraperitoneally to the renally impaired patient. Another important factor which questions the usefulness of i.v. admixture guidelines, is whether this information is in fact relevant to i.p. administration. Drug combinations which are known to produce a precipitate, for example gentamicin sulphate and heparin sodium, would be contraindicated for i.v. administration (63), but does this physico-chemical incompatibility also contraindicate i.p. administration?

Three reviews of the therapeutic management of peritonitis have been published which have collated a limited amount of data on drug stability in peritoneal dialysis fluids (64-66). None represents a complete review of the literature in this area, and the application of the information presented is limited by the lack of detail, for example storage conditions not specified, drug concentration not stated or peritoneal dialysis fluid formulation not stated. In some instances the authors have drawn conclusions which the

cited studies do not support, including instances where stability has been inferred from pharmacokinetic studies rather than having been demonstrated using controlled stability studies (64, 65). This over-simplified presentation of a portion of the literature is of little value to hospital pharmacists needing to make decisions concerning the viability of drugs administered to the peritoneal cavity.

1.2 Aims

The aims of this study were: (i) to conduct a literature review of the stability of antibiotics in peritoneal dialysis fluids, and (ii) to collate the published information and present it in a format which would serve as a useful reference for hospital pharmacists.

1.3 Methods

1.3.1 Literature review

Access to stability studies was obtained through Index Medicus, Medline database, correspondence with drug companies, and references contained in related journal articles.

1.3.2 Collation and presentation of the data

The stability studies were analysed and the data was collated and presented in a format which would facilitate its use as a reference for hospital pharmacists. The features chosen for this presentation were:

Drug monographs

All the data relevant to a particular drug was collated under the name of the drug. When

a study examined a combination of two or more drugs, the data was presented under the name of each drug. Drug monographs were arranged in alphabetical order.

Tabulated data

The data collated for each drug was presented in tabulated format. The tables contained a reference to each study, details of the study parameters, the method used to determine drug stability and a brief description of the results of each study.

CAPD fluid versus concentrated peritoneal dialysis fluids

To facilitate analysis of the data, the stability studies were divided into two categories:

(i) Those studies conducted in peritoneal dialysis fluids containing between 0.5% and 4.5% glucose. These fluids were collectively referred to as "CAPD fluids". Although these fluids are used most commonly in CAPD, the bags can also be connected in series and used with automatic cycler machines for CCPD and intermittent peritoneal dialysis.

(ii) Those studies conducted in concentrated peritoneal dialysis fluids containing 30% or 50% glucose. These fluids were collectively referred to as "peritoneal dialysis fluid concentrates". Since no patients were reported to be using reverse osmosis dialysis machines in Australia in October 1986 (16), few, if any, would be expected to be currently using peritoneal dialysis fluid concentrates. However, stability studies conducted in peritoneal dialysis fluid concentrates were presented because the review was designed to be relevant to practices in other countries as well as in Australia. Another issue which favoured the collation of this information, is the predicted increase in popularity of some form of semi-automated, semi-ambulatory peritoneal dialysis (such as CCPD and variations of this technique), resulting from efforts to increase dialytic efficiency and to reduce the incidence of peritonitis which has proved to be so much of a problem with CAPD (2, 4, 14, 67). If this were to happen, a renewed interest in automated proportioning systems could be expected because such systems would eliminate the risk of contamination associated with multiple serial connections of 2 L

peritoneal dialysis fluid containers.

Stability studies versus efficacy studies

Three methods have been used to investigate the stability of antibiotics in peritoneal dialysis fluids:

(i) Visual analysis for evidence of physical incompatibility

(ii) Stability determined by assaying for unchanged drug

(iii) Stability determined by measuring change in drug activity over time

Also included in this review were studies which examined the susceptibility of a test organism to peritoneal dialysis fluid or peritoneal dialysis effluent containing an antibiotic. These were collectively referred to as "efficacy studies", and were not true indicators of antibiotic stability in these fluids. Efficacy studies aim to mimic the conditions during a peritonitis episode, in which an antibiotic is added to the dialysis fluid in order to eradicate an organism residing within the peritoneal cavity. The activity of the antibiotic under these conditions is therefore of clinical relevance and may be an important factor in predicting treatment outcome (51). The feature which distinguishes efficacy studies from stability studies, is that the peritoneal dialysis fluid or effluent is not only the test solution to which the antibiotic is added, but also the growth medium for the test organism. The fate of a population of test organisms under these conditions reflects in part the effect of the dialysis fluid or effluent on this population. In the absence of controls designed to quantify this activity, the effect of the dialysis fluid or effluent on the activity of the antibiotic cannot be differentiated. None of the efficacy studies included in this review used controls to quantify the activity of peritoneal dialysis fluid or effluent on the test population, however this activity has been reported elsewhere in the literature. Several studies have demonstrated that CAPD fluids inhibit the growth of staphylococci (68-72). Some investigators concluded that CAPD fluid was bactericidal. Others found that while CAPD fluid inhibited the growth of staphylococci,

the organisms remained viable. The effect of CAPD fluids on other bacteria is less clear (68-71). Some studies found that *E. coli* and *P. aeruginosa* did not grow in CAPD fluids, while others found that these bacteria grew well. All studies demonstrated that peritoneal dialysis effluent was a more favourable growth medium than unused CAPD fluid for all the organisms tested.

Three methods have been used to investigate the efficacy of antibiotics in peritoneal dialysis fluids and peritoneal dialysis effluent:

(i) Measurement of the minimum inhibitory concentration of the antibiotic

(ii) Measurement of the minimum bactericidal concentration of the antibiotic

(iii) Analysis of the bacterial population as a function of time (time/kill curves)

The method and results of efficacy studies were tabulated in italics to distinguish them from stability studies.

Summary

To conclude each monograph, a summary of the tabulated data was presented for studies conducted in CAPD fluids and studies conducted in peritoneal dialysis fluid concentrates. Information on the stability and/or efficacy of the drug alone in peritoneal dialysis fluid was presented first, followed by information on its stability and/or efficacy when combined with other drugs. When applicable, the summary included comments on conflicting data, and comments on factors which may limit the application of the data to the clinical setting.

Guide to interpreting the data

A detailed guide to interpreting the tabulated data was provided in the introductory pages of the review. This included information on CAPD fluids and peritoneal dialysis fluid concentrates, stability and efficacy studies, study methods, drug nomenclature, order of presentation, standardisation of expression and units of measurement, abbreviations and

content of the appendices. Recommendations for the appropriate use of the document were provided, and limitations associated with the application of the information were highlighted.

1.4 Results

A document containing monographs for 33 antibiotics was produced and is presented in Appendix 1.

1.5 Discussion

Despite the routine use of i.p. antibiotics for the treatment of peritonitis, there are few studies which have investigated the stability of antibiotics in peritoneal dialysis fluids. Antibiotic combinations and antibiotics in combination with heparin and/or insulin are used frequently, yet the stability and compatibility of these combinations in dialysis fluids has received little attention. Some of the drugs for which stability information is available, are rarely used in today's clinical setting, for example carbenicillin. On the other hand, there is little or no stability information available for many of the drugs commonly used in renal units in Australia, for example flucloxacillin and co-trimoxazole. Despite the increasing incidence of fungal peritonitis and the increased interest in the use of i.p. antifungal agents, there is no information on the stability of antifungal agents in peritoneal dialysis fluids.

Of particular concern is the lack of well designed stability studies. Many of the studies reviewed failed to define many of the important variables which can affect drug stability in solution, for example drug concentration, storage temperature, peritoneal dialysis fluid container and peritoneal dialysis fluid composition. In addition, none of the studies reviewed provided evidence of the stability-indicating capability of the assay, in other

words the ability of the assay to unequivocally distinguish and quantitate unchanged drug in the presence of decomposition products.

The stability and compatibility of drugs in peritoneal dialysis fluids has not received the same attention that has been given to intravenously administered drugs. Intraperitoneal drug combinations are used, and i.p. admixtures are stored in the absence of stability data and, in many cases, in contravention of accepted i.v. admixture guidelines. In some centres, visual evidence of a physico-chemical incompatibility, for example haze or precipitate formation, is not regarded as contraindicating i.p. administration. Precipitation is expected to occur with some admixtures and occasionally attracts the additional instruction to "shake the bag" prior to instillation into the peritoneal cavity. This liberal approach to i.p. drug administration arises from the knowledge that a physico-chemical incompatibility resulting in precipitation will not produce a life-threatening situation. One disadvantage of this approach must be the risk of compromising the therapeutic efficacy of drugs administered to the peritoneal cavity, thereby compromising a rapid and successful treatment outcome.

An as yet unknown factor, which may prove to be an even greater disadvantage of this approach, is the effect of precipitates, decomposition products and reaction products on the peritoneal membrane. Sterile peritonitis and eosinophilic peritonitis have a high incidence in the peritoneal dialysis population (13). The cause of these phenomena is unknown, but chemical irritation of the peritoneal membrane by intraperitoneally administered compounds has been demonstrated (55, 56). Uncertainty also surrounds those factors which reduce the long term viability of the peritoneal membrane. Chemical irritation and irritation due to particulate matter have been suggested as possible contributing factors (33, 34, 73, 74).

Greater knowledge of the stability of drugs in peritoneal dialysis fluids, and the effects

of precipitates on the peritoneal membrane, is clearly required. Peritoneal dialysis patients are dependent on efficacious drug treatment to reduce the morbidity of peritonitis, and they are dependent on maintaining the function and integrity of the peritoneal membrane for their survival.

CHAPTER 2

STABILITY OF MICONAZOLE IN PERITONEAL DIALYSIS FLUID

2.1 Introduction

2.1.1 Fungal peritonitis: characterisation and incidence

Fungal peritonitis is a rare infectious complication usually occurring in one of two settings: (i) abdominal surgery or perforation, and (ii) peritoneal dialysis. It has been reported with increasing frequency since the advent of CAPD in 1976, and the subsequent increased use of peritoneal dialysis for the treatment of patients with end-stage renal disease (40, 75-78). Yeasts, particularly *Candida spp.*, are the most common organisms causing fungal peritonitis. Infections due to filamentous fungi have rarely been reported (38). Fungal peritonitis is associated with a high morbidity and mortality, and poses a difficult management problem (79-81).

The incidence of fungal peritonitis in the CAPD population in Australia is unknown, however peritonitis was directly responsible for thirty five deaths in peritoneal dialysis patients during the three year period to October 1988, and ten of these were due to fungal infection (15, 16, 82).

A special report of the National CAPD Registry of the United States of America has examined the characteristics of successive peritonitis episodes in a population who were commenced on CAPD during the period from January 1984 to June 1986 (n=6 335), (83). Fungal infection was present in only 2.7% of first peritonitis episodes, however following an initial fungal infection, 50% of recurrent infections also cultured fungi. Although each peritonitis episode was reported as a new and distinct

event, the high probability for a recurrent infection to also culture fungi, may be due in part to relapse. It can be difficult to distinguish between relapse and reinfection, especially as the time interval between peritonitis episodes shortens. This study reported a median time interval of two months between the first and second fungal infection.

The incidence of fungal peritonitis has been reported by several individual renal units during the period from 1983 to 1987 (76, 78-80, 84-86). These have ranged from 3.5% of all peritonitis episodes during a three and a half year period, to 15% during a two year period (78, 84).

2.1.2 Risk factors for fungal peritonitis

Impairment of host defence mechanisms during chronic renal failure, and the presence of a permanent indwelling catheter, are considered to contribute to the emergence of *Candida* as an important pathogen. *Candida* peritonitis in peritoneal dialysis patients can occasionally be attributed to obvious predisposing factors, such as bowel perforation or gross contamination of the dialysis system. In most cases, however, it is probable that multiple interacting factors are involved. Several risk factors have been proposed in the literature, foremost of which is the recent administration of antibiotics (within one month prior to the onset of fungal peritonitis). This is usually associated with an episode of bacterial peritonitis (40, 75, 77, 87-90). Other risk factors which have been proposed include recurrent episodes of bacterial peritonitis and frequent antibiotic administration (76, 78, 88, 91), hospitalisation (40), immunosuppressive therapy (40, 76), and diabetes (77, 90).

A study of seventeen cases of fungal peritonitis in CAPD patients failed to identify any epidemiologic, demographic or clinical factors which characterise patients developing this type of infection (80). In view of the relatively low incidence of fungal peritonitis,

large prospective studies would be required to test the validity of proposed risk factors.

2.1.3 Treatment of fungal peritonitis

The treatment of fungal peritonitis is based on the need to eradicate the infection as rapidly and safely as possible, while considering the need to preserve the peritoneum as a dialysing membrane. Many different treatment recommendations have been published since the early reports of this complication in patients with chronic indwelling catheters. The three main approaches to treatment are: (i) systemic and/or i.p. antifungal chemotherapy with catheter *in situ,* (ii) removal of the catheter plus supplementary antifungal chemotherapy, and (iii) removal of the catheter.

(i) Antifungal chemotherapy with catheter in situ

The successful treatment of fungal peritonitis using an i.p. antifungal agent with a chronic indwelling catheter *in situ,* was described as early as 1975, prior to the introduction of CAPD (92). Several more recent studies have also reported the successful treatment of fungal peritonitis using systemic and/or i.p. antifungal chemotherapy in patients with chronic indwelling catheters *in situ* (77, 84, 88, 89, 93-95). Advantages of this treatment option include uninterrupted peritoneal dialysis, preservation of the peritoneum for dialysis (by preventing the formation of adhesions), reduction in the demand for haemodialysis, and elimination of the need for surgery.

The best route of administration for antifungal chemotherapy has attracted considerable discussion in the literature. Some authors have commented on the therapeutic advantage of i.p. administration, reporting treatment successes with i.p. administration (88), or treatment failures with i.v. administration (91). Others have drawn attention to treatment failures when i.p. administration was used alone, and suggest that combination therapy with systemic antifungals or catheter removal is necessary to achieve cure (93).

Successful treatment has also been reported using oral chemotherapy in patients without interrupting CAPD (85).

Some antifungal agents can cause local irritation when instilled into the peritoneal cavity. Intraperitoneal amphotericin is frequently reported as causing pain (76, 84, 89-91, 96, 97), and it has been suggested that its use is associated with peritoneal fibrosis (40). There are isolated reports of local irritation due to flucytosine and miconazole (80, 92, 98).

(ii) Antifungal chemotherapy plus catheter removal

Early catheter removal has been identified by many authors as the most important step in a combined approach with antifungal chemotherapy, for the successful treatment of fungal peritonitis (75, 78, 86, 90, 97, 99). This is emphasised by reports of persistent fungal colonisation of the catheter after seemingly adequate chemotherapy had produced sterile peritoneal effluent (78, 97).

Intraperitoneal adhesions and abscess formation are problems associated with catheter removal and interruption of peritoneal dialysis. Often the dialysing capacity of the peritoneum is impaired and it is frequently not possible to resume peritoneal dialysis after resolution of the infection (79, 81, 95). Early or immediate replacement of the catheter enables early resumption of peritoneal dialysis, and has been recommended as a solution to these problems (100).

(iii) Catheter removal

It has been reported that removal of the peritoneal catheter alone will achieve cure in some cases (75, 93). Peritonitis episodes in which antifungal chemotherapy was unsuccessful, have been cured by removal of the catheter concurrent with cessation of chemotherapy (101). Maintenance of a better nutritional status has been identified as

another factor in favour of ceasing peritoneal dialysis (99).

There is no general consensus regarding the treatment of choice for fungal peritonitis in peritoneal dialysis patients. The approach to treatment depends on a number of variables, including organism identification, feasibility of haemodialysis, need to continue peritoneal dialysis, history of peritonitis, and concurrent illness. Accordingly, some authors have advocated a more flexible approach to the management of fungal peritonitis, and have recommended that an initial trial period with antifungal agents may be warranted prior to catheter removal (40, 76, 102). Two other controversial issues of treatment are the choice of antifungal agent and the use of peritoneal lavage. Probably the most serious problems in the management of fungal peritonitis are delayed diagnosis, and failure to initiate therapy quickly (40).

2.1.4 Stability of antifungal agents in peritoneal dialysis fluids

Despite the interest in i.p. antifungal chemotherapy, there is little information on the stability or compatibility of antifungal agents in peritoneal dialysis fluids (103). Amphotericin is known to precipitate in electrolyte and/or acidic solutions (63), and precipitation in peritoneal dialysis fluid has occasionally been reported (93). The effect of amphotericin precipitation on the peritoneal membrane, or on antifungal activity *in vivo,* is unknown.

2.1.5 Miconazole in the treatment of fungal peritonitis

Miconazole is an imidazole derivative possessing broad spectrum antifungal activity and some gram positive antibacterial activity (Figure 2.1). Clinical efficacy has been demonstrated against *Candida*, *Coccidioides*, *Cryptococcus* and *Paracoccidioides spp.* It acts by inhibiting the biosynthesis of membrane lipids, causing disruption to the permeability and integrity of fungal cell membranes (104). Miconazole has been administered intraperitoneally for the treatment of fungal peritonitis in concentrations ranging from 2 to 50 mg per litre of dialysate (84, 90, 93, 95, 99). Although dilutions of miconazole in 0.9% sodium chloride and 5% glucose injections are reported to be stable for 24 hours at room temperature, no information is available concerning the stability of miconazole in plastic containers (105), or in peritoneal dialysis fluids (103).

2.2 Aims

The aim of this study was to investigate the stability of miconazole in peritoneal dialysis fluid (PDF). The following aspects were examined:

(i) The stability-indicating capability of the assay

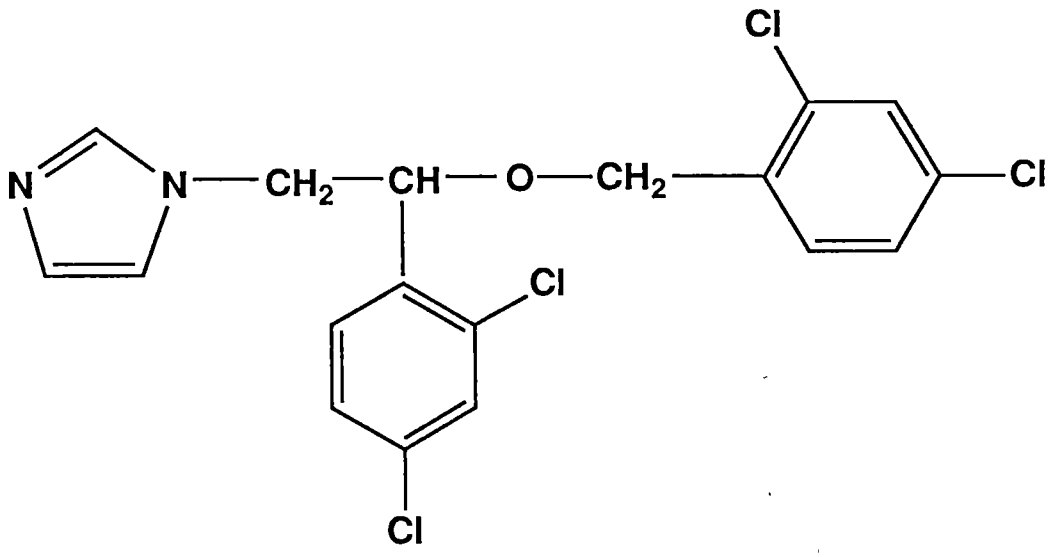
(ii) The stability of miconazole in PDF when stored in 2 L polyvinyl chloride (PVC) bags

(iii) The stability of miconazole in PDF when stored in glass ampoules

(iv) The sorption of miconazole by a 2 L PVC container

Figure 2.1 Miconazole

1-(2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl)-1H-imidazole



2.3 Methods

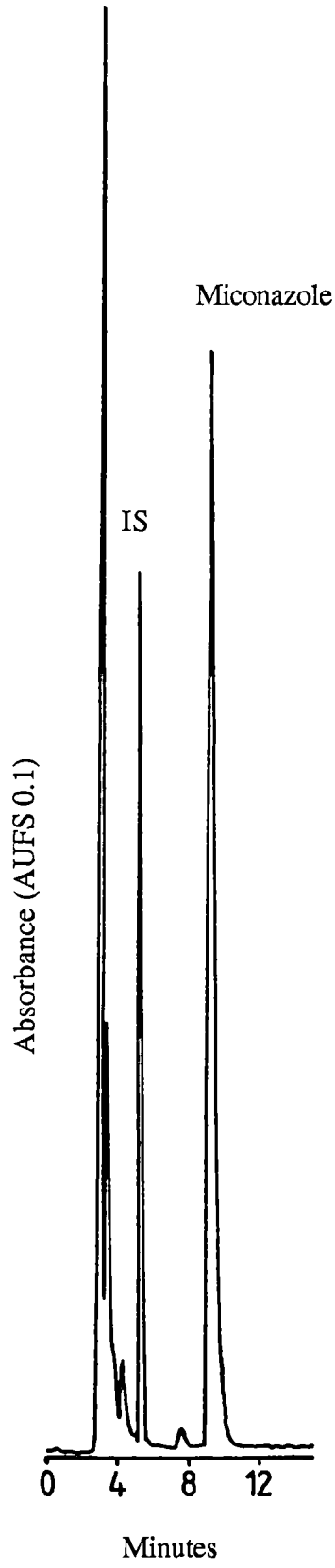
2.3.1 Materials

1. Miconazole injection 10 mg/mL (Daktarin®, Janssen, Belgium) Batch 85F11/031
2. PDF containing glucose 4.25%, sodium 132 mmol/L, calcium 1.75 mmol/L, magnesium 0.25 mmol/L, chloride 96 mmol/L and lactate 40 mmol/L. Osmolarity 485 milliosmoles/L (Dianeal® PD-2, Travenol, Australia) Batch A39H1
3. Miconazole nitrate (Janssen, Belgium) Batch ZR14889H 1001, donated by Janssen, Australia.
4. Methanol, HPLC grade (Waters Associates, MA, USA)
5. Ammonium dihydrogen phosphate, laboratory reagent grade (L.R.)
6. p-Dichlorobenzene, L.R.
7. Sulphuric acid, L.R.
8. Sodium hydroxide, L.R.

2.3.2 Analysis of miconazole

A high performance liquid chromatographic (HPLC) assay modified from that described by McGookin et al (106), was used to determine miconazole concentrations, using p-dichlorobenzene as an internal standard. Figure 2.2 shows a typical chromatogram of miconazole in PDF. The retention time for miconazole was approximately 8 minutes.

Figure 2.2 Chromatogram of miconazole in PDF (~20 mg/L) with internal standard (IS)



2.3.2.1 Instrumentation

Column:	μBondapak C18 stainless steel 3.9 mm i.d. x 30 cm (Waters Associates)
Guard column:	Bondapak C18/Corasil 37-50 μm (Waters Associates)
Solvent delivery system:	Waters Associates Model M45
Absorbance detector:	Waters Associates Model 441

2.3.2.2 Operating parameters

Mobile phase:	15% v/v 0.05M ammonium dihydrogen phosphate (pH 4.6) in methanol, filtered through a 0.45 μm membrane filter and degassed under vacuum before use.
Flow rate:	1.0 mL/min
Absorbance wavelength:	229 nm
Temperature:	20 ± 2°C

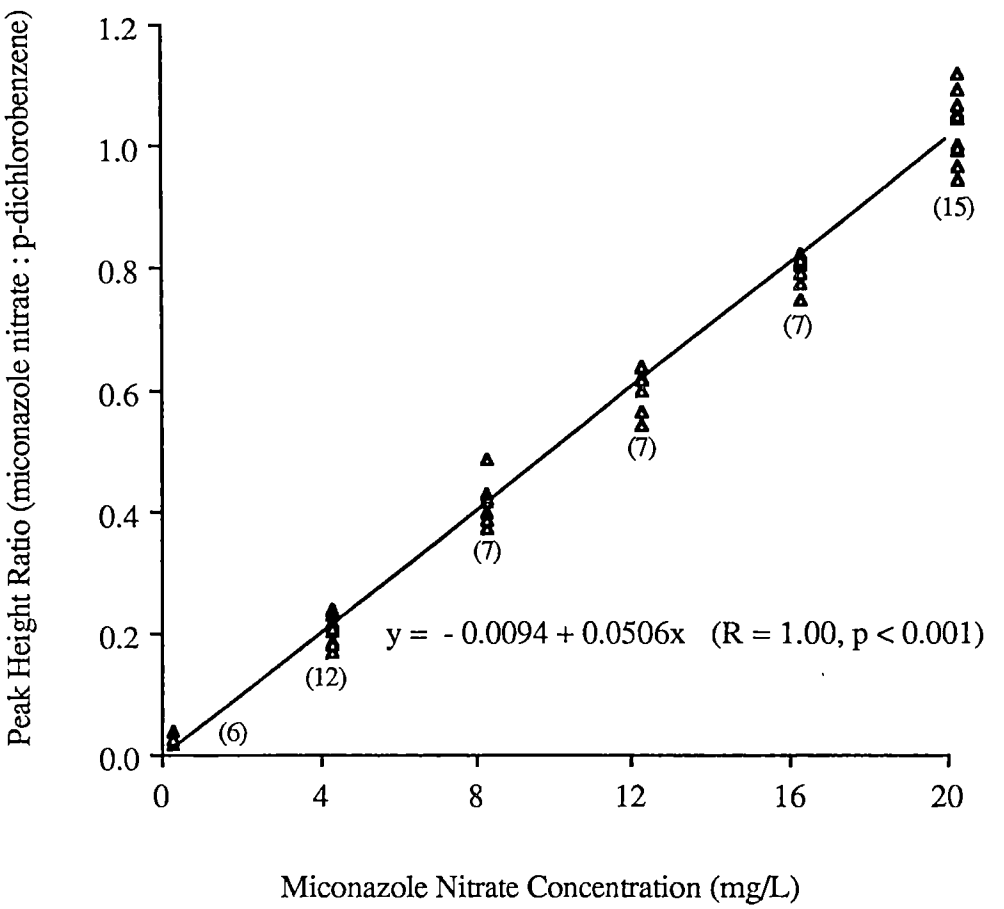
2.3.2.3 Calibration curve

A stock solution containing miconazole nitrate 2 g/L in methanol was prepared on the first day of the study. Aliquots of 50, 100, 150, 200 and 250 μL were pipetted into 25 mL volumetric flasks and adjusted to volume with PDF. This produced standard solutions containing 4, 8, 12, 16 and 20 mg/L of miconazole nitrate respectively. Each standard solution was assayed immediately after preparation.

A calibration curve was constructed by plotting the peak height ratio of miconazole nitrate to internal standard, against miconazole nitrate concentration (Figure 2.3). Each point on the calibration curve was determined at least once on each day of the study.

Figure 2.3 Calibration curve for miconazole nitrate

(The number of data points for each concentration is indicated in brackets)



The intra-day coefficient of variation was 3.6% at 20 mg/L (n=6), and 5.8% at 4 mg/L (n=6). The inter-day coefficient of variation was 3.9% at 20 mg/L (n=6), and 11.8% at 4 mg/L (n=6).

2.3.2.4 Sample preparation

A 200 µL sample of a solution of miconazole in PDF was combined with 200 µL of internal standard (p-dichlorobenzene 4 mg/L in methanol). A 20 µL aliquot of the resulting mixture was injected onto the column. Assays were performed immediately after sample preparation.

2.3.3 Stability-indicating capability of the assay

Two hundred microlitres of miconazole injection were pipetted into a 100 mL volumetric flask and adjusted to volume with PDF to produce a concentration of approximately 20 mg/L of miconazole. The resulting solution had a pH of approximately 6.0. Duplicate samples of the solution were assayed immediately to determine the initial miconazole concentration. Of the remaining solution:

(i) 2 mL was transferred into each of two glass ampoules and sealed

(ii) A portion was acidified to pH~2 with 1M H_2SO_4; 2 mL of the acidified solution was transferred into each of two glass ampoules and sealed

(iii) A portion was rendered alkaline to pH~11 with 1M NaOH; 2 mL of the alkaline solution was transferred into each of two glass ampoules and sealed

PDF without added miconazole was treated in a similar manner. The ampoules were then autoclaved for 1 hour at 118°C. Duplicate samples from each ampoule were assayed to determine the miconazole concentration. Numerous samples from each ampoule were also chromatographed without internal standard. The chromatograms of

all injections were compared and examined for changes suggesting the presence of decomposition products of miconazole.

2.3.4 Stability of miconazole in PDF stored in PVC bags

The method of preparation of admixtures used in this stability study was designed to simulate actual use conditions. Four millilitres of miconazole injection were measured in a 5 mL capacity plastic syringe and injected via the additive port into a commercially available PVC bag containing approximately 2080 mL of PDF. This produced a concentration of approximately 20 mg/L of miconazole. The bag was shaken vigorously by hand for one minute and a sample of the solution was assayed immediately, in duplicate, to determine the initial miconazole concentration. At 2, 4, 6, 12, 24, 48, 72, 120 and 216 hours after admixture, the bag was shaken gently by hand for one minute and a sample of the solution was assayed immediately, in duplicate, to determine the miconazole concentration. On each occasion approximately 1 mL samples were drawn from the bag via the additive port using a glass syringe. The additive port was swabbed with 70% alcohol before and after puncture, and sterile syringes and needles were used to maintain the sterility of the admixture. The bag was stored at 20 ± 2°C, exposed to ambient light, and was undisturbed between sampling times. The experiment was performed in duplicate.

2.3.5 Stability of miconazole in PDF stored in glass ampoules

Two hundred microlitres of miconazole injection were pipetted into a 100 mL volumetric flask and adjusted to volume with PDF to produce a concentration of approximately 20 mg/L of miconazole. Four samples of the resulting solution were assayed immediately to determine the initial miconazole concentration. One millilitre aliquots of the remaining solution were transferred into 1 mL glass ampoules and sealed. At 24, 48,

72, 168 and 216 hours after admixture, two ampoules were opened and the solution in each was assayed immediately, in duplicate, to determine the miconazole concentration. The ampoules were stored at 20 ± 2°C and exposed to ambient light. Care was taken not to shake or disturb the ampoules during storage to prevent contamination of the solution by decomposition products which may have been generated at the ampoule tip during the heat sealing process.

2.3.6 Sorption of miconazole by a PVC container

A solution of miconazole in PDF stored in a 2 L PVC bag was retained from the previously described study (2.3.4). The bag had been stored on a bench top at 20 ± 2°C and exposed to ambient light. Twenty one days after admixture, the bag was drained and duplicate samples of the solution were assayed to determine the miconazole concentration. The bag was cut along the seam into two halves. The inner surface of the plastic was rinsed with running distilled water and dried. Two 1 cm^2 sections and two 2 cm^2 sections of plastic were cut from an unprinted area of the bag. Each section was placed in a glass vial containing 4 mL of methanol and agitated. After 18 hours and 42 hours agitation, a sample of methanolic solution from each vial was assayed in duplicate to determine the miconazole concentration. A 2 L PVC bag containing PDF without added miconazole, was prepared in a similar manner and acted as a control. The inner surface area of each bag was calculated geometrically to be 1 120 cm^2.

2.4 Results

2.4.1 Stability-indicating capability of the assay

Chromatograms of the following solutions are illustrated in Figure 2.4:

(a) Miconazole in PDF (pH~6) assayed immediately after preparation

(b) Miconazole in PDF (pH~6) autoclaved for 1 hour at 118°C

(c) Miconazole in PDF (pH adjusted to ~2) autoclaved for 1 hour at 118°C

(d) Miconazole in PDF (pH adjusted to ~11) autoclaved for 1 hour at 118°C

The concentration of miconazole in the autoclaved solutions at unadjusted, acid and alkaline pH was 93%, 92% and 81%, respectively, of the initial concentration (19.4 mg/L) measured in solution (a).

The appearance of the chromatograms in the region of the solvent front varied significantly after autoclaving under different pH conditions. These changes were identical to those observed in chromatograms of the corresponding control solutions, shown in Figure 2.5 at reduced absorbance detector sensitivity, and may be associated with decomposition products of components of the PDF, for example glucose (107). These changes did not interfere with the peaks due to miconazole or internal standard. No extra peaks or changes, suggesting the presence of decomposition products of miconazole, were apparent in any of the chromatograms.

Figure 2.4 Chromatograms of miconazole (Mic) in PDF in glass ampoules

Internal standard (IS)

(a) Miconazole in PDF (pH~6) assayed immediately after preparation

(b) Miconazole in PDF (pH~6) autoclaved for 1 hour at 118°C

(c) Miconazole in PDF (pH adjusted to ~2) autoclaved for 1 hour at 118°C

(d) Miconazole in PDF (pH adjusted to ~11) autoclaved for 1 hour at 118°C

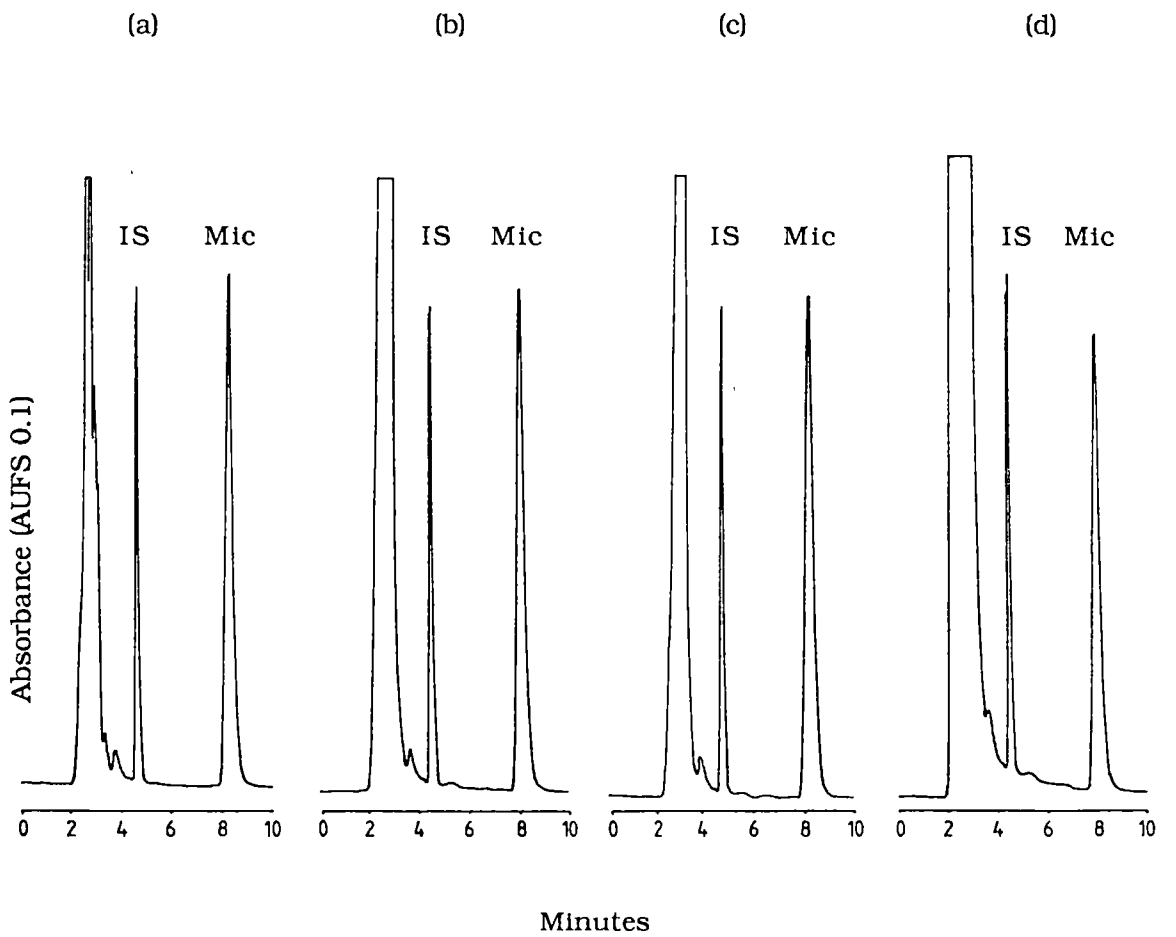


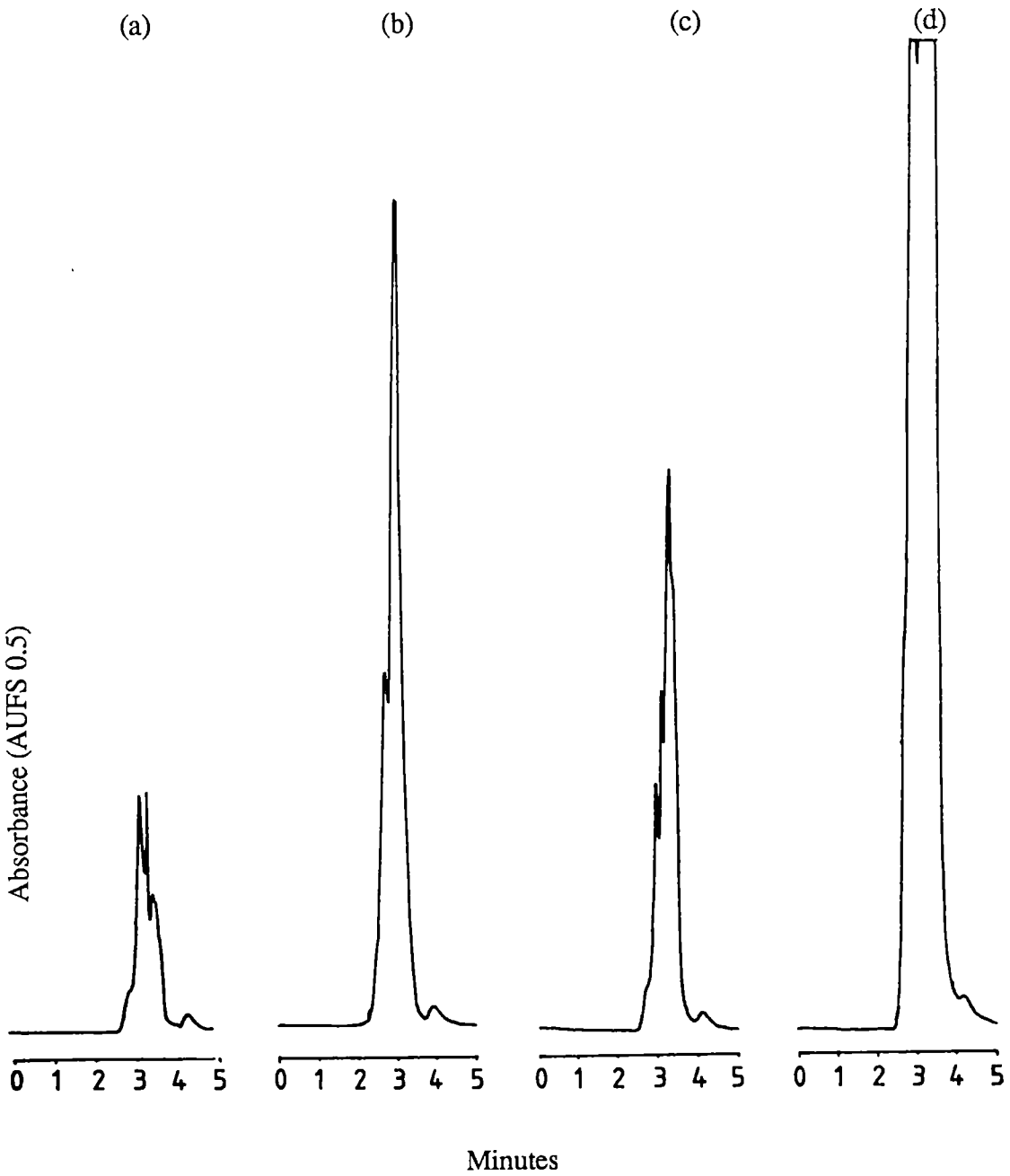
Figure 2.5 Chromatograms of PDF in glass ampoules without added miconazole (no internal standard)

(a) PDF (pH~6)

(b) PDF (pH~6) autoclaved for 1 hour at 118°C

(c) PDF (pH adjusted to ~2) autoclaved for 1 hour at 118°C

(d) PDF (pH adjusted to ~11) autoclaved for 1 hour at 118°C



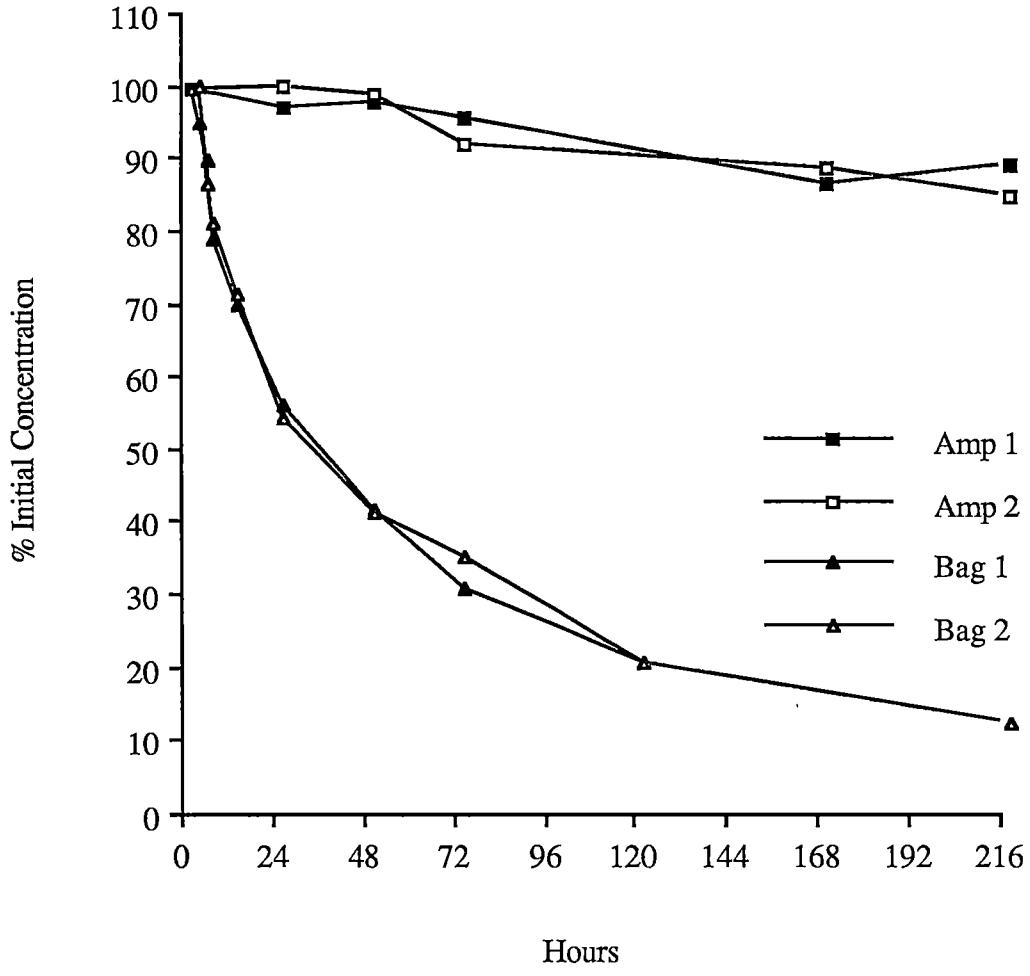
2.4.2 Stability of miconazole in PDF stored in PVC bags

The percentages of miconazole remaining in PDF stored in PVC bags are illustrated in Figure 2.6. A decline in miconazole concentration occurred in each bag during the study period, the rate of loss being greatest during the first 24 hours. Less than 90% of the initial concentration remained in each bag 4 hours after admixture. Less than 11% of the initial concentration remained in the solutions 216 hours (9 days) after admixture. No visible evidence of precipitation was observed in the solutions during the study period. When the pooled data (replicate assays from duplicate bags) was plotted semi-logarithmically (log [% initial concentration remaining] versus time), a curved plot was obtained indicating that monoexponential or simple first-order kinetics did not adequately model the loss of miconazole from solution. Feathering or resolving this curve as residuals yielded two straight line segments. The first-order rate constants for this biexponential rate profile of miconazole loss from PDF were 0.05 h^{-1} and 0.006 h^{-1}.

2.4.3 Stability of miconazole in PDF stored in glass ampoules

The percentages of miconazole remaining in PDF stored in glass ampoules are illustrated in Figure 2.6. A gradual decline in miconazole concentration occurred in each ampoule during the study period. Greater than 90% of the initial concentration was maintained for 3 days in each ampoule. Greater than 10% loss of initial concentration was observed in both ampoules 168 hours (7 days) after admixture. No visible evidence of precipitation was observed in the solutions during the study period.

Figure 2.6 Miconazole concentrations in admixtures stored in PVC bags and glass ampoules *



* Refer to Appendix 2 for data

2.4.4 Sorption of miconazole by a PVC container

The concentration of miconazole remaining in solution 21 days after admixture was 1.5 mg/L, which represented 7.5% of the initial concentration. The results of the methanolic extraction of miconazole from plastic are shown in Table 2.1. The quantity of miconazole extracted was greater per unit surface area from 1 cm^2 sections compared to 2 cm^2 sections, and slightly more miconazole was extracted from the plastic after 42 hours of agitation than after 18 hours. The mean quantity of miconazole recovered from the plastic by this method accounted for 28.3 ± 3.1% (mean ± SD, n=8) of the loss observed in the solution. Methanolic extracts of the corresponding controls showed no detectable peaks when assayed.

2.5 Discussion

Miconazole was found to be remarkably stable under conditions of extreme heat and pH which were intentionally applied in an attempt to promote its decomposition. Failure of these conditions to cause any substantial degree of chemical decomposition, means that it is not possible to unequivocally describe the ability of the assay to detect decomposition products of miconazole. However, it also indicates that substantial chemical decomposition is highly unlikely to occur under the relatively mild storage conditions employed in the stability studies conducted in both plastic and glass containers. The application of higher temperatures and prolonged heating may have produced greater decomposition of miconazole. To do so would have been of doubtful further benefit in assessing the ability of the assay to determine miconazole stability in solutions stored at room temperature. Such extreme conditions could, for instance, lead to the formation of decomposition products by mechanisms not relevant to storage at room temperature.

Table 2.1 Recovery of miconazole from plastic after methanolic extraction

Dimensions of plastic sample strip (cm)	Extraction time (hours)	Total miconazole recovered from sample strip * (μg)	Total miconazole in plastic *† (mg)	Percent miconazole loss recovered from plastic §	
				Mean	Range
1 x 1	18	12.1	13.6	29.8	1.4
1 x 1	42	12.8	14.3	31.4	2.5
2 x 1	18	20.2	11.3	24.8	4.4
2 x 1	42	22.1	12.4	27.1	2.2

* Mean of duplicate determinations

† Based on calculated total area of plastic = 1120 cm^2

§ Mean and range of duplicate determinations

This study demonstrates that a significant loss of miconazole (>10% of initial concentration) occurs within 4 hours when the drug is added to PDF containing 4.25% glucose and stored in PVC bags at 20 ± 2°C. A similar admixture was stable for at least 3 days when stored in glass ampoules under the same conditions. These findings alone suggest that the loss of miconazole observed in PVC bags is due largely to an interaction with the container, rather than chemical decomposition in solution. This proposition is supported by the results of the experiment designed to assess the stability-indicating capability of the assay (2.4.1). In the clinical situation, the rapid loss of miconazole from PDF stored in PVC bags would demand that such admixtures be prepared immediately prior to administration.

PVC is one of many polymers employed in the pharmaceutical industry for the manufacture of drug containers and delivery systems. Polymers are generally combined with one or more additives to improve the properties of the plastic, or to reduce its unit cost. Some of the more common additives are antioxidants, antisag agents, antistatic agents, colours, cross-linking agents, flame retardants, plasticisers, stabilisers and reinforcing agents (108). Numerous studies have reported the interaction of drugs with their containers and delivery systems. Autian and Brewer in 1958 were among the first to give attention to drug-plastic interactions when they reported the effect of a large number of parenteral products on disposable plastic-hubbed syringes (109). The mechanism, quantification and prediction of such interactions have been the focus of many subsequent studies (110 and references cited therein).

Four types of drug-plastic interactions have been identified: (i) permeation, (ii) leaching, (iii) sorption, and (iv) chemical reaction. Each of these processes can cause significant changes in the properties of the plastic. Conversely, subtle changes in the properties of the plastic, for example by polymer degradation or variation in plasticiser content, can have a significant effect on drug-container interactions (108, 111).

(i) Permeation

No plastic currently used in the pharmaceutical industry presents such a complete barrier to gases and other types of molecules as does an all-glass container. Oxygen and other gases in the external environment may enter the drug solution by passing through the plastic container wall. Conversely, a volatile constituent within the container may pass through the container wall to the external environment. Other solutes may also permeate the container, thereby reducing the concentration of that component in solution.

(ii) Leaching

Leaching refers to the migration of a component from the plastic into the solution in contact with it. A component leached from the plastic may remain in solution, or form a suspension of discrete particles.

(iii) Sorption

Sorption refers to the movement of a solute from the solution into the polymeric structure of the drug container or delivery system. Sorption consists of the processes of adsorption (interaction of a solute at the drug/plastic interface) and absorption (entrance of the solute into the body of the polymer). The forces of interaction are generally of the physical type, although chemical interaction or "chemisorption" has occasionally been reported. Sorption is a prerequisite to permeation.

(iv) Chemical reaction

A solute may react chemically with a constituent of the plastic. The solute most frequently involved in this type of interaction is a decomposition product generated in the solution after periods of storage, and the constituent of the plastic is usually an additive rather than the polymer. This interaction often results in discolouration of the plastic.

In this study, approximately 28% of the miconazole lost from solution could be recovered from the plastic by methanolic extraction. This represents sorption of miconazole by the PVC container. The loss of miconazole from the solution showed a biexponential rate profile. Since extremely long times (weeks or months) are generally required to attain or even approach an equilibrium situation during sorption of solutes by plastic infusion systems (112, 113), this biexponential profile may represent a loss of miconazole by the separate processes of partition and diffusion, as discussed by Polack et al (114).

The miconazole lost from the solution and not recovered from the plastic, may be due to: (i) incomplete extraction of miconazole from the plastic, (ii) chemical reaction of miconazole with components of the plastic, (iii) loss of miconazole by permeation, and/or (iv) chemical decomposition of miconazole.

McGookin et al have studied the sorption of miconazole dissolved in 0.9% sodium chloride injection by an i.v. infusion bag and various administration sets (106). The percentage sorption observed after transfer of the solution through the administration sets ranged from 1 to 10% of the initial concentration, with a mean of 4.8%. Sorption of miconazole after 24 hours storage in PVC infusion bags was of the order of 5%. The loss of miconazole observed in this study was assumed to be due to sorption, however McGookin et al did not investigate other mechanisms of loss, or prove sorptive loss *per se*. They concluded that the interaction of miconazole with plastic containers and administration sets is unlikely to be clinically significant. In contrast, this study demonstrates that the interaction of miconazole with a PVC container may result in a clinically significant loss from the solution.

In 1971, Autian proposed many factors which influence the permeation and sorption of drugs by plastic containers and delivery systems (108). These included temperature,

physico-chemical properties of the polymer (for example degree of crystallinity), physico-chemical properties of the drug (for example solubility, polarity and molecular weight), solution volume, solvent, pH, degree of drug ionisation, drug concentration, and the presence of other constituents in the solution.

Numerous studies have subsequently investigated the importance of many of these factors in controlling the rate and extent of drug-plastic interactions. For example, it has been demonstrated that different polymers exhibit different potentials to interact with drugs in solution. The loss of nitroglycerin and many of the benzodiazepines in PVC infusion systems has been extensively reported (115-123). However, nitroglycerin and diazepam have been shown to be stable in polyethylene (119, 121), and polypropylene containers (120). Similar findings have been reported for other solutes (120, 124), and have identified PVC as the polymer most frequently associated with sorption of drugs by containers and delivery systems (110).

Increased temperature has been reported by many authors to cause an increase in the rate and/or extent of uptake of various drugs by plastic infusion systems (121, 125-128). Uptake of solutes has also been demonstrated to increase with an increase in the surface area to volume ratio of the infusion bag (116, 120, 127). Lipid solubility and degree of ionisation have been identified as two important physico-chemical properties of the drug which influence its ability to interact with plastic infusion systems, with uptake into plastic generally limited to unionised, lipid soluble molecules (118, 129, 130).

The effect of concentration on the uptake of solutes by plastic infusion systems is less clear. Several studies have shown that the percentage loss of organic nitrates and diazepam from PVC bags was independent of the initial concentration (116, 120, 121, 131). However, the percentage loss of warfarin sodium and chlormethiazole from PVC bags was reported to be concentration dependent (111, 125). Factors which make

concentration an important variable in the uptake of some drugs and not others, are largely unknown, but appear to be associated with two different rate controlling processes, one being the diffusion of drug in the plastic matrix, and the other being a saturable binding or adsorptive process (132). It is possible that some drugs may enhance their own sorption by interacting with the polymer, for example the plasticisation of PVC by chlormethiazole (111). The investigation of the effect of concentration on the sorptive loss of a solute is complicated by the effect which a change in concentration can have on the pH of the solution (120, 132)

Many questions also surround the importance of other constituents in the solution and their influence on solute uptake by plastic infusion systems. Moorhatch and Chiou demonstrated that the sorption of vitamin A acetate was enhanced in the presence of 0.9% sodium chloride compared to water, and that the sorption of both warfarin sodium and vitamin A acetate was enhanced in the presence of 5% glucose (125). However, comparisons of 0.9% sodium chloride and 5% glucose injections as diluents have shown no influence on the rate of uptake of a variety of organic nitrates and benzodiazepines by plastic infusion systems (116, 117, 123, 131, 133).

Variation in one or more of the many factors which influence the uptake of drugs by plastic infusion systems may be responsible for the difference between the results of this study and those of McGookin et al (106). Possible differences between the polymer composition of the PVC bags used in this and McGookin et al's study may cause variation in sorptive loss, and the polymer type of the administration sets used in the latter study was not stated. The different characteristics of PDF and 0.9% sodium chloride injection as diluents may also cause variation in sorptive loss. PDF is more acidic than 0.9% sodium chloride injection, and a decrease in pH would be expected to decrease the sorptive loss of miconazole (a weak base) to plastic infusion systems. Therefore the difference in diluent pH alone cannot explain the different results of these

studies. The concentration of miconazole, however, will also affect the pH of the admixture, since miconazole i.v. solution has a pH in the range 3.7 to 5.7 (134). The volume of the infusion solution, the concentration of miconazole, and the pH of the admixture, are important variables which are not stated in McGookin et al's report, but which are essential for making a critical comparison with the present study.

CHAPTER 3

STABILITY OF CO-TRIMOXAZOLE IN PERITONEAL DIALYSIS FLUID

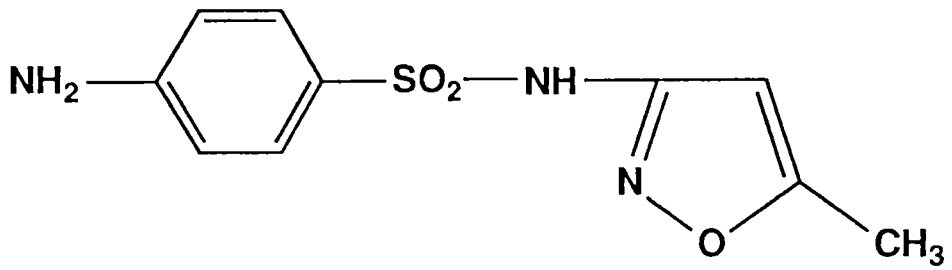
3.1 Introduction

A combination of the two antibacterial agents, sulphamethoxazole and trimethoprim, in a fixed 5:1 ratio, is commonly known as co-trimoxazole (Figure 3.1). Co-trimoxazole is active against a wide range of gram-negative and gram-positive organisms, including *E.coli* and *Staphylococcus spp*. Sulphamethoxazole inhibits the bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the enzyme dihydrofolate reductase. Hence co-trimoxazole exerts its effect by blocking two consecutive steps in the pathway by which microorganisms synthesise tetrahydrofolic acid. It is this reduced form of folic acid which is essential for cellular metabolism, including the synthesis of purines and DNA (135). Co-trimoxazole has been administered intraperitoneally for the treatment of peritonitis in concentrations ranging from 5 to 40 mg of trimethoprim, and 25 to 200 mg of sulphamethoxazole, per litre of dialysate (53, 136-138). Despite the use of i.p. co-trimoxazole, both alone and in combination with other drugs, there is no information on the stability or compatibility of co-trimoxazole in PDF's (103).

Figure 3.1

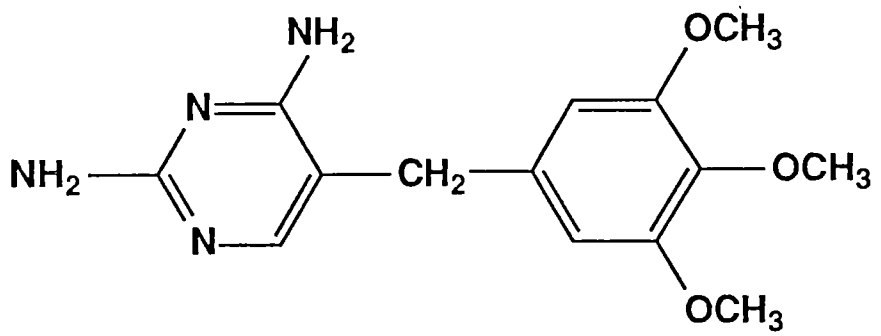
Sulphamethoxazole

3-(4-aminobenzenesulphonamido)-5-methylisoxazole



Trimethoprim

2,4-diamino-5-(3,4,5-trimethoxybenzyl) pyramidine



3.2 Aims

The aim of this study was to investigate the stability of co-trimoxazole in PDF. The following aspects were examined:

(i) The stability-indicating capability of the assay

(ii) The stability of co-trimoxazole in PDF when stored in 2 L PVC bags

(iii) The stability of co-trimoxazole in PDF when stored in glass ampoules

(iv) Identification of a decomposition product present in co-trimoxazole/PDF admixtures

3.3 Methods

3.3.1 Materials

1. Co-trimoxazole injection containing 400 mg of sulphamethoxazole and 80 mg of trimethoprim in 5 mL (Bactrim ®, Roche, Switzerland) Batch B1004
2. PDF containing glucose 4.25%, sodium 132 mmol/L, calcium 1.75 mmol/L, magnesium 0.25 mmol/L, chloride 96 mmol/L, lactate 40 mmol/L. Osmolarity 485 milliosmoles/L (Dianeal ® PD-2, Travenol, Australia) Batch A39H1
3. Sulphamethoxazole (Sigma, MO, USA) Lot 101F-0243
4. Trimethoprim (donated by Roche, Australia) Lot 771 840
5. Sulphadimidine B.P. (Central Medical Store, Hobart)
6. Acetonitrile, HPLC grade (Waters Associates, MA, USA)
7. Methanol, HPLC grade (Waters Associates, MA, USA)
8. Disodium hydrogen phosphate, analytical reagent grade (A.R.), (May and Baker, Australia)
9. Potassium dihydrogen phosphate A.R. (May and Baker, Australia)
10. Sulphanilic acid L.R. (BDH Chemicals, England)
11. Glacial acetic acid L.R. (BDH Chemicals, England)

12. Acetic anhydride L.R. (Ajax Chemicals, Australia)
13. Sulphuric acid A.R. (Ajax Chemicals, Australia)
14. Sodium hydroxide A.R. (May and Baker, Australia)
15. Diethyl ether A.R. (May and Baker, Australia)
16. Pentafluoropropionic anhydride (Pierce, U.S.A.)
17. Bis(trimethylsilyl)trifluoroacetamide (Pierce, U.S.A.)
18. Ethanol (C.S.R., Australia)
19. Dichloromethane A.R. (Ajax Chemicals, Australia)
20. Ammonia solution A.R. (BDH Chemicals, England)
21. Anhydrous sodium carbonate A.R. (Standard Laboratories, Australia)
22. Ethyl acetate A.R. (May and Baker, Australia)
23. Benzene, re-distilled
24. 5-Methyl-3-isoxazolamine was synthesised using the method described by Manzo et al (139). Sulphamethoxazole (500 mg) was dissolved in a mixture of glacial acetic acid (20 mL) and acetic anhydride (5 mL) and boiled for 5 minutes. When cool, the solution was combined with distilled water and ice. The precipitate produced was collected and dried to yield a weight of approximately 390 mg. The precipitate was dissolved in 2.5 mL of 40% w/v sulphuric acid and boiled for 3 minutes. The cooled solution was rendered alkaline with 10% w/v sodium hydroxide solution and extracted with 3 x 4 mL volumes of diethyl ether. The pooled extracts were evaporated to dryness. A sample of the resulting compound was analysed by mass spectrometry (MS). A second sample was dissolved in ethanol and analysed by UV spectrometry.

3.3.2 Analysis of co-trimoxazole

An HPLC assay modified from that described by Rumble (140), was used to determine sulphamethoxazole and trimethoprim concentrations, using sulphadimidine as an internal standard. Figure 3.2 shows a typical chromatogram of co-trimoxazole in PDF. The retention times for trimethoprim and sulphamethoxazole were approximately 16 and 18 minutes respectively.

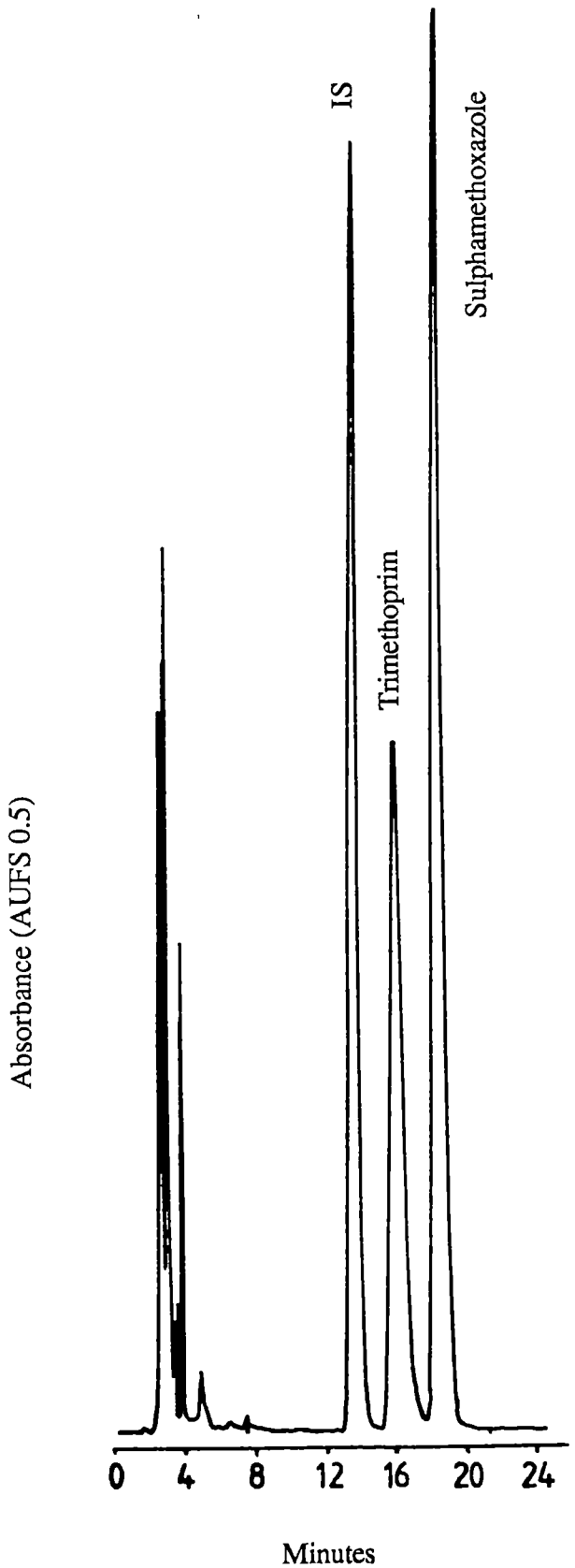
3.3.2.1 Instrumentation

Column:	μBondapak C18 stainless steel 3.9 mm i.d. x 30 cm (Waters Associates)
Guard column:	Bondapak C18/Corasil 37-50 μm (Waters Associates)
Solvent delivery system:	Waters Associates Model M45
Absorbance detector:	Waters Associates Model 441

3.3.2.2 Operating parameters

Mobile phase:	17% v/v acetonitrile in 0.067M phosphate buffer (pH 6.2), filtered through a 0.45 μm membrane filter and degassed under vacuum before use.
Flow rate:	1.0 mL/min
Absorbance wavelength:	229 nm
Temperature:	20 ± 2°C

Figure 3.2 Chromatogram of co-trimoxazole in PDF with internal standard (IS) (~100/20 mg/L sulphamethoxazole/trimethoprim)



3.3.2.3 Calibration curves

A stock solution containing sulphamethoxazole 10 g/L and trimethoprim 2 g/L in methanol was prepared on the first day of the study. Aliquots of 50, 100, 150, 200 and 250 µL were pipetted into 25 mL volumetric flasks and adjusted to volume with PDF. This produced standard solutions containing 20/4, 40/8, 60/12, 80/16, and 100/20 mg/L of sulphamethoxazole / trimethoprim respectively. Each standard solution was assayed immediately after preparation.

A calibration curve for sulphamethoxazole was constructed by plotting the peak height ratio of sulphamethoxazole to internal standard, against sulphamethoxazole concentration (Figure 3.3). The intra-day coefficient of variation was 2.0% at 100 mg/L (n=6), and 2.5% at 20 mg/L (n=6). The inter-day coefficient of variation was 0.8% at 100 mg/L (n=4), and 1.1% at 20 mg/L (n=4).

A calibration curve for trimethoprim was constructed by plotting the peak height ratio of trimethoprim to internal standard, against trimethoprim concentration (Figure 3.4). The intra-day coefficient of variation was 3.9% at 20 mg/L (n=7), and 3.1% at 4 mg/L (n=6). The inter-day coefficient of variation was 3.0% at 20 mg/L (n=4), and 3.7% at 4 mg/L (n=4).

3.3.2.4 Sample preparation

A 200 µL sample of a solution of co-trimoxazole in PDF was combined with 200 µL of internal standard (sulphadimidine 52 mg/L in methanol). A 20 µL aliquot of the resulting mixture was injected onto the column. Assays were performed immediately after sample preparation.

Figure 3.3 Calibration curve for sulphamethoxazole

(The number of data points for each concentration is indicated in brackets)

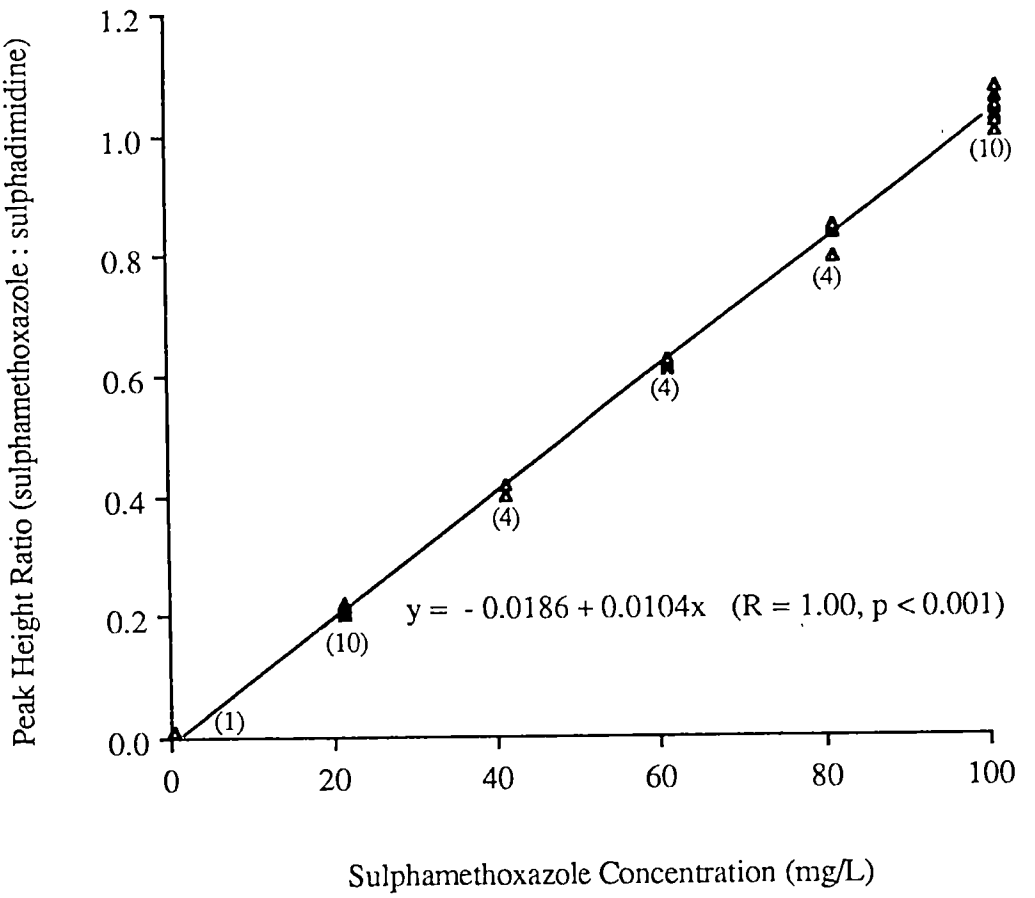
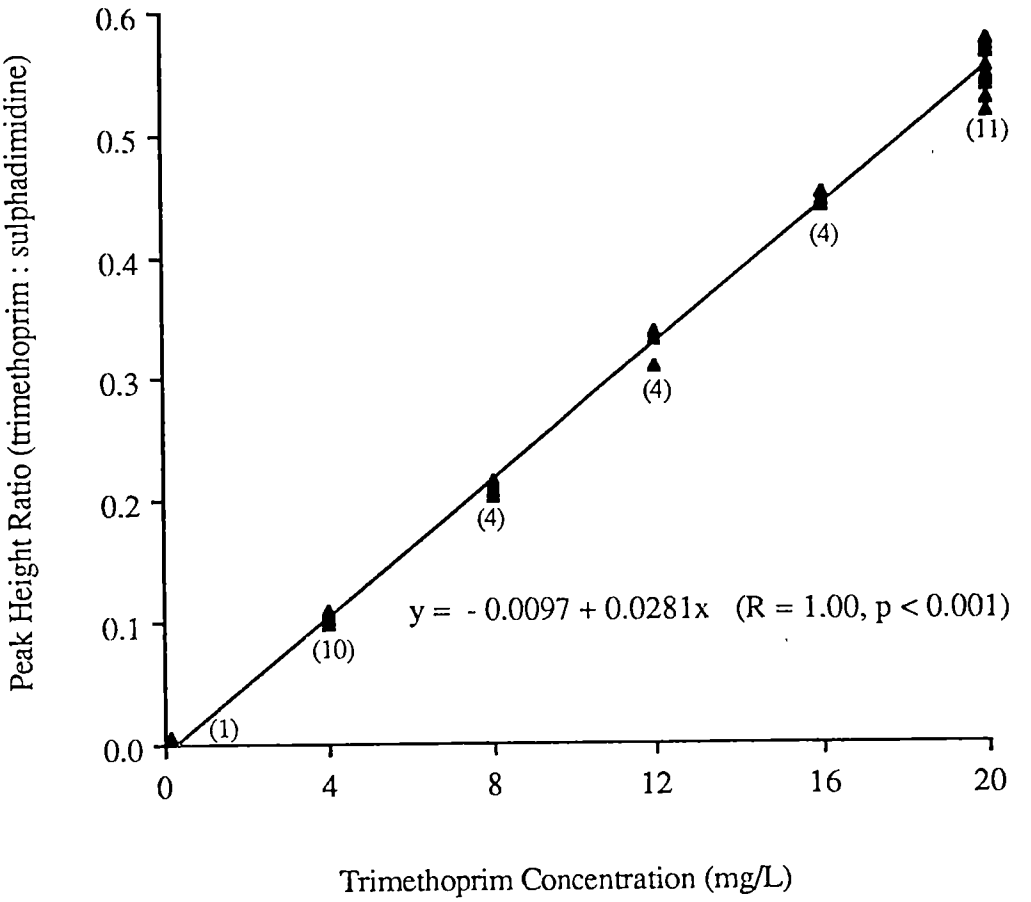


Figure 3.4 Calibration curve for trimethoprim

(The number of data points for each concentration is indicated in brackets)



3.3.3 Stability-indicating capability of the assay

A 250 µL aliquot of co-trimoxazole injection was pipetted into a 200 mL volumetric flask and adjusted to volume with PDF to produce a concentration of approximately 100 mg/L of sulphamethoxazole, and 20 mg/L of trimethoprim. The resulting solution had a pH of approximately 6.0. Four samples of the solution were assayed immediately to determine the initial sulphamethoxazole and trimethoprim concentrations. Of the remaining solution:

(i) 2 mL was transferred into each of two glass ampoules and sealed

(ii) A portion was acidified to pH~2 with 1M H_2SO_4; 2 mL of the acidified solution was transferred into each of two glass ampoules and sealed

(iii) A portion was rendered alkaline to pH~11 with 1M NaOH; 2 mL of the alkaline solution was transferred into each of two glass ampoules and sealed

The ampoules were then autoclaved for 1 hour at 118°C. Duplicate samples from each ampoule were assayed to determine the sulphamethoxazole and trimethoprim concentrations. Numerous samples from each ampoule were also chromatographed without internal standard. The chromatograms of all injections were compared and examined for changes suggesting the presence of decomposition products of co-trimoxazole.

3.3.4 Stability of co-trimoxazole in PDF stored in PVC bags

The method of preparation of admixtures used in this stability study was designed to simulate actual use conditions. A 2.5 mL volume of co-trimoxazole injection was measured in a 2.5 mL capacity plastic syringe and injected via the additive port into a commercially available PVC bag containing approximately 2080 mL of PDF. This produced concentrations of approximately 100 mg/L of sulphamethoxazole and 20 mg/L

of trimethoprim. The bag was shaken vigorously by hand for one minute and a sample of the solution was assayed immediately, in duplicate, to determine the initial sulphamethoxazole and trimethoprim concentrations. At 2, 6, 12, 24, 48, 72 and 216 hours after admixture, the bag was shaken gently by hand for one minute and a sample of the solution was assayed immediately, in duplicate, to determine the sulphamethoxazole and trimethoprim concentrations. On each occasion approximately 1 mL samples were drawn from the bag via the additive port using a glass syringe. The additive port was swabbed with 70% alcohol before and after puncture, and sterile syringes and needles were used to maintain the sterility of the admixture. The bag was stored at 20 ± 2°C, exposed to ambient light, and was undisturbed between sampling times. The experiment was performed in duplicate.

3.3.5 Stability of co-trimoxazole in PDF stored in glass ampoules

A 250 µL aliquot of co-trimoxazole injection was pipetted into a 200 mL volumetric flask and adjusted to volume with PDF to produce a concentration of approximately 100 mg/L of sulphamethoxazole, and 20 mg/L of trimethoprim. Four samples of the resulting solution were assayed immediately to determine the initial sulphamethoxazole and trimethoprim concentrations. One millilitre aliquots of the remaining solution were transferred into 1 mL glass ampoules and sealed. At 2, 6, 12, 24, 48, 72, and 216 hours after admixture, two ampoules were opened and the solution in each was assayed immediately, in duplicate, to determine the sulphamethoxazole and trimethoprim concentrations. The ampoules were stored at 20 ± 2°C and exposed to ambient light. Care was taken not to shake or disturb the ampoules during storage to prevent contamination of the solution by decomposition products which may have been generated at the ampoule tip during the heat sealing process.

3.3.6 Identification of a decomposition product in co-trimoxazole/PDF admixtures

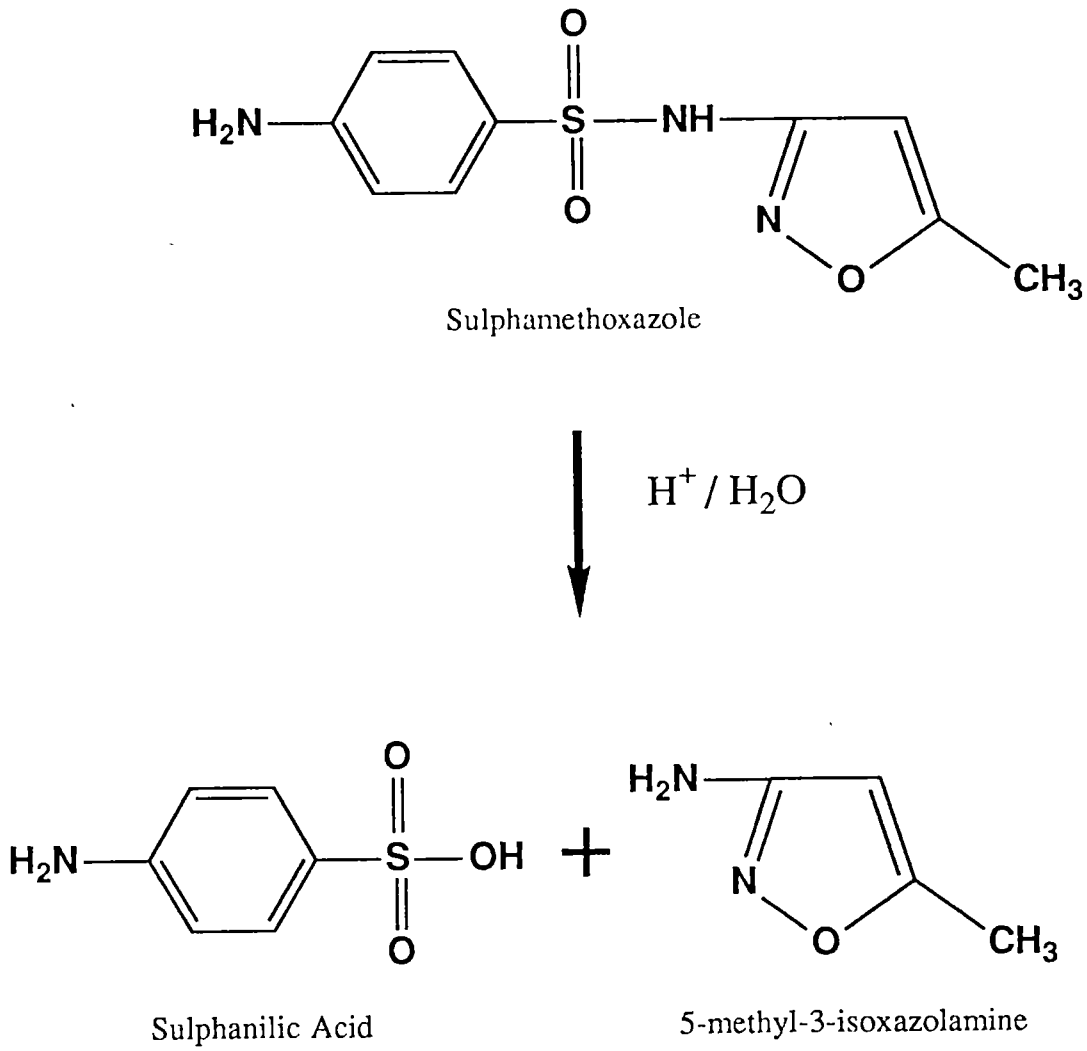
In an acid environment, sulphamethoxazole has been shown to hydrolyse yielding sulphanilic acid and 5-methyl-3-isoxazolamine, and on extended heating additional diazotisable products are formed (141). The initial approach to identifying an unknown decomposition product present in co-trimoxazole/PDF admixtures after storage, was directed towards the known decomposition products of sulphamethoxazole, namely sulphanilic acid and 5-methyl-3-isoxazolamine (Figure 3.5). Subsequent experiments to identify the decomposition product were based on its extraction and isolation from co-trimoxazole/PDF admixtures. Each of the admixtures used in these experiments had an initial concentration of approximately 100 mg/L of sulphamethoxazole and 20 mg/L of trimethoprim.

3.3.6.1 Comparison with known decomposition products

Solutions of sulphanilic acid (~10 mg/L in PDF) and 5-methyl-3-isoxazolamine (~20 mg/L in PDF) were prepared and analysed by HPLC. Chromatograms of these solutions were compared with chromatograms of co-trimoxazole/PDF admixtures after various storage intervals in both PVC bags and glass ampoules.

Sulphanilic acid and 5-methyl-3-isoxazolamine were co-chromatographed with (i) co-trimoxazole/PDF admixtures after various storage intervals in both PVC bags and glass ampoules, and (ii) co-trimoxazole/PDF admixtures which had undergone accelerated degradation under conditions of extreme heat and pH.

Figure 3.5 Hydrolysis of sulphamethoxazole



Sulphamethoxazole

Sulphanilic Acid

5-methyl-3-isoxazolamine

3.3.6.2 Direct probe MS analysis

A 5 mL sample of a solution of co-trimoxazole in PDF, stored for 10 days in a PVC bag, was reduced by evaporation under vacuum and azeotrope formation with ethyl acetate and benzene. Evaporation to dryness did not prove possible under these conditions because of the high glucose content of the sample. The resulting residue was subjected to direct probe MS analysis

3.3.6.3 Extraction of column effluent fractions: gas chromatography/mass spectrometry analysis

Four samples of a solution of co-trimoxazole in PDF, stored for 10 days in a PVC bag, were injected onto the HPLC column. Fractions of the column effluent, corresponding to the elution of the unknown decomposition product, were collected between 5 and 7 minutes after injection of each sample. The pooled fractions (~8 mL) were rendered alkaline with ammonia solution and extracted with 3 x 20 mL volumes of dichloromethane. The pooled extracts were dried over anhydrous sodium carbonate, filtered and evaporated to dryness. The extract was derivatised with pentafluoropropionic anhydride (PFPA), and bis(trimethylsilyl)trifluoroacetamide (BSTFA), and analysed by gas chromatography/mass spectrometry (GCMS). GCMS was carried out using a Hewlett Packard 5890 GC coupled with an HP 5970 mass selective detector and an HP 59970A data system. A 25 m x 0.32 mm internal diameter fused silica capillary column (HP-5 Ultra) of film thickness 0.52 μm was used with helium carrier gas at a linear velocity of 40 cm/sec at 60°C. The oven temperature was programmed from 60°C to 290°C at 10°/min. The injector temperature was 250°C, and the detector temperature was 290°C. The capillary injector was operated in the splitless mode.

3.3.6.4 Extraction with dichloromethane: HPLC and GCMS analysis

Three 10 mL samples of a solution of co-trimoxazole in PDF, stored for 16 days in a PVC bag, were obtained. One 10 mL sample was acidified to pH~2 with 1M H_2SO_4. A second sample was rendered alkaline to pH~11 with ammonia solution, and the remaining sample was unadjusted (pH~6). Each sample was extracted with 2 x 20 mL volumes of dichloromethane. The aqueous phase of each sample remaining after extraction was reserved and analysed by HPLC. The extracts were dried over anhydrous sodium carbonate, filtered and evaporated to dryness. The extracts were derivatised with PFPA and BSTFA and analysed by GCMS, as previously described (3.3.6.3). Three 10 mL samples of PDF without added co-trimoxazole, were extracted and analysed in a similar manner as reagent blanks.

3.4 Results

3.4.1 Stability-indicating capability of the assay

Chromatograms of the following solutions are illustrated in Figure 3.6:

(a) Co-trimoxazole in PDF (pH~6) assayed immediately after preparation

(b) Co-trimoxazole in PDF (pH~6) autoclaved for 1 hour at 118°C

(c) Co-trimoxazole in PDF (pH adjusted to ~2) autoclaved for 1 hour at 118°C

(d) Co-trimoxazole in PDF (pH adjusted to ~11) autoclaved for 1 hour at 118°C

Changes which are evident in the chromatograms of the autoclaved solutions include a reduction in the peak heights of sulphamethoxazole and trimethoprim, and the appearance of several additional peaks between 2 and 12 minutes after injection.

Figure 3.6 Chromatograms of co-trimoxazole in PDF in glass ampoules

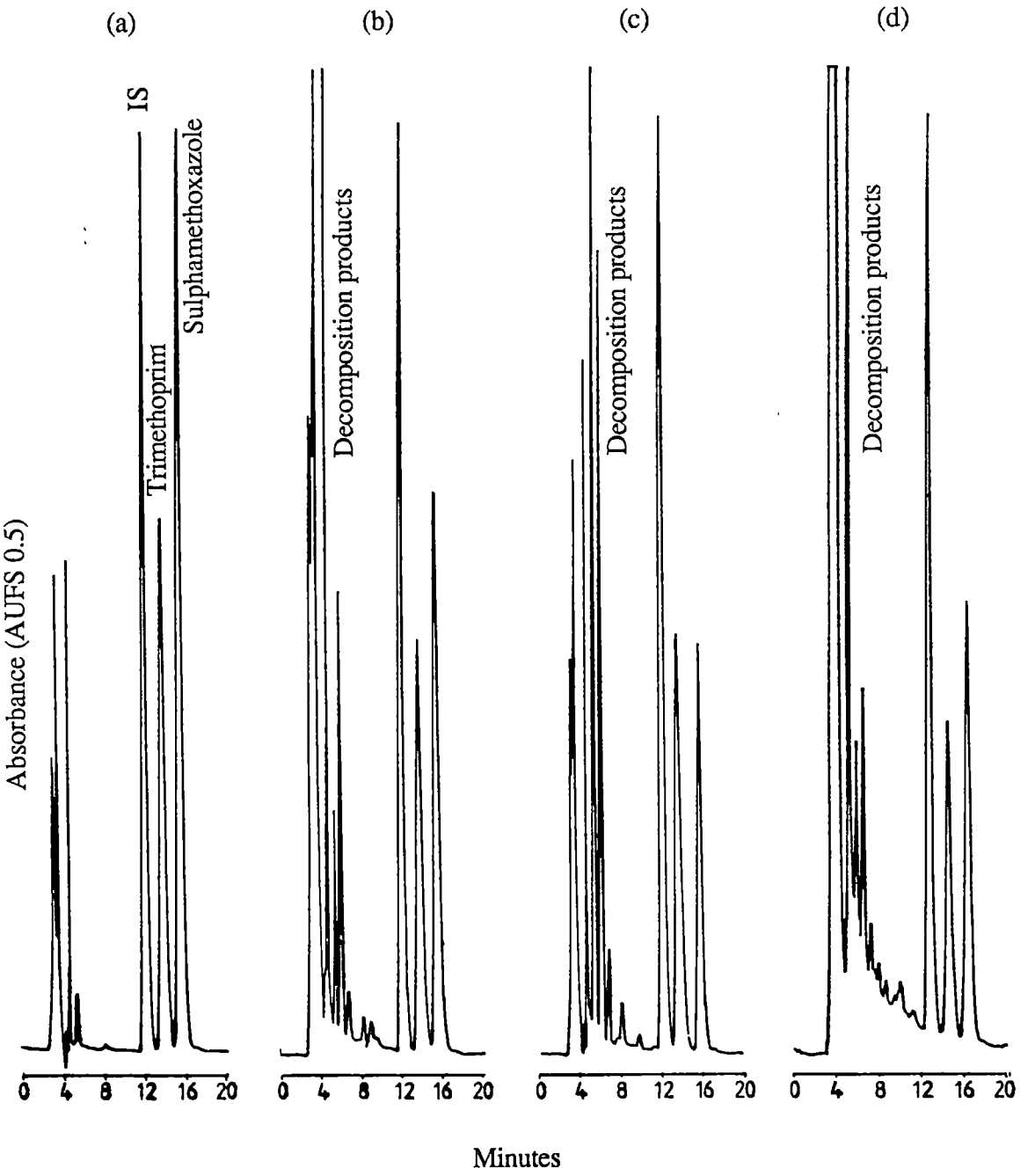
Internal standard (IS)

(a) Co-trimoxazole in PDF (pH~6) assayed immediately after preparation

(b) Co-trimoxazole in PDF (pH~6) autoclaved for 1h at 118°C

(c) Co-trimoxazole in PDF (pH adjusted to ~2) autoclaved for 1h at 118°C

(d) Co-trimoxazole in PDF (pH adjusted to ~11) autoclaved for 1h at 118°C



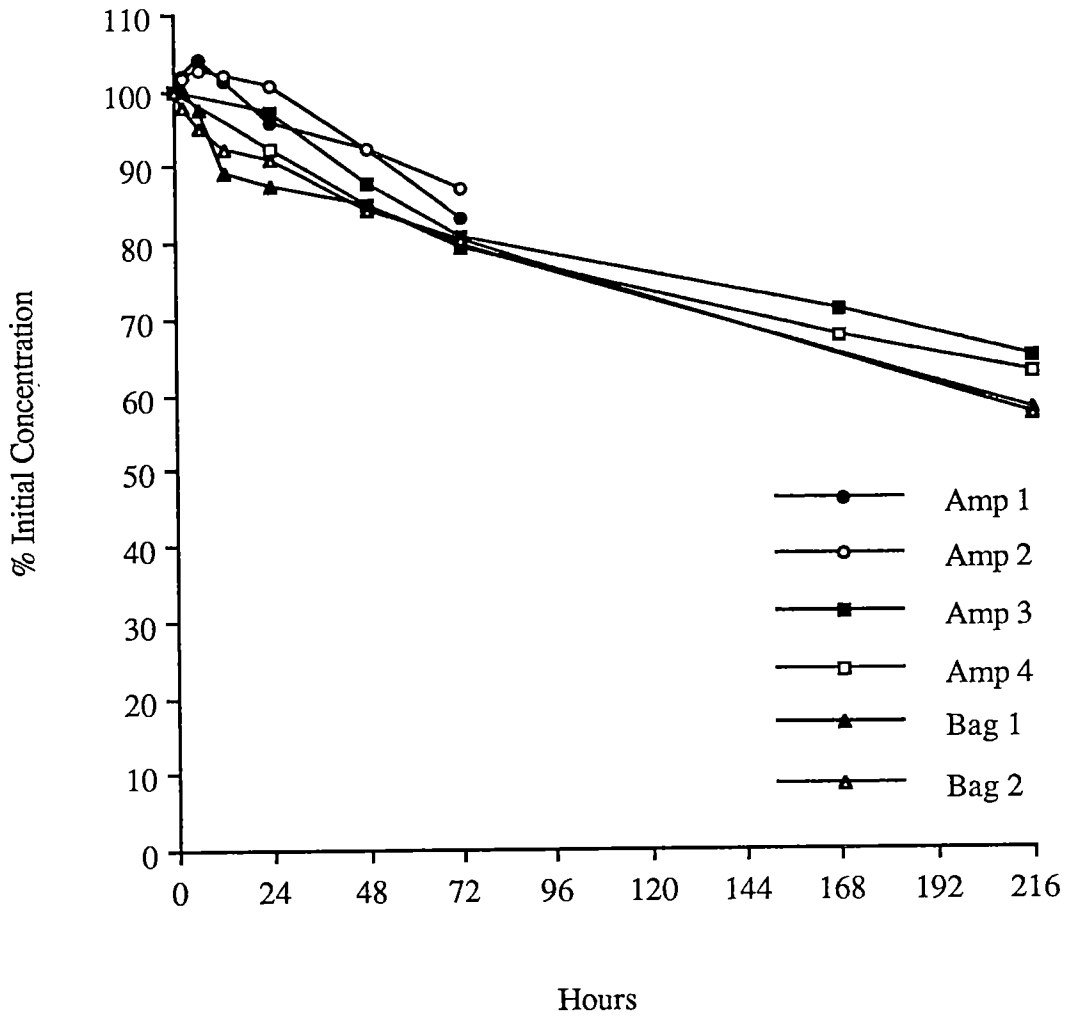
The concentration of sulphamethoxazole in the autoclaved solutions at unadjusted, acid and alkaline pH was 69%, 50% and 54%, respectively, of the initial concentration (86.4 mg/L) measured in solution (a). The concentration of trimethoprim in the autoclaved solutions at unadjusted, acid and alkaline pH was 93%, 92% and 72%, respectively, of the initial concentration (17.5 mg/L) measured in solution (a). The assay is therefore able to detect a decrease in the concentration of sulphamethoxazole and trimethoprim resulting from their decomposition in conditions of extreme heat and pH. At least some of the products formed under these conditions are detectable by this assay and appear as additional peaks in the chromatograms.

3.4.2 Stability of co-trimoxazole in PDF stored in PVC bags

The percentages of sulphamethoxazole remaining in PDF stored in PVC bags are illustrated in Figure 3.7. A decline in sulphamethoxazole concentration occurred in each bag during the study period. Greater than 10% loss of initial concentration was observed in one bag at 12 hours, and in both bags 48 hours after admixture. A 20% loss of initial concentration was observed in each bag 72 hours after admixture. Approximately 57% of the initial concentration remained in the solutions 216 hours (9 days) after admixture. When the pooled data (replicate assays from duplicate bags) was plotted semi-logarithmically (log [% initial concentration remaining] versus time), visual inspection of the resulting straight line suggested a time to 90% initial concentration of approximately 17 hours. Some deviation from linearity was observed in the data prior to 12 hours.

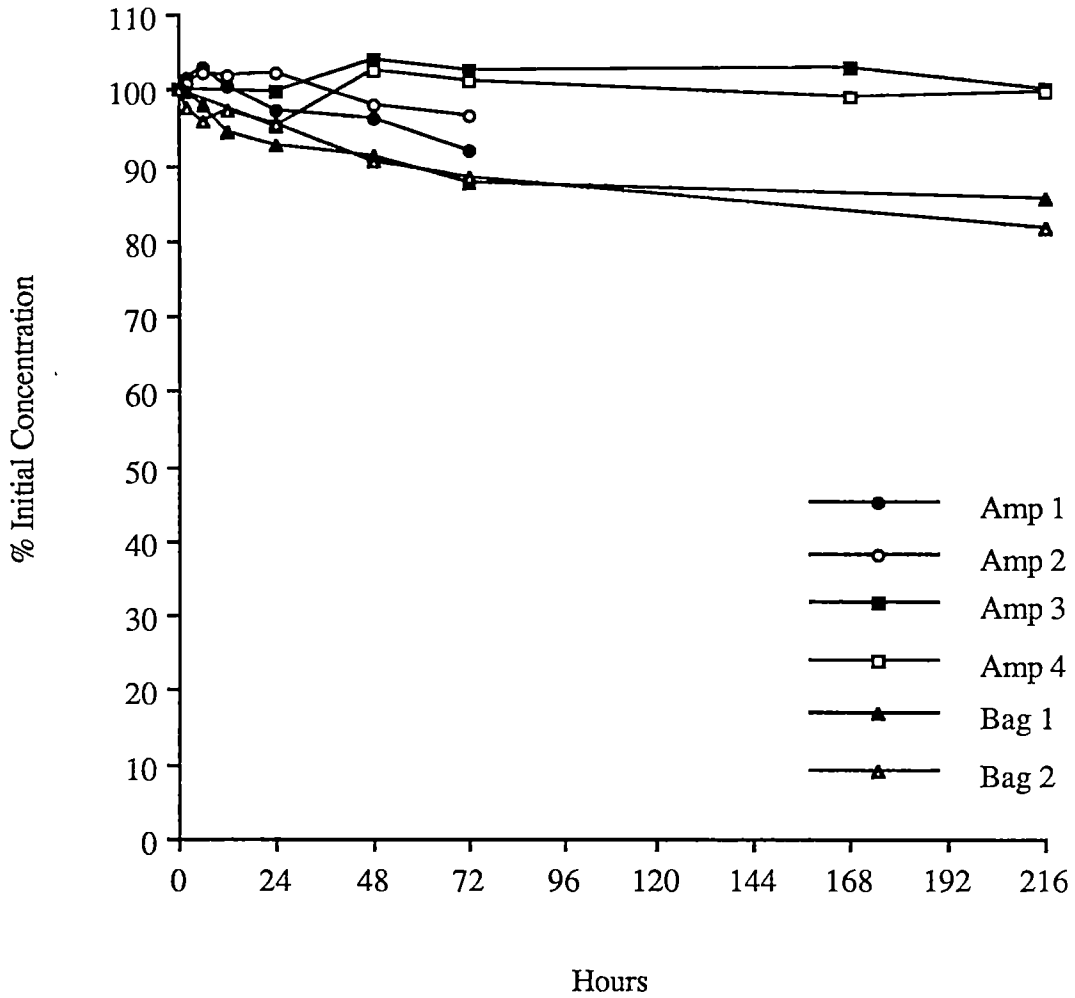
The percentages of trimethoprim remaining in PDF stored in PVC bags are illustrated in Figure 3.8. Greater than 10% loss of initial concentration was observed in each bag 72 hours after admixture. Approximately 84% of the initial concentration remained in the solutions 216 hours (9 days) after admixture.

Figure 3.7 Sulphamethoxazole concentrations in admixtures stored in PVC bags and glass ampoules *



* Refer to Appendix 3 for data

Figure 3.8 Trimethoprim concentrations in admixtures stored in PVC bags and glass ampoules *



* Refer to Appendix 3 for data

A new peak, attributed to a decomposition product, was present in the chromatograms of all solutions 2 hours or more after admixture. This peak eluted approximately 6 minutes after injection of the sample, and gradually increased in size at each sampling time during the study period (Figure 3.9). Figure 3.10 shows this peak in a chromatogram of a solution stored for 72 hours. No visible evidence of precipitation was observed in the solutions during the study period.

3.4.3 Stability of co-trimoxazole in PDF stored in glass ampoules

A malfunction in the solvent delivery system prevented the assay of the 216 hour samples during the initial stability experiment. A repeat experiment was performed in which samples were assayed in duplicate at 0, 24, 48, 72, 168 and 216 hours after admixture. The results of both experiments are presented.

The percentages of sulphamethoxazole remaining in PDF stored in glass ampoules are illustrated in Figure 3.7. A decline in sulphamethoxazole concentration occurred in each ampoule during the study period. Greater than 10% loss of initial concentration was observed in two ampoules 48 hours after admixture, and in all ampoules 72 hours after admixture. The repeat experiment showed that approximately 64% of the initial concentration remained in the solutions 216 hours (9 days) after admixture.

The percentages of trimethoprim remaining in PDF stored in glass ampoules are illustrated in Figure 3.8. Greater than 90% of the initial concentration was measured in each ampoule at all sampling times during the study period.

A decomposition product, previously detected in solutions stored in PVC bags, was also detected in solutions stored in glass ampoules. This was represented by a new peak in the chromatograms of all solutions 2 hours or more after admixture. This peak eluted

Figure 3.9 Peak height ratio of unknown decomposition product in admixtures stored in PVC bags and glass ampoules. (Each point is the mean of duplicate determinations, range ≤ 0.04)

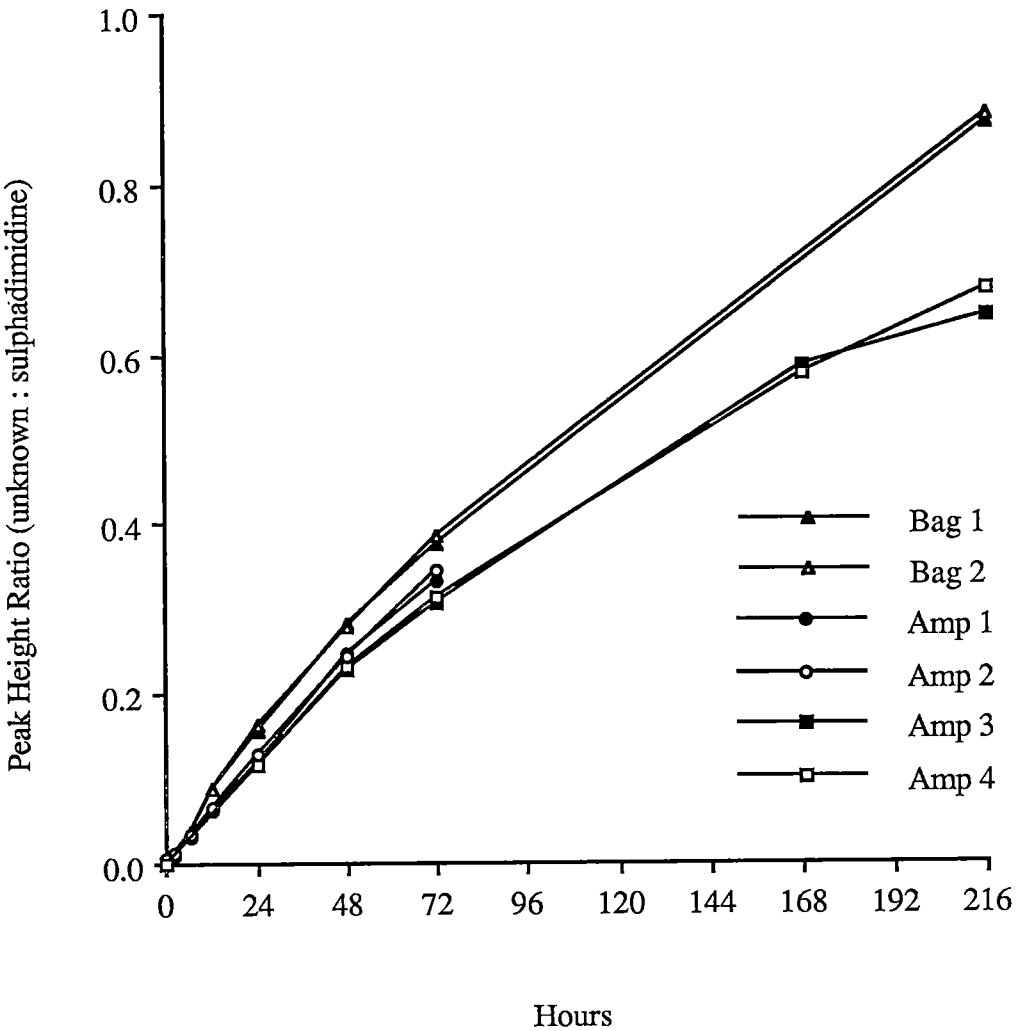
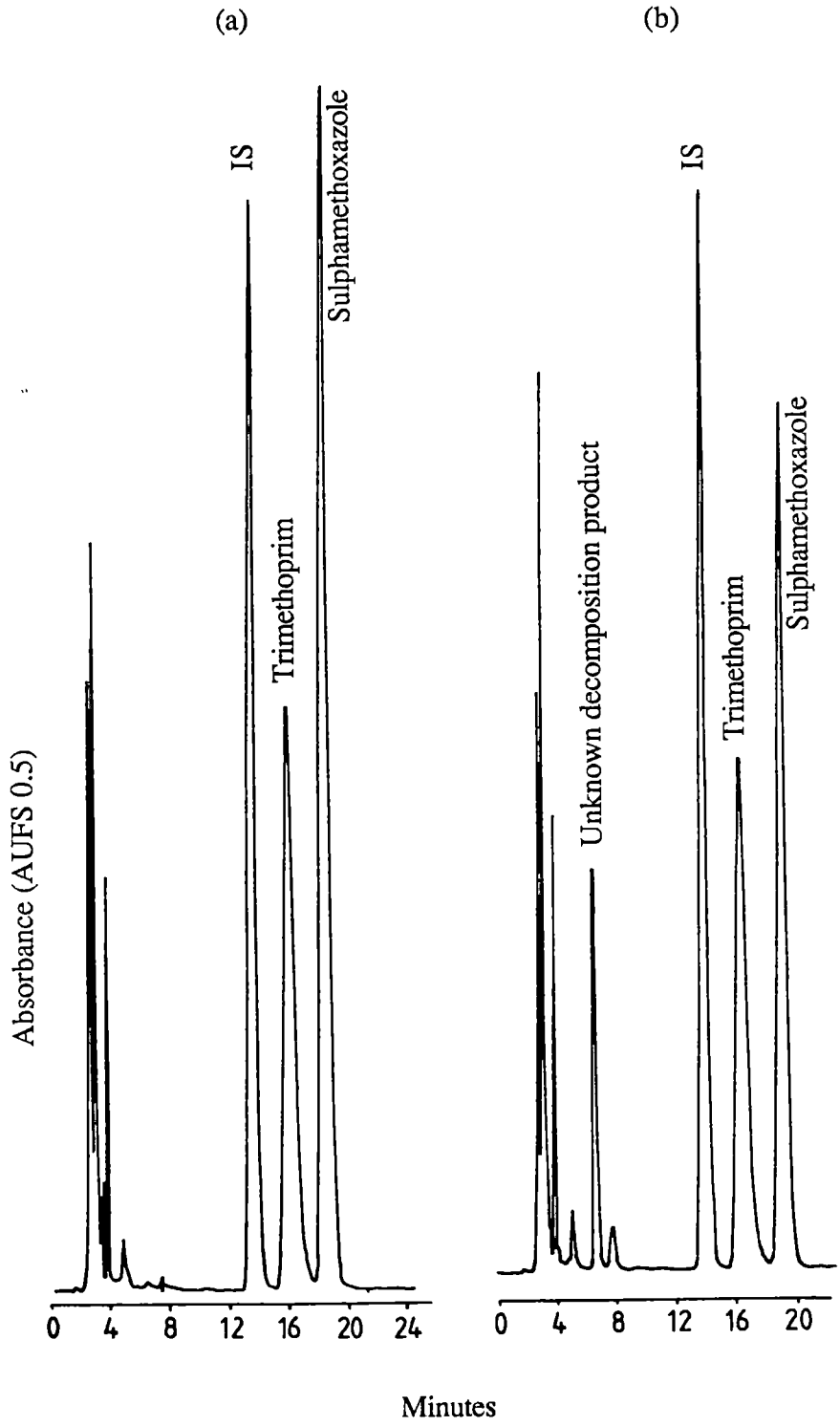


Figure 3.10 Chromatograms of co-trimoxazole in PDF in PVC bags

(a) Immediately after admixture

(b) 72 hours after admixture

Internal standard (IS)



approximately 6 minutes after injection of the sample, and gradually increased in size at each sampling time during the study period (Figure 3.9). No visible evidence of precipitation was observed in any of the solutions during the study period.

3.4.4 Identification of a decomposition product in co-trimoxazole/PDF admixtures

3.4.4.1 Comparison with known decomposition products

Sulphanilic acid

Chromatograms of the following solutions are illustrated in Figure 3.11.

(a) PDF

(b) Sulphanilic acid in PDF

(c) Co-trimoxazole in PDF after storage for 10 days in a glass ampoule

Sulphanilic acid present in solution (b) eluted with the solvent front, approximately 3 minutes after injection of the sample. The unknown decomposition product present in solution (c) had a retention time of approximately 6 minutes. The unknown decomposition product was therefore not sulphanilic acid. It is possible that sulphanilic acid may have been present in the stored admixtures, but was not visible in the chromatograms because of the peaks due to PDF and the solvent front. Figure 3.12 shows the chromatograms of a co-trimoxazole/PDF admixture before and after the addition of sulphanilic acid. Sulphanilic acid clearly produced a change in the chromatogram approximately 3 minutes after injection of the sample, while the size and shape of the unknown peak remained unchanged. This supports the conclusion that the unknown decomposition product is not sulphanilic acid.

Figure 3.11 Chromatograms which demonstrate that the unknown decomposition product present in co-trimoxazole/PDF admixtures is not sulphanilic acid

(a) PDF

(b) Sulphanilic acid in PDF

(c) Co-trimoxazole in PDF after storage for 10 days

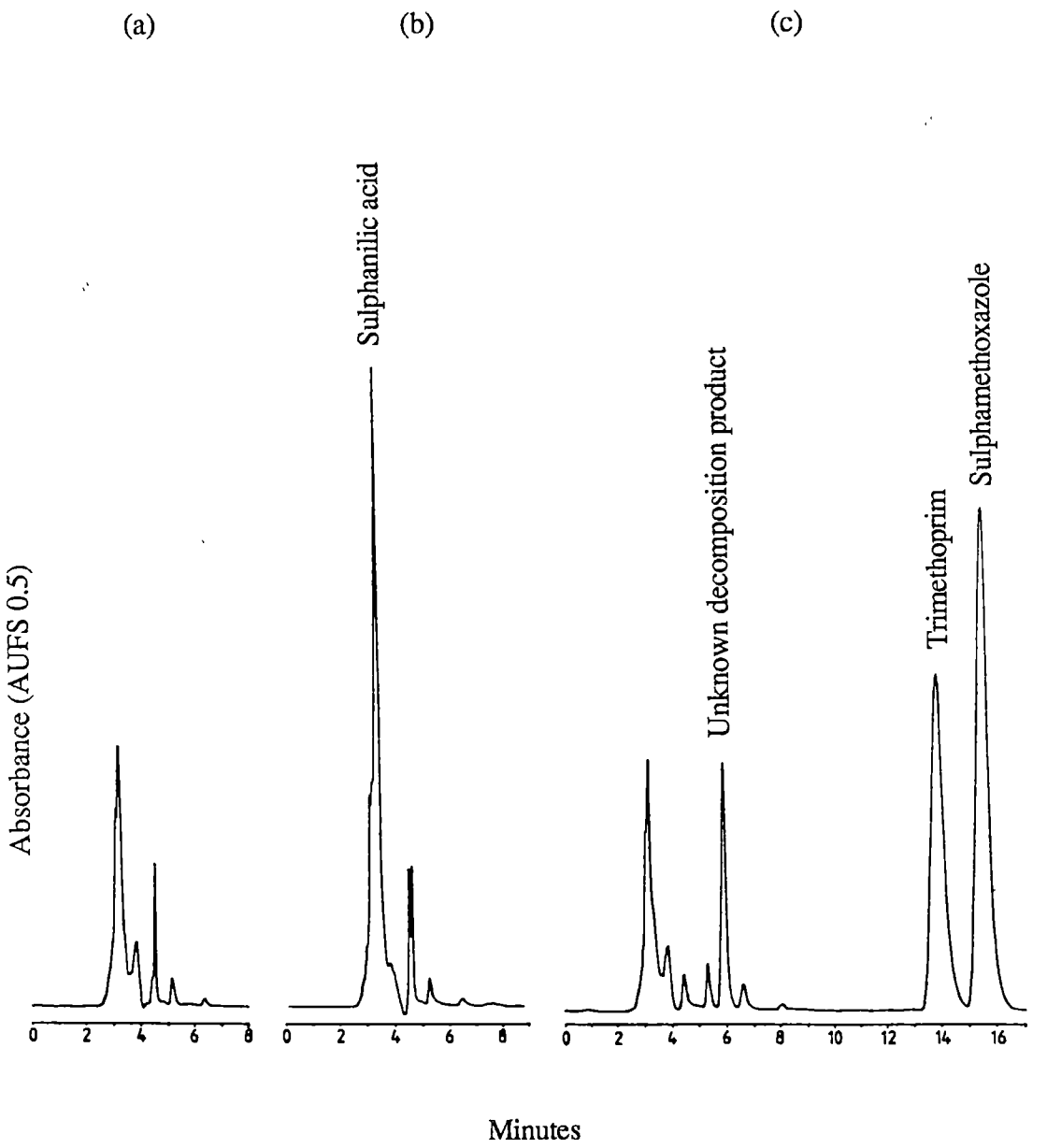


Figure 3.12 Chromatograms which demonstrate that the unknown decomposition product present in co-trimoxazole/PDF admixtures is not sulphanilic acid

(a) Co-trimoxazole in PDF after storage for 10 days

(b) Solution (a) plus sulphanilic acid

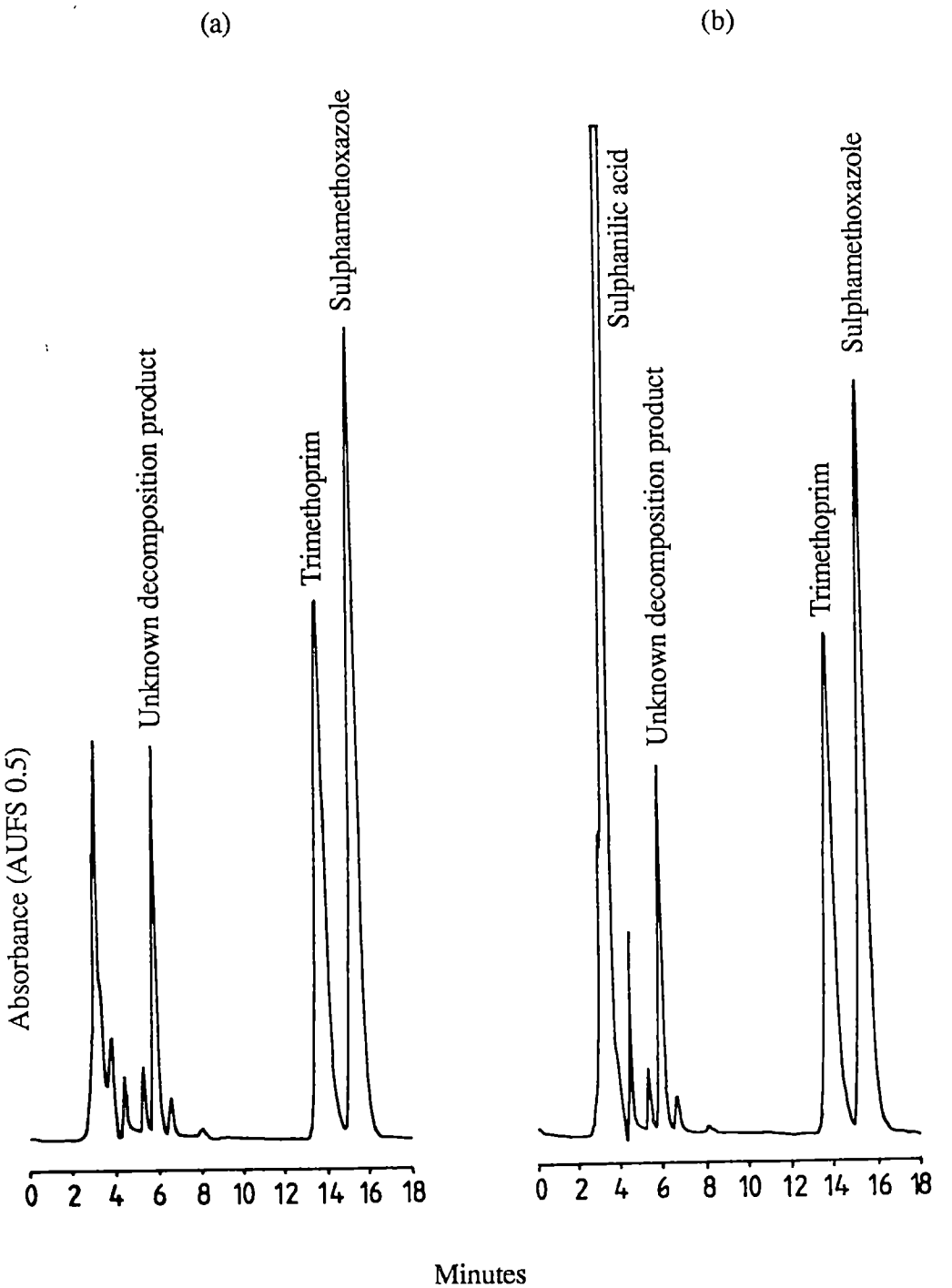
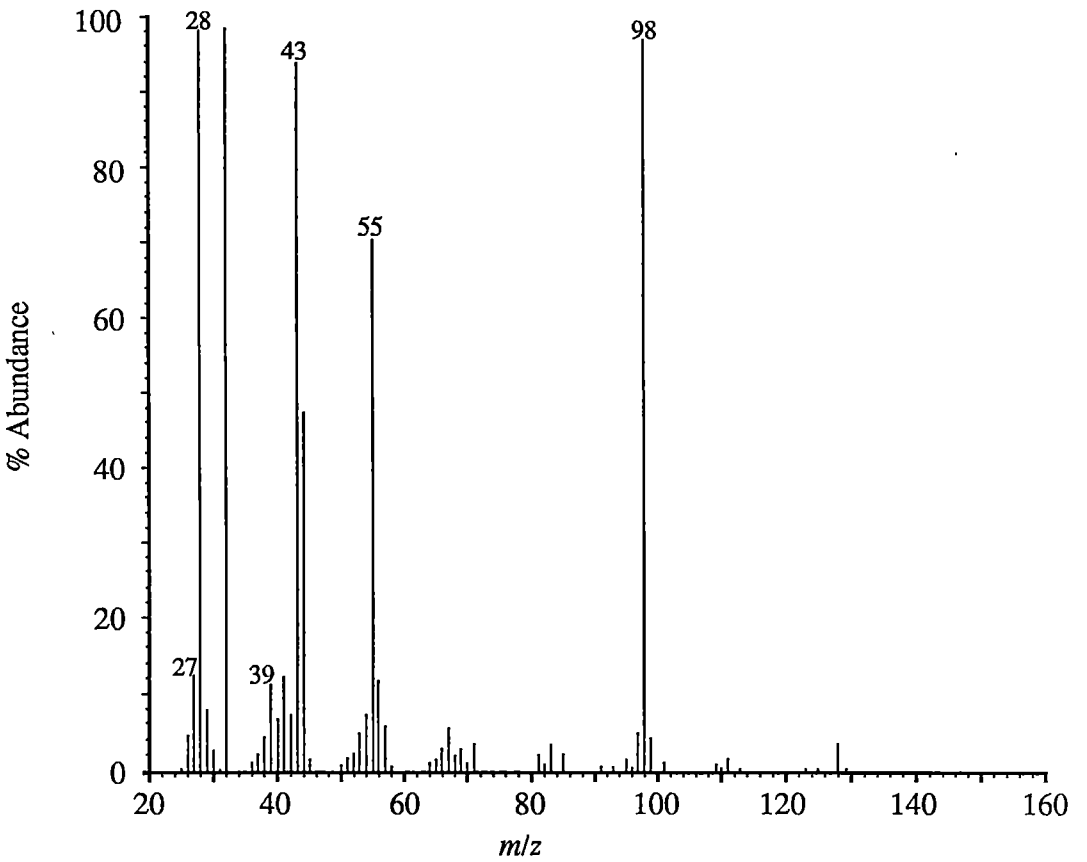


Figure 3.13 Mass spectrum of synthetic 5-methyl-3-isoxazolamine



5-Methyl-3-isoxazolamine

The mass spectrum of the synthetic 5-methyl-3-isoxazolamine is shown in Figure 3.13. The spectrum shows a molecular ion at *m/z* 98 and is identical to a reference spectrum of 5-methyl-3-isoxazolamine (142). The UV spectrum of 5-methyl-3-isoxazolamine is illustrated in Figure 3.14. Maximum absorbance occurred at 208 nm. Significant absorbance was evident at 230 nm, suggesting that this compound will be detected at the HPLC wavelength employed in this study.

Chromatograms of the following solutions are illustrated in Figure 3.15.

(a) 5-Methyl-3-isoxazolamine in PDF

(b) Co-trimoxazole in PDF after storage for 16 days in a PVC bag

(c) Solution (a) and (b) combined

5-Methyl-3-isoxazolamine present in solutions (a) and (c) eluted approximately 4.8 minutes after injection. The unknown decomposition product present in solutions (b) and (c) had a retention time of approximately 6 minutes. The unknown decomposition product was therefore not 5-methyl-3-isoxazolamine. 5-Methyl-3-isoxazolamine was not detected in any of the stored admixtures, and this provides indirect evidence that sulphanilic acid was probably not present either.

Chromatograms of co-trimoxazole/PDF admixtures which had undergone accelerated degradation under conditions of extreme heat and pH (Figure 3.6), showed a large number of decomposition products eluting between 3 and 8 minutes after injection. It was possible that the unknown decomposition product (detected in admixtures stored at room temperature) was among these, however due to the complexity of the chromatograms in this region, it was difficult to confirm its presence. It was also not possible to confirm the presence of sulphanilic acid or 5-methyl-3-isoxazolamine, despite co-chromatographing these compounds with the autoclaved solutions.

Figure 3.14 UV spectrum of synthetic 5-methyl-3-isoxazolamine

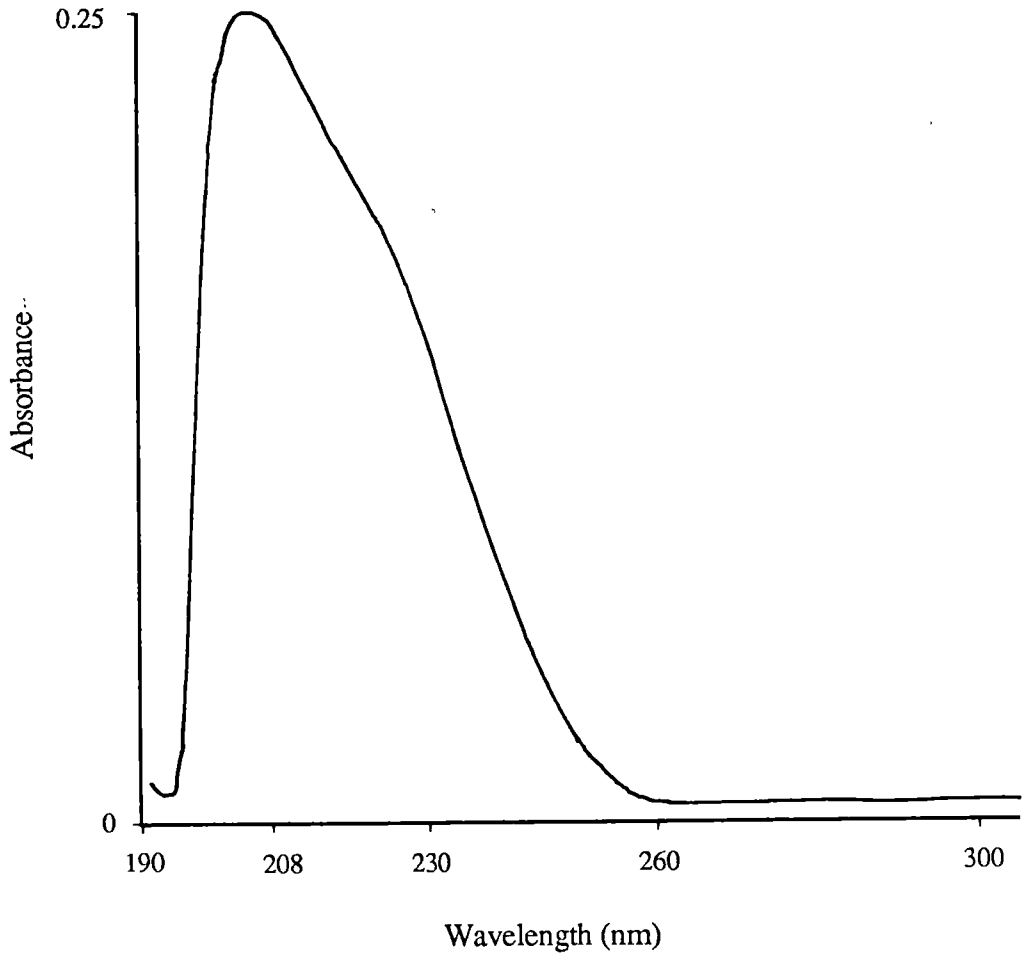
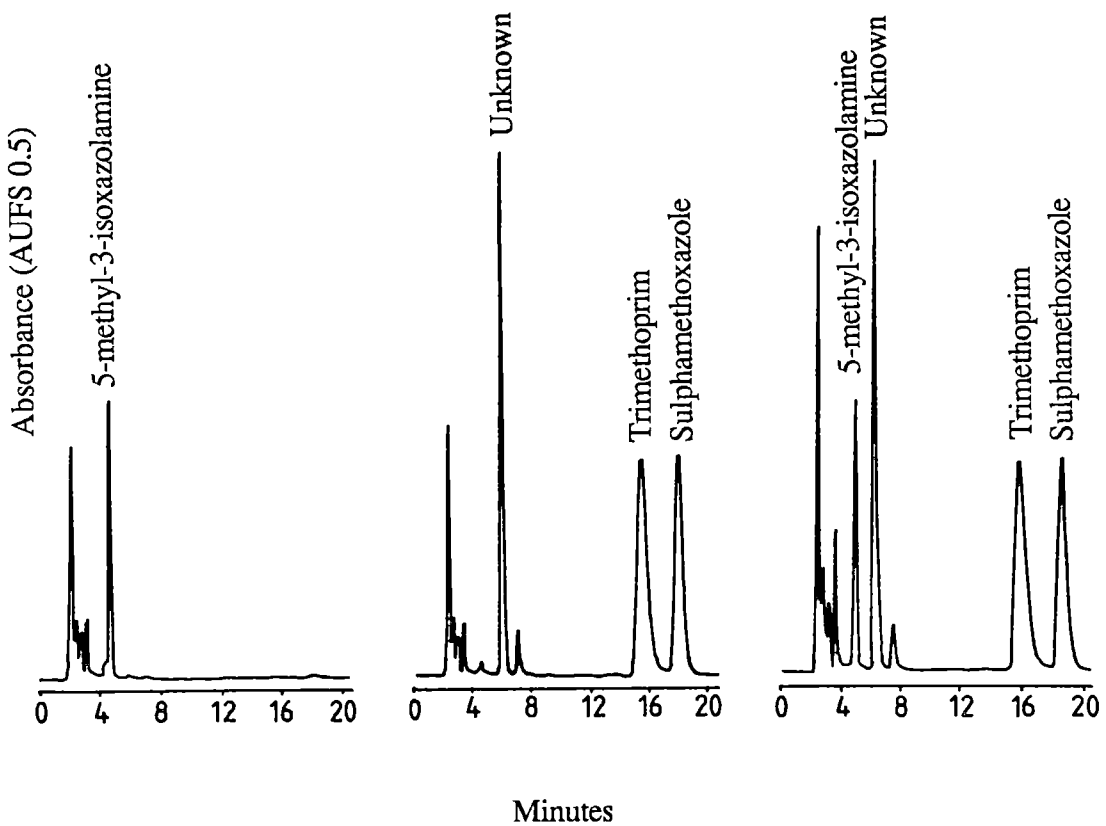


Figure 3.15 Chromatograms which demonstrate that the unknown decomposition product present in co-trimoxazole/PDF admixtures is not 5-methyl-3-isoxazolamine

(a) 5-Methyl-3-isoxazolamine in PDF

(b) Co-trimoxazole in PDF after storage for 16 days

(c) Solution (a) and (b) combined



3.4.4.2 Direct probe MS analysis

Because of the large amounts of glucose present in the co-trimoxazole/PDF admixture, the mass spectrum of the concentrated sample introduced directly on the probe showed only the spectrum of glucose, and it was not possible to obtain any information regarding the structure of the unknown decomposition product.

3.4.4.3 Extraction of column effluent fractions: GCMS analysis

GCMS results of this experiment were inconclusive.

3.4.4.4 Extraction with dichloromethane: HPLC and GCMS analysis

Chromatograms (HPLC) of the following solutions are illustrated in Figure 3.16:

(a) Co-trimoxazole in PDF after storage for 16 days in a PVC bag (pH~6)

(b) Solution (a) extracted with dichloromethane

(c) Solution (a), (pH adjusted to ~2), extracted with dichloromethane

(d) Solution (a), (pH adjusted to ~11), extracted with dichloromethane

The unknown decomposition product was extracted most effectively from the acidified solution, with a reduction in peak height of approximately 65%. Very little change in peak height occurred after extraction under unadjusted and alkaline conditions. This indicates that the unknown decomposition product is acidic in nature.

Figure 3.17 shows the mass spectrum of the major chromatographic peak resulting from GCMS analysis of the extract of the acidified solution. High resolution mass spectrometry confirmed a molecular formula of $C_{10}H_{15}NO_2S$, consistent with N-butylbenzenesulphonamide. The mass spectrum was found to be identical with a

Figure 3.16 Chromatograms showing extraction of unknown decomposition product at various pH's using dichloromethane

(a) Co-trimoxazole in PDF after storage for 16 days (pH~6)

(b) Solution (a) extracted with dichloromethane

(c) Solution (a), (pH adjusted to ~2), extracted with dichloromethane

(d) Solution (a), (pH adjusted to ~11), extracted with dichloromethane

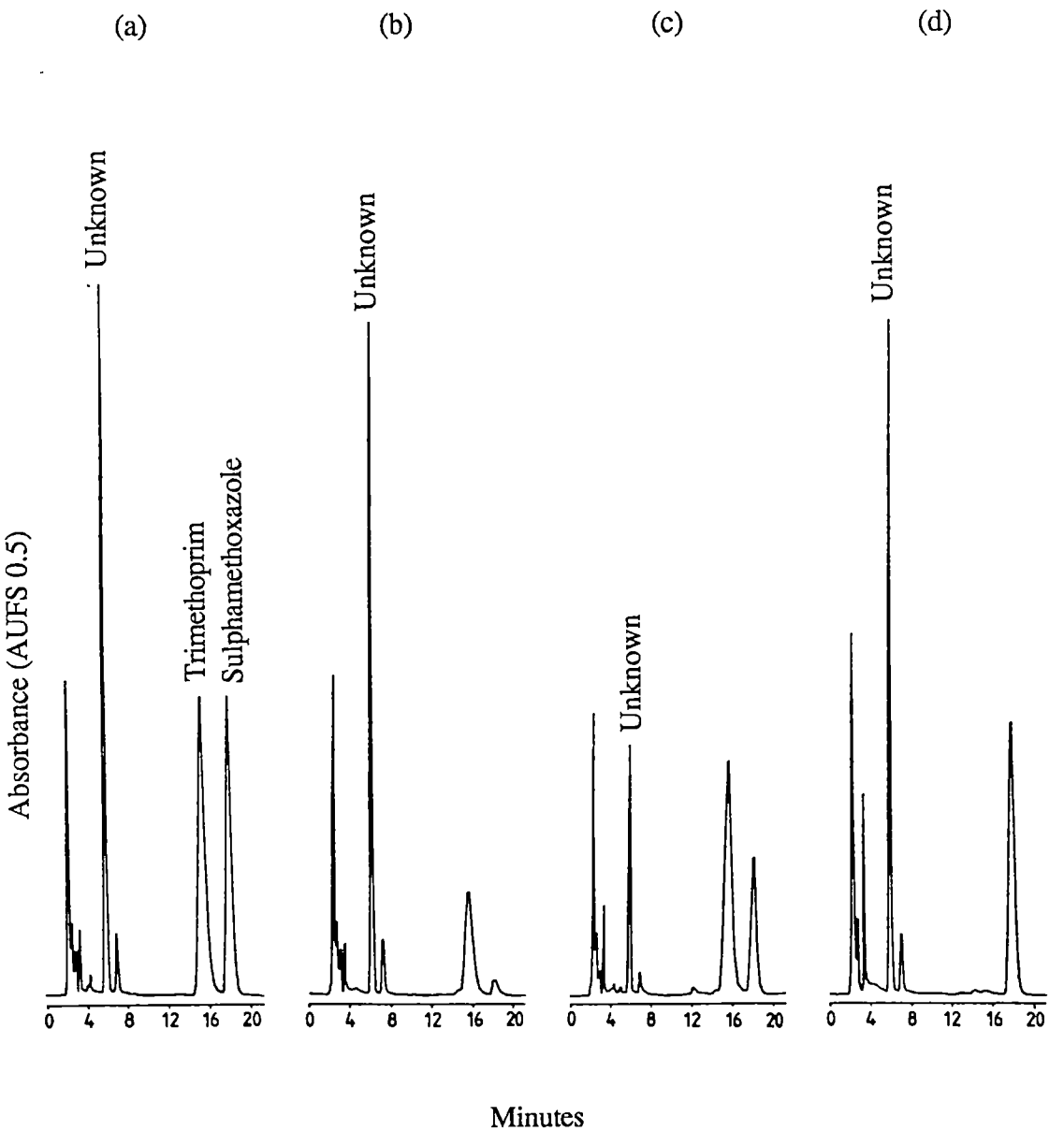
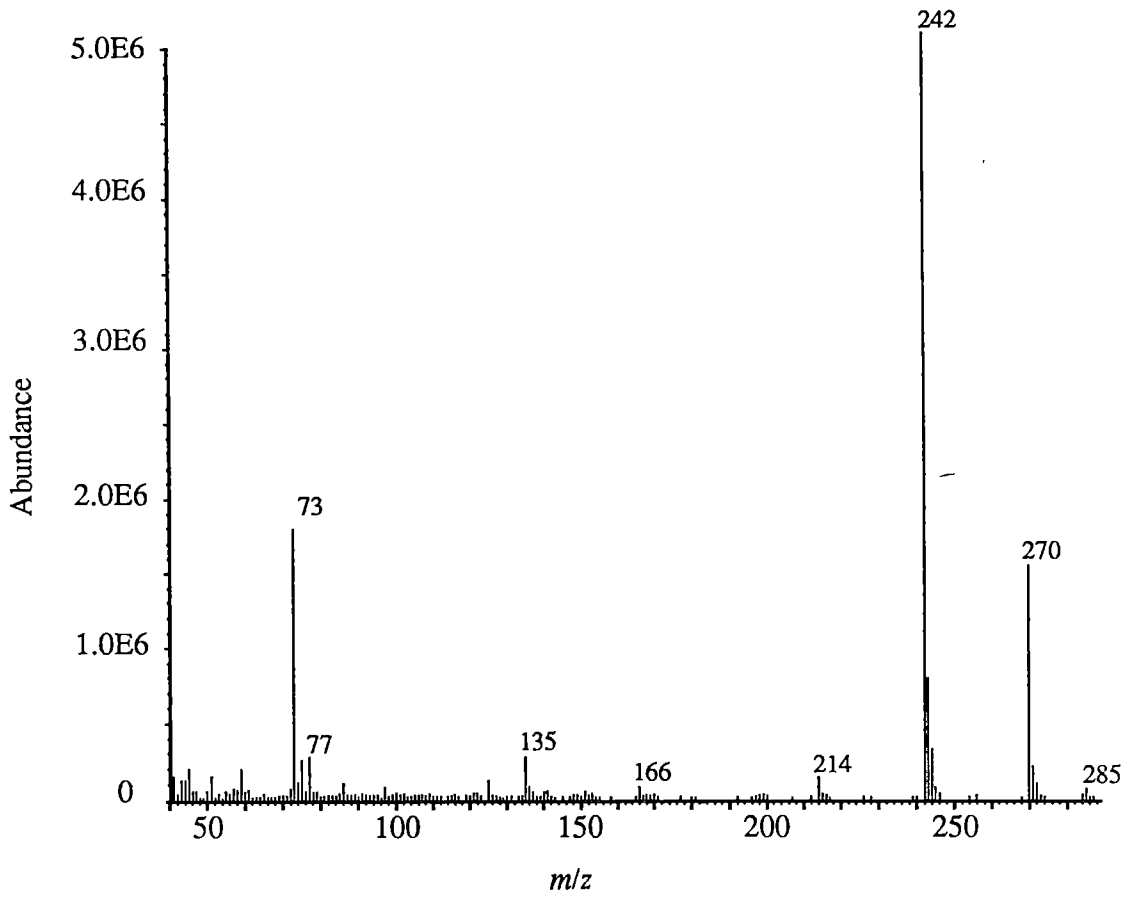


Figure 3.17 Mass spectrum of the major GC peak resulting from GCMS analysis of an extract of a co-trimoxazole/PDF admixture. The admixture was stored for 16 days in a PVC bag and extracted under acidic conditions.



reference spectrum of that compound (143). Although N-butylbenzenesulphonamide bears some structural relationship to sulphamethoxazole, it was also identified in approximately equal amounts in the reagent blanks (PDF without added co-trimoxazole). It is possible that N-butylbenzenesulphonamide, which is used as a plasticiser (144), may have leached from the PVC bags during storage. No further information regarding the identity of the decomposition product was obtained from these experiments.

3.5 Discussion

The inherent advantage of HPLC as an analytical technique for stability studies, lies in its ability to separate and detect distinct chemical entities. However, HPLC analysis may not be stability indicating when, for example, decomposition products elute with the intact drug, or when other drugs or solution components elute with or interfere with the intact drug (145). The HPLC assay used in these stability experiments was able to quantitate the intact drug in the presence of decomposition products which were produced when an admixture of co-trimoxazole in PDF was subjected to intense heat and extreme pH to intentionally decompose it. This provides evidence of the stability-indicating capability of the assay.

A significant loss of sulphamethoxazole (> 10% of initial concentration) occurred within 48 hours when an admixture of co-trimoxazole in PDF containing 4.25% glucose was stored in PVC bags at 20 ± 2°C. Greater than 10% loss of initial concentration was observed in one bag at 12 hours. A comparison of the stability experiments conducted in PVC bags and glass ampoules provides some insight into the mechanism of loss of sulphamethoxazole from co-trimoxazole/PDF admixtures. If the loss of sulphamethoxazole was due to an interaction with the container, such as sorption or permeation, then the stability of sulphamethoxazole in PVC bags and glass ampoules would be expected to be dissimilar. However, in these experiments, sulphamethoxazole

stability seemed to be unrelated to the container type, with similar losses occurring from admixtures stored in PVC bags and glass ampoules. This suggests that the mechanism of this loss is primarily chemical decomposition in solution. Further evidence for this proposition was the time dependent increase in concentration of an unknown decomposition product in admixtures stored in both plastic and glass, and this may have been a decomposition product of sulphamethoxazole. The loss of sulphamethoxazole from admixtures stored in PVC bags showed some deviation from first-order kinetics prior to 12 hours, suggesting that an initial, more rapid loss of sulphamethoxazole may have occurred by some other process.

The loss of trimethoprim from admixtures stored in PVC bags was greater than from admixtures stored in glass ampoules throughout the study period. Greater than 10% loss of the initial concentration occurred within 3 days in admixtures stored in PVC bags, whereas trimethoprim was stable for at least 9 days when similar admixtures were stored in glass ampoules under the same conditions. This suggests that the loss of trimethoprim from admixtures stored in PVC bags may be due to an interaction with the container. Kowaluk et al found that there was negligible loss due to sorption when trimethoprim dissolved in 0.9% sodium chloride injection (25 mg/L) was stored in PVC bags for one week at 15-20°C (118). Negligible loss due to sorption was also observed during simulated infusion through a burette chamber and PVC tubing, and when solutions were stored in polyolefin syringes for 24 hours (132).

This study demonstrates that the shelf-life of an admixture of co-trimoxazole in PDF is limited by the stability of the sulphamethoxazole component, since the rate of loss of sulphamethoxazole was greater than the rate of loss of trimethoprim during the study period. A greater number of studies and sampling times would enable a more accurate determination of the time for 10% decomposition, however the present study conservatively indicates a shelf-life of only 12 hours, since greater than 10% loss of the

initial sulphamethoxazole concentration had occurred in this time in one of the bags examined.

Co-trimoxazole injection must be diluted prior to i.v. administration, and studies of the stability of co-trimoxazole in various i.v. infusion fluids have produced highly divergent results. Trissel has reviewed two studies which have examined the stability of co-trimoxazole in 5% glucose injection (3.2 / 0.64 g/L sulphamethoxazole/trimethoprim) at 22-25°C (63). One study concluded that the admixture was physically and chemically stable for 24 hours, while the second study observed turbidity and precipitation at 4 hours, and 28% loss of trimethoprim in 24 hours. A more recent study reported that similar admixtures were stable for 48 hours (146), while the manufacturer advises that the administration of such admixtures must be completed within 2 hours (147). These studies have also produced conflicting information regarding the stability of more concentrated solutions of co-trimoxazole, and the compatibility of co-trimoxazole with other diluents. Even the manufacturers information differs with respect to the suitability of various infusion fluids as diluents. Information provided by the manufacturer in Australia includes 0.9% sodium chloride injection as a suitable diluent (147), however manufacturers information quoted in American sources advise that co-trimoxazole should not be admixed with any infusion fluids apart from 5% glucose injection (63, 148). Turbidity and precipitation in i.v. admixtures is well recognised and has been shown to be dependent on the concentration of co-trimoxazole, the duration of storage and the diluent employed (146). Most studies have identified trimethoprim as the stability limiting component (63, 146). Few direct comparisons can be made between these studies and the present stability study conducted in PDF. In addition to the different characteristics of the diluents, there are the large differences in the concentrations of co-trimoxazole examined. The concentrations of co-trimoxazole employed in admixtures for i.v. administration are much greater than those employed for i.p. administration. These differences, plus the conflicting information which exists for

co-trimoxazole stability in i.v. infusion fluids, emphasise the importance of conducting stability studies in PDF for intraperitoneally administered drugs.

The unknown decomposition product present in co-trimoxazole /PDF admixtures stored in both PVC bags and glass ampoules, was not present when PDF alone was stored in PVC bags for prolonged periods at 20°C. It was therefore a decomposition or reaction product of sulphamethoxazole, trimethoprim, or excipients in the co-trimoxazole injection. Identification of this unknown decomposition product may have provided information on the fate of sulphamethoxazole or trimethoprim in the stored admixtures. It was suspected that the compound was a derivative of sulphamethoxazole, because an increase in concentration of this compound was associated with a decrease in concentration of sulphamethoxazole in admixtures stored in both plastic and glass. The concentration of trimethoprim, on the other hand, decreased in plastic and remained constant in glass, and was therefore seemingly unrelated to the emergence of the unknown compound. Although it did not prove possible to identify this decomposition product, it was demonstrated that it was not sulphanilic acid or 5-methyl-3-isoxazolamine, which have previously been identified as decomposition products of sulphamethoxazole under acid conditions.

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APPENDIX 1

Stability of Antibiotics in Peritoneal Dialysis Fluids

STABILITY OF ANTIBIOTICS IN PERITONEAL DIALYSIS FLUIDS

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SCHOOL OF PHARMACY
UNIVERSITY OF TASMANIA
HOBART, TASMANIA

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CONTENTS

INTRODUCTION

The frequent occurrence of peritonitis continues to be a major complication of peritoneal dialysis in the treatment of patients with end stage renal disease. Peritonitis is the major impediment to the prolonged success of this dialysis technique. This has been illustrated by a recent survey of continuous ambulatory peritoneal dialysis (CAPD) patients in Australia which found that 64% of patients transferring from CAPD to another form of dialysis, did so because of peritonitis (40).

Effective antibiotic therapy must not only provide adequate serum and tissue drug levels, but must be able to eradicate organisms that may persist in stagnant residual pools of dialysate within the peritoneal cavity. The intraperitoneal (i.p.) administration of antibiotics is convenient and has the potential advantage of producing high local drug concentrations. Therapeutic serum levels of many antibiotics can be achieved and maintained by i.p. administration alone (41). Although it has become routine practice to administer antibiotics to the peritoneal cavity via the dialysate, there are few studies documenting the stability of antibiotics in these fluids. Peritoneal dialysis fluid contains electrolytes including sodium, chloride, calcium and magnesium, either acetate or lactate as a source of bicarbonate, and an osmotically active agent, usually glucose. It has an acid pH, usually in the range 5.0-5.5. Stability and compatibility guidelines available for IV admixtures may not be appropriate for peritoneal dialysis fluids nor relevant to i.p. administration. Several reviews have included a small amount of stability data (30, 31, 32, 48). The application of this data is limited by a lack of detail and, in some cases, the authors have drawn conclusions which their cited studies do not support. Stability has sometimes been inferred from pharmacokinetic studies. This review has collated the stability and efficacy studies which have been conducted in peritoneal dialysis fluids and presents them in tables under the name of each antibiotic for which data exists. For each antibiotic a summary of the data is presented.

The majority of patients undergoing peritoneal dialysis use pre-mixed "ready to use" proprietary dialysis solutions which contain between 0.5% and 4.5% glucose. Antibiotics for i.p. administration are added directly to the peritoneal dialysis fluid prior to its instillation into the peritoneal cavity. To facilitate analysis of stability studies, peritoneal dialysis fluids containing between 0.5% and 4.5% glucose have been grouped together and are collectively referred to as "CAPD fluids". Although these fluids are mainly used in continuous ambulatory peritoneal dialysis (CAPD), they can also be used with automated cycler equipment for continuous cyclic peritoneal dialysis (CCPD), and intermittent peritoneal dialysis (IPD).

Stability studies conducted in concentrated peritoneal dialysis fluids have also been reviewed. These fluids contain 30% or 50% glucose and are intended for use with automated proportioning systems. One such system is the reverse osmosis dialysis machine which uses reverse osmosis to convert a tap water supply into sterile, apyrogenic water, and an automated proportioning system for using the water so produced to accurately dilute the concentrated dialysis fluid. The delivered dialysis fluid generally contains between 0.5% and 4.5% glucose. Antibiotics for i.p. administration are generally added to the concentrated dialysis fluid prior to its passage through the automated proportioning system. The use of reverse osmosis dialysis machines and concentrated dialysis fluids obviates the need for the large volume of "ready to use" dialysis fluid normally required for one IPD session. Their use has declined due to the popularity of CAPD and there were no patients using reverse osmosis dialysis machines in Australia as at October 1986 (40). An increase in the popularity of CCPD, or variations of this technique, may see a renewed interest in automated proportioning systems (41). To facilitate analysis of stability studies, peritoneal dialysis fluids containing 30% or 50% glucose have been grouped together and are collectively referred to as "peritoneal dialysis fluid concentrates".

The studies reviewed can be classified as either stability or efficacy studies, and these are described in detail below.

Stability of antibiotics in peritoneal dialysis fluids

Three methods have been used to investigate the stability of antibiotics in peritoneal dialysis fluids:

1. Physical compatibility

A drug is described as physically compatible with a peritoneal dialysis fluid if there is no visible evidence of an incompatibility. Visible evidence of an incompatibility includes the formation of a precipitate, haze or opalescence. Other visible changes (for example a colour change) may also constitute a physical incompatibility. A drug demonstrated to be physically compatible with a peritoneal dialysis fluid is not necessarily stable under the same test conditions.

2. Stability determined by direct analysis

The extent of decomposition of a drug can be measured using an assay which is specific for the chemical entity of the unchanged drug. Drugs which demonstrate ≤10% decomposition in peritoneal dialysis fluid are described as stable over the test period.
The following analytical techniques have been referred to in this review:

enzyme multiplied immunoassay (EMIT)
fluorescence immunoassay (FIA)
high performance liquid chromatography (HPLC)
radioimmunoassay (RIA)
spectrophotometry (S)

3. Stability determined by measuring drug activity

The stability of a drug can be investigated by measuring the change in drug activity over time. This method is restricted to drugs which have an activity which is readily quantifiable. An investigation of heparin stability, for example, can be made by measuring its effect on the clotting time of blood (CT).

Bioassay (B) is the term used for the measurement of antibiotic activity against a test organism. The activity of the antibiotic can be related to the concentration of antibiotic in the test solution in several ways, but only two techniques have been used by the studies included in this review.

(i) Agar well-diffusion technique
This involves adding samples of test solution to holes punched in an agar medium which has been spread with a culture of test organisms. Following incubation, zones of inhibition form around these agar wells, their diameter depending on the concentration of antibiotic in the test solution. The concentration can be determined by reference to a standard curve which has been prepared by measuring the zone diameter around solutions containing a known concentration of antibiotic.

(ii) Minimum inhibitory concentration
A sample of test solution is serially diluted with a growth medium and innoculated with test organisms. The minimum inhibitory dilution is the highest dilution of the test solution capable of preventing visible growth of the test organisms. At this dilution, the antibiotic is at its minimum inhibitory concentration (MIC). At this concentration the test organisms remain viable, so that if transferred to a more favourable environment they would continue to grow.

Changes in antibiotic activity over time, as determined by bioassay, have been assessed in two ways:

(i) by comparing the activity of the antibiotic after a test period in peritoneal dialysis fluid to its initial activity in peritoneal dialysis fluid.

(ii) by comparing the activity of the antibiotic after a test period in peritoneal dialysis fluid to its activity after the same time in normal saline.

Antibiotics which retain ≥90% of their initial activity in peritoneal dialysis fluid are described as stable over the test period. However, it is possible that these antibiotics have an activity in peritoneal dialysis fluid which is considerably less than their activity in normal saline over the same test period. This is demonstrated by one study which found that all the antibiotics tested maintained their initial activity for 4 hours in peritoneal dialysis fluid concentrate, suggesting that these antibiotics are stable in peritoneal dialysis fluid concentrate over this test period. However, the study also found that the initial activity of several antibiotics in peritoneal dialysis fluid concentrate was significantly less than their initial activity in normal saline, (9).

Efficacy of antibiotics in peritoneal dialysis fluids

Included in this review are studies which investigate the fate of a test organism in peritoneal dialysis fluid or peritoneal dialysis effluent containing an antibiotic. These studies aim to mimic the conditions during a peritonitis episode, therefore the activity of the antibiotic under these conditions may be of clinical relevance. They are not, however, true indicators of antibiotic stability in peritoneal dialysis fluid or peritoneal dialysis effluent.

The difference between these studies and the stability studies already described is that peritoneal dialysis fluid or peritoneal dialysis effluent is not only the test solution in which the antibiotic is dissolved, but also the growth medium for the test organism. The results reflect in part the effect of the dialysis fluid or effluent on the test organism. In the absence of controls designed to quantify this activity, the effect of the dialysis fluid or effluent on the activity of the antibiotic cannot be differentiated. This has been the case with the efficacy studies included in this review. The activity of dialysis fluid and effluent alone against bacteria has been reported elsewhere in the literature. Several studies have demonstrated that CAPD fluids inhibit the growth of staphylococci (8, 21, 42, 43, 44, 45). Some investigators concluded that CAPD fluid was bactericidal. Others found that while CAPD fluid inhibited the growth of staphylococci, the organisms remained viable. The effect of CAPD fluids on other bacteria is not as clear (8, 21, 42, 43). Some studies found that E.coli and P.aeruginosa did not grow in CAPD fluids, while others found these bacteria grew well. All studies demonstrated that peritoneal dialysis effluent was a more favourable growth medium than unused CAPD fluid for all test organisms.

Three methods, described below, have been used to determine the susceptibility of a test organism to peritoneal dialysis fluid or effluent containing an antibiotic. These have been collectively termed bioactivity methods, *(b), which appears in the tables in italics:*

(i) Minimum inhibitory concentration (MIC)
The lowest concentration of antibiotic capable of preventing the visible growth of an innoculum of test organisms. At this concentration the organisms remain viable, so that if transferred to a more favourable environment they would continue to grow.

(ii) Minimum bactericidal concentration (MBC)
The lowest concentration of antibiotic capable of killing ≥99.9% of the population of test organisms.

(iii) Time/kill curves
A study of the bacterial population as a function of time.

INTERPRETATION OF THE TABLES

Drug [1]	Mfr [2]	Drug [3]	Mfr [4]	Solution [5]	Mfr [6]	Method [7]	Results [8]	Ref [9]

[10]

[1] Drug to which the table refers and the concentration tested.
[2] Manufacturer of the reference drug.
[3] Drug(s) used in combination with the reference drug and the concentration(s) tested.
[4] Manufacturer(s) of the drug(s) used in combination with the reference drug.
[5] Peritoneal dialysis fluid (PDF) or peritoneal dialysis (PD) effluent in which the drug or drug combination was tested.
[6] Manufacturer of the peritoneal dialysis fluid.
[7] Method used to assess the stability or efficacy of each drug or drug combination.
[8] A description of the results of the study.
[9] Reference to the original study.
[10] Summary

Drug and concentration [1], [3]

When a study has specified the use of a salt of a drug or a drug base, this has been stated in the table e.g. Amikacin sulphate, Amikacin base. When this information is not available then the drug name appears in the table as it appears in the original article e.g. Amikacin. Drugs used in combination with the reference drug appear in column [3] in alphabetical order. Studies of drug combinations have been reported under the name of each antibiotic used in the combination.

The concentration of each drug has been expressed in terms of mg or g per litre to facilitate comparison between the various studies. This does not necessarily mean that the drugs were tested in 1L volumes of solution. Some tests were performed in test tubes using small volumes e.g. 10mL. Other investigators added the drugs to volumes of solution normally instilled into the peritoneal cavity i.e. 2L. Tests performed in plastic bags have been identified in the results when this information is available from the original article. There is no implication that the test concentration is appropriate for the treatment of peritonitis. A dash (-) indicates that the concentration of the drug was not stated.

Manufacturer abbreviations [2], [4], [6]

AB	Abbott
BE	Beecham
BR	Bristol
BS	Biosedra Laboratory
CSL	Commonwealth Serum Laboratories
GL	Glaxo
HO	Hoechst-Roussel
LE	Lederle
LI	Eli Lilly
MG	American McGaw
MI	Miles
ML	Merrell Dow
MSD	Merck Sharp & Dohme
PD	Parke-Davis
PF	Pfizer
RI	Riker
RR	Roerig
SC	Schering
SI	Sigma
TR	Travenol
UP	Upjohn
WY	Wyeth
-	Manufacturer not stated

Solution [5]

Test solutions containing between 0.5% and 4.5% glucose are grouped together in a table headed "CAPD fluids". Included in this table are tests conducted in peritoneal dialysis effluent. Test solutions containing 30% or 50% glucose are grouped together in a table headed "Peritoneal dialysis fluid concentrates". The glucose concentration of the test solution is stated in the table. Letters A-G refer to Appendix 1 where full details of the composition of the solution are given. If the composition of the test solution is not specified in the study, this is stated in the table.

Method [7]

The following abbreviations refer to the method used to assess the stability or efficacy of each drug or drug combination :

B	bioassay
b	*bioactivity (measure of the efficacy of peritoneal dialysis fluid or peritoneal dialysis effluent containing an antibiotic)*
CT	clotting time of fresh whole blood
EMIT	enzyme multiplied immunoassay
FIA	fluorescence immunoassay
HPLC	high performance liquid chromatography
RIA	radioimmunoassay
S	spectrophotometry
V	visual examination (macroscopic)
-	method not stated

When both drugs of a drug combination have been tested, the first method appearing in the column is applicable to the reference drug. Subsequent method(s) appearing in brackets refer to the drug(s) used in combination with the reference drug. When two methods have been used to assess the stability or efficacy of one drug, these are both specified e.g.

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method
Gentamicin sulphate 5mg/L and 8mg/L	SC			PDF containing 2.5% glucose (Dianeal), A.	TR	RIA,* EMIT*
Gentamicin sulphate 8mg/L	-	Cefazolin 75mg/L Heparin 1000units/L	- -	PDF containing 1.5% glucose (composition not stated)	-	FIA≈ (HPLC)† (-) §

* Gentamicin concentration determined by radioimmunoassay and enzyme multiplied immunoassay.

≈ Gentamicin concentration determined by fluorescence immunoassay.
† Cefazolin concentration determined by high performance liquid chromatography.
§ Method for determining heparin stability not stated.

Results [8]

The results of efficacy studies have been printed in italics to distinguish them from stability studies.
Tests performed in plastic bags have been identified when specified in the original article. Evidence or lack of evidence of a physical incompatibility has been reported when specified in the study; no comment on physical compatibility indicates that this was not examined. The time for 10% decomposition has been stated if this was determined. The temperature at which the test was conducted has been reported as specified in the study.

Summary [10]

A summary of the tabulated information is presented for each drug. The summary is intended as a brief overview of the available stability information and as such would be a useful first reference. In general, however, the summary should be used in conjunction with the tables where greater detail is provided. The original study should be consulted when more information is required. The summary includes comments on conflicting information where applicable, and mention may be made of those points which limit the application of the information. Within the context of the summary, storage temperatures in the range 20°C-25°C inclusive have been referred to as "room temperature".

Abbreviations

A complete list of the abbreviations used in this text appears in Appendix 2.

Limitations

As a consequence of the small number of stability studies conducted in peritoneal dialysis fluids, several studies have been reviewed which would otherwise have been discarded due to lack of detailed information. Drug concentration, storage temperature and solution composition are three of many important variables which affect drug stability in solution. Studies which lack this information are easily recognised in the tables and their limitations may be mentioned in the relevant summaries. Caution must be exercised when using stability information from few studies, or from studies which lack detailed information. This review is intended as an aid to professional judgement. Factors which have received little attention in the literature include the stability and compatibility of drug combinations in peritoneal dialysis fluids, and the effect of precipitation on the peritoneal membrane. Until more information is available in this area, guidelines available for IV admixtures will remain a valuable reference.

AMIKACIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Amikacin (-)	-			PDF containing 1.5% glucose (composition not stated)	-	B	Initial activity retained for 24h at room temperature.	52
Amikacin 25mg/L	BR			PDF containing 1.5% glucose (Dianeal), A PDF containing 1.5% glucose (Dianeal) pH adjusted to 7.4 PD effluent collected after a 6h i.p. dwell, G	TR TR	*b*	*MBC against P.aeruginosa 16-32 times greater in PDF than in buffered PDF and Mueller-Hinton broth. MBC against P.aeruginosa 8 times greater in PD* effluent than in Mueller-Hinton broth. *Time for >99.9% kill (amikacin 25mg/L) was 1h in Mueller-Hinton broth, 2h in PD effluent, 6h in buffered PDF and 24h in PDF at 37°C.*	3
Amikacin 20mg/L	-	Azlocillin 500mg/L	-	PDF containing 1.5% glucose (Dianeal), A, pH adjusted to 7.2	TR	EMIT (HPLC)	Amikacin lost 10% of initial concentration in 30min and 30% in 8h in 1L plastic bags containing dialysate and azlocillin at 37°C. Initial concentration of azlocillin retained for 8h.	47
Amikacin sulphate 25mg/L	BR	Cefamandole nafate 125mg/L	LI	PD effluent collected after a 6h i.p. dwell of PDF containing 1.5% glucose (Dianeal), F		*b* *(b)*	*Antibiotic combination in PD effluent at 37°C more rapidly lethal than either drug alone against E.coli, P.aeruginosa and S.aureus.*	6
Amikacin sulphate 25mg/L	BR	Cefazolin sodium 125mg/L	LI	PD effluent collected after a 6h i.p. dwell of PDF containing 1.5% glucose (Dianeal), F		*b* *(b)*	*Antibiotic combination in PD effluent at 37°C more rapidly lethal than either drug alone against E.coli, P.aeruginosa and S.aureus.*	6
Amikacin sulphate 25mg/L	BR	Cefoxitin sodium 125mg/L	MSD	PD effluent collected after a 6h i.p. dwell of PDF containing 1.5% glucose (Dianeal), F		*b* *(b)*	*Antibiotic combination in PD effluent at 37°C more rapidly lethal than either drug alone against E.coli, P.aeruginosa and S.aureus.*	6

Amikacin

Only one study has investigated amikacin stability in CAPD fluid and few details are provided. Amikacin was stable in CAPD fluid containing 1.5% glucose for 24h at room temperature, however the concentration tested is unknown (52). One study investigating the efficacy of intraperitoneal amikacin found that the activity of amikacin against P.aeruginosa was significantly inhibited in CAPD fluid and peritoneal dialysis effluent. This was demonstrated in peritoneal dialysis fluid and effluent of relatively low glucose concentration (≤1.5%), (3).

Amikacin in combination

Significant decomposition of amikacin occurred within 30min when combined with azlocillin in pH adjusted CAPD fluid at 37°C. Azlocillin was stable for 8h. Physical compatibility was not commented on (47). [...continued next page]

Synergistic activity against E.coli, P.aeruginosa and S.aureus was demonstrated when amikacin was combined with cefamandole, cefazolin or cefoxitin in peritoneal dialysis effluent. This does not imply synergism against other bacterial species or exclude the possibility of significant inactivation of one antibiotic by the other (6).

Peritoneal dialysis fluid concentrates

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Amikacin sulphate 0.6g/L	BR			PDF concentrate containing 30% glucose, H	TR	B	Activity after 4h in PDF concentrate similar to initial activity in normal saline. Temperature not stated.	9
Amikacin base 10mg/L and 50mg/L	BR			PDF concentrate containing 50% glucose, D	MG	B	25-30% loss of initial activity in 7h and 50-62% loss of initial activity in 24h at room temperature. Loss of activity was greater at the lower amikacin concentration.	1
Amikacin (-)	-			PDF concentrate containing 30% or 50% glucose (composition not stated) pH 5.7 PDF concentrate containing 30% or 50% glucose (composition not stated) pH adjusted to 6.8	- -	B	42% loss of initial activity in 24h in PDF concentrate containing 50% glucose, pH 6.8. 25% loss of initial activity in 24h in all other solutions. Temperature not stated.	27
Amikacin sulphate 0.6g/L	BR	Heparin sodium 2500 units/L	RI	PDF concentrate containing 30% glucose, H	TR	B (-)	Activity of amikacin maintained for 4h in PDF concentrate containing heparin. Heparin not studied. Temperature not stated.	9

Amikacin

Three studies have investigated amikacin stability in PDF concentrates. Amikacin 6g/L was stable for 4h in PDF concentrate containing 30% glucose (9). Significant loss of activity occurred within 24h at lower amikacin concentrations (1), and higher glucose concentration (1, 27).

Amikacin in combination

Amikacin 6g/L was stable for 4h when combined with heparin in PDF concentrate containing 30% glucose. The effect of the combination on heparin activity is unknown. Physical compatibility was not commented on (9).

AMPICILLIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Ampicillin 50mg/L	BR			PDF containing 4.25% glucose (Dianeal 137, PD2), B, C	TR	B	Initial activity retained for 48h in 1L or 2L plastic bags containing dialysate at 25°C.	5
Ampicillin 50mg/L	BR	Heparin 500 units/L	-	PDF containing 4.25% glucose (Dianeal 137, PD2), B, C	TR	B (-)	Initial activity of ampicillin retained for 48h in 1L or 2L plastic bags containing dialysate and heparin at 25°C. Heparin not studied.	5

Ampicillin

One study has demonstrated that ampicillin 50mg/L is stable in CAPD fluids containing 4.25% glucose for 48h at room temperature (5).

Ampicillin in combination

Ampicillin was stable for 48h at room temperature when combined with heparin in CAPD fluids containing 4.25% glucose. The effect of the combination on heparin activity is unknown. Physical compatibility was not commented on (5).

Peritoneal dialysis fluid concentrates

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Ampicillin sodium 2.5g/L	BR			PDF concentrate containing 30% glucose, H	TR	B	Significant loss of activity occurred within 10min in PDF concentrate compared to normal saline (128 fold increase in MIC against E.coli). No further loss of activity was evident at 4h. Temperature not stated.	9
Ampicillin (-)	-			PDF concentrate containing 30% or 50% glucose (composition not stated) pH 5.7 PDF concentrate containing 30% or 50% glucose (composition not stated) pH adjusted to 6.8	- -	B	Up to 75% loss of initial activity in 24h in all solutions. This loss was greater and faster in solutions of high glucose concentration and high pH. Temperature not stated.	27
Ampicillin sodium 2.5g/L	BR	Gentamicin sulphate 100mg/L	SC	PDF concentrate containing 30% glucose, H	TR	B (B)	The activity of the antibiotic combination against E.coli after 4h in PDF concentrate was the same as its activity after 10min. The combined activity was significantly greater than the activity of either antibiotic alone. Temperature not stated.	9

Peritoneal dialysis fluid concentrates (continued)

Ampicillin sodium 2.5g/L	BR	Gentamicin sulphate 100mg/L Heparin sodium 2500 units/L	SC RI	PDF concentrate containing 30% glucose, H	TR	B (B) (-)	The activity of the antibiotic combination against E.coli was significantly inhibited after 10min in PDF concentrate containing heparin. No further loss of activity was evident at 4h. Heparin not studied. Temperature not stated.	9
Ampicillin sodium 2.5g/L	BR	Heparin sodium 2500 units/L	RI	PDF concentrate containing 30% glucose, H	TR	B (-)	Ampicillin alone in PDF concentrate compared to normal saline showed significant loss of activity within 10min (128 fold increase in MIC against E.coli). No further loss of activity was evident at 10min or 4h when combined with heparin. Heparin not studied. Temperature not stated.	9

Ampicillin

Two studies have investigated ampicillin stability in PDF concentrates. One study demonstrated that ampicillin was not stable for 24h in PDF concentrates containing 30% or 50% glucose, however the concentration tested and the storage temperature are unknown (27). A second study demonstrated that a significant loss of ampicillin activity occurs within 10min in PDF concentrate when compared to its activity in normal saline (9).

Ampicillin in combination

Only one study has attempted to investigate ampicillin in combination with other drugs in PDF concentrate (9). The initial activity of the ampicillin plus gentamicin combination was maintained for 4h in PDF concentrate containing 30% glucose. Synergistic activity against E.coli was demonstrated when ampicillin was combined with gentamicin. This does not imply synergism against other bacterial species or exclude the possibility of significant inactivation of one or both antibiotics. Physical compatibility was not commented on.

Heparin had no effect on the activity of ampicillin, but inhibited the combined activity of ampicillin plus gentamicin after only 10min in PDF concentrate containing 30% glucose. The effect of the combinations on heparin activity is unknown. Physical compatibility was not commented on.

AZLOCILLIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Azlocillin 200mg/L	MI			PDF containing 4.25% glucose (Dianeal 137, PD2), B, C	TR	B	Initial activity retained for 48h in 1L or 2L plastic bags containing dialysate at 25°C.	5
Azlocillin 200mg/L	MI			PDF containing 1.5% glucose (Dianeal), A PDF containing 1.5% glucose (Dianeal) pH adjusted to 7.4 PD effluent collected after a 6h i.p. dwell, G	TR TR	*b*	*MBC against P.aeruginosa more than 16 times greater in PDF and PD effluent than in Mueller-Hinton broth. MBC against P.aeruginosa 2-4 times greater in buffered PDF than in Mueller-Hinton broth.* *Time for >99.9% kill (azlocillin 200mg/L) was 6h in Mueller-Hinton broth at 37°C. Bactericidal activity was not demonstrated in 24h in PDF, buffered PDF or PD effluent.*	3
Azlocillin 500mg/L	-	Amikacin 20mg/L	-	PDF containing 1.5% glucose (Dianeal), A, pH adjusted to 7.2	TR	HPLC (EMIT)	Azlocillin stable for 8h in 1L plastic bags containing dialysate and amikacin at 37°C. Amikacin lost 10% of its initial concentration in 30min and 30% in 8h.	47
Azlocillin 500mg/L	-	Gentamicin 8mg/L	-	PDF containing 1.5% glucose (Dianeal), A, pH adjusted to 7.2	TR	HPLC (EMIT)	Azlocillin stable for 8h in 1L plastic bags containing dialysate and gentamicin at 37°C. Initial concentration of gentamicin maintained for 6h. >10% loss of initial concentration occurred within 8h.	47
Azlocillin 200mg/L	MI	Heparin 500 units/L	-	PDF containing 4.25% glucose (Dianeal 137, PD2), B, C	TR	B (-)	Initial activity of azlocillin retained for 48h in 1L or 2L plastic bags containing dialysate and heparin at 25°C. Heparin not studied.	5
Azlocillin 500mg/L	-	Netilmicin 7.5mg/L	-	PDF containing 1.5% glucose (Dianeal), A, pH adjusted to 7.2	TR	HPLC (EMIT)	Azlocillin stable for 8h in 1L plastic bags containing dialysate and netilmicin at 37°C. Initial concentration of netilmicin maintained for 6h. >10% loss of initial concentration occurred within 8h.	47

Azlocillin

One study has demonstrated that azlocillin 200mg/L is stable in CAPD fluids containing 4.25% glucose for 48h at room temperature (5). Another study investigating the efficacy of intraperitoneal azlocillin found that the activity of azlocillin against P.aeruginosa was significantly inhibited in CAPD fluid and peritoneal dialysis effluent. This was demonstrated in peritoneal dialysis fluid and effluent of relatively low glucose concentration (≤1.5%), (3).

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Azlocillin in combination

Azlocillin was stable for 8h at 37°C when combined with amikacin in pH adjusted CAPD fluid, however significant decomposition of amikacin occurred within 30min. Physical compatibility was not commented on (47).

Azlocillin was stable for 8h at 37°C when combined with gentamicin in pH adjusted CAPD fluid, however significant decomposition of gentamicin occurred after 6h. Physical compatibility was not commented on (47).

Azlocillin was stable for 8h at 37°C when combined with netilmicin in pH adjusted CAPD fluid, however significant decomposition of netilmicin occurred after 6h. Physical compatibility was not commented on (47).

Azlocillin was stable for 48h at room temperature when combined with heparin in CAPD fluids containing 4.25% glucose. The effect of the combination on heparin activity is unknown. Physical compatibility was not commented on (5).

CARBENICILLIN

Peritoneal dialysis fluid concentrates

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Carbenicillin disodium 2g/L	RR			PDF concentrate containing 30% glucose, H	TR	B	Significant loss of activity occurred within 10min in PDF concentrate compared to normal saline (four-fold increase in MIC against E.coli). No further loss of activity was evident at 4h. Temperature not stated.	9
Carbenicillin (-)	-			PDF concentrate containing 30% or 50% glucose (composition not stated) pH 5.7 PDF concentrate containing 30% or 50% glucose (composition not stated) pH adjusted to 6.8	- -	B	Up to 75% loss of initial activity in 24h in all solutions. This loss was greater and faster in solutions of high glucose concentration and high pH. Temperature not stated.	27
Carbenicillin disodium 2g/L	RR	Gentamicin sulphate 100mg/L	SC	PDF concentrate containing 30% glucose, H	TR	B (B)	The activity of the antibiotic combination against E.coli after 4h in PDF concentrate was the same as its activity after 10min. The combined activity was similar to, but no greater than, the activity of either antibiotic alone. Temperature not stated.	9

Peritoneal dialysis fluid concentrates (continued)

Carbenicillin disodium 2g/L	RR	Gentamicin sulphate 100mg/L Heparin sodium 2500 units/L	SC RI	PDF concentrate containing 30% glucose, H	TR	B (B) (-)	The activity of the antibiotic combination against E.coli was unaffected by the presence of heparin after 10min and 4h in PDF concentrate. The combined activity was similar to, but no greater than, the activity of either antibiotic alone. Heparin not studied. Temperature not stated.	9
Carbenicillin disodium 2g/L	RR	Heparin sodium 2500 units/L	RI	PDF concentrate containing 30% glucose, H	TR	B (-)	Carbenicillin alone in PDF concentrate compared to normal saline showed significant loss of activity within 10min (four-fold increase in MIC against E.coli). No further loss of activity was evident at 10min or 4h when combined with heparin. Heparin not studied. Temperature not stated.	9

Carbenicillin

Two studies have investigated carbenicillin stability in PDF concentrates. One study demonstrated that carbenicillin was not stable for 24h in PDF concentrates containing 30% or 50% glucose, however the concentration tested and the storage temperature are unknown (27). A second study demonstrated that a significant loss of carbenicillin activity occurs within 10min in PDF concentrate when compared to its activity in normal saline (9).

Carbenicillin in combination

Only one study has attempted to investigate carbenicillin in combination with other drugs in PDF concentrate (9). The initial activity of the carbenicillin plus gentamicin combination was maintained for 4h in PDF concentrate containing 30% glucose. Synergistic activity against E.coli was not demonstrated when carbenicillin was combined with gentamicin, however this combination may be synergistic against other bacterial species or provide broader activity against a variety of bacterial species. Physical compatibility was not commented on.

Heparin had no effect on the activity of carbenicillin, or on the combined activity of carbenicillin plus gentamicin in PDF concentrate containing 30% glucose. The effect of the combinations on heparin activity is unknown. Physical compatibility was not commented on.

CEFAMANDOLE

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Cefamandole 8mg/L	-			PDF containing 1.5% glucose (Dianeal 137), B	TR	B	Initial activity retained for 24h at room temperature.	12
Cefamandole 2g/L	-			PDF containing 2.5% glucose, E	MG	V	No visible precipitation in 3h at room temperature.	8
Cefamandole nafate 125mg/L	LI	Amikacin sulphate 25mg/L	BR	PD effluent collected after a 6h i.p. dwell of PDF containing 1.5% glucose (Dianeal), F		*b* *(b)*	*Antibiotic combination in PD effluent at 37°C more rapidly lethal than either drug alone against E.coli, P.aeruginosa and S.aureus.*	6
Cefamandole nafate 125mg/L	LI	Gentamicin sulphate (-)	SC	PD effluent collected after a 6h i.p. dwell of PDF containing 1.5% glucose (Dianeal), F		*b* *(b)*	*Antibiotic combination in PD effluent at 37°C more rapidly lethal than either drug alone against E.coli, P.aeruginosa and S.aureus.*	6
Cefamandole nafate 125mg/L	LI	Tobramycin sulphate (-)	LI	PD effluent collected after a 6h i.p. dwell of PDF containing 1.5% glucose (Dianeal), F		*b* *(b)*	*Antibiotic combination in PD effluent at 37°C more rapidly lethal than either drug alone against E.coli, P.aeruginosa and S.aureus.*	6

Cefamandole

One study has demonstrated that cefamandole 8mg/L is stable in CAPD fluid containing 1.5% glucose for 24h at room temperature (12). Cefamandole 2g/L was physically compatible with peritoneal dialysis fluid containing 2.5% glucose for 3h at room temperature (8).

Cefamandole in combination

Synergistic activity against E.coli, P.aeruginosa and S.aureus was demonstrated when cefamandole was combined with amikacin, gentamicin or tobramycin in peritoneal dialysis effluent. This does not imply synergism against other bacterial species or exclude the possibility of significant inactivation of one antibiotic by the other (6).

CEFAMANDOLE (continued)

Peritoneal dialysis fluid concentrates

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Cefamandole nafate 2g/L	LI			PDF concentrate containing 30% or 50% glucose, D	MG	B, V	Initial activity retained for 48h at 25°C and 96h at 5°C. No visible precipitation in 24h at 25°C; haze observed within 24h in solutions stored at 5°C.	13
Cefamandole nafate 5g/L	LI			PDF concentrate containing 30% or 50% glucose, D	MG	B, V	Initial activity retained for 48h at 25°C and 96h at 5°C. Haze observed within 24h in solutions stored at 5°C and 25°C.	13
Cefamandole (-)	-			PDF concentrate containing 30% or 50% glucose (composition not stated) pH 5.7 PDF concentrate containing 30% or 50% glucose (composition not stated) pH adjusted to 6.8	- -	B	Initial activity retained for 24h in all solutions. Temperature not stated.	27
Cefamandole nafate 2g/L	-			PDF concentrate containing 30% glucose, H	TR	B	Significant loss of activity occurred within 10min in PDF concentrate compared to normal saline (256 fold increase in MIC against E.coli). No further loss of activity was evident at 4h. Temperature not stated.	9
Cefamandole nafate 2g/L	-	Heparin sodium 2500 units/L	RI	PDF concentrate containing 30% glucose, H	TR	B (-)	Cefamandole alone in PDF concentrate compared to normal saline showed significant loss of activity within 10min (256 fold increase in MIC against E.coli). No further loss of activity was evident at 10min or 4h when combined with heparin. Heparin not studied. Temperature not stated.	9

Cefamandole

Three studies have investigated cefamandole stability in PDF concentrates containing 30% or 50% glucose. Cefamandole 2g/L was stable for 48h at room temperature, however physical incompatibility was observed at a higher cefamandole concentration (5g/L) or a lower storage temperature (5°C), (13). A second study, in which the test concentration and storage temperature are not specified, concluded that cefamandole was stable for 24h (27). A significant loss of cefamandole activity occurred within 10min in PDF concentrate when compared to its activity in normal saline (9).

Cefamandole in combination

Heparin had no effect on the activity of cefamandole in PDF concentrate containing 30% glucose. The effect of the combination on heparin activity is unknown. Physical compatibility was not commented on (9).

CEFAPIRIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Cefapirin 125mg/L	BR			PDF containing 1.5% or 4.25% glucose (Dianeal 137), B	TR	B	At least 95% of initial activity retained for 24h in 1L plastic bags containing dialysate at 25°C.	10
Cefapirin 125mg/L	BR			PDF containing 4.25% glucose (Dianeal 137, PD2), B, C	TR	B	Initial activity retained for 48h in 1L or 2L plastic bags containing dialysate at 25°C.	5
Cefapirin 500mg/L	BR			PDF containing 4.25% glucose (Dianeal 137), B	TR	B	16% loss of initial activity in 24h in 1L or 2L plastic bags containing dialysate at 35°C.	5
Cefapirin 2g/L	-			PDF containing 2.5% glucose, E	MG	V	No visible precipitation in 3h at room temperature.	8
Cefapirin 125mg/L	BR	Heparin 500 units/L	-	PDF containing 4.25% glucose (Dianeal 137, PD2), B, C	TR	B (-)	Initial activity of cefapirin retained for 48h in 1L or 2L plastic bags containing dialysate and heparin at 25°C. Heparin not studied.	5
Cefapirin 500mg/L	BR	Tobramycin 65mg/L	LI	PDF containing 4.25% glucose (Dianeal 137), B	TR	B (B)	Initial activity of each antibiotic retained for 24h in 1L or 2L plastic bags containing dialysate at 25°C.	5
Cefapirin 500mg/L	BR	Tobramycin 65mg/L	LI	PDF containing 4.25% glucose (Dianeal 137), B	TR	B (B)	Cefapirin lost 16% of initial activity and tobramycin lost 12% of initial activity within 24h when combined in 1L or 2L plastic bags containing dialysate at 35°C.	5

Cefapirin

Two studies have demonstrated that cefapirin 125mg/L is stable in CAPD fluids of various glucose concentrations for 24h at room temperature (5, 10). At increased temperature, cefapirin 500mg/L was not stable for 24h (5). Cefapirin 2g/L was physically compatible with peritoneal dialysis fluid containing 2.5% glucose for 3h at room temperature (8).

Cefapirin in combination

Cefapirin was stable for 48h at room temperature when combined with heparin in CAPD fluids containing 4.25% glucose. The effect of the combination on heparin activity is unknown. Physical compatibility was not commented (5).

Cefapirin and tobramycin were stable for 24h at room temperature when combined in CAPD fluid containing 4.25% glucose. At increased temperature, a significant loss of activity of each drug occurred within 24h (5).

CEFAZOLIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Cefazolin 2g/L	-			PDF containing 2.5% glucose, E	MG	V	No visible precipitation in 3h at room temperature.	8
Cefazolin 0.25-16mg/L	SI			Mueller-Hinton agar reconstituted with PD effluent collected after an overnight dwell of PDF containing 2.5% glucose (composition not stated)		*b*	*The MIC of cefazolin in Mueller-Hinton agar was not adversely affected by the addition of PD effluent when measured against coagulase-positive or coagulase-negative staphylococci.* *	49
Cefazolin sodium 125mg/L	LI	Amikacin sulphate 25mg/L	BR	PD effluent collected after a 6h i.p. dwell of PDF containing 1.5% glucose (Dianeal), F		*b* *(b)*	*Antibiotic combination in PD effluent at 37°C more rapidly lethal than either drug alone against E.coli, P.aeruginosa and S.aureus.*	6
Cefazolin sodium 125mg/L	LI	Gentamicin sulphate (-)	SC	PD effluent collected after a 6h i.p. dwell of PDF containing 1.5% glucose (Dianeal), F		*b* *(b)*	*Antibiotic combination in PD effluent at 37°C more rapidly lethal than either drug alone against E.coli, P.aeruginosa and S.aureus.*	6
Cefazolin 75mg/L and 150mg/L	-	Gentamicin sulphate 8mg/L Heparin 1000 units/L	- -	PDF containing 1.5% glucose (composition not stated)	-	V, HPLC (FIA) (-)	Cefazolin and gentamicin stable for 48h at 4°C, 26°C and 37°C in 1L plastic bags containing dialysate and heparin. No visible precipitation. Heparin not studied.	34
Cefazolin 75mg/L and 150mg/L	-	Heparin 1000 units/L	-	PDF containing 1.5% glucose (composition not stated)	-	V, HPLC (-)	Cefazolin stable for 48h at 4°C, 26°C and 37°C in 1L plastic bags containing dialysate and heparin. No visible precipitation. Heparin not studied.	34
Cefazolin 50mg/L	-	Moxalactam disodium 30mg/L	LI	PDF containing 1.5% glucose (Dianeal), A	TR	- (HPLC)	Moxalactam stable in solutions stored for 6h at 25°C then heated to 37°C for 30min. Cefazolin not studied.	50

CAPD fluids (continued)

Cefazolin 50mg/L	-	Moxalactam disodium 30mg/L Vancomycin 25mg/L	LI -	PDF containing 1.5% glucose (Dianeal), A	TR	- (HPLC) (-)	Moxalactam stable in solutions stored for 6h at 25°C then heated to 37°C for 30min. Cefazolin and vancomycin not studied.	50
Cefazolin sodium 125mg/L	LI	Tobramycin sulphate (-)	LI	PD effluent collected after a 6h i.p. dwell of PDF containing 1.5% glucose (Dianeal), F		*b* *(b)*	*Antibiotic combination in PD effluent at 37°C more rapidly lethal than either drug alone against E.coli, P.aeruginosa and S.aureus.*	6

Cefazolin

No studies have investigated the stability of cefazolin alone in CAPD fluids. Cefazolin 2g/L was physically compatible with peritoneal dialysis fluid containing 2.5% glucose for 3h at room temperature (8). One study investigating the efficacy of intraperitoneal cefazolin found that the activity of cefazolin against staphylococci was not inhibited by peritoneal dialysis effluent (49).

* Coagulase-positive staphylococci includes S.aureus. Coagulase-negative staphylococci includes S.epidermidis.

Cefazolin in combination

Cefazolin, gentamicin and heparin were physically compatible when combined in CAPD fluid containing 1.5% glucose. Both antibiotics were stable for 48h at temperatures up to 37°C. The effect of the combination on heparin activity is unknown (34).

Moxalactam was stable after storage for 6h at room temperature followed by heating to 37°C for 30min when combined with cefazolin, and cefazolin plus vancomycin, in CAPD fluid containing 1.5% glucose. The effect of the combinations on cefazolin and vancomycin stability is unknown. Physical compatibility was not commented on (50).

Synergistic activity against E.coli, P.aeruginosa and S.aureus was demonstrated when cefazolin was combined with amikacin, gentamicin or tobramycin in peritoneal dialysis effluent. This does not imply synergism against other bacterial species or exclude the possibility of significant inactivation of one antibiotic by the other (6).

Cefazolin and heparin were physically compatible when combined in CAPD fluid containing 1.5% glucose. Cefazolin was stable for 48h at temperatures up to 37°C. The effect of the combination on heparin activity is unknown (34).

CEFAZOLIN (continued)

Peritoneal dialysis fluid concentrates

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Cefazolin (-)	-			PDF concentrate containing 30% or 50% glucose (composition not stated) pH 5.7 PDF concentrate containing 30% or 50% glucose (composition not stated) pH adjusted to 6.8	- -	B	Initial activity retained for 24h in all solutions. Temperature not stated.	27

Cefazolin

Only one study has investigated cefazolin stability in PDF concentrates and few details are provided. Cefazolin was stable for 24h in PDF concentrates containing 30% or 50% glucose, however the concentration tested and the storage temperature are unknown (27).

CEFMENOXIME

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Cefmenoxime 4mg/L	-			PDF containing 1.5% glucose (Dianeal 137), B	TR	B	Initial activity retained for 24h at room temperature.	12

Cefmenoxime

One study has demonstrated that cefmenoxime 4mg/L is stable in CAPD fluid containing 1.5% glucose for 24h at room temperature (12).

CEFOPERAZONE

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Cefoperazone 4mg/L	-			PDF containing 1.5% glucose (Dianeal 137), B	TR	B	Initial activity retained for 24h at room temperature.	12
Cefoperazone 1g/L	-			PDF containing 1.5% glucose (composition not stated)	-	B	Initial activity retained for 10h at 37°C. 10% loss of initial activity in 24h at 37°C.	51
Cefoperazone (-)	-			PDF (composition not stated) and PD effluent (composition not stated)	-	*b*	*MIC's against a variety of test organisms in PDF and PD effluent similar to MIC's determined in Mueller-Hinton broth.*	26

Cefoperazone

Two studies have investigated cefoperazone stability in CAPD fluids containing 1.5% glucose. Cefoperazone 4mg/L was stable for 24h at room temperature (12). A more concentrated solution of cefoperazone was stable for 10h at 37°C, but was not stable for 24h (51). One study investigating the efficacy of intraperitoneal cefoperazone found that the activity of cefoperazone against a variety of bacterial species was not inhibited in CAPD fluid or peritoneal dialysis effluent (26).

CEFOTAXIME

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Cefotaxime 125mg/L	HO			PDF containing 4.25% glucose (Dianeal 137, PD2), B, C	TR	B	Initial activity retained for 24h in 1L or 2L plastic bags containing dialysate at 25°C. 20% loss of initial activity in 48h at 25°C.	5
Cefotaxime 4mg/L	-			PDF containing 1.5% glucose (Dianeal 137), B	TR	B	Initial activity retained for 24h at room temperature.	12
Cefotaxime 2g/L	-			PDF containing 2.5% glucose, E	MG	V	No visible precipitation in 3h at room temperature.	8
Cefotaxime 125mg/L	HO	Heparin 500 units/L	-	PDF containing 4.25% glucose (Dianeal 137, PD 2), B, C	TR	B (-)	Initial activity of cefotaxime retained for 24h in 1L or 2L plastic bags containing dialysate and heparin at 25°C. 20% loss of initial activity in 48h at 25°C. Heparin not studied.	5

Cefotaxime

Two studies have investigated cefotaxime stability in CAPD fluids of various glucose concentrations. Cefotaxime was stable for 24h at room temperature (5, 12), but was not stable for 48h (5). Cefotaxime 2g/L was physically compatible with peritoneal dialysis fluid containing 2.5% glucose for 3h at room temperature (8).

Cefotaxime in combination

Cefotaxime was stable for 24h at room temperature when combined with heparin in CAPD fluids containing 4.25% glucose, but was not stable for 48h. The effect of the combination on heparin activity is unknown. Physical compatibility was not commented on (5).

CEFOXITIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Cefoxitin 8mg/L	-			PDF containing 1.5% glucose (Dianeal 137), B	TR	B	Initial activity retained for 24h at room temperature.	12
Cefoxitin sodium 100mg/L	-			PDF (Dianeal), A, glucose composition not stated	TR	HPLC	Stable for 24h at 37°C.	39
Cefoxitin 2g/L	-			PDF containing 2.5% glucose, E	MG	V	No visible precipitation in 3h at room temperature.	8
Cefoxitin sodium 125mg/L	MSD	Amikacin sulphate 25mg/L	BR	PD effluent collected after a 6h i.p. dwell of PDF containing 1.5% glucose (Dianeal), F		*b* *(b)*	*Antibiotic combination in PD effluent at 37°C more rapidly lethal than either drug alone against E.coli, P.aeruginosa and S.aureus.*	6
Cefoxitin sodium 125mg/L	MSD	Gentamicin sulphate (-)	SC	PD effluent collected after a 6h i.p. dwell of PDF containing 1.5% glucose (Dianeal), F		*b* *(b)*	*Antibiotic combination in PD effluent at 37°C more rapidly lethal than either drug alone against E.coli, P.aeruginosa and S.aureus.*	6
Cefoxitin sodium 125mg/L	MSD	Tobramycin sulphate (-)	LI	PD effluent collected after a 6h i.p. dwell of PDF containing 1.5% glucose (Dianeal), F		*b* *(b)*	*Antibiotic combination in PD effluent at 37°C more rapidly lethal than either drug alone against E.coli, P.aeruginosa and S.aureus.*	6

Cefoxitin

Two studies have investigated cefoxitin stability in CAPD fluids. Cefoxitin 8mg/L was stable in CAPD fluid containing 1.5% glucose for 24h at room temperature (12). A more concentrated solution of cefoxitin in CAPD fluid of unknown glucose concentration was stable for 24h at 37°C (39). Cefoxitin 2g/L was physically compatible with peritoneal dialysis fluid containing 2.5% glucose for 3h at room temperature (8).

Cefoxitin in combination

Synergistic activity against E.coli, P.aeruginosa and S.aureus was demonstrated when cefoxitin was combined with amikacin, gentamicin or tobramycin in peritoneal dialysis effluent. This does not imply synergism against other bacterial species or exclude the possibility of significant inactivation of one antibiotic by the other (6).

CEFOXITIN (continued)

Peritoneal dialysis fluid concentrates

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Cefoxitin (-)	-			PDF concentrate containing 30% or 50% glucose (composition not stated) pH 5.7 PDF concentrate containing 30% or 50% glucose (composition not stated) pH adjusted to 6.8	- -	B	Initial activity retained for 24h in all solutions. Temperature not stated.	27

Cefoxitin

Only one study has investigated cefoxitin stability in PDF concentrates and few details are provided. Cefoxitin was stable for 24h in PDF concentrates containing 30% or 50% glucose, however the concentration tested and the storage temperature are unknown (27).

CEFSULODIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Cefsulodin 100mg/L	AB			PDF containing 1.5% glucose (Dianeal), A PDF containing 1.5% glucose (Dianeal) pH adjusted to 7.4 PD effluent collected after a 6h i.p. dwell, G	TR TR	*b*	*MBC against P.aeruginosa 4-8 times greater in PDF than in buffered PDF and Mueller-Hinton broth. MBC against P.aeruginosa 16-32 times greater in PD effluent than in Mueller-Hinton broth.* *Time for >99.9% kill (cefsulodin 100mg/L) was 24h in Mueller-Hinton broth at 37°C. Bactericidal activity was not demonstrated in 24h in PDF, buffered PDF or PD effluent.*	3

Cefsulodin

No studies have investigated the stability of cefsulodin in CAPD fluids. One study investigating the efficacy of intraperitoneal cefsulodin found that the activity of cefsulodin against P.aeruginosa was significantly inhibited in CAPD fluid and peritoneal dialysis effluent. This was demonstrated in peritoneal dialysis fluid and effluent of relatively low glucose concentration, (≤1.5%), (3).

CEFTAZIDIME

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Ceftazidime 8mg/L	-			PDF containing 1.5% glucose (Dianeal 137), B	TR	B	Initial activity retained for 24h at room temperature.	12
Ceftazidime 100mg/L	GL			PDF containing 1.5% glucose (Dianeal), A PDF containing 1.5% glucose (Dianeal) pH adjusted to 7.4 PD effluent collected after a 6h i.p. dwell, G	TR TR	*b*	*MBC against P.aeruginosa 8-16 times greater in PDF than in buffered PDF and Mueller-Hinton broth. MBC against P.aeruginosa 32 times greater in PD effluent than in Mueller-Hinton broth.* *Time for >99.9% kill (ceftazidime 100mg/L) was 6h in Mueller-Hinton broth at 37°C. Bactericidal activity was not demonstrated in 24h in PDF, buffered PDF or PD effluent.*	3

Ceftazidime

One study has demonstrated that ceftazidime 8mg/L is stable in CAPD fluid containing 1.5% glucose for 24h at room temperature (12). Another study investigating the efficacy of intraperitoneal ceftazidime found that the activity of ceftazidime against P.aeruginosa was significantly inhibited in CAPD fluid and peritoneal dialysis effluent. This was demonstrated in peritoneal dialysis fluid and effluent of relatively low glucose concentration (≤1.5%), (3).

CEFTRIAXONE

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Ceftriaxone 4mg/L	-			PDF containing 1.5% glucose (Dianeal 137), B	TR	B	Initial activity retained for 24h at room temperature.	12
Ceftriaxone (-)	-			PDF (composition not stated)	-	HPLC	16% loss of initial concentration in 5.5h and 25% loss of initial concentration in 6.75h at 37°C.	38

Ceftriaxone

Two studies have investigated ceftriaxone stability in CAPD fluids. Ceftriaxone 4mg/L was stable in CAPD fluid containing 1.5% glucose for 24h at room temperature (12). At increased temperature significant decomposition occurred within 6h in CAPD fluid of unknown composition (38).

CEFUROXIME

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Cefuroxime 13mg/L	-			PDF containing 1.5% glucose (Dianeal 137), B PD effluent (composition not stated) pH 6.5	TR	-	Initial activity retained for 24h in all solutions stored at 20°C. 13.7-16.6% loss of initial activity in 6h in solutions stored at 37°C. No further loss evident at 24h.	17
Cefuroxime 50mg/L, 100mg/L, 150mg/L, 200mg/L	-			PDF containing 1.5% glucose (Dianeal), A	TR	B, HPLC	Cefuroxime was added to dialysate in plastic bags and instilled immediately into the peritoneal cavity. Concentrations measured in solutions left behind in the plastic bags varied from 44.3% to 1351% of the calculated initial concentration. Binding of cefuroxime to the dialysate container was not assessed. Temperature not stated.	2

Cefuroxime

One study has demonstrated that cefuroxime 13mg/L is stable in CAPD fluid containing 1.5% glucose for 24h at room temperature. At increased temperature a significant loss of activity occurred within 6h (17). A second study concludes that a uniform mixture of cefuroxime in CAPD fluid may be difficult to achieve. Binding of cefuroxime to the plastic dialysate container was proposed as a possible cause, but this was not investigated (2).

CEPHALOTHIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Cephalothin 2g/L	-			PDF containing 2.5% glucose, E	MG	V	No visible precipitation in 3h at room temperature.	8
Cephalothin (-)	-			PDF (composition not stated) and PD effluent (composition not stated)	-	*b*	*MIC's against a variety of test organisms in PDF and PD effluent similar to MIC's determined in Mueller-Hinton broth.*	26
Cephalothin sodium 250mg/L	LI			PDF containing 1.5% or 4.25% glucose (Dianeal 137), B	TR	HPLC	A 2L plastic bag of PDF containing cephalothin was emptied over 18min through a CAPD administration set containing a 0.22µm filter (Peridex CAPD Filter Set). Binding of cephalothin to the administration set was not significant. Binding of cephalothin to the dialysate container was not assessed. Temperature not stated.	25

Cephalothin

No studies have investigated the stability of cephalothin in CAPD fluids. Cephalothin 2g/L was physically compatible with peritoneal dialysis fluid containing 2.5% glucose for 3h at room temperature (8). Binding of cephalothin to an administration set containing an in-line 0.22µm filter was not significant (25). One study investigating the efficacy of intraperitoneal cephalothin found that the activity of cephalothin against a variety of bacterial species was not inhibited in CAPD fluid or peritoneal dialysis effluent (26).

Peritoneal dialysis fluid concentrates

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Cephalothin 100mg/L	-			PDF concentrate containing 50% glucose, D	MG	B	60% loss of initial activity in 24h. Temperature not stated.	20
Cephalothin (-)	-			PDF concentrate containing 30% or 50% glucose (composition not stated) pH 5.7 PDF concentrate containing 30% or 50% glucose (composition not stated) pH adjusted to 6.8	- -	B	Initial activity retained for 24h in all solutions. Temperature not stated.	27

Peritoneal dialysis fluid concentrates (continued)

Cephalothin sodium 2g/L	-			PDF concentrate containing 30% glucose, H	TR	B	Significant loss of activity occurred within 10min in PDF concentrate compared to normal saline (8 fold increase in MIC against E.coli). No further loss of activity was evident at 4h Temperature not stated.	9
Cephalothin sodium 2g/L	-	Gentamicin sulphate 100mg/L	SC	PDF concentrate containing 30% glucose, H	TR	B (B)	The activity of the antibiotic combination against E.coli after 4h in PDF concentrate was the same as its activity after 10min. The combined activity was similar to, but no greater than, the activity of either antibiotic alone. Temperature not stated.	9
Cephalothin sodium 2g/L	-	Heparin sodium 2500 units/L	RI	PDF concentrate containing 30% glucose, H	TR	B (-)	Cephalothin alone in PDF concentrate compared to normal saline showed significant loss of activity within 10min (8 fold increase in MIC against E.coli). No further loss of activity was evident at 10min or 4h when combined with heparin. Heparin not studied. Temperature not stated.	9
Cephalothin sodium 2g/L	-	Tobramycin sulphate 100mg/L	LI	PDF concentrate containing 30% glucose, H	TR	B (B)	The activity of the antibiotic combination against E.coli after 4h in PDF concentrate was the same as its activity after 10min. The combined activity was significantly greater than the activity of tobramycin alone, but no greater than the activity of cephalothin alone. Temperature not stated.	9
Cephalothin sodium 2g/L	-	Tobramycin sulphate 100mg/L Heparin sodium 2500 units/L	LI RI	PDF concentrate containing 30% glucose, H	TR	B (B) (-)	The activity of the antibiotic combination against E.coli was unaffected by the presence of heparin after 10min and 4h in PDF concentrate. The combined activity was significantly greater than the activity of tobramycin alone, but no greater than the activity of cephalothin alone. Heparin not studied. Temperature not stated.	9

Cephalothin

Information concerning the stability of cephalothin in PDF concentrates is conflicting. One study found that cephalothin 100mg/L was not stable for 24h in PDF concentrate containing 50% glucose, however the storage temperature is unknown (20). A second study concluded that cephalothin was stable for 24h in PDF concentrates containing 30% or 50% glucose, however the concentration tested and the storage temperature are unknown (27). A third study demonstrated that a significant loss of cephalothin activity occurs within 10min in PDF concentrate containing 30% glucose when compared to its activity in normal saline (9).

Cephalothin in combination

Only one study has attempted to investigate cephalothin in combination with other drugs in PDF concentrate (9). The initial activity of the cephalothin plus gentamicin combination and the cephalothin plus tobramycin combination was maintained for 4h in PDF concentrate containing 30% glucose. Physical compatibility was not commented on. [...continued next page]

Synergistic activity against E.coli was not demonstrated when cephalothin was combined with gentamicin or tobramycin, however these combinations may be synergistic against other bacterial species or provide broader activity against a variety of bacterial species.

Heparin had no effect on the activity of cephalothin, or on the combined activity of cephalothin plus tobramycin in PDF concentrate containing 30% glucose. The effect of the combinations on heparin activity is unknown. Physical compatibility was not commented on.

CIPROFLOXACIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Ciprofloxacin 2mg/L	MI			PDF containing 1.5% glucose (Dianeal), A PDF containing 1.5% glucose (Dianeal) pH adjusted to 7.4 PD effluent collected after a 6h i.p. dwell, G	TR TR	*b*	*MBC against P.aeruginosa 32-64 times greater in PDF than in buffered PDF and Mueller-Hinton broth. MBC against P.aeruginosa 8 times greater in PD effluent than in Mueller-Hinton broth.* *Time for >99.9% kill (ciprofloxacin 2mg/L) was 1h in PD effluent, 2h in Mueller-Hinton broth and 24h in buffered PDF at 37°C. Bactericidal activity was not demonstrated in 24h in PDF.*	3
Ciprofloxacin 0.25-16mg/L	MI			Mueller-Hinton agar reconstituted with PD effluent collected after an overnight dwell of PDF containing 2.5% glucose (composition not stated)		*b*	*The MIC of ciprofloxacin in Mueller-Hinton agar was not adversely affected by the addition of PD effluent when measured against coagulase-positive staphylococci. The addition of PD effluent raised the MIC of ciprofloxacin against coagulase-negative staphylococci in 66% of the isolates tested (n=50). **	49

Ciprofloxacin

No studies have investigated the stability of ciprofloxacin in CAPD fluids. Two studies have investigated the efficacy of intraperitoneal ciprofloxacin. CAPD fluid and peritoneal dialysis effluent significantly inhibited the activity of ciprofloxacin against P.aeruginosa (3). Peritoneal dialysis effluent inhibited the activity of ciprofloxacin against the majority of coagulase-negative staphylococci tested, however the MIC values obtained were within clinically achievable levels. Peritoneal dialysis effluent generally had no adverse effect on the activity of ciprofloxacin against coagulase-positive staphylococci (49).

* Coagulase-positive staphylococci includes S.aureus. Coagulase-negative staphylococci includes S.epidermidis.

CLINDAMYCIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Clindamycin 10mg/L	UP			PDF containing 4.25% glucose (Dianeal 137, PD 2), B, C	TR	B	Initial activity retained for 48h in 1L or 2L plastic bags containing dialysate at 25°C.	5
Clindamycin 10mg/L	UP	Heparin 500 units/L	-	PDF containing 4.25% glucose (Dianeal 137, PD 2), B, C	TR	B (-)	Initial activity of clindamycin retained for 48h in 1L or 2L plastic bags containing dialysate and heparin at 25°C. Heparin not studied.	5

Clindamycin

One study has demonstrated that clindamycin 10mg/L is stable in CAPD fluids containing 4.25% glucose for 48h at room temperature (5). A later study by the same investigators, (not tabulated), has examined the therapeutic implications of incomplete hydrolysis of clindamycin phosphate to its bioactive form in peritoneal dialysis fluids (11).

Clindamycin in combination

Clindamycin was stable for 48h at room temperature when combined with heparin in CAPD fluids containing 4.25% glucose. The effect of the combination on heparin activity is unknown. Physical compatibility was not commented on (5).

GENTAMICIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Gentamicin 10mg/L	SC			PDF containing 1.5% or 4.25% glucose (Dianeal 137), B	TR	B	At least 95% of initial activity retained for 24h in 1L plastic bags containing dialysate at 25°C.	10
Gentamicin sulphate 5mg/L and 8mg/L	SC			PDF containing 2.5% glucose (Dianeal), E	TR	RIA, EMIT	Stable for 24h at 23°C.	4
Gentamicin (-)	-			PDF (composition not stated) and PD effluent (composition not stated)	-	*b*	*MIC against P.aeruginosa four times greater in PD effluent than in PDF and Mueller-Hinton broth.*	26
Gentamicin sulphate 30mg/L	SC			PDF containing 1.5% glucose (Dianeal 137), B	TR	HPLC	A 2L plastic bag of PDF containing gentamicin was emptied over 18min through a CAPD administration set containing a 0.22µm filter (Peridex CAPD Filter Set). 7.5% of the gentamicin was bound to the administration set. Binding of gentamicin to the dialysate container was not assessed. Temperature not stated.	25
Gentamicin sulphate 30mg/L	SC			PDF containing 4.25% glucose (Dianeal 137), B	TR	HPLC	A 2L plastic bag of PDF containing gentamicin was emptied over 18min through a CAPD administration set containing a 0.22µm filter (Peridex CAPD Filter Set). 25% of the gentamicin was bound to the administration set. Binding of gentamicin to the dialysate container was not assessed. Temperature not stated.	25
Gentamicin 8mg/L	-	Azlocillin 500mg/L	-	PDF containing 1.5% glucose (Dianeal), A, pH adjusted to 7.2	TR	EMIT (HPLC)	Gentamicin stable for 6h in 1L plastic bags containing dialysate and azlocillin at 37°C. >10% loss of initial concentration occurred within 8h. Initial concentration of azlocillin maintained for 8h.	47
Gentamicin sulphate (-)	SC	Cefamandole nafate 125mg/L	LI	PD effluent collected after a 6h i.p. dwell of PDF containing 1.5% glucose (Dianeal), F		*b* *(b)*	*Antibiotic combination in PD effluent at 37°C more rapidly lethal than either drug alone against E.coli, P.aeruginosa and S.aureus.*	6

CAPD fluids (continued)

Gentamicin sulphate (-)	SC	Cefazolin sodium 125mg/L	LI	PD effluent collected after a 6h i.p. dwell of PDF containing 1.5% glucose (Dianeal), F		*b* *(b)*	*Antibiotic combination in PD effluent at 37°C more rapidly lethal than either drug alone against E.coli, P.aeruginosa and S.aureus.*	6
Gentamicin sulphate 8mg/L	-	Cefazolin 75mg/L Heparin 1000units/L	- -	PDF containing 1.5% glucose (composition not stated)	-	V, FIA (HPLC) (-)	Gentamicin and cefazolin stable for 48h at 4°C, 26°C and 37°C in 1L plastic bags containing dialysate and heparin. No visible precipitation. Heparin not studied.	34
Gentamicin sulphate 8mg/L	-	Cefazolin 150mg/L Heparin 1000units/L	- -	PDF containing 1.5% glucose (composition not stated)	-	V, FIA (HPLC) (-)	Gentamicin and cefazolin stable for 48h at 4°C, 26°C and 37°C in 1L plastic bags containing dialysate and heparin. No visible precipitation. Heparin not studied.	34
Gentamicin sulphate (-)	SC	Cefoxitin sodium 125mg/L	MSD	PD effluent collected after a 6h i.p. dwell of PDF containing 1.5% glucose (Dianeal), F		*b* *(b)*	*Antibiotic combination in PD effluent at 37°C more rapidly lethal than either drug alone against E.coli, P.aeruginosa and S.aureus.*	6
Gentamicin sulphate 8mg/L	-	Heparin 1000 units/L	-	PDF containing 1.5% glucose (composition not stated)	-	V, FIA (-)	Gentamicin stable for 48h at 4°C, 26°C and 37°C in 1L plastic bags containing dialysate and heparin. No visible precipitation. Heparin not studied.	34
Gentamicin 10mg/L	-	Heparin 1000units/L	-	PDF containing 1.5% glucose (Dianeal), A	TR	V, B (S, CT)	Solutions were prepared in two ways: (i) one drug added to a dilute solution of the other in PDF (ii) two drugs combined in concentrated solution to produce a precipitation reaction, then added to PDF The activity of gentamicin after 4-6h in both solutions was unaffected by the presence of heparin. The UV absorbance of heparin after 4-6h in both solutions was unaffected by the presence of gentamicin. In the absence of a precipitate the anticoagulant activity of heparin after 4-6h was unaffected by the presence of gentamicin . The anticoagulant activity of heparin was significantly reduced in solutions which had formed a precipitate, even though the precipitate redissolved. Temperature not stated.	18 19

Gentamicin

Two studies have demonstrated that gentamicin 5-10mg/L is stable in CAPD fluids of various glucose concentrations for 24h at room temperature (4, 10). Administration of CAPD fluid containing gentamicin through an administration set containing an in-line 0.22µm filter may result in significant binding to the administration set (25). One study investigating the efficacy of intraperitoneal gentamicin found that the activity of gentamicin against P.aeruginosa was significantly inhibited in peritoneal dialysis effluent (26).

Gentamicin in combination

Gentamicin, cefazolin and heparin were physically compatible when combined in CAPD fluid containing 1.5% glucose. Both antibiotics were stable for 48h at temperatures up to 37°C. The effect of the combination on heparin activity is unknown (34).

Gentamicin and azlocillin were stable for 6h at 37°C when combined in pH adjusted CAPD fluid. Significant decomposition of gentamicin occurred within 8h. Physical compatibility was not commented on (47).

Synergistic activity against E.coli, P.aeruginosa and S.aureus was demonstrated when gentamicin was combined with cefamandole, cefazolin or cefoxitin in peritoneal dialysis effluent. This does not imply synergism against other bacterial species or exclude the possibility of significant inactivation of one antibiotic by the other (6).

Gentamicin and heparin are potentially physically incompatible. A precipitate may be avoided by combining the two drugs in dilute solution. Gentamicin was stable for 48h at temperatures up to 37°C when combined with heparin in CAPD fluid containing 1.5% glucose. Heparin activity was maintained for 4-6h provided a precipitate did not form (34, 18, 19).

Peritoneal dialysis fluid concentrates

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Gentamicin sulphate 100mg/L	SC			PDF concentrate containing 30% glucose, H	TR	B	Significant loss of activity occurred within 10min in PDF concentrate compared to normal saline (four-fold increase in MIC against E.coli). No further loss of activity was evident at 4h. Temperature not stated.	9
Gentamicin sulphate 160mg/L	SC			PDF concentrate containing 30% glucose, H	TR	EMIT	Time for 10% decomposition calculated as 11 days at 23°C.	4
Gentamicin sulphate 160mg/L	SC			PDF concentrate containing 30% glucose, H	TR	RIA	Time for 10% decomposition calculated as 2.7 days at 23°C.	4
Gentamicin sulphate 3mg/L and 10mg/L	SC			PDF concentrate containing 50% glucose, D	MG	B	11-19% loss of initial activity in 7h and 24-49% loss of initial activity in 24h at room temperature. Loss of activity was greater at the lower gentamicin concentration.	1

Peritoneal dialysis fluid concentrates (continued)

Gentamicin sulphate 160mg/L	SC			PDF concentrate containing 50% glucose, H	TR	EMIT	10% decomposition in 41.4h at 23°C.	4
Gentamicin sulphate 160mg/L	SC			PDF concentrate containing 50% glucose, H	TR	RIA	10% decomposition in 37.6h at 23°C.	4
Gentamicin 200mg/L	-			PDF concentrate containing 50% glucose, D	MG	B	20% loss of initial activity in 24h. Temperature not stated.	20
Gentamicin (-)	-			PDF concentrate containing 30% or 50% glucose (composition not stated) pH 5.7 PDF concentrate containing 30% or 50% glucose (composition not stated) pH adjusted to 6.8	- -	B	25% loss of initial activity in 6h and 30% loss of initial activity in 24h in all solutions. Temperature not stated.	27
Gentamicin sulphate 100mg/L	SC	Ampicillin sodium 2.5g/L	BR	PDF concentrate containing 30% glucose, H	TR	B (B)	The activity of the antibiotic combination against E.coli after 4h in PDF concentrate was the same as its activity after 10min. The combined activity was significantly greater than the activity of either antibiotic alone. Temperature not stated.	9
Gentamicin sulphate 100mg/L	SC	Ampicillin sodium 2.5g/L Heparin sodium 2500 units/L	BR RI	PDF concentrate containing 30% glucose, H	TR	B (B) (-)	The activity of the antibiotic combination against E.coli was significantly inhibited after 10min in PDF concentrate containing heparin. No further loss of activity was evident at 4h. Heparin not studied. Temperature not stated.	9
Gentamicin sulphate 100mg/L	SC	Cephalothin sodium 2g/L	-	PDF concentrate containing 30% glucose, H	TR	B (B)	The activity of the antibiotic combination against E.coli after 4h in PDF concentrate was the same as its activity after 10min. The combined activity was similar to, but no greater than, the activity of either antibiotic alone. Temperature not stated.	9

Peritoneal dialysis fluid concentrates (continued)

Gentamicin sulphate 100mg/L	SC	Carbenicillin disodium 2g/L	RR	PDF concentrate containing 30% glucose, H	TR	B (B)	The activity of the antibiotic combination against E.coli after 4h in PDF concentrate was the same as its activity after 10min. The combined activity was similar to, but no greater than, the activity of either antibiotic alone. Temperature not stated.	9
Gentamicin sulphate 100mg/L	SC	Carbenicillin disodium 2g/L Heparin sodium 2500 units/L	RR RI	PDF concentrate containing 30% glucose, H	TR	B (B) (-)	The activity of the antibiotic combination against E.coli was unaffected by the presence of heparin after 10min and 4h in PDF concentrate. The combined activity was similar to, but no greater than, the activity of either antibiotic alone. Heparin not studied. Temperature not stated.	9
Gentamicin sulphate 100mg/L	SC	Heparin sodium 2500 units/L	RI	PDF concentrate containing 30% glucose, H	TR	B (-)	Gentamicin alone in PDF concentrate compared to normal saline showed significant loss of activity within 10min (four-fold increase in MIC against E.coli). No further loss of activity was evident at 10min or 4h when combined with heparin. Heparin not studied. Temperature not stated.	9
Gentamicin sulphate 100mg/L	SC	Penicillin G potassium 500 000 units/L	PD	PDF concentrate containing 30% glucose, H	TR	B (B)	The activity of the antibiotic combination against S.aureus after 4h in PDF concentrate was the same as its activity after 10min. The combined activity was significantly greater than the activity of penicillin G alone. Temperature not stated.	9
Gentamicin sulphate 100mg/L	SC	Penicillin G potassium 500 000 units/L Heparin sodium 2500 units/L	PD RI	PDF concentrate containing 30% glucose, H	TR	B (B) (-)	The activity of the antibiotic combination against S.aureus was unaffected by the presence of heparin after 10min and 4h in PDF concentrate. The combined activity was significantly greater than the activity of penicillin G alone. Heparin not studied. Temperature not stated	9
Gentamicin sulphate 100mg/L	SC	Vancomycin hydrochloride 750mg/L	LI	PDF concentrate containing 30% glucose, H	TR	B (B)	The activity of the antibiotic combination against S.aureus after 4h in PDF concentrate was the same as its activity after 10min. The combined activity was similar to, but no greater than, the activity of vancomycin alone. Temperature not stated.	9

Peritoneal dialysis fluid concentrates (continued)

Gentamicin sulphate 100mg/L	SC	Vancomycin hydrochloride 750mg/L	LI	PDF concentrate containing 30% glucose, H	TR	B (B)	The activity of the antibiotic combination against S.aureus was unaffected by the presence of heparin after 10min and 4h in PDF concentrate. The combined activity was similar to, but no greater than, the activity of vancomycin alone. Heparin not studied.	9
		Heparin sodium 2500 units/L	RI			(-)	Temperature not stated.	

Gentamicin

Information concerning the stability of gentamicin in PDF concentrates is conflicting. One study, using two direct analytical techniques, demonstrated that gentamicin was stable for 24h at room temperature in PDF concentrates containing 30% or 50% glucose (4). Three studies using bioassay as a measure of stability have demonstrated that a significant loss of activity occurs within 24h (1, 20, 27), and probably occurs within 7h (1, 27). One study demonstrated that a significant loss of gentamicin activity occurs within 10min in PDF concentrate when compared to its activity in normal saline (9).

Gentamicin in combination

Only one study has attempted to investigate gentamicin in combination with other drugs in PDF concentrate (9). This study measures the activity of antibiotics and antibiotic combinations against one of two test organisms, E.coli and S.aureus. The synergism or lack of synergism of antibiotic combinations compared to either drug alone is demonstrated. However, because both test organisms are sensitive, to some extent, to all of the antibiotics tested, any synergism demonstrated by an antibiotic combination does not exclude the possibility of significant inactivation of one or both antibiotics. The inactivation of aminoglycosides by beta-lactam antibiotics in parenteral admixtures is well documented (46).
Therefore, interpretation of the results of this study should take into consideration three factors:

(i) synergism of an antibiotic combination does not exclude the possibility of significant inactivation of one or both antibiotics,
(ii) synergism of an antibiotic combination against the stated test organism does not imply synergism against other bacterial species,
(iii) an antibiotic combination which is not synergistic against the stated test organism may be synergistic against other bacterial species or provide broader activity against a variety of bacterial species.

The initial activity of each antibiotic combination tested was maintained for 4h in PDF concentrate containing 30% glucose. Synergistic activity against E.coli was demonstrated when gentamicin was combined with ampicillin, but not when combined with cephalothin or carbenicillin. Synergistic activity against S.aureus was demonstrated when gentamicin was combined with penicillin G, but not when combined with vancomycin. Physical compatibility was not commented on.

Heparin inhibited the combined activity of gentamicin plus ampicillin after only 10min in PDF concentrate containing 30% glucose. Heparin had no effect on the activity of gentamicin alone, or on the combined activity of gentamicin plus carbenicillin, gentamicin plus penicillin G, or gentamicin plus vancomycin. The effect of the combinations on heparin activity is unknown. Physical compatibility was not commented on.

IMIPENEM

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Imipenem 0.01mg/L and 0.1mg/L	MSD			PD effluent (composition not stated)		*b*	*MIC and MBC against S.aureus at 37°C was the same in PD effluent as in Mueller-Hinton broth.*	21

Imipenem

No studies have investigated the stability of imipenem in CAPD fluids. One study investigating the efficacy of intraperitoneal imipenem found that the activity of imipenem against S.aureus was not inhibited in peritoneal dialysis effluent (21).

KANAMYCIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Kanamycin (-)	-			PDF containing 1.5% glucose (Formular 1) (composition not stated)	BS	B	13% loss of activity in 6h and 29% loss of activity in 24h at 18°C.	29

Kanamycin

One study has investigated the stability of kanamycin in peritoneal dialysis fluid containing 1.5% glucose and it was conducted prior to the introduction of CAPD. The test concentration and details of the solution composition are unknown. A significant loss of kanamycin activity occurred within 6h at 18°C (29).

MEZLOCILLIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Mezlocillin 200mg/L	MI			PDF containing 4.25% glucose (Dianeal 137, PD2), B, C	TR	B	Initial activity retained for 48h in 1L or 2L plastic bags containing dialysate at 25°C.	5
Mezlocillin 200mg/L	MI	Heparin 500 units/L	-	PDF containing 4.25% glucose (Dianeal 137, PD2), B, C	TR	B (-)	Initial activity of mezlocillin retained for 48h in 1L or 2L plastic bags containing dialysate and heparin at 25°C. Heparin not studied.	5

Mezlocillin

One study has demonstrated that mezlocillin 200mg/L is stable in CAPD fluids containing 4.25% glucose for 48h at room temperature (5).

Mezlocillin in combination

Mezlocillin was stable for 48h at room temperature when combined with heparin in CAPD fluids containing 4.25% glucose. The effect of the combination on heparin activity is unknown. Physical compatibility was not commented on (5).

MOXALACTAM

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Moxalactam 8mg/L	-			PDF containing 1.5% glucose (Dianeal 137), B	TR	B	Initial activity retained for 24h at room temperature.	12
Moxalactam disodium 30mg/L	LI			PDF containing 1.5% glucose (Dianeal), A	TR	HPLC	Stable in solutions stored for 6h at 25°C then heated to 37°C for 30min.	50
Moxalactam 2g/L	-			PDF containing 2.5% glucose, E	MG	V	No visible precipitation in 3h at room temperature.	8
Moxalactam disodium 30mg/L	LI	Cefazolin 50mg/L	-	PDF containing 1.5% glucose (Dianeal), A	TR	HPLC (-)	Moxalactam stable in solutions stored for 6h at 25°C then heated to 37°C for 30min. Cefazolin not studied.	50
Moxalactam disodium 30mg/L	LI	Cefazolin 50mg/L Vancomycin 25mg/L	- -	PDF containing 1.5% glucose (Dianeal), A	TR	HPLC (-) (-)	Moxalactam stable in solutions stored for 6h at 25°C then heated to 37°C for 30min. Cefazolin and vancomycin not studied.	50

Moxalactam

Two studies have investigated moxalactam stability in CAPD fluids containing 1.5% glucose. Moxalactam 8mg/L was stable for 24h at room temperature (12), and moxalactam 30mg/L was stable after storage for 6h at room temperature followed by heating to 37°C for 30min (50). Moxalactam 2g/L was physically compatible with peritoneal dialysis fluid containing 2.5% glucose for 3h at room temperature (8).

Moxalactam in combination

Moxalactam was stable after storage for 6h at room temperature followed by heating to 37°C for 30min when combined with cefazolin, and cefazolin plus vancomycin, in CAPD fluid containing 1.5% glucose. The effect of the combinations on cefazolin and vancomycin stability is unknown. Physical compatibility was not commented on (50).

MOXALACTAM (continued)

Peritoneal dialysis fluid concentrates

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Moxalactam disodium 2g/L	-			PDF concentrate containing 30% glucose, H	TR	B	Significant loss of activity occurred within 10min in PDF concentrate compared to normal saline (32 fold increase in MIC against E.coli). No further loss of activity was evident at 4h. Temperature not stated.	9
Moxalactam disodium 2g/L	-	Heparin sodium 2500 units/L	RI	PDF concentrate containing 30% glucose, H	TR	B (-)	Moxalactam alone in PDF concentrate compared to normal saline showed significant loss of activity within 10min (32 fold increase in MIC against E.coli) No further loss of activity was evident at 10min or 4h when combined with heparin. Heparin not studied. Temperature not stated.	9

Moxalactam

One study has demonstrated that a significant loss of moxalactam activity occurs within 10min in PDF concentrate containing 30% glucose when compared to its activity in normal saline, (9).

Moxalactam in combination

Heparin had no effect on the activity of moxalactam in PDF concentrate containing 30% glucose. The effect of the combination on heparin activity is unknown. Physical compatibility was not commented on (9).

NAFCILLIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Nafcillin 100mg/L	WY			PDF containing 4.25% glucose (Dianeal 137, PD2), B, C	TR	B	Initial activity retained for 24h in 1L or 2L plastic bags containing dialysate at 25°C. 15% loss of initial activity in 48h at 25°C.	5
Nafcillin 100mg/L	WY			PDF containing 1.5% or 4.25% glucose (Dianeal 137), B	TR	B	At least 95% of initial activity retained for 24h in 1L plastic bags containing dialysate at 25°C.	10
Nafcillin 100mg/L	WY	Heparin 500 units/L	-	PDF containing 4.25% glucose (Dianeal 137, PD2), B, C	TR	B (-)	Initial activity of nafcillin retained for 24h in 1L or 2L plastic bags containing dialysate and heparin at 25°C. 15% loss of initial activity in 48h at 25°C. Heparin not studied.	5

Nafcillin

Two studies have demonstrated that nafcillin 100mg/L is stable in CAPD fluids of various glucose concentrations for 24h at room temperature (5, 10). A significant loss of activity occurred within 48h at room temperature (5).

Nafcillin in combination

Nafcillin was stable for 24h at room temperature when combined with heparin in CAPD fluids containing 4.25% glucose, but was not stable for 48h. The effect of the combination on heparin activity is unknown. Physical compatibility was not commented on (5).

Peritoneal dialysis fluid concentrates

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Nafcillin 200mg/L	-			PDF concentrate containing 50% glucose, D	MG	B	Approximately 40% loss of initial activity in 24h. Temperature not stated.	20
Nafcillin (-)	-			PDF concentrate containing 30% or 50% glucose (composition not stated) pH 5.7 PDF concentrate containing 30% or 50% glucose (composition not stated) pH adjusted to 6.8	- -	B, V	Precipitation observed within 6h in solutions at pH 5.7 Up to 75% loss of initial activity in 24h in all solutions. This loss was greater and faster in solutions of high glucose concentration and high pH. Temperature not stated.	27

Nafcillin

Two studies have investigated nafcillin stability in PDF concentrates. Nafcillin was not stable for 24h in PDF concentrates containing 30% or 50% glucose (20, 27), and physical incompatibility was observed within 6h (27). The storage temperature was not specified in either study.

NETILMICIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Netilmicin 10mg/L	SC			PDF containing 1.5% glucose (Dianeal), A PDF containing 1.5% glucose (Dianeal) pH adjusted to 7.4 PD effluent collected after a 6h i.p. dwell, G	TR TR	*b*	*MBC against P.aeruginosa 2-4 times greater in PDF than in buffered PDF and Mueller-Hinton broth. MBC against P.aeruginosa 4-8 times greater in PD effluent than in Mueller-Hinton broth.* *Time for >99.9% kill (netilmicin 10mg/L) was 1h in Mueller-Hinton broth, 2h in PD effluent, 6h in buffered PDF and 24h in PDF at 37°C.*	*3*
Netilmicin 7.5mg/L	-	Azlocillin 500mg/L	-	PDF containing 1.5% glucose (Dianeal), A, pH adjusted to 7.2	TR	EMIT (HPLC)	Netilmicin stable for 6h in 1L plastic bags containing dialysate and azlocillin at 37°C. >10% loss of initial concentration occurred within 8h. Initial concentration of azlocillin maintained for 8h.	47

Netilmicin

No studies have investigated the stability of netilmicin alone in CAPD fluids. One study investigating the efficacy of intraperitoneal netilmicin found that the activity of netilmicin against P.aeruginosa was significantly inhibited in CAPD fluid and peritoneal dialysis effluent. This was demonstrated in peritoneal dialysis fluid and effluent of relatively low glucose concentration (≤1.5%), (3).

Netilmicin in combination

Netilmicin and azlocillin were stable for 6h at 37°C when combined in pH adjusted CAPD fluid. Significant decomposition of netilmicin occurred within 8h. Physical compatibility was not commented on (47).

Peritoneal dialysis fluid concentrates

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Netilmicin sulphate 3mg/L and 10mg/L	SC			PDF concentrate containing 50% glucose, D	MG	B	11-19% loss of initial activity in 7h and 24-49% loss of initial activity in 24h at room temperature. Loss of activity was greater at the lower netilmicin concentration.	1

Netilmicin

One study has demonstrated that netilmicin was not stable for 7h at room temperature in PDF concentrate containing 50% glucose. The netilmicin concentrations tested were well below those used in the treatment of peritonitis (1).

OXACILLIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Oxacillin 0.25-16mg/L	BR			Mueller-Hinton agar reconstituted with PD effluent collected after an overnight dwell of PDF containing 2.5% glucose (composition not stated)		*b*	*The MIC of oxacillin in Mueller-Hinton agar was not adversely affected by the addition of PD effluent when measured against coagulase-positive and coagulase-negative staphylococci.* *	49

Oxacillin

No studies have investigated the stability of oxacillin in CAPD fluids. One study investigating the efficacy of intraperitoneal oxacillin found that the activity of oxacillin against staphylococci was not inhibited by peritoneal dialysis effluent (49).

* Coagulase-positive staphylococci includes S.aureus. Coagulase-negative staphylococci includes S.epidermidis.

Peritoneal dialysis fluid concentrates

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Oxacillin (-)	-			PDF concentrate containing 30% or 50% glucose (composition not stated) pH 5.7 PDF concentrate containing 30% or 50% glucose (composition not stated) pH adjusted to 6.8	- -	B	Up to 75% loss of initial activity in 24h in all solutions. This loss was greater and faster in solutions of high glucose concentration and high pH. Temperature not stated.	27

Oxacillin

Only one study has investigated oxacillin stability in PDF concentrates and few details are provided. Oxacillin was not stable for 24h in PDF concentrates containing 30% or 50% glucose, however the concentration tested and the storage temperature are unknown (27).

PENICILLIN G

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Penicillin G 6mg/L	PF			PDF containing 1.5% or 4.25% glucose (Dianeal 137), B	TR	B	25% loss of initial activity in 24h in 1L plastic bags containing dialysate at at 25°C.	10

Penicillin G

One study has demonstrated that penicillin G 6mg/L is not stable for 24h at room temperature in CAPD fluids of various glucose concentrations (10).

Peritoneal dialysis fluid concentrates

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Penicillin G potassium 500 000 units/L	PD			PDF concentrate containing 30% glucose, H	TR	B	Significant loss of activity occurred within 10min in PDF concentrate compared to normal saline (64 fold increase in MIC against S.aureus). No further loss of activity was evident at 4h. Temperature not stated.	9
Penicillin G 100mg/L	-			PDF concentrate containing 50% glucose, D	MG	B	60% loss of initial activity in 24h. Temperature not stated.	20
Penicillin G potassium 500 000 units/L	PD	Gentamicin sulphate 100mg/L	SC	PDF concentrate containing 30% glucose, H	TR	B (B)	The activity of the antibiotic combination against S.aureus after 4h in PDF concentrate was the same as its activity after 10min. The combined activity was significantly greater than the activity of penicillin G alone. Temperature not stated.	9
Penicillin G potassium 500 000 units/L	PD	Gentamicin sulphate 100mg/L Heparin sodium 2500 units.L	SC RI	PDF concentrate containing 30% glucose, H	TR	B (B) (-)	The activity of the antibiotic combination against S.aureus was unaffected by the presence of heparin after 10min and 4h in PDF concentrate. The combined activity was significantly greater than the activity of penicillin G alone. Heparin not studied. Temperature not stated.	9
Penicillin G potassium 500 000 units/L	PD	Heparin sodium 2500 units/L	RI	PDF concentrate containing 30% glucose, H	TR	B (-)	Penicillin G alone in PDF concentrate compared to normal saline showed significant loss of activity within 10min (64 fold increase in MIC against S.aureus). No further loss of activity was evident at 10min or 4h when combined with heparin. Heparin not studied. Temperature not stated.	9

Penicillin G

Two studies have investigated penicillin G stability in PDF concentrates. One study demonstrated that penicillin G 100mg/L was not stable for 24h in PDF concentrate containing 50% glucose, however the storage temperature is unknown (20). A second study demonstrated that a significant loss of penicillin G activity occurs within 10min in PDF concentrate when compared to its activity in normal saline (9).

Penicillin G in combination

Only one study has attempted to investigate penicillin G in combination with other drugs in PDF concentrate (9). The initial activity of the penicillin G plus gentamicin combination was maintained for 4h in PDF concentrate containing 30% glucose. Synergistic activity against S.aureus was demonstrated when penicillin G was combined with gentamicin. This does not imply synergism against other bacterial species or exclude the possibility of significant inactivation of one or both antibiotics. Physical compatibility was not commented on.

Heparin had no effect on the activity of penicillin G, or on the combined activity of penicillin G plus gentamicin in PDF concentrate containing 30% glucose. The effect of the combinations on heparin activity is unknown. Physical compatibility was not commented on.

PIPERACILLIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Piperacillin 200mg/L	LE			PDF containing 4.25% glucose (Dianeal 137, PD2), B, C	TR	B	Initial activity retained for 48h in 1L or 2L plastic bags containing dialysate at 25°C.	5
Piperacillin 200mg/L	LE			PDF containing 1.5% glucose (Dianeal), A PDF containing 1.5% glucose (Dianeal) pH adjusted to 7.4 PD effluent collected after a 6h i.p. dwell, G	TR TR	*b*	*MBC against P.aeruginosa 4-8 times greater in buffered PDF than in Mueller-Hinton broth. MBC against P.aeruginosa more than 16 times greater in PDF and PD effluent than in Mueller-Hinton broth.* *Time for >99.9% kill (piperacillin 200mg/L) was 6h in Mueller-Hinton broth at 37°C. Bactericidal activity was not demonstrated in 24h in PDF, buffered PDF or PD effluent.*	3
Piperacillin 200mg/L	LE	Heparin 500 units/L	-	PDF containing 4.25% glucose (Dianeal 137, PD2), B, C	TR	B (-)	Initial activity of piperacillin retained for 48h in 1L or 2L plastic bags containing dialysate and heparin at 25°C. Heparin not studied.	5

Piperacillin

One study has demonstrated that piperacillin 200mg/L is stable in CAPD fluids containing 4.25% glucose for 48h at room temperature (5). Another study investigating the efficacy of intraperitoneal piperacillin found that the activity of piperacillin against P.aeruginosa was significantly inhibited in CAPD fluid and peritoneal dialysis effluent (3).

Piperacillin in combination

Piperacillin was stable for 48h at room temperature when combined with heparin in CAPD fluids containing 4.25% glucose. The effect of the combination on heparin activity is unknown. Physical compatibility was not commented on (5).

SISOMICIN

Peritoneal dialysis fluid concentrates

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Sisomicin sulphate 3mg/L and 10mg/L	SC			PDF concentrate containing 50% glucose, D	MG	B	11-19% loss of initial activity in 7h and 24-49% loss of initial activity in 24h at room temperature. Loss of activity was greater at the lower sisomicin concentration.	1

Sisomicin

One study has demonstrated that sisomicin was not stable for 7h at room temperature in PDF concentrate containing 50% glucose. The sisomicin concentrations tested were well below those used in the treatment of peritonitis (1).

TEICOPLANIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Teicoplanin 0.09-6mg/L	ML			Mueller-Hinton agar reconstituted with PD effluent collected after an overnight dwell of PDF containing 2.5% glucose (composition not stated)		*b*	*The MIC of teicoplanin in Mueller-Hinton agar was not adversely affected by the addition of PD effluent when measured against coagulase-positive staphylococci and oxacillin resistant coagulase-negative staphylococci. The addition of PD effluent raised the MIC of teicoplanin against oxacillin sensitive coagulase-negative staphylococci in 50% of the isolates tested (n=10).**	49

Teicoplanin

No studies have investigated the stability of teicoplanin in CAPD fluids. One study investigating the efficacy of intraperitoneal teicoplanin found that the activity of teicoplanin against staphylococci was generally not adversely affected by peritoneal dialysis effluent. Peritoneal dialysis effluent did inhibit the activity of teicoplanin against some oxacillin sensitive coagulase-negative staphylococci, however the number of isolates in this test group was small and the MIC values obtained were within clinically achievable levels (49).

* Coagulase-positive staphylococci includes S.aureus. Coagulase-negative staphylococci includes S.epidermidis.

TICARCILLIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Ticarcillin 200mg/L	BE			PDF containing 1.5% or 4.25% glucose (Dianeal 137), B	TR	B	At least 95% of initial activity retained for 24h in 1L plastic bags containing dialysate at 25°C.	10

Ticarcillin

One study has demonstrated that ticarcillin 200mg/L is stable in CAPD fluids of various glucose concentrations for 24h at room temperature (10).

TOBRAMYCIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Tobramycin sulphate 5mg/L and 8mg/L	LI			PDF containing 2.5% glucose (Dianeal), E	TR	RIA, EMIT	Stable for 24h at 23 deg C.	4
Tobramycin 10mg/L	LI			PDF containing 4.25% glucose (Dianeal 137, PD 2), B, C	TR	B	Initial activity retained for 48h in 1L or 2L plastic bags containing dialysate at 25°C.	5
Tobramycin 65mg/L	LI			PDF containing 4.25% glucose (Dianeal 137), B	TR	B	12% loss of initial activity in 24h in 1L or 2L plastic bags containing dialysate at 35°C.	5
Tobramycin 8mg/L	LI			PDF containing 1.5 % glucose (Dianeal), A PDF containing 1.5% glucose (Dianeal) pH adjusted to 7.4 PD effluent collected after a 6h i.p. dwell, G	TR TR	*b*	*MBC against P.aeruginosa 8-16 times greater in PDF and PD effluent than in buffered PDF and Mueller-Hinton broth.* *Time for >99.9% kill (tobramycin 8mg/L) was 1h in Mueller-Hinton broth, 2h in PD effluent, 6h in buffered PDF and 24 h in PDF at 37°C.*	3
Tobramycin 0.1mg/L	LI			PD effluent (composition not stated)		*b*	*Bactericidal activity against S.aureus at 37°C was reduced by 90% when PD effluent was used as the growth medium instead of Mueller-Hinton broth.*	21

CAPD fluids (continued)

Tobramycin (-)	-			PDF (composition not stated) and PD effluent (composition not stated)	-	*b*	*MIC against P.aeruginosa four times greater in PD effluent than in PDF and Mueller-Hinton broth.*	26
Tobramycin sulphate (-)	LI	Cefamandole nafate 125mg/L	LI	PD effluent collected after a 6h i.p. dwell of PDF containing 1.5% glucose (Dianeal), F		*b (b)*	*Antibiotic combination in PD effluent at 37°C more rapidly lethal than either drug alone against E.coli, P.aeruginosa and S.aureus.*	6
Tobramycin sulphate (-)	LI	Cefazolin sodium 125mg/L	LI	PD effluent collected after a 6h i.p. dwell of PDF containing 1.5% glucose (Dianeal), F		*b (b)*	*Antibiotic combination in PD effluent at 37°C more rapidly lethal than either drug alone against E.coli, P.aeruginosa and S.aureus.*	6
Tobramycin sulphate (-)	LI	Cefoxitin sodium 125mg/L	MSD	PD effluent collected after a 6h i.p. dwell of PDF containing 1.5% glucose (Dianeal), F		*b (b)*	*Antibiotic combination in PD effluent at 37°C more rapidly lethal than either drug alone against E.coli, P.aeruginosa and S.aureus.*	6
Tobramycin 65mg/L	LI	Cefapirin 500mg/L	BR	PDF containing 4.25% glucose (Dianeal 137), B	TR	B (B)	Initial activity of each antibiotic retained for 24h in 1L or 2L plastic bags containing dialysate at 25°C.	5
Tobramycin 65mg/L	LI	Cefapirin 500mg/L	BR	PDF containing 4.25% glucose (Dianeal 137), B	TR	B (B)	Tobramycin lost 12% of initial activity and cefapirin lost 16% of initial activity within 24h when combined in 1L or 2L plastic bags containing dialysate at 35°C.	5
Tobramycin 10mg/L	LI	Heparin 500 units/L	-	PDF containing 4.25% glucose (Dianeal 137, PD 2), B, C	TR	B (-)	Initial activity of tobramycin retained for 48h in 1L or 2L plastic bags containing dialysate and heparin at 25°C. Heparin not studied.	5

Tobramycin

Two studies have demonstrated that tobramycin 5-10mg/L is stable in CAPD fluids of various glucose concentrations for 24h at room temperature (4, 5). At increased temperature, tobramycin 65mg/L was not stable for 24h (5). Three studies have investigated the efficacy of intraperitoneal tobramycin. Peritoneal dialysis effluent significantly inhibited the activity of tobramycin against P.aeruginosa (3, 26), and S.aureus (21).

Tobramycin in combination

Tobramycin and cefapirin were stable for 24h at room temperature when combined in CAPD fluid containing 4.25% glucose. At increased temperature, a significant loss of activity of each drug occurred within 24h (5).

Synergistic activity against E.coli, P.aeruginosa and S.aureus was demonstrated when tobramycin was combined with cefamandole, cefazolin or cefoxitin in peritoneal dialysis effluent. This does not imply synergism against other bacterial species or exclude the possibility of significant inactivation of one antibiotic by the other (6).

Tobramycin was stable for 48h at room temperature when combined with heparin in CAPD fluids containing 4.25% glucose. The effect of the combination on heparin activity is unknown. Physical compatibility was not commented on (5).

TOBRAMYCIN (continued)

Peritoneal dialysis fluid concentrates

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Tobramycin sulphate 100mg/L	LI			PDF concentrate containing 30% glucose, H	TR	B	Significant loss of activity occurred within 10min in PDF concentrate compared to normal saline (four-fold increase in MIC against E.coli). No further loss of activity was evident at 4h. Temperature not stated.	9
Tobramycin sulphate 160mg/L	LI			PDF concentrate containing 30% glucose, H	TR	EMIT	Time for 10% decomposition calculated as 2.1 days at 23°C.	4
Tobramycin sulphate 160mg/L	LI			PDF concentrate containing 30% glucose, H	TR	RIA	10% decomposition in 14.8h at 23°C.	4
Tobramycin base 3mg/L and 10mg/L	LI			PDF concentrate containing 50% glucose, D	MG	B	34-48% loss of initial activity in 7h and 70-85% loss of initial activity in 24h at room temperature. Loss of activity was greater at the lower tobramycin concentration.	1
Tobramycin sulphate 160mg/L	LI			PDF concentrate containing 50% glucose, H	TR	EMIT	10% decomposition in 21.1h at 23°C.	4
Tobramycin sulphate 160mg/L	LI			PDF concentrate containing 50% glucose, H	TR	RIA	10% decomposition in 9.4h at 23°C.	4
Tobramycin (-)	-			PDF concentrate containing 30% or 50% glucose (composition not stated) pH 5.7 PDF concentrate containing 30% or 50% glucose (composition not stated) pH adjusted to 6.8	- -	B	42% loss of initial activity in 24h in all solutions. Temperature not stated.	27

Peritoneal dialysis fluid concentrates (continued)

Tobramycin sulphate 100mg/L	LI	Cephalothin sodium 2g/L	-	PDF concentrate containing 30% glucose, H	TR	B (B)	The activity of the antibiotic combination against E.coli after 4h in PDF concentrate was the same as its activity after 10min. The combined activity was significantly greater than the activity of tobramycin alone, but no greater than the activity of cephalothin alone. Temperature not stated.	9
Tobramycin sulphate 100mg/L	LI	Cephalothin sodium 2g/L Heparin sodium 2500 units/L	- RI	PDF concentrate containing 30% glucose, H	TR	B (B) (-)	The activity of the antibiotic combination against E.coli was unaffected by the presence of heparin after 10min and 4h in PDF concentrate. The combined activity was significantly greater than the activity of tobramycin alone, but no greater than the activity of cephalothin alone. Heparin not studied. Temperature not stated.	9
Tobramycin sulphate 100mg/L	LI	Heparin sodium 2500units/L	RI	PDF concentrate containing 30% glucose, H	TR	B (-)	Tobramycin alone in PDF concentrate compared to normal saline showed significant loss of activity within 10min (four-fold increase in MIC against E.coli). No further loss of activity was evident at 10min or 4h when combined with heparin. Heparin not studied. Temperature not stated.	9

Tobramycin

Four studies have investigated tobramycin stability in PDF concentrates. One study, using two direct analytical techniques, produced conflicting results concerning the stability of tobramycin in PDF concentrate containing 30% glucose. Tobramycin was found to be stable for 24h using one analytical technique, but not stable using another (4). Overwhelming evidence suggests that tobramycin is not stable for 24h in PDF concentrates containing either 30% or 50% glucose (1, 4, 27). One study demonstrated that a significant loss of tobramycin activity occurs within 10min in PDF concentrate when compared to its activity in normal saline (9).

Tobramycin in combination

Only one study has attempted to investigate tobramycin in combination with other drugs in PDF concentrate (9). The initial activity of the tobramycin plus cephalothin combination was maintained for 4h in PDF concentrate containing 30% glucose. Synergistic activity against E.coli was not demonstrated when tobramycin was combined with cephalothin, however this combination may be synergistic against other bacterial species or provide broader activity against a variety of bacterial species. Physical compatibility was not commented on.

Heparin had no effect on the activity of tobramycin, or on the combined activity of tobramycin plus cephalothin in PDF concentrate containing 30% glucose. The effect of the combinations on heparin activity is unknown. Physical compatibility was not commented on.

VANCOMYCIN

CAPD fluids

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Vancomycin 15mg/L	LI			PDF containing 1.5% or 4.25% glucose (Dianeal 137), B	TR	B	At least 95% of initial activity retained for 24h in 1L plastic bags containing dialysate at 25°C.	10
Vancomycin 20mg/L	LI			PDF containing 4.25% glucose (Dianeal 137, PD 2), B, C	TR	B	Initial activity retained for 24h in 1L or 2L plastic bags containing dialysate at 25°C. 15% loss of initial activity in 48h at 25°C.	5
Vancomycin hydrochloride 30mg/L	LI			PDF containing 1.5% or 4.25% glucose (Dianeal), A	TR	B	Initial activity retained for 24h in 1L plastic bags containing dialysate at 4°C and 23-24°C.	16
Vancomycin 0.09-6mg/L	SI			Mueller-Hinton agar reconstituted with PD effluent collected after an overnight dwell of PDF containing 2.5% glucose (composition not stated)		*b*	*The MIC of vancomycin in Mueller-Hinton agar was not adversely affected by the addition of PD effluent when measured against coagulase-positive staphylococci. The addition of PD effluent raised the MIC of vancomycin against coagulase-negative staphylococci in 77% of the isolates tested (n=50).* *	49
Vancomycin 20mg/L	LI	Heparin 500 units/L	-	PDF containing 4.25% glucose (Dianeal 137, PD 2), B, C	TR	B (-)	Initial activity of vancomycin retained for 24h in 1L or 2L plastic bags containing dialysate and heparin at 25°C. 15% loss of initial activity in 48h at 25°C. Heparin not studied.	5
Vancomycin hydrochloride 30mg/L	LI	Heparin sodium 500 units/L	CSL	PDF containing 1.5% glucose (Dianeal), A	TR	V	Solutions stored in glass at 4°C and 21-22°C demonstrated no visible precipitation in 24h and no change in pH in 48h.	16
Vancomycin hydrochloride 30mg/L	LI	Heparin sodium 500 units/L	CSL	PDF containing 1.5% or 4.25% glucose (Dianeal), A	TR	B (-)	Initial activity of vancomycin retained for 24h in 1L plastic bags containing dialysate and heparin at 4°C and 23-24°C. Heparin not studied.	16
Vancomycin 25mg/L	-	Moxalactam disodium 30mg/L Cefazolin 50mg/L	LI -	PDF containing 1.5% glucose (Dianeal), A	TR	- (HPLC) (-)	Moxalactam stable in solutions stored for 6h at 25°C then heated to 37°C for 30min. Vancomycin and cefazolin not studied.	50

Vancomycin

Three studies have demonstrated that vancomycin 15-30mg/L is stable in CAPD fluids of various glucose concentrations for 24h at room temperature (5, 10, 16). A significant loss of activity occurred within 48h at room temperature (5). One study investigating the efficacy of intraperitoneal vancomycin found that the activity of vancomycin against coagulase-positive staphylococci was not inhibited by peritoneal dialysis effluent. Peritoneal dialysis effluent may inhibit the activity of vancomycin against coagulase-negative staphylococci (49).
* Coagulase-positive staphylococci includes S.aureus. Coagulase-negative staphylococci includes S.epidermidis.

Vancomycin in combination

Vancomycin was stable for 24h at room temperature when combined with heparin in CAPD fluids of various glucose concentrations (5, 16), but was not stable for 48h (5).
The combination was physically compatible at 4°C and 21-22°C (16). The effect of the combination on heparin activity is unknown (5, 16).

Moxalactam was stable after storage for 6h at room temperature followed by heating to 37°C for 30min when combined with vancomycin plus cefazolin in CAPD fluid containing 1.5% glucose. The effect of the combination on vancomycin and cefazolin stability is unknown. Physical compatibility was not commented on (50).

Peritoneal dialysis fluid concentrates

Drug	Mfr	Drug	Mfr	Solution	Mfr	Method	Results	Ref
Vancomycin hydrochloride 750mg/L	LI			PDF concentrate containing 30% glucose, H	TR	B	Activity after 4h in PDF concentrate similar to initial activity in normal saline. Temperature not stated.	9
Vancomycin hydrochloride 10mg/L and 50mg/L	LI			PDF concentrate containing 50% glucose, D	MG	B	93-100% of initial activity was retained for 24h at room temperature. Stability was greater at the higher vancomycin concentration.	1
Vancomycin (-)	-			PDF concentrate containing 30% or 50% glucose (composition not stated) pH 5.7 PDF concentrate containing 30% or 50% glucose (composition not stated) pH adjusted to 6.8	- -	B	Initial activity retained for 24h in all solutions. Temperature not stated.	27
Vancomycin hydrochloride 750mg/L	LI	Gentamicin sulphate 100mg/L	SC	PDF concentrate containing 30% glucose, H	TR	B (B)	The activity of the antibiotic combination against S.aureus after 4h in PDF concentrate was the same as its activity after 10min. The combined activity was similar to, but no greater than, the activity of vancomycin alone. Temperature not stated	9

Peritoneal dialysis fluid concentrates (continued)

Vancomycin hydrochloride 750mg/L	LI	Gentamicin sulphate 100mg/L Heparin sodium 2500 units/L	SC RI	PDF concentrate containing 30% glucose, H	TR	B (B) (-)	The activity of the antibiotic combination against S.aureus was unaffected by the presence of heparin after 10min and 4h in PDF concentrate. The combined activity was similar to, but no greater than, the activity of vancomycin alone. Heparin not studied. Temperature not stated.	9
Vancomycin hydrochloride 750mg/L	LI	Heparin sodium 2500 units/L	RI	PDF concentrate containing 30% glucose, H	TR	B (-)	Activity of vancomycin maintained for 4h in PDF concentrate containing heparin. Heparin not studied. Temperature not stated.	9

Vancomycin

Three studies have investigated vancomycin stability in PDF concentrates. Vancomycin 10mg/L and 50mg/L was stable for 24h at room temperature in PDF concentrate containing 50% glucose (1). A second study, in which the test concentration and storage temperature are not specified, concluded that vancomycin was stable for 24h in PDF concentrates containing 30% or 50% glucose (27). A third study demonstrated that there was no significant loss of vancomycin activity after 4h in PDF concentrate when compared to its activity in normal saline (9).

Vancomycin in combination

Only one study has attempted to investigate vancomycin in combination with other drugs in PDF concentrate (9). The initial activity of the vancomycin plus gentamicin combination was maintained for 4h in PDF concentrate containing 30% glucose. Synergistic activity against S.aureus was not demonstrated when vancomycin was combined with gentamicin, however this combination may be synergistic against other bacterial species or provide broader activity against a variety of bacterial species. Physical compatibility was not commented on.

Heparin had no effect on the activity of vancomycin, or on the combined activity of vancomycin plus gentamicin in PDF concentrate containing 30% glucose. The effect of the combinations on heparin activity is unknown. Physical compatibility was not commented on.

APPENDIX 1

The following formulations were obtained from the studies reviewed and do not necessarily represent a comprehensive list of the solutions available.

A. Dianeal (Travenol Laboratories)

Glucose	1.5%, 4.25%
Sodium	141 mmol/L
Chloride	101 mmol/L
Calcium	1.75 mmol/L
Magnesium	0.75 mmol/L
Lactate	45 mmol/L
pH	5.4-5.6

B. Dianeal 137 (Travenol Laboratories)

Glucose	1.5%, 4.25%
Sodium	132 mmol/L
Chloride	102 mmol/L
Calcium	1.75 mmol/L
Magnesium	0.75 mmol/L
Lactate	35 mmol/L
pH	5.0-5.4

C. PD2 (Travenol Laboratories)

Glucose	4.25%
Sodium	132 mmol/L
Chloride	96 mmol/L
Calcium	1.75 mmol/L
Magnesium	0.25 mmol/L
Lactate	40 mmol/L
pH	5.0-5.4

D. Peritoneal dialysis fluid concentrate (McGaw Laboratories)

Glucose	30%, 50%
Sodium	2600 mmol/L
Chloride	2000 mmol/L
Calcium	35 mmol/L
Magnesium	10 mmol/L
Acetate	690 mmol/L
pH	5.4-5.8

E. Peritoneal dialysis fluid concentrate diluted 1 in 20.

Glucose	2.5%
Sodium	130 mmol/L
Chloride	100 mmol/L
Calcium	1.75 mmol/L
Magnesium	0.5 mmol/L
Acetate	34.5 mmol/L

F. Peritoneal dialysis effluent collected after a 6h i.p. dwell of Dianeal containing 1.5% glucose

Calcium	1.12 mmol/L
Magnesium	0.66 mmol/L
Cholesterol	10 mg/L
Protein	1.46 g/L
Osmolarity	266 mOsm/kg
pH	7.2
sterile	

G. Peritoneal dialysis effluent collected after a 6h i.p. dwell

Glucose	0.24-0.33%
Calcium	1.05-1.55 mmol/L
Magnesium	0.6-0.8 mmol/L
Protein	1.56-2.11 g/L
Osmolarity	279-298 mOsm/L
pH	7.4-7.54
sterile	

H. Peritoneal dialysis fluid concentrate (Travenol Laboratories)

Glucose	30%, 50%
Sodium	2600 mmol/L
Chloride	2000 mmol/L
Calcium	35 mmol/L
Magnesium	10 mmol/L
Acetate	690 mmol/L
pH	5.4-5.8

APPENDIX 2

ABBREVIATIONS

B	bioassay
b	*bioactivity (measure of efficacy)*
CAPD	continuous ambulatory peritoneal dialysis
CCPD	continuous cyclic peritoneal dialysis
CT	clotting time
EMIT	enzyme multiplied immunoassay
FIA	fluorescence immunoassay
HPLC	high performance liquid chromatography
h	hour(s)
i.p.	intraperitoneal
IPD	intermittent peritoneal dialysis
MBC	minimum bactericidal concentration
mfr	manufacturer
MIC	minimum inhibitory concentration
min	minutes
PD	peritoneal dialysis
PDF	peritoneal dialysis fluid
RIA	radioimmunoassay
S	spectrophotometry
V	visual examination (macroscopic)
-	not stated

Manufacturer Abbreviations

AB	Abbott
BE	Beecham
BR	Bristol
BS	Biosedra Laboratory
CSL	Commonwealth Serum Laboratories
GL	Glaxo
HO	Hoechst-Roussel
LE	Lederle
LI	Eli Lilly
MG	American McGaw
MI	Miles
ML	Merrell Dow
MSD	Merck Sharp & Dohme
PD	Parke-Davis
PF	Pfizer
RI	Riker
RR	Roerig
SC	Schering
SI	Sigma
TR	Travenol
UP	Upjohn
WY	Wyeth
-	Manufacturer not stated

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APPENDIX 2

Miconazole concentrations in PDF admixtures stored in PVC bags and glass ampoules

Miconazole (Mic) concentrations* in PDF admixtures stored in PVC bags and glass ampoules

	Bag 1		Bag 2		Amp 1		Amp 2	
Initial conc.	20.6 mg/L		20.0 mg/L		21.6 mg/L		22.1 mg/L	
Sample time (hours)	% Initial Mic concentration		% Initial Mic concentration		% Initial Mic concentration		% Initial Mic concentration	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range
0	100.0	5.5	100.0	0.2	100.0	2.0	100.0	2.0
2	93.3	0.6	98.3	0.4	-	-	-	-
4	88.4	1.2	85.0	0.3	-	-	-	-
6	77.4	4.5	79.5	5.1	-	-	-	-
12	68.4	5.3	69.8	1.3	-	-	-	-
24	54.8	2.8	52.7	1.6	95.5	2.2	98.3	7.6
48	40.3	1.0	39.8	3.0	96.2	1.3	97.3	3.2
72	29.2	1.0	33.8	2.8	94.1	1.5	90.4	3.2
120	19.0	0.5	19.1	0.2	-	-	-	-
168	-	-	-	-	85.1†	-	87.2	5.1
216	10.8	0.0	10.7	0.1	87.7	2.0	83.3	5.4

* Miconazole nitrate concentrations were determined using the calibration curve, and converted to equivalent concentrations of miconazole by multiplying by the molecular weight ratio (416.1/479.2)

† Single determination only

APPENDIX 3

Sulphamethoxazole and trimethoprim concentrations in PDF admixtures stored in PVC bags and glass ampoules

Sulphamethoxazole (SMX) concentrations in PDF admixtures stored in PVC bags and glass ampoules

	Bag 1		Bag 2		Amp 1		Amp 2		Amp 3		Amp 4	
Initial conc.	94.6 mg/L		95.9 mg/L		87.4 mg/L		85.6 mg/L		85.0 mg/L		87.8 mg/L	
Sample time	% Initial SMX concentration		% Initial SMX concentration		% Initial SMX concentration		% Initial SMX concentration		% Initial SMX concentration		% Initial SMX concentration	
(hours)	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
0	100.0	0.5	100.0	0.3	100.0	0.6	100.0	0.2	100.0	1.6	100.0	1.0
2	100.2	0.5	97.7	1.0	101.9	1.2	101.6	1.4	-	-	-	-
6	97.3	0.9	95.0	2.8	104.1	3.7	102.7	0.3	-	-	-	-
12	89.1	0.8	92.3	2.4	101.3	1.0	101.9	2.5	-	-	-	-
24	87.5	3.9	90.8	0.2	95.6	2.8	100.6	0.2	97.0	0.1	92.4	0.9
48	85.1	0.4	84.4	1.2	92.1	0.4	92.2	1.5	87.6	0.8	84.8	2.1
72	79.8	0.5	80.5	1.2	83.2	2.3	86.9	1.7	80.7	1.2	79.3	1.3
168	-	-	-	-	-	-	-	-	70.9	2.8	67.5	0.9
216	57.8	0.3	57.0	0.5	-	0.4	-	0.2	64.6	1.7	62.5	2.8

Trimethoprim (TMP) concentrations in PDF admixtures stored in PVC bags and glass ampoules

	Bag 1		Bag 2		Amp 1		Amp 2		Amp 3		Amp 4	
Initial conc.	19.5 mg/L		19.7 mg/L		18.4 mg/L		17.9 mg/L		17.3 mg/L		17.6 mg/L	
Sample time (hours)	% Initial TMP concentration		% Initial TMP concentration		% Initial TMP concentration		% Initial TMP concentration		% Initial TMP concentration		% Initial TMP concentration	
	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range	Mean	Range
0	100.0	0.0	100.0	0.4	100.0	1.0	100.0	1.2	100.0	0.4	100.0	0.4
2	99.8	0.6	97.6	0.7	101.4	1.0	100.8	0.8	-	-	-	-
6	97.8	1.1	95.9	2.8	102.9	2.5	102.1	0.6	-	-	-	-
12	94.4	0.0	97.2	3.0	100.4	0.2	101.8	2.8	-	-	-	-
24	92.5	2.4	95.4	0.6	97.2	2.3	102.1	0.6	99.9	1.0	95.1	3.0
48	91.4	1.9	90.5	0.7	96.1	0.6	98.1	1.8	103.9	0.4	102.5	1.4
72	87.6	0.2	88.3	1.1	92.0	1.9	96.6	0.8	102.6	1.4	101.3	1.4
168	-	-	-	-	-	-	-	-	102.9	3.3	99.0	1.2
216	85.6	5.1	81.8	2.4	-	-	-	-	100.0	0.4	99.7	3.4