ความเข้ากันได้ของสารละลายอาหารที่ให้ทางหลอดเลือดดำของโรงพยาบาลรามาธิบดี กับยาในกลุ่มเซฟาโลสปอรินส์

นางสาว ตวงพร สุวรรณอำไพ

สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเภสัชศาสตรมหาบัณฑิต
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ลิขสิทธิ์ของจุฬาลงกรณ์มหาวิทยาลัย

COMPATIBILITY OF PARENTERAL NUTRIENT SOLUTIONS OF RAMATHIBODI HOSPITAL WITH CEPHALOSPORINS

Miss Tuangporn Suwanampai

สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

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Field of Study	Food Chemistry and Medical Nutrition
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ตวงพร สุวรรณอำไพ: ความเข้ากันได้ของสารละลายอาหารที่ให้ทางหลอดเลือดดำของโรงพยาบาลรามาธิบดีกับยาในกลุ่มเซฟาโลสปอรินส์ (COMPATIBILITY OF PARENTERAL NUTRIENT SOLUTIONS OF RAMATHIBODI HOSPITAL WITH CEPHALOSPORINS) อ. ที่ปรึกษา: ผศ.ดร. วรางคณา วารีสน้อยเจริญ, อ.ที่ปรึกษาร่วม: ภญ. ยุพา จรรยงค์วรกุล, 117 หน้า. ISBN 974-17-3910-9.

ผู้ป่วยที่รับการรักษาอยู่ในโรงพยาบาลที่ได้รับสารอาหารทางหลอดเลือดดำ ส่วนใหญ่มักได้รับการรักษาด้วยยาฉีดทางหลอดเลือดดำร่วมด้วย การให้ยาร่วมกับอาหารที่ให้ทางหลอดเลือดดำมีข้อดีสำหรับผู้ป่วยที่มีหลอดเลือดจำกัดสำหรับให้ยาและผู้ป่วยที่ต้องจำกัดปริมาณของเหลวเข้าสู่ร่างกาย จุดมุ่งหมายของการศึกษาครั้งนี้เพื่อศึกษาความเข้ากันได้และความคงตัวของยาในกลุ่มเซฟาโลสปอรินส์กับสารละลายอาหารที่ให้ทางหลอดเลือดดำส่วนกลางและหลอดเลือดดำส่วนปลายของโรงพยาบาลรามาธิบดี วิธีการศึกษาจะนำสารละลายของยาเซฟาโลสปอรินส์แต่ละชนิดผสมกับสารละลายอาหารที่ให้ทางหลอดเลือดดำทั้งสูตรสำหรับหลอดเลือดดำส่วนกลางและหลอดเลือดดำส่วนปลายในอัตราส่วน 1:1 โดยปริมาตร และศึกษาความเข้ากันไม่ได้ทางกายภาพโดยดูด้วยตาเปล่าและวัดค่าความขุ่นของสารละลายผสม ศึกษาความเข้ากันไม่ได้ทางเคมีของสารละลายผสมโดยวัดการเปลี่ยนแปลงของค่าความเป็นกรดด่าง ศึกษาความคงตัวของยาเซฟาโซลินและเซ็บทาซิดีมในสารละลายอาหารที่ให้ทางหลอดเลือดดำโดยใช้เทคนิคไฮเพอร์ฟอร์แมนซ์ลิควิดโครมาโตรกราฟี ผลการศึกษาพบว่าเซฟาโซลิน เซฟอซิทิน และเซ็บทาซิดีม มีความเข้ากันได้ทางกายภาพกับสารละลายอาหารที่ให้ทางหลอดเลือดดำเป็นเวลา 48 ชั่วโมงที่อุณหภูมิห้อง อย่างไรก็ตามพบว่าเมื่อผสมยาเซฟอแทกซิม และเซ็บไตรอะโซน กับสารละลายอาหารที่ให้ทางหลอดเลือดดำจะเกิดตะกอนและขุ่นในเวลา 48 และ 12 ชั่วโมงตามลำดับ ค่าความเป็นกรดด่างของสารละลายผสมของยากับสารละลายอาหารที่ให้ทางหลอดเลือดดำทุกตัวมีค่าใกล้เคียงกันและอยู่ในช่วง 6-7 ปริมาณที่คงเหลืออยู่ของยาเซฟาโซลินและเซ็บทาซิดีมที่ได้จากการวิเคราะห์ยังคงมีค่าสูงกว่า ร้อยละ 90 ของความเข้มข้นเริ่มต้น ที่เวลา 24 และ 8 ชั่วโมงตามลำดับ ผลการศึกษาที่ได้สามารถใช้เป็นแนวทางในการให้ยาสำหรับผู้ป่วยที่จำเป็นต้องได้รับยาในกลุ่มเซฟาโลสปอรินส์ร่วมกับสารละลายอาหารที่ให้ทางหลอดเลือดดำผ่านทางตำแหน่งวายของชุดบริหารยา โดยเซฟาโซลิน เซฟอซิทิน และเซ็บทาซิดีม มีความเหมาะสมที่จะให้ร่วมกับสารละลายอาหารทางหลอดเลือดดำได้ ในทางตรงกันข้ามเซฟอแทกซิม และเซ็บไตรอะโซน ควรจะบริหารยาโดยแยกจากสารละลายอาหารที่ให้ทางหลอดเลือดดำเพื่อป้องกันปัญหาความเข้ากันไม่ได้

สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

ภาควิชา อาหารเคมี ลายมือชื่อนิสิต.....

สาขาวิชา อาหารเคมีและโภชนศาสตร์ทางการแพทย์ ลายมือชื่ออาจารย์ที่ปรึกษา.....

ปีการศึกษา 2546 ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

4476572733 MAJOR: FOOD CHEMISTRY
KEY WORD: PARENTERAL NUTRIENT SOLUTION/ CEPHALOSPORINS/ COMPATIBILITY/ STABILITY

TUANGPORN SUWANAMPAI: COMPATIBILITY OF PARENTERAL NUTRIENT SOLUTIONS OF RAMATHIBODI HOSPITAL WITH CEPHALOSPORINS. THESIS ADVISOR: ASST. PROF. WARANGKANA WARISNOICHAROEN, Ph.D., THESIS CO-ADVISOR: EUPAR CHANYONGVORAKUL, M.Sc. in Pharm. 117pp. ISBN 974-17-3910-9.

The hospitalized patients who required parenteral nutrition frequently need to receive parenteral medication as well. The use of combination of drugs and parenteral nutrient (PN) solution may be beneficial when there is limited venous access and/or the patient is fluid restricted. The purpose of this study was to determine the compatibility and stability of cephalosporins in solutions for total and peripheral parenteral nutrition, TPN and PPN, typically used in Ramathibodi Hospital. Each of cephalosporin solutions was combined with either TPN or PPN solutions at a volume ratio of 1:1. Determinations of physical incompatibility were performed by visual observation and measurement of degree of turbidity. Chemical incompatibility was determined by the measurement of pH. The stability of cephalosporins (cefazolin and ceftazidime) in PN solutions was measured by HPLC technique. The results of physical incompatibility studies indicated that cefazolin, cefoxitin, and ceftazidime were physically compatible with PN solutions for 48 hours at room temperature. However, cefotaxime and ceftriaxone in combination with PN solutions showed visible precipitate and haze in 48 and 12 hours, respectively. The pH values of all drugs combined with PN solutions were similar, and in the range of 6-7. The amount of cefazolin and ceftazidime obtained from analysis remained greater than 90% of the initial concentration at 24 and 8 hours, respectively. The findings might be use as the guidelines for patients who require the co-administration of cephalosporins and PN solutions through a Y-injection site in the administration set. Cefazolin, cefoxitin, and ceftazidime were suitable to be coadministered with PN solutions. In contrast, cefotaxime and ceftriaxone should be administered through a separate line with PN solutions to avoid the potential for incompatibilities.

สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

Department Food Chemistry Student's signature……
Field of study Food Chemistry and Medical Nutrition Advisor's signature……
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LIST OF ABBREVIATIONS

AA	= amino acid
AIO	= all-in-one
ANOVA	= analysis of variance
^{o}C	= degree celsius
%CV	= percent coefficient of variation
d	= day
D5W	= 5% dextrose in water
EFA	= essential fatty acid
FTU	= formazine turbidity unit
g	= gram
hr	= hour
HPLC	= high-performance liquid chromatography
IM	= intramuscular injection
IU	= international unit
IV	= intravenous injection
kcal	= kilocalorie
kg	= kilogram
kJ	= kilojoule
L	= liter
M	= molarity
MB	= multiple bottle system
mEq	= milliequivalent
mg	= milligram
min	= minute
ml	= milliliter
mm	= millimeter
mmol	= millimole
mo	= month
mOsmol	= milliosmole
MW	= molecular weight
nm	= nanometer
NTU	= nephelometric turbidity unit
PBPs	= penicillin-binding-proteins

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pH	= the negative logarithm of the dissociation ion
pK_a	= the negative logarithm of the dissociation constant
PN	= parenteral nutrition
PPN	= peripheral parenteral nutrition
psi	= pounds per square inch
r^2	= coefficient of determination
REE	= resting energy expenditure
SD	= standard deviation
TNA	= total nutrient admixture
TPN	= total parenteral nutrition
UV	= ultraviolet
yr	= year
µg	= microgram
µl	= microliter
µm	= micrometer

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CHAPTER I

INTRODUCTION

Malnutrition has many causes and manifestations; it comprises a group of clinical conditions that arise from abnormalities associated with nutrient intake, digestion, absorption, metabolism, and excretion. Malnutrition represents a continuum beginning with a problem in one or more of these determinants of nutrient availability and progressing to gross structural and functional changes that adversely affect health and quality of life (Jelliffe, 1997; Ziegler et al., 1997).

The most common nutritional deficiency observed in hospitalized patients is protein-energy malnutrition. As many as 50% of patients may demonstrate moderate malnutrition, with 5% to 10% of patients classified as severely malnourished. When malnutrition with depletion of body cell mass and impaired tissue and organ function is undetected and thus not treated, weakness, compromised immunity, decreased wound healing, and complications are more likely to occur. Such patients have increased morbidity and mortality rates and require longer hospitalization. Thus, the selection of proper nutrients and route of administration are important for the patients (Klein et al., 1997; Taylor et al., 2003).

Normally, there are two major routes for supplying adequate nutrients to patients: enteral and parenteral routes. Major considerations for selecting the feeding route and nutrition support formula include gastrointestinal function, expected duration of nutrition therapy, aspiration risk, and the actual development of organ dysfunction. Patients who will not, should not, or cannot eat but who have a functional gastrointestinal tract are candidates for enteral nutrition support. Benefits of enteral feeding are the maintenance of gastrointestinal structure and functional integrity, enhanced utilization of nutrients, ease and safety of administration, and lower cost (American Society for Parenteral and Enteral Nutrition [A.S.P.E.N.], 1986, 1993; Woodcock et al., 2001).

Parenteral nutrition support is used for patients with diffuse peritonitis, intestinal obstruction that prohibits use of the bowel, intractable vomiting, paralytic ileus, severe pancreatitis, enterocutaneous fistulae, gastrointestinal ischemia, sever diarrhea that makes metabolic management difficult and who are not candidates for enteral

support. Peripheral parenteral nutrition (PPN) may be used in selected patients to provide partial or total nutrition support for patients who are not able to ingest adequate calories orally or enterally, or when central-vein parenteral nutrition is not feasible. PPN is typically used for a short time (up to 2 weeks) because of limited patient tolerance and few suitable peripheral veins. The lack of peripheral venous sites that can withstand long—term nutrition infusion makes repletion levels of nutrition support difficult to attain by this route. The concentrations (osmolarity) of nutrients are limited in order to avoid thrombophlebitis and fluid overload. Therefore, PPN is not the optimal choice for feeding patients with significant malnutrition, severe metabolic stress, large amount of nutrient or electrolyte needs, fluid restriction, and/or the need for prolonged intravenous nutrition support (Allwood, 2000; Jeejeebhoy, 2001).

Parenteral nutrition via central vein is used to provide nutrients at greater concentrations and smaller fluid volumes than is possible with PPN. Central venous access can be maintained for prolonged periods (weeks to years) with a variety of catheters that must be surgically placed and maintained using strictly aseptic techniques (A.S.P.E.N., 1993).

Because patients who required parenteral nutrition frequently are critically ill and often need to receive parenteral medications as well. Where possible, these should be given separately from the parenteral nutrition solution but this is not always possible, particularly in areas where the number of intravenous drugs required exceeds the access sites available such as in cancer and intensive care unit patients. In these cases, Y-injection site connection should become a necessity when there is no other route or parenteral access available (Thomson, Naysmith, and Lindsay, 2000).

The advantages of infusing parenteral drugs into parenteral nutrition solution at a Y-injection site include a decrease in total fluid administration to fluid-restricted patients, fewer venipuncture sites especially in patients with limited venous access, convenience for the patient, saving in nursing time and decreased cost (Melnik, 1997). However, the problem of drug and parenteral nutrition incompatibilities has been known for years (Hasegawa, 1994; Allwood and Kearney, 1998). Incompatibility may result in loss of therapeutic activity, unexpected adverse effects, precipitate formation resulting in platelet aggregation, anaphylactoid reactions, and multiple and minute pulmonary infractions (Newton, 1978; Food and Drug Administration, 1994; Minton, Barnett, and Cosslett, 1998).

The compatibility of numerous drugs with disparate formulations of parenteral nutrition solutions has been tested and reported (Gura, 1993). In 1990, the chemical stability and compatibility of imipenem-cilastatin sodium in two different total parenteral nutrient (TPN) solutions were determined. A physical color change from colorless to dark orange appeared in TPN solutions over the 24 hours and seemed to be correlated with the degradation of imipenem and/or cilastatin (Zaccardelli et al., 1990).

Previous studies found that the stability of ciprofloxacin (pH 3.3-3.9) decrease markedly when the pH of the solution approaches its isoelectric point (7.4) (Goodwin et al., 1991). Because commonly used components of TPN solutions have pH values ranging from 5.0 to 8.0 and therefore could be incompatible with ciprofloxacin. Thus, pharmacists should avoid adding high-pH drug products to ciprofloxacin. However, Percy and Rho (1993) reported that ciprofloxacin was visually compatible with the tested components of TPN solutions for two hours at room temperature.

Trissel et al. (1997) reported that four representative parenteral nutrient solutions were compatible with 82 of 102 drugs for four hours at 23 $^{\circ}$C. Twenty drugs were incompatible with one or more of the parenteral nutrient solutions. In 1999, they reported that most of 106 drugs tested were physically compatible with the 3-in-1 parenteral nutrition admixtures for four hours at 23 $^{\circ}$C. The drugs that showed any incompatibilities should not be administered simultaneously with the parenteral nutrition admixtures via a Y-injection site (Trissel et al., 1999).

Most of the studies on the compatibility of drug and parenteral nutrition solution; however, are mostly based on visual finding only. Some compatibility results of the same drugs are sometimes different from those reported previously. Differences in drug concentrations, formulations of parenteral nutrient solution, methods of evaluation, and interpretations of observed phenomena may all play a role in the disparities (Clark and Lew, 1997; Trissel et al., 1997).

Cephalosporins are β-lactam antibiotic derivatives of Cephalosporin C. Cephalosporins are usually antibiotics acting as an inhibitor of mucopeptide synthesis in the bacterial cell wall. Cephalosporins are mainly administered via parenteral route and are commonly used in multiinfected septic patients. In some cases, they are considered to given in combination with the parenteral nutrient solutions. The compatibility of

cephalosporins with a number of standard intravenous solutions has been studied. From an extensive literature search, little information has been published on the stability of cephalosporins in admixtures with parenteral nutrient solutions in Thailand. If cephalosporins could be administered as a continuous infusion in parenteral nutrient solution, parenteral nutrition therapy would not be interrupted and the cost of drug administration would be reduced.

The purpose of this study was to determine the compatibility and stability of cephalosporins in two different parenteral nutrient solutions typically used in hospitalized patients who require the co-administration of cephalosporins through a Y-injection site in the administration set.

Objectives

The objectives of this study were:

1. To determine the physical and chemical incompatibilities of standard parenteral nutrient solutions of Ramathibodi Hospital with selected cephalosporins.

2. To determine the stability of selected cephalosporins when coadministered with standard parenteral nutrient solutions by high-performance liquid chromatography.

Research hypothesis

From the objectives above, three hypotheses should be tested for each solution.

1. pH of a solution was changed from baseline over time (t= 2, 4, 8, 12, 24, and 48 hours).

2. Turbidity of a solution was changed from baseline over time (t= 2, 4, 8, 12, 24, and 48 hours).

3. Concentrations of cefazolin and ceftazidime were changed from baseline over time (t= 2, 4, 8, 12, and 24 hours).

Significance of the study

The study was designed to determine physical and chemical incompatibilities of PN solutions and cephalosporins, which included cefazolin, cefoxitin, cefotaxime, ceftazidime, and ceftriaxone, in 5% dextrose injection. In addition, the stability of cefazolin and ceftazidime in 5% dextrose injection in combination with PN solutions were studied. The results can be served as the guidelines for patients who require the coadministration of cephalosporins and PN solutions.

Scope and limitations

The compatibility study confined to determine physical and chemical incompatibilities. The physical incompatibility was indicated by visual observation and degree of turbidity and chemical incompatibility was indicated by pH measurement.

Limitations of the study were:

1. The samples in the study were prepared at the initial of study period then the same samples were drawn at any time of experiment. Hence, the differences in the components of the test solutions may occur.

2. The components in the PN solutions were not analyzed to see whether there was any degradation, which might be a factor affecting the compatibility.

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CHAPTER II

LITERATURE REVIEW

Parenteral Nutrition

Parenteral nutrition (PN) means that nutrients are provided intravenously. Therefore, when PN is considered, venous access is necessary and an appropriate infusion technique is mandatory for successful feeding. PN is indicated for patients who cannot be adequately fed enterally (Williams, 1993; Buchman, 1997). The use of parenteral nutrition in hospitalized patients has been recommended according to the clinical symptoms and, in some cases, the method of treatment such as chemotherapy (National Advisory Group on Standard and Practice Guidelines for Parenteral Nutrition, 1998). Guidelines for the use of parenteral nutrition in the hospitalized adult patient are shown in Table 1.

The primary objective of parenteral nutrition is the maintenance or improvement of the nutritional and metabolic status of patients who, for a critical period of time, cannot be adequately nourished by oral or tube feeding. In most instances, parenteral nutrition functions as a therapy adjuvant to primary treatments such as surgery, antibiotics, and other medical therapies (National Advisory Group on Standard and Practice Guidelines for Parenteral Nutrition, 1998; Font-Noguera, Cercos-Lleti, and Llopis-Salvia, 2001).

The malnourished surgical or cancer patient is strengthened with parenteral nutrition in the attempt to restore immune defenses and to help the patient tolerate further therapy. The hypercatabolic patient, such as a burned or septic patient, often requires total parenteral nutrition to prevent rapid nutritional depletion. Home total parenteral nutrition is a long - term alternative for the patient with no bowel function. The decision to undertake parenteral nutrition requires the weighing of several factors and consideration for the patient's diagnosis and prognosis (Shils, 1994; Takala, 1997).

Table 1. Guidelines for the use of parenteral nutrition in the hospitalized adult patient (adapted from A.S.P.E.N., 1986)

General guideline	Specific clinical settings
PN should be a part of routine care	Patients with massive small bowel resection, diseases of the small intestine, radiation enteritis, severe diarrhea, intractable vomiting; patients undergoing high-dose chemotherapy, radiation, and bone marrow transplant; moderate to severe acute pancreatitis; severe malnutrition in the face of a nonfunctional gastrointestinal tract; severely catabolic patients with or without malnutrition when the gastrointestinal tract will not be usable within 5-7 days.
PN usually would be helpful	Major surgery, moderate stress, enterocutaneous fistulae, inflammatory bowel disease, hyperemesis gravidarum, patients in whom adequate enteral nutrition cannot be established within 7-10 days, patients with inflammatory adhesions with small bowel obstruction, patients receiving intensive cancer chemotherapy.
PN is of limited value	Minimal stress and trauma in well-nourished patients when the gastrointestinal tract will be usable within a 10-day period, immediate postoperative period, proven or suspected untreatable diarrhea.
PN should not be used	Patients who have a functional and usable gastrointestinal tract; patients whose prognosis does not warrant aggressive nutritional support; the risks of PN are judged to exceed the potential benefits.

Administration of parenteral nutrition

Parenteral nutrition may be delivered either by central or peripheral venous access (Figure 1). Central parenteral nutrition or total parenteral nutrition (TPN) formulas typically have 150-250 g of dextrose per liter of solution. In patients with no known history of glucose intolerance, parenteral nutrition may be initiated at a rate of

40-50 ml/h and advanced until the desired final rate of infusion is achieved. In patients with known glucose intolerance, the infusion rate should be advanced more slowly to allow for evaluation of blood glucose, the administration of insulin (if indicated), and adaptation to the dextrose infusion (Teasley-Strausburg, 1992).

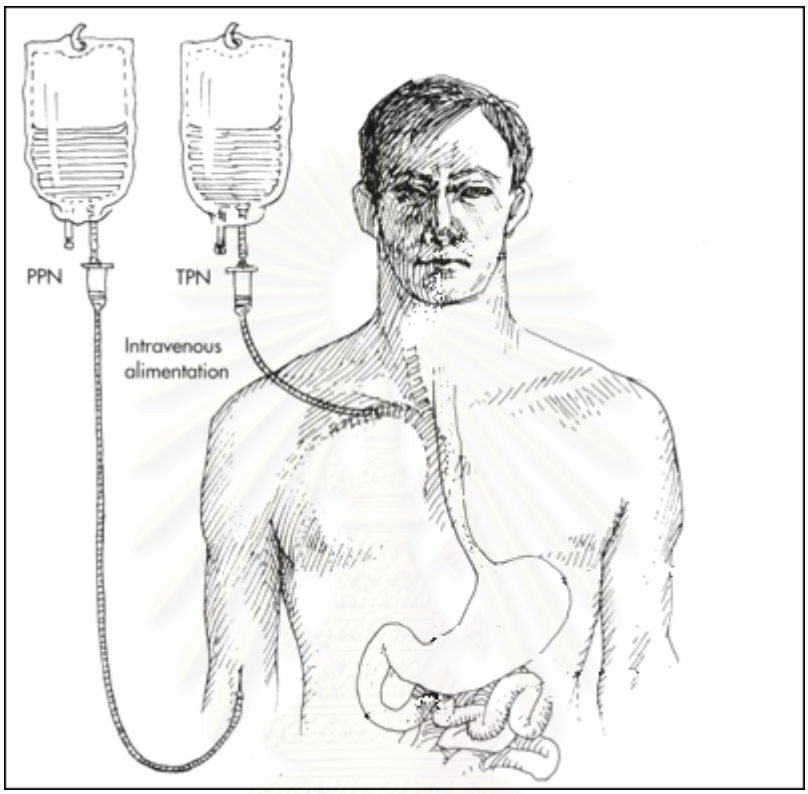

Figure 1. Routes of administration of parenteral nutrition
(PPN = peripheral parenteral nutrition, TPN = total parenteral nutrition)

Peripheral parenteral nutrition (PPN) formulas typically contain not more than 100 g of dextrose per liter of solution. Consequently, with this relatively low concentration of dextrose, peripheral parenteral nutrition solutions may be initiated at the rate necessary to infuse the complete 24-hour volume of parenteral nutrition. Peripheral parenteral nutrition may be discontinued without tapering the rate. Peripheral parenteral nutrition has the primary advantage of avoiding the use of central venous access device and its associated potential complications. However, Peripheral parenteral nutrition is limited by the tolerance of peripheral vein to hypertonic solutions. Consequently, a parenteral nutrition solution that can be administered by peripheral vein must be relatively dilute (osmolarity $\leq$ 900 mOsmol/L). A more dilute peripheral parenteral nutrition solution will provide fewer calories and less protein per volume and the concentrations of electrolytes that can be admixed will also be limited.

Therefore, the volume of peripheral parenteral nutrition solution required to meet a given patient's nutrient requirements may exceed the patient's fluid tolerance. Furthermore, in many patients requiring parenteral nutrition, peripheral venous access is limited because of poor peripheral vein status (e.g., those who have had multiple courses of chemotherapy, elderly patients, malnourished patients), such that peripheral vein access is exhausted before the need for parenteral nutrition has been eliminated. The determining factors in the choice of central versus peripheral veins parenteral nutrition are summarized in Table 2.

Table 2. Comparison of central versus peripheral veins parenteral nutrition (Teasley-Strausburg, 1992)

Criteria	Peripheral vein PN	Central vein PN
Vascular access	Limited to PN solutions with an osmolarity of $\leq$ 900 mOsmol/l in order to prevent vein damage	Highly concentrated, hypertonic solutions
Duration of PN therapy	Usually limited to $\leq$ 2 weeks because of irritation of peripheral veins by the PN solution and frequent need to change the infusion site	May be used indefinitely, especially if a tunneled vascular access is used
Nutritional requirements	Because dilute solutions must be used, a high volume of PN solution will be required to meet the nutritional requirements; supplemental nutrition can usually be met with a reasonable amount fluid	Regimen can be specific to the patient's nutritional requirements using either highly concentrated solutions or more dilute solutions as determined by the patient's fluid requirements
Risks	Technical complications associated with peripheral vascular access, metabolic and nutritional complications associated with infusing PN solution	Technical complications associated with establishing and maintaining central vascular access, metabolic and nutritional complications associated with infusing PN solution

System for parenteral nutrition

1. Multiple bottle system

In the early days of parenteral nutrition, a multiple bottle system (MB) is used, where amino acids, glucose and fat emulsion are administered in parallel. Minerals and vitamins are added to different bottles and infused at different times. It is common to have 6-8 bottle changes every day, and it is necessary to set up different irregular flow rates and make many additions. The common complications found are hyperglycemia and electrolyte disorders, so frequent controls of glycemia and plasma electrolytes are required in patients receiving parenteral nutrition. The only advantages of MB are flexibility and ease of adjustment to patient needs. It has been claimed that, using the MB system, it is easy to overcome compatibility problems with no limitation on mineral and electrolyte dosage, because incompatible elements could be added to separate bottles. However, it is known that untested simultaneous administration of nutrients increases the risk of physicochemical incompatibilities.

In some countries, amino acids and glucose are mixed in the same bottle, also called 2-in-1, thus reducing the number of connections and allowing simultaneous infusion of most daily fluids, reducing also the hyperglycemia. Fat is infused separately, sometimes into a peripheral vein, or through a Y-site connector, every second day or once a week (Pertkiewicz, 2000).

2. All-in-One system

The All-in-One (AIO, 3-in-1) system, and total nutrient admixture (TNA) are additional terms used to describe the combination of dextrose, amino acids, fat emulsion, electrolytes, trace elements, and multivitamins in one container. These components are mixed in one bag and provide a total nutrient supply for 24 hours. Concerns regarding stability and compatibility still remain an issue when compounding with an opaque solution, which may mask visualization of precipitate formation. There are several advantages to the TNA system. One container per day with one flow rate decreases the nursing time involved in intravenous set-up and tubing changes. Fewer manipulations decrease the risk of touch contamination. There is also less time consuming during preparation of only one TPN bag per day per patient. Ultimate time

saving and the fewer materials needed result in an economic advantage of this system (Johnson and Anderson, 1992; Pichard et al., 2000).

Energy requirements

The human body can draw energy from carbohydrates, lipids, and proteins. Generally, the majority of energy is taken in as carbohydrates and lipids while proteins provide 15-20% of total energy per day. In practice, daily energy requirements of hospitalized patients can be estimated by several methods, such as the Harris-Benedict equation. Approximately 30 kcal (7.2 kJ) per kg body weight per day should be sufficient to maintain weight for the relatively unstressed middle-aged patient in an acceptable weight range whose activity is restricted and who has no fever or other hypermetabolic condition. The formula content of the ratio of grams of protein nitrogen to nonprotein calories (g/kcal) of approximately 1:250 to 1:300 is appropriate for such a patient. Malnourished nonhypercatabolic adults can be placed into positive nitrogen balance on a caloric intake approximately equal to 1.3 times higher than resting energy expenditure (REE). The provision of 28-30 kcal/kg body weight may be utilized to estimate basal energy requirements of adult patients. To allow for weight gain, more calories are required depending on the weight gain desired. To minimize or help regain loss of lean body mass in adult patients acutely stressed by trauma, burns, or infection, the N/kcal ratio is generally increased. Caloric provision to such adult patients may be as high as 40 to 45 kcal/kg body weight or occasionally higher. Care must be taken not to exceed caloric expenditure consistently (Shils, 1994).

All essential and nonessential amino acids should be provided in amounts needed for adequate protein synthesis. Essential fatty acids should be supplied regularly. Macrominerals, trace elements, and vitamin intakes should meet individual requirements without excessive wastage or toxicity. However, it is important to note that energy needs vary due to patient's activity, severity of illness, age, and the presence or absence of malnutrition (Chiolero, Revelly, and Tappy, 1997).

Nutrient requirements during PN (Phillips and Odgers, 1982; Dudrick and Latifi, 1994; Bloch and Mueller, 2000)

1. Amino acid solutions

Amino acid (AA) solutions serve as the protein source in PN. Proteins are vital to every nutrition regimen because of the many essential functions they perform. Proteins are essentially structural components of all cells, are important in maintaining the output of digestive enzymes and peptide hormones, and are needed to synthesize plasma proteins, which function in maintaining osmotic balance, transporting substances through blood, and maintaining immunity. Protein, in the absence of adequate nonprotein calories or in the setting of altered metabolism, can also serve as an energy source. Proteins within the body undergo a constant process of breakdown and resynthesis. Therefore, as a substrate for the continual synthesis of the many protein-dependent structures and substances, protein is a critical component of the diet.

Protein, in the form of crystalline AA solutions for PN, is an essential component of every nutrition-support regimen. Individual AA may perform specific physiological functions (Table 3). The estimated protein requirement in an individual patient depends on age, level of activity, nutritional status, renal function, hepatic function, and presence or absence of hypermetabolism. General guidelines exist for meeting a patient's protein requirements under these varying conditions (Table 4).

In addition to quantitative differences in the protein requirements for varying age groups and disease states, there may also be differences in the requirements for specific AAs. The optimal provision of AAs during PN is dependent on both the total quantity provided as well as the specific AA composition (Rassin, 1986; Stein, 1986)

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Table 3. Characteristics and physiological function of selected amino acids (Teasley-Strausburg, 1992; Furst, 2000)

Amino acids	Characteristics and physiological function
Arginine	Important in immune function, especially thymus mass and T-lymphocyte number and function. Able to function directly or via ornithine for which it is the precursor.
Aromatic amino acids (phenylalanine, tryptophan, tyrosine)	Being precursors to neurotransmitters including dopamine, epinephrine, norepinephrine, and serotonin; dependent on hepatic function for metabolism. Able to accumulate in hepatic failure.
Branched-chain amino acids (isoleucine, leucine, valine)	Oxidized in extrahepatic tissues, primarily skeletal muscle; regulating protein turnover. Being a preferential energy source in hypermetabolic states.
Cysteine	Synthesized from methionine and subsequently to taurine. Essential amino acids in neonates which the metabolic pathways may not be mature.
Glutamine	Trophic effects on the pancreas and intestinal crypt cells preserving gut integrity in the absence of enteral feeding.
Ornithine	Important in immune function, especially thymus mass and T-lymphocyte number and function.
Taurine	Synthesized from methionine via cysteine. Essential in neonates which this metabolic pathway may not be mature. Involved functions in bile acid conjugation.

Table 4. Approximate protein requirements during nutrition support (Crim and Munro, 1994; National Advisory Group on Standard and Practice Guidelines for Parenteral Nutrition, 1998)

Clinical condition	Daily protein intake in g/ kg body weight		
	Infants 0-1 yr	Children 1-10 yr	Children ≥10 yr and adults
Normal	1.6-2.2	1.0-1.2	0.8-1.0
Low stress			
Maintenance	2.0-2.5	2.0-2.5	1.0-1.2
Anabolic	2.5-3.0	2.5-3.0	1.3-1.7
Hypermetabolic stress	2.5-3.5	2.5-3.5	1.5-2.5
Severe burn injury	2.5-3.5	2.5-3.5	2.0-3.0
Renal failure			
No dialysis	1.6-2.0	1.0-1.8	0.6-1.0
With dialysis	3.0-4.0	1.5-3.6	1.2-2.7

2. Carbohydrate solutions

Carbohydrate serves as an energy substrate for the body. The provision of carbohydrate calories via PN has been shown to suppress gluconeogenesis from endogenous substances such as amino acids. The effect is called as protein-sparing in that these amino acids remain available for reincorporation into new protein. There is a maximal rate of glucose infusion at which gluconeogenesis will be maximally suppressed. In each patient, consideration must be given to the goal of nutrition support specific to the amount of carbohydrate being provided in order to avoid undesirable effects of excess carbohydrate administration such as glucose intolerance, excess carbon dioxide production, lipogenesis, and hepatotoxicity.

Dextrose is used almost exclusively in PN solutions as the source of carbohydrate calories. It offers the advantages of being readily available, inexpensive, and efficiently metabolized in most patients. Other sources of parenteral carbohydrate

and carbohydrate-like substances such as fructose, sorbitol, mannitol and xylitol have been used in a variety of settings. However, hepatotoxicity has been associated with the use of many of these non-dextrose carbohydrates. Parenteral carbohydrate and carbohydrate-like substance used are shown in Table 5.

Brain and red blood cells have an obligatory metabolic requirement for glucose. Therefore, carbohydrate serves as a principal energy substrate in PN, but rather conditions that may warrant a reduced intake of dextrose because of preexisting glucose intolerance. These conditions include diabetes mellitus, pancreatitis, hypermetabolic stress as in sepsis, major trauma, or burn injury, low-birthweight infants, and drug-induced hyperglycemia, e.g., from corticosteroids or thiazide diuretics.

There is no specific minimum requirement for carbohydrate during PN. The optimum dose of dextrose differs for infants, children, and adults. In general, for a balanced PN regimen that includes amino acids, dextrose and fat, dextrose is used to provide 40-60% of the total caloric intake. In adults, the optimum dose for maximal suppression of gluconeogenesis and glucose oxidation is 2-5 mg/kg/min. The usual dextrose intake in neonates and infants is 10-14 mg/kg/min. In older children up to age 16, the usual dextrose intake is 6-9 mg/kg/min.

Adverse effects associated with parenteral dextrose administration are dose dependent. Excess carbohydrate administration will result in lipid synthesis. The process of glucose conversion to fat is accompanied by a higher rate of carbon dioxide production and oxygen consumption than is glucose oxidation. In the patient with poor pulmonary function the infusion of excessive dextrose may result in a significant ventilatory load of carbon dioxide, which may cause further respiratory impairment. In the ventilator-dependent patient, it may complicate weaning the patient from the ventilator. A high rate of fat synthesis from excess dextrose intake may result in fatty liver and altered hepatic function.

Table 5. Parenteral carbohydrates and carbohydrate-like substrates (Teasley-Strausburg, 1992)

Substrates	Characteristics
Dextrose	Commercially available; most frequently used source of intravenous carbohydrate; used in solution as dextrose monohydrate, which provides 3.4 kcal/g; suppress gluconeogenesis; high-dose intake resulting in hyperglycemia, excess carbon dioxide production, and fatty liver
Fructose	Naturally occurring monosaccharide; not insulin-dependent for phosphorylation and conversion to glucose; yielding energy of 3.75-4 kcal/g; toxicity including hyperuricemia, lactic acidosis, hepatomegaly, and hypophosphatemia; not recommended for routine parenteral use, contraindicated in fructose intolerance
Glycerol	Naturally occurring sugar alcohol; yielding energy of 4.32 kcal/g; protein-sparing when administered concomitantly with amino acids; possibly safe in adult use with no experience in infants and children
Invert sugar	Composed of equal parts of dextrose and fructose; commercially available but no reported experience with use for parenteral nutrition; yielding energy of approximately 4 kcal/g
Sorbitol	Naturally occurring sugar alcohol; not insulin dependent; able to be utilized without resultant hyperglycemia; toxicities include lactic acidosis, hyperuricemia, depletion of liver adenosine triphosphate, and hyperbilirubinemia
Xylitol	Naturally occurring sugar alcohol; not insulin dependent; able to be utilizable without resultant hyperglycemia; toxicities include lactic acidosis, hyperuricemia, depletion of liver adenosine triphosphate, and hyperbilirubinemia

3. Lipid emulsions

Lipid emulsions serve two primary purposes in the PN regimen as a source of calories and of essential fatty acids (EFAs). Fat is the most calorically dense substrate available, having more than twice the caloric density of carbohydrate and protein and providing approximately 9 kcal/g. Fat emulsions, therefore, have the practical advantage of providing more calories per volume at a lower osmolarity. Fat emulsions provide varying amounts of linoleic and linolenic acids sufficient to prevent or treat EFA deficiency. Arachidonic acid, which is also essential in humans, can be synthesized from linoleic acid. Fatty acids participate in numerous metabolic processes besides energy production. They serve as precursors for many important biologically active compounds such as prostaglandins and corticosteroids, and as structural integrity of cell membranes and lipoproteins. Physiological functions of lipids are shown in Table 6.

Table 6. Physiological functions of lipids (Teasley-Strausburg, 1992)

Function	Characteristics
Energy substrate	Primary source of stored energy in mammals; providing high energy content (9 kcal/g); stored in the anhydrous state
Structural functions	Essential component of cell membranes with consequent role in platelet function, wound healing, immunocompetence, and integrity of skin and hair; providing insulation against heat loss; providing padding for critical organ; storage of fat-soluble vitamins in fatty tissues
Precursors to regulatory compound	Precursors to prostaglandins, glucocorticoids, mineralocorticoids, estrogens, androgensm and bile acids

Lipid emulsions should be part of every PN regimen in quantities sufficient to prevent EFA deficiency. Lipid emulsions are also indicated as a source of fat calories for meeting energy requirements. In most patients, lipid should represent part of the daily nonprotein caloric intake in order to provide a balanced substrate intake that optimizes protein utilization. Lipid has a particular metabolic advantage over carbohydrate in patients with glucose intolerance, such as the patient with diabetes mellitus or stress-induced glucose intolerance. In the ventilator-dependent patient in

whom carbon dioxide retention, lipid emulsion will be a potential benefit because less carbon dioxide is produced upon fat oxidation than upon glucose oxidation. Lipid emulsions also provide an advantage to the patient in whom peripheral veins PN is indicated in that the emulsions are a highly concentrated source of calories. Some guidelines for lipid requirement are summarized in Table 7.

Adverse reactions to intravenous lipid emulsions have been reported to occur in a variety of settings. Soybean oil and safflower oil emulsions have been reported to have acute reactions including allergic reactions, fever, chills, vomiting, and chest or back pain.

Table 7. Guidelines for lipid requirement during PN (Teasley-Strausburg, 1992)

Condition for lipid intake	Daily lipid intake (% of total daily caloric requirement)	
	Infants and children	Adults
Minimum for essential fatty acid requirements	2-4	2-4
Optimum for protein utilization and avoidance of intolerance and adverse effects	20-40	20-40 or $\leq$ 1.0 g/kg/d
Maximum for avoidance of intolerance and adverse effects	$\leq$ 60 or $\leq$ 4.0 g/kg/d	$\leq$ 60 or $\leq$ 2.5 g/kg/d

4. Electrolyte solutions

Electrolytes play a critical role in almost of the body's physiological functions (Table 8). Disorders of electrolyte homeostasis are associated with many disease states. Consequently, in the patient who requires nutrition support of any form, the clinician usually encounters abnormal electrolyte concentration that reflects either the primary disease state, complications, or treatment. Management of electrolyte status in these patients can be one of the most time consuming aspects of monitoring and managing nutrition support. The keys to minimize electrolyte complications associated

with nutrition support are close monitoring, awareness of the factors that predispose a patient to electrolyte imbalance.

Table 8. Physiological functions of electrolytes (Schultz and Angaran, 1989; Teasley-Strausburg, 1992)

Electrolytes	Function
Calcium	Preservation and function of cell membranes, propagation of neuromuscular activity, regulation of endocrine and exocrine secretory functions, blood coagulation cascade, platelet adhesion process, bone metabolism, muscle cell excitation/contraction coupling, and mediation of the electrophysiologic slow-channel response in cardiac and smooth muscle tissue
Magnesium	Cofactor of hundreds of enzymatic systems, including all phosphate transfer reactions involving adenosine triphosphate; modulator of the neuromuscular activity of the calcium ion
Phosphorus	Essential element of phospholipid in cell membranes, nucleic acids and phosphoproteins required for mitochondrial function; regulates the intermediary metabolism of carbohydrates, fat and proteins; regulates enzymatic reactions including glycolysis, ammoniogenesis, and hydroxylation of 25-hydroxyvitamin D; source of high-energy bonds of adenosine triphosphate; important in muscle contractility, electrolyte transport, and neurologic function
Potassium	Role in cell metabolism, participating in such processes as protein and glycogen synthesis; determination of the resting potential across cell membranes from its concentration ratio inside the cell versus the extracellular fluid
Sodium	Important in the major osmotic force of the extracellular compartment accompanied by chloride and bicarbonate

The general guidelines for electrolyte requirements during PN (Table 9), individualization is often required to maintain electrolyte homeostasis. Sodium and potassium requirements for a given patient are highly variable and generally not limited by compatibility restraints. In general, sodium and potassium requirements in adult PN formulation are 1 to 2 mEq/kg/d but should be customized to meet individual patient needs. Chloride and acetate content should be adjusted to maintain acid-base balance.

Omission of a given electrolyte is usually indicated only if the patient has a preexisting hyperelectrolyte state or a condition such as severe renal failure in which the renal clearance of sodium, potassium, magnesium, chloride, and phosphorus is impaired (National Advisory Group on Standard and Practice Guidelines for Parenteral Nutrition, 1998).

Table 9. Daily electrolyte requirements during PN (National Advisory Group on Standard and Practice Guidelines for Parenteral Nutrition, 1998)

Electrolytes	Daily electrolyte requirements		
	Infants $\leq$ 1 yr	Children > 1 yr	Adolescents
Sodium	2-5 mEq/kg	2-6 mEq/kg	60-100 mEq
Chloride	1-5 mEq/kg	2-5 mEq/kg	*
Potassium	1-4 mEq/kg	2-3 mEq/kg	60-100 mEq
Calcium	3-4 mEq/kg	1-2.5 mEq/kg	10-20 mEq
Phosphorus	1-2 mmol/kg	0.5-1 mmol/kg	10-40 mmol
Magnesium	0.3-0.5 mEq/kg	0.3-0.5 mEq/kg	10-30 mEq
Acetate	*	*	*

* As needed to maintain acid-base balance

5. Vitamin Solutions

Vitamins are organic compounds essential to normal tissue growth, maintenance, and function. They are involved in enzymatic processes that are important to energy and macronutrient metabolism. Vitamins function primarily as coenzymes of energy-yielding nutrients as well as cofactors in the storage and utilization of energy. Based on their chemical properties, vitamins are classified as either fat-soluble, which are capable of being stored by the body in fatty tissues, or water-soluble, which have limited storage by the body. Vitamins cannot be synthesized by the body, therefore, must be provided through dietary sources. Guidelines for parenteral vitamin requirements in adults are shown in Table 10. The American Medical Association (AMA) does not include vitamin K as part of the multivitamin formulation in order to avoid

interactions in patients receiving oral anticoagulants. However, patients receiving PN, especially those receiving antibiotic therapy, may need vitamin K supplementation.

Table 10. Daily vitamin supplementation to adult PN formulations (American Medical Association Department of Foods and Nutrition, 1979)

Vitamins	Daily vitamin requirement*
Thiamin (B_1)	3 mg
Riboflavin (B_2)	3.6 mg
Niacin (B_3)	40 mg
Folic acid	400 μg
Pantothenic acid	15 mg
Pyridoxine (B_6)	4 mg
Cyanocobalamin (B_{12})	5 μg
Biotin	60 μg
Ascorbic acid (C)	100 mg
Vitamin A	3300 IU [a]
Vitamin D	200 IU [b]
Vitamin E	10 IU [c]

* Vitamin K supplementation 2-4 mg/week in PN patients not receiving oral anticoagulation therapy.

[a] 3.33 IU vitamin A = 1 retinol equivalent

[b] 40 IU vitamin D = 1 μg of cholecalciferol

[c] 1.49 IU vitamin E = 1 mg α- tocopherol

Vitamins should be provided as part of any form of nutrition support. Their key role in numerous metabolic processes makes their inclusion critical to the appropriate and efficient use of other nutrients. Parenteral vitamins may also be indicated for patients with diseases such as inflammatory bowel disease, short-bowel syndrome, radiation enteritis, tropical spure, and scleroderma, which interfere with the normal absorption of selected vitamins, especially vitamins A, K, B_{12} and folic acid (Green et al., 1988).

6. Trace mineral solutions

The trace minerals that have been identified as essential in humans perform a variety of biological functions (Table 11). They participate in carbohydrate, lipid, and protein metabolism, immune function, cell membrane integrity, oxygen transport, and hormone activity. The trace minerals for which human deficiency states have been defined are copper, chromium, iodine, iron, manganese, molybdenum, selenium, and zinc (Teasley-Strausburg, 1992).

There are numerous case reports in the medical literature of trace mineral deficiency syndromes, particularly in individuals receiving PN. Usually the deficiency can be attributed to the absence or inadequacy of trace mineral supplementation. Recommendations exist for the daily requirement of most trace minerals during PN (Table 12). However, it is recognized that approximation, and individual variations exist (American Medical Association Department of Foods and Nutrition, 1979; Shils, 1994).

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Table 11. Physiological functions of essential trace minerals (Teasley-Strausburg, 1992)

Trace minerals	Physiological function
Chromium	Participates in glucose metabolism, potentiates the action of insulin, potentiates in regulation of lipoprotein metabolism
Copper	Participates in oxygen utilization; functions including energy metabolism, cholesterol metabolism, catecholamine metabolism, erythropoiesis, leucopoiesis, skeletal mineralization, elastin and collagen synthesis and antioxidant
Iodine	Participates in the synthesis of thyroid hormones, thyroxine and triiodothyronine
Iron	Component of metalloproteins and metalloenzymes including hemoglobin, myoglobin, and cytochromes; principal function in the transport, storage, and utilization of oxygen
Manganese	Component of metalloenzymes: Mn-superoxide dismutase and pyruvate carboxylase; an ionic cofactor in certain metabolic reactions; functions in energy metabolism, antioxidant protection, formation of connective tissue, and synthesis of mucopolysaccharides
Molybdenum	Component of metalloenzymes: xanthine oxidase, sulfite oxidase, and aldehyde oxidase, participating in oxidation-reduction reaction
Selenium	Constituent of glutathione peroxidase, which catalyzes the reaction of hydrogen peroxide to water, as an antioxidant protecting cell membrane and hemoglobin from oxidative damage and hemolysis
Zinc	Component of metalloenzymes, including carbonic anhydrase, alkaline phosphatase, lactic acid dehydrogenase, alcohol dehydrogenase, and some peptidases; functions include protein, carbohydrate, and lipid metabolism, membrane stabilization, and RNA conformation

Table 12. Daily trace mineral requirements during PN (American Medical Association Department of Foods and Nutrition, 1979)

Trace mineral	Requirement of trace minerals per day		
	Adults and children >5 yr	Children weighing ≥3 kg and <5 yr (per kg body weight)	Infants weighing <3 kg (per kg body weight)
Chromium (μg)	10-15	0.14-0.2	0.14-0.2
Copper (mg)	0.5-1.5	0.02	0.02
Iodine (μg)	100-140	1	1
Iron (mg)	0.5	0 (in newborn) 0.1 (>3 mo)	0
Manganese (μg)	150-800	1-10	1-10
Molybdenum (μg)	20-120	0.25	0.25
Selenium (μg)	20-40	2-3	2-3
Zinc (mg)	2.5-4.0	0.25 (in newborn) 0.1 (>3 mo)	0.3-0.4

7. Fluid requirements

Water constitutes over one-half of body weight in normal individual, and it functions as a structural component, a medium for chemical reactions, and a vehicle for interchange between the body cells and organ. Fluid requirements are highly individualized and are dependent on numerous factors including the patient's hydrational status, size, environment, and disease state. Daily fluid requirements estimates based on body weight are shown in Table 13. Fluid status must be frequently assessed after initiating fluid therapy by evaluating the patient for signs and symptoms of fluid overload or dehydration and measuring daily fluid intake and output.

Table 13. Daily fluid requirements during PN (Holiday and Seger, 1957; National Advisory Group on Standards and Practice Guidelines for Parenteral Nutrition, 1998)

Human body weight	Amount of fluid
< 1500 g	130-150 ml/kg
1500-2000 g	110-130 ml/kg
2.5-10 kg	100 ml/kg
> 10 kg-20 kg	1000 ml for 10 kg + 50 ml/kg for each kg > 10
> 20 kg	1500 ml for 20 kg + 20 ml/kg for each kg > 20

Complications of parenteral nutrition

Parenteral nutrition can be safe and effective in restoring and/or maintaining nutritional status in patients who are unable to consume or tolerate oral or enteral feeding. However, parenteral nutrition is complex and has a unique set of associated complications, some of which can be serious or even life threatening. The complication rate can be minimized through careful patient selection and by having experts in specialized nutrition support oversee the feeding program.

Complications may categorized in to four groups which are (1) mechanical or technical (involving catheters, pumps, and other apparatus for administration), (2) infectious (complicated further by underlying conditions requiring parenteral nutrition and by the infection risk associated with parenteral nutrition), (3) metabolic (glucose, fluid, electrolyte, acid-base imbalances, and organ dysfunction), and (4) nutritional (deficiency and/or excess of macronutrients, electrolytes, vitamins, and trace elements) (A.S.P.E.N., 1993).

Prevention of complications or other adverse effects, such as overfeeding from increased carbohydrate (eg., increased carbon dioxide production) requires clinical monitoring and adherence to protocols for aseptic care and maintenance of the access site (catheter), proper preparation and storage of solutions, procedures for administration of the parenteral nutrition regimen, and routine monitoring at intervals appropriate to the clinical status of the patient. Moreover, an understanding of the potential complications and their treatment is also important (Colomb et al., 2000; Cowl et al., 2000; Maroulis and Kalfarentzos, 2000).

Parenteral nutrition for drug delivery

The use of PN as a drug delivery system may be beneficial when there is limited venous access and/or the patient is fluid restricted. Other effects of drug addition to PN are savings in nursing and pharmacy time, and decreased cost (Akers, 1987; Melnik, 1997). Cost assessment of the potential and real-cost savings by the addition of drugs to PN solutions has also promoted the addition of medication (Pearson and King, 1992).

In the critical care patients such as in cancer and intensive care unit patients, who are receiving PN often need to receive concurrent parenteral antibiotics as well. Where possible, these should be given separately from the PN solution but this is not always possible. These patients may have limited access sites for drug administration especially when other intravenous fluids are being administered concomitantly. In these cases, there may be unavailable to administer the drug simultaneously with the PN solution (Driscoll et al., 1991; Gura, 1993). In addition the Y-site injection (Figure 2) should become a necessity when there is no other route or parenteral access available and drugs that cannot be given together in the same solution (Allen, Levinson, and Phisutsinthop, 1977).

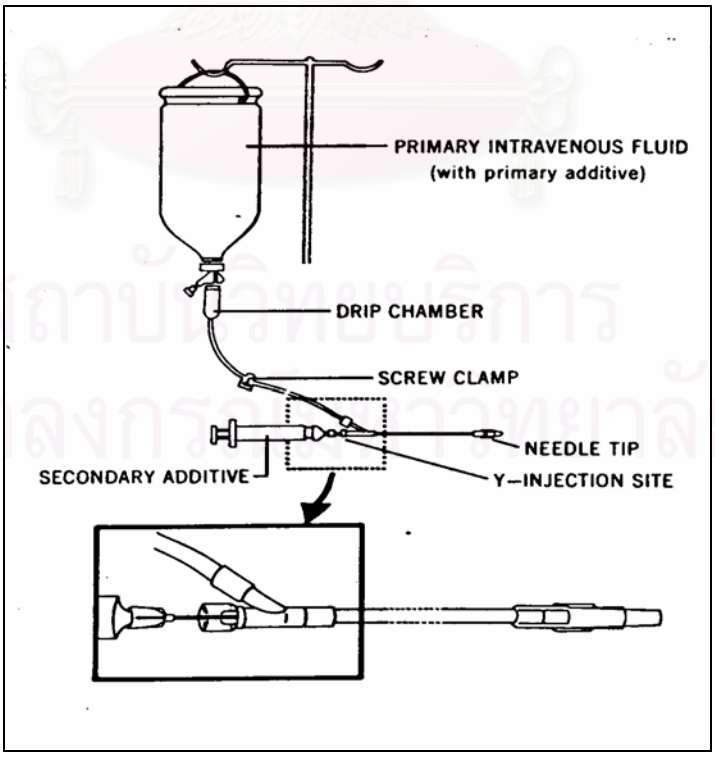

Figure 2. The Y-injection site of the administration set

In addition, the increased line manipulation increases the potential for sepsis, and other complications. It would be beneficial to the patients if these medications could be administered via PN solution. It reduced the number of direct intravenous line into the patient, resulting in decreased line and site maintenance by nursing staff (Bullock et al., 1989).

The major problem associated with the addition of drugs to PN is the potential for incompatibilities (Bussell et al., 1997). Incompatibilities come from undesirable physicochemical phenomena which most commonly manifest themselves as solvent effects and acid-base reactions. They can usually be avoided through the judicious admixing of parenteral drugs and solutions. In contrast, instability, such as hydrolysis or oxidation, may be retarded to a clinically acceptable extent, but not absolutely averted. In practical context, the general term incompatibility encompasses instability as is evidenced in the monographs (King and Catania, 1994; Trissel, 1994).

There are many factors influencing on compatibility of drugs with parenteral nutrient solution. Differences in drug concentrations, nutrient formulations, temperatures, contact times, and acidity of the solution may all play a role in the disparities (Trissel et al., 1997).

Incompatibility can be divided into 2 main types, physical and chemical incompatibilities (Newton, 1978; Mierzwa, 1986).

Physical incompatibilities are mainly from inadequate solubility, and from acid-base reactions, which produce poorly soluble nonionized drug species or coprecipitates of oppositely charged drug ions. They are typified by precipitation, color change, evolution of gas, turbidity or cloudiness.

Chemical incompatibility is the irreversible degradation of drugs to produce therapeutically inactive or otherwise toxic product. It may or may not be visibly evident. In clinical practice, parenteral drugs may usually be administered providing that less than 10% decomposition or inactivation has occurred (Driscoll, 1997; Allwood, 2002).

Compatibility studies of drugs and PN solution

Compatibility of drugs and PN admixtures should be evaluated to minimize the possibility of complications and/or therapeutic failures. Physicochemical interference with either a nutrient or a drug through complexation, precipitation, or degradation reaction within the PN admixture must be avoided. The physicochemical compatibilities and stabilities of various chemical combinations are diverse and require close monitoring and routine evaluation (Thomson, Naysmith, and Lindsay, 2000; Allwood and Kearney, 1998).

The compatibility of various drugs with selected intravenous admixtures at the Y-injection site of an intravenous administration set was studied. The mixing volumes of the drugs and the intravenous admixture at the Y-injection site to the needle tip were approximately equal. Most of the drugs studied were found to be physically compatible except phenytoin sodium, diazepam and methylprednisolone sodium succinate (Allen, Levinson, and Phisutinthop, 1977).

In 1985, the compatibility of total nutrient admixtures and antibiotics was studied. Of all nutrient-antibiotic admixtures tested, only the mixture containing tetracycline hydrochloride exhibited signs of creaming, oiling out, and phase separation. No other antibiotics (ampicillin, cefamandole, cefazolin, cefoxitin, cephapirin, clindamycin, erythromycin, gentamicin, kanamycin, oxacillin, penicillin G, ticarcillin, and tobramycin) disrupted the integrity of lipid emulsion, as evidenced by the complete absence of creaming, oiling out, and phase separation. Additionally, no appreciable pH changes occurred in any of these antibiotic-nutrient mixtures after four hours (Baptista and Lawrence, 1985).

In 1987, the stability of ticarcillin, mezlocillin, and piperacillin in three total parenteral nutrient solutions at concentrations commonly used in adults was determined. Solutions were assayed for antibiotic concentration by high-performance liquid chromatography. Ticarcillin, mezlocillin, and piperacillin were stable for 24 hours in the TPN solutions studied (Perry, Khalidi, and Sanders, 1987). These antibiotics may be added to these TPN solutions when administration of the antibiotic via a secondary infusion is not possible.

Bullock et al. (1989) found that gentamicin and tobramycin were stable in eight different total nutrient admixtures with no significant effect on emulsion particle size or stability. Amikacin was incompatible with all total nutrient admixtures, resulting in visual breaking of all emulsions within 1 hr. Eight different total nutrient admixtures contain varying concentrations of dextrose, amino acid, and fat emulsion.

Nahata (1989) found that vancomycin hydrochloride (at concentrations 1 and 6 mg/ml) appeared to be stable in TPN solutions containing either 1.65% or 4.25% amino acids with various electrolytes, multivitamins, and trace elements when stored for four hours at room temperature.

Zaccardelli et al. (1990) found that imipenem-cilastatin sodium at a concentration of 5 mg/ml was stable for 15 minutes in TPN solutions consisted of 4.25% amino acids with 25% dextrose or consisted of 5% amino acids with 35% dextrose.

The solubility of ciprofloxacin (pH 3.3-3.9) decreases markedly when the pH of the solution approaches the isoelectric point of ciprofloxacin (pH 7.4). The admixtures of ciprofloxacin with clindamycin phosphate (pH 6.3) have been found to precipitate immediately. The admixtures of ciprofloxacin with aminophylline (pH 8.6) showed precipitation within four hours of mixing (Goodwin et al., 1991). The pH values of the commonly used components in TPN solutions were ranging from 5.0 to 8.0 and therefore could be incompatible with ciprofloxacin. However, Percy and Rho (1993) have reported that ciprofloxacin was visually compatible with the tested components of TPN solutions for two hours at room temperature.

Veltri and Lee (1996) found that 16 of 21 parenteral drugs commonly prescribed in the neonatal intensive care unit were compatible with the pediatric PN solutions. Acetazolamide, acyclovir, aminophylline, ampicillin, and chlorothiazide were incompatible and all reacted with PN solutions. All incompatibilities were the formation of a fine white precipitate. The order of mixing had no impact on the compatibility of these drug-PN mixtures, and each instance of incompatibility was observed at the time of mixing.

Trissel et al. (1997) reported that four representative PN solutions were compatible with 82 of 102 drugs for four hours at 23 $^{\circ}$C. Twenty drugs were incompatible with one or more of the PN solutions. Later in 1999, they reported that

most of 106 drugs tested were physically compatible with the 3-in-1 parenteral nutrition admixtures for 4 hours at 23 $^{\circ}$C. However, 23 drugs exhibited various incompatibilities, resulting in the formation of precipitate, disruption of the emulsion with oiling out (Trissel et al., 1999).

Antibiotics administration via parenteral nutrient solutions

Antibiotics frequently added to PN solution. In critical care patients, who are receiving parenteral nutrition often need to receive concurrent antibiotics for sepsis (Perry, Khalidi, and Sanders, 1987; Zaccardelli et al., 1990). As sepsis is the main complication of central venous catheter used for parenteral nutrition (Goulet et al., 1990; Schmidt-Sommerfeld et al., 1990). The treament of catheter-related infections relies primarily on antibiotic therapy (Nahata et al., 1988; Maroulis and Kalfarentzos, 2000). However, addition of antibiotics to the PN solution can only be used if the antibiotic remains stable in the PN solution and is compatible with all PN solution components (Louie and Niemiec, 1986).

There are several studies addressing the compatibility of various antibiotics added to PN solutions have been published. Antibiotics frequently added to PN solutions include penicillins, aminoglycosides, quinolones, and cephalosporins (Manning and Washington, 1992; Tounian et al., 1999; Thomson, Naysmith, and Lindsay, 2000). Cephalosporins, a broad spectrum antibiotic, are the most commonly used in the septic patient. The adverse effects of cephalosporins are less than other β-lactam antibiotics and, in recommended doses, rarely produce significant renal toxicity. In the present study, cephalosporins used as representative drugs.

Cephalosporins

Cephalosporins, semisynthetic antibiotic derivatives of cephalosporin C, produced by the fungus *Cephalosporium acremonium*. Cephalosporins are usually bactericidal in action. The antibacterial activity of the cephalosporins, like penicillin, carbacephems, and cephamycins, results from inhibition of mucopeptide synthesis in the bacterial cell wall. Although the exact mechanisms of action of cephalosporins have not been fully elucidated, the drugs bind to several enzymes in the bacterial cytoplasmic membrane (e.g., carboxypeptidases, endopeptidases, transpeptidases) that are involved in cell wall synthesis and cell division. It has been hypothesized that β-lactam

antibiotics act as substrate analogs of acyl-D-alanyl-D-alanine, the substrate for these enzymes. This interferes with cell wall synthesis and results in the formation of defective cell walls and osmotically unstable spheroplasts. Cell death following exposure to β-lactam antibiotics usually results from lysis, which appears to be mediated by bacterial autolysis such as peptidoglycan hydrolases.

The target enzymes of β-lactam antibiotics have been classified as penicillin-binding-proteins (PBPs) and appear to vary substantially among bacterial species. The affinities of various β-lactam antibiotics for different PBPs appear to explain the differences in morphology that occur in susceptible organisms following exposure to different β-lactam antibiotics. They may also explain differences in the spectrum of activity of β-lactam antibiotics that are not caused by the presence or absence of β-lactamases. In general, cepholosporins are active *in vitro* against many gram-positive aerobic bacteria, some gram-negative aerobic bacteria, and some anaerobic bacteria; however, there are substantial differences among the cephalosporins in spectra of activity as well as levels of activity against susceptible bacteria. Cephalosporins are inactive against fungi and viruses (The United State Pharmacopeial Convention, 2000; The Board of directors of the American Society of Health-System Pharmacists, 2002).

Classification of cephalosporins

Cephalosporins may be classified by their chemical structure, clinical pharmacology, resistance to β-lactamases, or antimicrobial spectrum, the well-accepted system of classification by generations is very useful (Hardman and Limbird, 2001). The classification by generations of cephalosporins is shown in Table 14.

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Table 14. The classification by generations of cephalosporins (Hardman and Limbird, 2001)

Generations	Agents	Antimicrobial spectrum
First	Cefazolin Cephalothin Cephalexin	- Streptococci except penicillin-resistant strains, *Staphylococcus aureus* except methicillin-resistant strain.
Second	Cefuroxime Cefaclor	- *Escherichia coli*, *Klebsiella*, *Proteus*, *Haemophilus influenzae*, *Moraxella catarrhalis*. Not as active against gram-positive organisms as first-generation agents.
	Cefoxitin Cefotetan	- Inferior activity against *S. aureus* compared to cefuroxime but superior activity against *Bacteroides fragilis* and other *Bacteroides* spp.
Third	Cefotaxime Ceftriaxone Ceftazidime	- Enterobacteriaceae; *Pseudomonas aeruginosa*; *Serratia*; *Neisseria gonorrhoeae*; activity for *S. aureus*: *Strepococcus pneumoniae* and *Streptococcus pyogenes* comparable to first-generation agents. Inferior activity against *Bacteroides* spp. than cefoxitin and cefotetan
Fourth	Cefepime	- Comparable to third-generation but more resistant to some β-lactamases

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Classification by generations is based on general features of antimicrobial activity. The first-generation cephalosporins, epitomized by cephalothin and cefazolin, have good activity against gram-positive bacteria and relatively modest activity against gram-negative microorganisms. Most gram-positive cocci (with the exception of enterococci, methicillin-resistant *S. aureus*, and *S. epidermidis*) are susceptible. Most oral cavity anaerobes are sensitive, but the *Bacteroides fragilis* group is resistant. Activity against *Moraxella catarrhalis*, *E. coli*, *K. pneumoniae*, and *P. mirabilis* is good. The second-generation cephalosporins have somewhat increased activity against gram-negative microorganisms, but are much less active than the third-generation agents. A subset of second-generation agents (cefoxitin, cefotetan, and cefamandole) also is active against the *B. fragilis* group. The third-generation cephalosporins generally are less active than first-generation agents against gram-positive cocci, but they are much more active to the Enterobacteriaceae, including β-lactamases producing strains. A subset of third-generation agents (ceftazidime) is also active against *P. aeruginosa* but less active than other third-generation agents against gram-positive cocci. The fourth-generation cephalosporins, such as cefepime, have an extended spectrum of activity compared to the third-generation and have increased stability from hydrolysis by plasmid and chromosomally mediated β-lactamases. Fourth-generation agents may prove to have particular therapeutic usefulness in the treatment of infections due to aerobic gram-negative bacilli resistant to third-generation cephalosporins.

Cefazolin

Cefazolin is a first-generation cephalosporin antibiotic. Cefazolin occurs as a white to off-white, crystalline powder which may have a faint odor or as a white to off-white lyophilized solid. The drug is freely soluble in water and very slightly soluble in alcohol. Each gram of cefazolin as the sodium salt contains approximately 2 mEq of sodium. When reconstituted as directed, cefazolin sodium solutions are light yellow to yellow and have a pH of 4.5-6. Commercially available frozen cefazolin sodium injections containing 500 mg or 1g of cefazolin in 50 mL of 5% dextrose injection have osmolalities of 260-320 or 310-380 mOsm/kg, respectively, and have a pH of 4.5-7.

Cefoxitin

Cefoxitin is a second-generation cephalosporin, and a semisynthetic cephamycin antibiotic derived from cephamycin C, a substance produced by *Streptomyces lactamdurans*. The drug is a β-lactam antibiotic structurally and pharmacologically related to cephalosporins and penicillins. Cefoxitin is commercially available as the sodium salt which occurs as a somewhat hygroscopic, white to off-white powder or granules having a slight characteristic odor. Cefoxitin sodium is very soluble in water and slightly soluble in alcohol. Each gram of cefoxitin as the sodium salt contains 2.3 mEq of sodium. Following reconstitution with sterile or bacteriostatic water for injection, 0.9% sodium chloride injection, or 5% dextrose injection, cefoxitin sodium solutions have a pH of 4.2-7 and are colorless to light amber.

Cefotaxime

Cefotaxime is a third-generation cephalosporin antibiotic. Cefotaxime is commercially available as the sodium salt. Potency of cefotaxime sodium is expressed in term of cefotaxime. Cefotaxime sodium occurs as an off-white to pale yellow, crystalline powder. Cefotaxime sodium is sparingly soluble in water, slightly soluble in alcohol, and has a pK_a of 3.4. The sodium salt of cefotaxime contains 2.2 mEq of sodium per gram of cefotaxime.

Commercially available cefotaxime sodium sterile powder for injection should stored at less than 30 $^{\circ}C$ and protected from excess heat and light. Discoloration of cefotaxime sodium powder or solutions may indicate a loss of potency.

Ceftazidime

Ceftazidime is a third-generation cephalosporin antibiotic. Some commercially available preparations of ceftazidime are sterile powder for injection containing a mixture of ceftazidime (as the pentahydrate) and sodium carbonate. In these formulations, sodium carbonate has been admixed with ceftazidime to facilitate its dissolution.

Ceftazidime occurs as a white to off-white powder. The drug has solubilities of 5 mg/mL in water and less than 1 mg/mL in alcohol. When reconstituted as directed, ceftazidime and ceftazidime sodium solutions have pHs of 5-7.5 and 5-8,

respectively, and are light yellow to amber in color depending on the diluent used, concentration of the drug, and length of storage. The commercially available sterile powders for injection should be stored at 15-30°C and protected from light. Ceftazidime powder and solutions of ceftazidime and ceftazidime sodium tend to darken depending on storage conditions; however, color changes do not necessarily indicate loss of potency.

Ceftriaxone

Ceftriaxone is a third-generation cephalosporin antibiotic. Ceftriaxone is commercially available as of the disodium salt and is referred to as ceftriaxone sodium. Potency of ceftriaxone sodium is expressed in term of ceftriaxone. Commercially available sterile ceftriaxone sodium occurs as a white to yellowish-orange crystalline powder. Ceftriaxone sodium is readily soluble in water, having an aqueous solubility of 400 mg/mL at 25°C. The drug has a solubility of 1 mg/mL in alcohol at 25°C.

Ceftriaxone sodium contains approximately 3.6 mEq of sodium per gram of ceftriaxone. When reconstituted as directed, solutions of the drug are light yellow to amber in color depending on the diluent used, concentration of the drug, and length of storage. Ceftriaxone sodium sterile powder for injection should be stored at 25°C or lower and protected from light.

A limited number of investigators have reported on the stability of cephalosporins in PN solution. In the few published reports, some cephalosporins stability data were based on physical compatibility while the chemical stability of the drugs was not assessed. Although the compatibility study of cephalosporins have been tested and reported with PN solutions. Unfortunately, these reports cite specific PN solutions, drug concentrations and contact times and thus cannot be accurately extrapolated to different PN solutions, drug concentrations or contact times.

CHAPTER III

MATERIALS AND METHODS

Study design

The present study was designed with one group repeated measurements and used model of the Y-injection site to simulate the administration of the drug via a running PN solution line.

The study was divided into three phases; (1) determination of physical incompatibility, (2) determination of chemical incompatibility, and (3) investigation of drug stability.

Materials and Instruments

1. Chemicals used in preparation of PN solutions

1.1 Macronutrients

- Dextrose 50% in water, 500 ml (Thai Otsuka Pharmaceutical, Co.,Ltd., Thailand, Lot no. 2E716)
- Dextrose 50% in water, 200 ml (Thai Otsuka Pharmaceutical, Co., Ltd., Thailand, Lot no. 2K842)
- Amiparen-10, 500 ml (Thai Otsuka Pharmaceutical, Co., Ltd., Thailand, Lot no. 3A973)

1.2 Micronutrients

- 8.71% Dipotassium phosphate injection, 20ml (Otsuka Pharmaceutical, Co., Ltd., Japan, Lot no. M2C89)
- 29.4% Potassium acetate injection, 20 ml (Thai Red Cross Society, Bangkok, Thailand, Lot no. 2002/0211)
- 3% Sodium chloride injection, 500 ml (General Hospital Products, Co., Ltd., Thailand, Lot no. 29-432-XL1)
- 50% Magnesium sulfate injection, 2 ml (Atlantic Pharmaceutical, Co., Ltd., Thailand, Lot no.023131)
- 10% Calcium gluconate injection, 10 ml (Govenmental Pharmaceutical Organization, Thailand, Lot no. J450047)

- Sterile water for injection, 1000 ml (Thai Otsuka Pharmaceutical, Co., Ltd., Thailand, Lot no. 2G991)

2. Drugs and solvent

2.1 Cefazolin 1 g (Fazolin®) (Siam Bheasach Co., Ltd., Thailand, Lot no. 92C187)

2.2 Cefoxitin 1 g (Cefxitin®) (Siam Bheasach Co., Ltd., Thailand, Lot no. 92C196)

2.3 Cefotaxime 1 g (Claraxim®) (Siam Bheasach Co., Ltd., Thailand, Lot no. 92C200)

2.4 Ceftazidime 1 g (Cef-4®) (Siam Bheasach Co., Ltd., Thailand, Lot no. 92C211)

2.5 Ceftriaxone 1 g (Cef-3®) (Siam Bheasach Co., Ltd., Thailand, Lot no. 92C092)

2.6 Dextrose 5% in water, 1000 ml (Thai Otsuka Pharmaceutical, Co., Ltd., Thailand, Lot no. 2E912)

3. Other chemicals

3.1 Sodium hydroxide (NaOH) (Merck, Germany, Lot no. B979898-205)

3.2 Potassium dihydrogen phosphate (KH_2PO_4) (Merck, Germany, Lot no. A262673-405)

3.3 Methanol (HPLC grade) (Labscan Asia, Thailand, Lot no. 02-09-0153)

3.4 Acetonitrile (HPLC grade) (J. T. Baker, USA, Lot no. 75-05-8)

3.5 Calibration solutions of the turbidity meter; primary standard 0 FTU and 10 FTU (Hanna instruments, Italy, Lot no. 587 and 1046)

3.6 Cleaning solution (Hanna instruments, Italy, Lot no. 1006)

3.7 Buffer solutions for pH meter (pH 4.00±0.02 and pH 7.00±0.02) (Merck, Germany, Lot no. 22745224 and 70237118)

4. Instruments and other materials

4.1 pH meter (Index ID 1000, Index, USA)

4.2 Turbidity meter (HI 93703, Hanna instruments, Hungary)

4.3 Filter paper, 0.45 μm (Sartorius AG, Germany)

4.4 Syringe filter, 0.2 μm (Gelman Science, USA)

4.5 High-performance liquid chromatography (LC-10ADVP type,Shimadzu Corporation, Japan)

4.6 HPLC column, Luna 5 μ C 18 (2), 250 x 4.60 mm (Phenomenex, USA)

4.7 Security guard (Phenomenex, USA)

4.8 Guard cartridge C18, (ODS, Octadecyl), 4 x 3.0 mm (Phenomenex, USA)

4.9 Horizontal laminar-airflow hood, Class 100 (Bassaire, England)

4.10 Disposable syringes (5, 10, 20 ml) (Nipro, Thailand, Lot no. 01L28, 02B22)

4.11 Needles (Nissho Nipro, Thailand, Lot no. 02C04)

4.12 Glass cuvette and cap (Hanna instruments, Hungary)

4.13 Halogen spot light (50 W, Model 99304 W)

Methods

1. Preparation of samples

The preparation of samples was performed at Faculty of Pharmaceutical Sciences, Chulalongkorn University.

1.1 Preparation of PN solution

The PN solutions were compounded manually using aseptic technique under a laminar-airflow hood (Barker, 1981). The PN solutions included standard formula for peripheral line infusion (PPN) and formula for central line infusion (TPN) were obtained from Professor Chulaporn Roongpisutthipong, M.D., Division of Nutrition and Biochemical Medicine, Department of Medicine, Ramathibodi Hospital. A standard formula of TPN contains 4% amino acids and 25% dextrose. Standard adult PPN formula has lower concentration of dextrose (10%) and amino acids (2.5%) (Siriruttanapruk et al., 1999). The compositions of the two PN solutions tested are presented in Table 15.

Table 15. Composition of parenteral nutrient solutions tested.

Component in 1 liter of PN solution	Standard Adult TPN Formula	Standard Adult PPN Formula
Amino acid (g)	40	25
Dextrose (g)	250	100
Sodium (mEq)	50	50
Potassium (mEq)	40	30
Chloride (mEq)	50	50
Phosphate (mM)	7.5	7.5
Calcium (mEq)	5	5
Magnesium (mEq)	8	8
Acetate (mM)	73	45
Total calorie (kcal) /liter	1010	440

Each formula was prepared by the following order of mixing. For standard adult TPN, 400 ml of 10% amino acids was added into 500 ml of 50% dextrose injection in solution bag. Then 15 ml of 8.71% dipotassium phosphate, 8.3 ml of 29.4% potassium acetate, 100 ml of 3% sodium chloride, 2 ml of 50% magnesium sulfate, and 10 ml of 10% calcium gluconate were added, respectively. Standard adult PPN was prepared by adding 250 ml of 10% amino acids into 200 ml of 50% dextrose injection. Then, adding 15 ml of 8.71% dipotassium phosphate, 5 ml of 29.4% potassium acetate, 100 ml of 3% sodium chloride, 2 ml of 50% magnesium sulfate, 10 ml of 10% calcium gluconate, and 418 ml of sterile water for injection respectively. After admixing, the solution bag was inverted six times to assure adequate mixing. The component of amino acid solution and individual commercially electrolyte solutions are detailed in Appendix B.

After preparation, the PN solutions were stored in a refrigerator (4 $^{\circ}$C) until time of mixing with the drug solutions. The PN solutions were used within 48 hours after preparation in order to avoid the possibility of inadvertently microbial contamination during admixture.

1.2 Preparation of drug solutions

According to the manufacturer's recommendations, a 1-g vial of each drug, namely, cefazolin (Fazolin®), cefoxitin (Cefxitin®), cefotaxime (Claraxim®), ceftazidime (Cef-4®), and ceftriaxone (Cef-3®), was reconstituted and diluted with 5% dextrose for injection to a final volume of 50 ml giving a drug concentration of 20 mg/ml which is a concentration commonly administered to a patient.

2. Determination of physical incompatibility

The samples were freshly prepared by adding the diluted drug solutions in each of the PN solutions. The drug solutions and the PN solution were mixed at the volume ratio of 1:1. The ratio has been shown to simulate the Y-site administration of the drug via a running PN solution line and has been used in other compatibility studies (Allen, Levinson and Phisutsinthop, 1977).

In the present study, 50 ml of drug solution was added to equal aliquots of each of PN solutions in glass bottles. The mixture was then shaken for six times to ensure the complete mixing. The prepared mixtures were then determined for incompatibility as follows.

2.1 Visual Observation

The samples were drug-PN solution combinations and prepared as described previously. The control was 20 mg/ml of drug in dextrose solution without any PN solution added. Duplicate determinations were made on three sets of each sample immediately and at 2, 4, 8, 12, 24, and 48 hours after mixing of drug and PN solutions at room temperature. All samples were examined firstly in a normal laboratory fluorescent light with the unaided eyes. Samples with no obviously visual incompatibility were examined further against a black and white background using a high-intensity light source to enhance visibility of any low-level haze and smaller particles. Incompatibility was defined as any visible particulate matter, haze or turbidity, color change, or gas evolution (Athanikar et al., 1979; Trissel et al., 1997).

2.2 Turbidity Measurement

The measurement of the extent of turbidity, any changes in haze intensity over time, was performed on the drug-PN solutions by using the turbidity meter. The samples were drug-PN solution combinations prepared as described in 3.1. The drug diluted with 5% dextrose injection only served as a control.

The turbidity meter functions by passing a beam of infrared light through a vial containing the sample being measured. The light source is a high emission infrared with a wavelength peaking at 890 nm, so as to ensure that the interference caused by colored samples is minimum. A sensor, positioned at 90° with respect to the direction of light, detects the amount of light scattered by the undissolved particle present in the sample. The microprocessor converts such readings into formazine turbidity unit (FTU) values, ranging from 0-10. The FTU is identical to another internationally recognized unit, the nephelometric turbidity unit (NTU).

Before any measurements, the turbidity meter was calibrated with 0 FTU and 10 FTU standard solutions. Duplicate determinations were made on three sets of each sample immediately and at 2, 4, 8, 12, 24, and 48 hours after mixing at room temperature. The turbidity meter was allowed to return to zero by washing with cleaning solution and rinsed with 0 FTU standard solution before next determination.

Conventional assessments of visual compatibility have been based on the absence of turbidity or any particulates. Consequently, there is no generally accepted definition of incompatibility based on a change in measured degree of turbidity. In this study, the interpretation of any changes in turbidity over time in terms of incompatibility was based on a change in FTU values. An increase or decrease of 0.5 FTU or more in drugs in PN solutions compared to drugs in 5% dextrose injection could be represented as an occurrence of incompatibility in drugs with PN solutions (Trissel and Bready, 1992; Trissel and Martinez, 1993; 1994).

3. Determination of chemical incompatibility by pH measurement

Chemical incompatibility is the irreversible degradation. It may either visibly or invisibly evident. The determinations of chemical incompatibility include measurement of pH changes and measurement of drug concentrations or drug stability

(Baumgartner et al., 1997). In this study, the drug concentration was measured using HPLC assay and the experimental detail was in the following topic.

For the pH measurement, each drug was diluted with 5% dextrose injection to a concentration of 20 mg/ml and then mixed with the PN solutions. A control was drug solution in dextrose solution at the same concentration above with in an absence of PN solutions.

The changes in acidity of the solution were measured by using pH meter and the volume of solutions used was at least 8 ml. Duplicate determinations were made on three sets of each sample immediately and at 2, 4, 8, 12, 24, and 48 hours after mixing at room temperature. Before any measurements, the pH meter was calibrated with standard buffer solutions, pH 4.00 and pH 7.00 and the electrode was rinsed two times with distilled water.

4. Stability of drug in PN solution

The drug concentrations in PN solution were measured by reversed-phase high-performance liquid chromatography (HPLC) using modified method described by Stiles, Tu, and Allen (1989). The HPLC system consisted of a liquid chromatography (LC-10ADVP), a degasser (DGU-14A), a system controller (SCL-10AVP), an UV visible light detector (SPD-10AVP), and an auto-injector (SIL-10A). The software for HPLC was CLASS-VP.

Cefazolin, a first generation cephalosporin antibiotic and ceftazidime, a third generation cephalosporin antibiotic were widely used in hospitalized patients. In this study, there were no physical and chemical incompatibilities in previous determinations. Cefazolin and ceftazidime were used for HPLC analysis. The samples were freshly prepared from reconstituting a 1-g vial of cefazolin or ceftazidime with 50 ml of 5% dextrose injection before admixing with 50 ml of the PN solution. The solutions were then diluted five times with distilled water. Samples were filtered through 0.2 μm syringe filter before injected through an auto-injector. Each drug was also reconstituted with 100 ml of 5% dextrose injection and was served as a control. The analysis was done immediately and at 2, 4, 8, 12, and 24 hours after mixing the drug and PN solutions at room temperature. Triplicate measurements were made for all samples.

4.1 Preparation of mobile phase

Mobile phase for cefazolin was composed of 20% acetonitrile and 80% 0.005 M phosphate buffer at pH 7.5. Mobile phase for ceftazidime was composed of 10% methanol and 90% 0.005 M phosphate buffer at pH 7.5. Freshly prepared mobile phase was filtering through 0.45 μm nylon membrane filter, then degassed by sonication for about 30 minutes.

Phosphate buffer pH 7.5

A 0.005 M potassium dihydrogen phosphate solution was prepared by accurately weighing 0.68 g of potassium dihydrogen phosphate. The salt was dissolved with distilled water. The pH of solution was adjusted to 7.5 using 2.0 M sodium hydroxide solution. The final solution was adjusted to 1000 ml in volumetric flask using distilled water. A 2.0 M sodium hydroxide solution was prepared by accurately weighing 8 g of sodium hydroxide pellets. Dissolve the pellets and adjust the volume to 100 ml with distilled water.

4.2 Chromatographic condition

The condition for analysis of cefazolin was presented as follows:

Column	: Luna 5 μ C 18 (2), 250 x 4.60 mm
Mobile phase	: 20:80 v/v of Acetonitrile : 0.005 M phosphate buffer pH7.5
UV detector	: 254 nm
Flow rate	: 1.0 ml/min
Injection volume	: 5 μl
Attenuation	: auto-attenuation
Pressure	: 3000 psi

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The condition for analysis of ceftazidime was presented as follows:

Column	: Luna 5 μ C 18 (2), 250 x 4.60 mm
Mobile phase	: 10:80 v/v of Methanol : 0.005 M phosphate buffer pH7.5
UV detector	: 254 nm
Flow rate	: 1.0 ml/min
Injection volume	: 2 μl
Attenuation	: auto-attenuation
Pressure	: 3000 psi

4.3 Preparation of standard solution

A stock solution of cefazolin or ceftazidime was a 1-g vial of each drug reconstituted with 5% dextrose injection. The contents of the vial was then transferred to a 100- ml volumetric flask and diluted with 5% dextrose injection to a final volume of 100 ml.

Standard solutions were prepared by pipetting 2.5, 5, 7.5, 10, 12.5 and 15 ml of cefazolin or ceftazidime stock solution and transferring to 50-ml volumetric flasks. The solutions were adjusted to volume with distilled water so that the concentrations of cefazolin or ceftazidime in standard solutions were 0.5, 1, 1.5, 2, 2.5 and 3 mg/ml.

4.4 Calibration curve

According to standard solutions with known concentration of cefazolin and ceftazidime, the calibration curves were evaluated by plotting the curve between the peak areas of drug obtained from HPLC versus the known concentrations of drug. Linear regression analysis was performed. The equation and the coefficient of determination (r^2) were calculated.

4.5 Validation of HPLC assay

The HPLC assay of cephalosporins was modified from the methods described by Stiles, Tu, and Allen (1989) and was validated under the following conditions.

4.5.1 Accuracy

Cefazolin solutions were prepared by reconstituting a 1-g vial of cefazolin and adjusted volume to 100 ml with 5% dextrose injection. The solutions were pipetted of 5, 10 and 15 ml of cefazolin solution and transferred to 50-ml volumetric flasks and then adjusted to required volume with distilled water. Three sets of solution were prepared to obtain cefazolin concentrations of 1, 2 and 3 mg/ml, respectively. Percentage of analytical recovery of each sample was detected and calculated. The determination of accuracy test for ceftazidime was followed the same procedure described for cefazolin.

4.5.2 Precision

a) Within run precision

The within run precision was determined by analyzing three sets of the calibration curves in the same day. Peak areas of cefazolin and ceftazidime were compared and the percent coefficient of variation (%CV) for each concentration was determined.

b) Between run precision

The between run precision was determined by comparing each concentration of three sets of the calibration curves prepared on different days. Peak areas for the three standard curves of both drugs injected on different days were determined and the percent coefficient of variation (%CV) for each concentration was calculated.

4.5.3 Specificity

Under the chromatographic conditions selected, the peaks of other components in the sample must not interfere with the peak of the drug sample. The instability of drugs results in uncertainty of the analysis due to peak interferences. The possible degradation parts of cefazolin and ceftazidime were prepared by reconstituting a 1-g vial of drugs with 5% dextrose injection and adjusted the volume to 100 ml. Then the solutions were incubated in a water bath at 45 ^{o}C for 72 hours. Chromatograms were evaluated by comparing with those of the standard solutions.

4.5.4 Linearity

The linearity of standard curve was evaluated by plotting the standard curve between the peak areas of cefazolin and ceftazidime versus the concentrations of cefazolin and ceftazidime, respectively. Linear regression analysis was performed. The equation and the coefficient of determination (r^2) were calculated.

4.6 Analysis of amount of drug

The drug concentrations and percent recovery for each sample were calculated. The chromatograms were expressed as peak areas. Sample concentrations were calculated from a line generated by least squares regression from the average of the standard curve according to the equation: y=ax + b; where y is the peak area, x is the drug concentration, a is a slope of the curve and b is the interception at Y-axis. Drug recovery at time zero was considered to be 100%. The concentrations of drug at various sampling times were calculated and were expressed as a percentage of the initial concentration. A decrease in amount of drug to be less than 90% of drug remaining was considered to possibly indicate instability (Perry, Khalidi, and Sanders, 1987).

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5. Statistic analysis

Statistical analysis was performed on SPSS version 10.0 to test the research hypotheses following:

1. pH of a solution was changed from baseline over time (t= 2, 4, 8, 12, 24, and 48 hours).

2. Turbidity of a solution was changed from baseline over time (t= 2, 4, 8, 12, 24, and 48 hours).

3. Concentrations of cefazolin and ceftazidime were changed from baseline over time (t= 2, 4, 8, 12, and 24 hours).

The statistical analysis used was a one-way analysis of variance (ANOVA). The level of significance was set at α= 0.05. In fact, an analysis of covariance (ANCOVA) with repeated measures or an analysis of variance with repeated measures for changes from baselines was recommended. However, it was improper to analyze the data obtained in the present study.

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CHAPTER IV

RESULTS AND DISSCUSSION

1. Determination of physical incompatibility

1.1 Visual observation

The visual observation in this study was examined for any visible particulate matter, haze or turbidity, color change, or gas evolution. Both of PN solutions (TPN and PPN) appeared clear, colorless, free-flowing with no visible particulate matter, or gas evolution in normal fluorescent room light and high intensity light source.

The overall results of visual observation found that all of the cephalosporins in 5% dextrose injection without PN solutions were no visible particulate matter, haze or turbidity, and gas evolution in normal fluorescent room light and high intensity light source in the observation period, 48 hours. However, all of cephalosporins showed some degree of color change during the observation periods and seemed to depend upon the type of drugs and the mixing times. The results of color change are shown in Table 16. Cefazolin in 5% dextrose injection changed from colorless to pale yellow in 24 hours. For the other drugs in dextrose solution, they were pale yellow in color and slightly changed within the time observed. Cefoxitin and ceftazidime in 5% dextrose injection showed some levels of to be less color change observed in 8 and 12 hours, respectively. The color of cefotaxime and ceftriaxone in 5% dextrose injection began change within 4 hours of study. After 48 hours, the appearance cefoxitin, cefotaxime, ceftazidime and ceftriaxone were orange, orange, dark yellow and dark orange, respectively.

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Table 16. Color change of cephalosporins in 5% dextrose injection alone and in combination with PN solutions

Drug and PN solutions	Color change of solutions at various sampling times						
	0 hr	2 hr	4 hr	8 hr	12 hr	24 hr	48 hr
Cefazolin							
- D5W	0	0	0	0	0	1	1
- TPN	0	0	0	0	0	1	1
- PPN	0	0	0	0	0	1	1
Cefoxitin							
- D5W	1	1	1	2	3	3	4
- TPN	1	1	1	2	2	3	4
- PPN	1	1	1	2	2	3	4
Cefotaxime							
- D5W	1	1	2	2	2	3	4
- TPN	1	1	2	2	3	4	5 (P)
- PPN	1	1	2	2	3	4	5 (P)
Ceftazidime							
-D5W	1	1	1	1	2	2	3
- TPN	1	1	2	2	3	4	4
- PPN	1	1	1	2	2	3	4
Ceftriaxone							
- D5W	1	1	2	3	3	4	5
- TPN	1	1	2	2	3	4	5
- PPN	1	1	2	3	4 (P)	4 (P)	5 (P)

Color rating scale: 0 (colorless), 1 (pale yellow), 2 (yellow), 3 (dark yellow), 4 (orange), 5 (dark orange); P = precipitate formed

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From the overall results, cefazolin, cefoxitin, and ceftazidime in 5% dextrose injection in combination with both PN solutions indicated no visible particulate matter, haze, and gas evolution. In contrast, cefotaxime and ceftriaxone solutions showed visible particulate matter and turbidity. The appearance of white precipitate indicated the incompatibility of drugs with PN solutions. It was found that cefotaxime precipitated with both TPN and PPN solutions in 48 hours and ceftriaxone precipitated with PPN solution in 12 hours at room temperature. The same results were not found when cefazolin, cefoxitin and ceftazidime were used. Therefore, it was considered that they were visual compatible with TPN and PPN used in the study.

For the cephalosporins in 5% dextrose injection in combination with PN solutions, color change during the observation periods was observed (Table 16). Cefazolin in combination with PN solution changed from colorless to pale yellow in 24 hours. Cefoxitin and ceftazidime in combination with PN solution changed from pale yellow to orange within 48 and 24 hours, respectively. Cefotaxime and ceftriaxone in combination with PN solution changed from pale yellow to dark orange with formation of fine white precipitate within 48 and 12 hours, respectively.

The results were correlated with those obtained from drug solutions in the absence of PN solutions. The color change was the least for cefazolin solution while cefotaxime and ceftriaxone solutions presented the change within 4 hours. The white precipitates were also formed for cefotaxime with TPN and PPN added and ceftriaxone with PPN added. In combination with both TPN and PPN solutions the color of cefoxitin solution changes was in 8 hours. Ceftazidime solution in combination with TPN solution seemed to enhance the discoloration compared to in combination with PPN solution due to the shorter period needed for color change.

The color change of drug may be an indication of an interaction between the drug and components in nutrient solutions and seemed to possibly be correlated with the degradation of the drugs. This result was consistent with a previous study of stability of imipenem and cilastatin sodium in TPN solution which the color changed to darken and appeared to be closely related to the degradation of imipenem and/or cilastatin (Zaccardelli et al., 1990).

1.2 Turbidity measurements

The measurement of degree of turbidity is to determine any changes in haze intensity of solutions using the turbidity meter. The turbidity measurements are a quantification of light scattered by the undissolved particle in the sample. Numerous factors influence the degree of light scattering, including particle size, particle shape, particle and liquid medium color, and concentration of particle (Trissel and Bready, 1992). The results of determination of turbidity of cephalosporins in 5% dextrose injection alone and in combination with PN solutions are summarized in Table 17. The changes in FTU values of drug-PN solutions compared to drugs in 5% dextrose injection are shown in Table 18. The changes in FTU values compared to the value at the initial time are tabulated for drugs in dextrose solution in the absence and presence of the PN solutions (Table 19).

From the results the degree of turbidity of all cephalosporins in 5% dextrose injection ranged from 0.2 to 1.0. Accordingly, the changes in degree of turbidity showed that none of the drugs had any differences in FTU greater than 0.5 during the observation periods compared to the initial time indicating suitability of using the dextrose solution as drug diluent.

For cephalosporins in combination with PN solutions, cefazolin, cefoxitin, and ceftazidime had the FTU values of less than 1.0 in all sampling times observed. The changes in the FTU values of drug solution with PN solutions were not greater or less than 0.5 compared to drugs in 5% dextrose injection exhibiting no evidence of incompatibility of cefazolin, cefoxitin, and ceftazidime in PN solutions.

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Table 17. Degree of turbidity of cephalosporins in 5% dextrose injection alone and in combination with PN solutions

Drug and PN solutions	Formazine Turbidity Units at various sampling times (mean±SD, n=6)						
	0 hr	2 hr	4 hr	8 hr	12 hr	24 hr	48 hr
Cefazolin							
- D5W	0.25±0.01	0.24±0.018*	0.21±0.01*	0.26±0.01	0.25±0.01	0.21±0.01*	0.28±0.01*
- TPN	0.19±0.04	0.17±0.03	0.17±0.06	0.18±0.04	0.03±0.03*	0.03±0.02*	0.01±0.01*
- PPN	0.31±0.02	0.27±0.02	0.24±0.02*	0.25±0.03*	0.23±0.03*	0.22±0.03*	0.17±0.02*
Cefoxitin							
- D5W	0.69±0.01	0.69±0.01	0.62±0.01*	0.60±0.01*	0.52±0.01*	0.75±0.01*	0.77±0.01*
- TPN	0.63±0.03	0.58±0.02	0.56±0.02	0.58±0.02	0.78±0.12*	0.73±0.10*	0.75±0.08*
- PPN	0.54±0.03	0.49±0.01*	0.49±0.01*	0.51±0.02*	0.52±0.01	0.54±0.02	0.87±0.05*
Cefotaxime							
- D5W	1.06±0.01	1.06±0.01	0.99±0.01*	0.98±0.01*	0.96±0.01*	0.88±0.01*	0.76±0.01*
- TPN	0.20±0.03	0.18±0.03	0.16±0.04	0.17±0.04	0.19±0.05	0.16±0.05	4.32±0.72*
- PPN	0.39±0.09	0.41±0.07	0.39±0.07	0.37±0.09	0.37±0.09	0.37±0.10	14.18±0.47*

Table 17 (continued)

Drug and PN solutions	Formazine Turbidity Units at various sampling times (mean±SD, n=6)						
	0 hr	2 hr	4 hr	8 hr	12 hr	24 hr	48 hr
Ceftazidime							
- D5W	0.20±0.01	0.17±0.01*	0.16±0.01*	0.13±0.01*	0.11±0.01*	0.10±0.01*	0.09±0.01*
- TPN	0.30±0.03	0.30±0.03	0.29±0.02	0.27±0.05	0.18±0.03*	0.19±0.03*	0.19±0.04*
- PPN	0.16±0.02	0.10±0.05*	0.08±0.05*	0.04±0.02*	0.07±0.02*	0.06±0.02*	0.25±0.08*
Ceftriaxone							
- D5W	0.35±0.01	0.35±0.01	0.39±0.01*	0.36±0.01	0.34±0.01*	0.40±0.01*	0.39±0.01*
- TPN	1.36±0.17	1.14±0.20*	1.10±0.22*	1.05±0.19*	1.06±0.20*	0.93±0.12*	1.01±0.08*
- PPN	0.79±0.05	0.80±0.06	0.74±0.08	0.77±0.09	4.25±0.91*	9.44±1.86*	21.32±7.76*

* Significant changes from baseline (0 hr), $p < 0.05$

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Table 18. The differences in turbidity of drug-PN solutions compared to drug in 5% dextose injection

Drug solutions	Differences[a] in turbidity (FTU) between drug-PN solution and drug in 5% dextrose injection						
	0 hr	2 hr	4 hr	8 hr	12 hr	24 hr	48 hr
Cefazolin							
- TPN	0.07	0.06	0.03	0.08	0.23	0.18	0.27
- PPN	0.05	0.04	0.04	0.01	0.03	0.01	0.11
Cefoxitin							
- TPN	0.06	0.11	0.06	0.03	0.26	0.03	0.02
- PPN	0.15	0.20	0.13	0.09	0	0.21	0.09
Cefotaxime							
- TPN	0.86	0.88	0.83	0.81	0.77	0.72	3.56
- PPN	0.67	0.65	0.60	0.61	0.59	0.51	13.62

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Table 18 (continued)

Drug solutions	Differences[a] in turbidity (FTU) between drug-PN solution and drug in 5% dextrose injection						
	0 hr	2 hr	4 hr	8 hr	12 hr	24 hr	48 hr
Ceftazidime							
- TPN	0.10	0.12	0.12	0.14	0.07	0.09	0.10
- PPN	0.04	0.07	0.08	0.09	0.04	0.04	0.16
Ceftriaxone							
- TPN	1.00	0.79	0.71	0.69	0.72	0.53	0.62
- PPN	0.43	0.45	0.35	0.41	3.91	9.05	20.94

[a] Differences between the mean values representing in absolute value

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Table 19. The differences in turbidity of cephalosporins in 5% dextrose injection alone and in combination with PN solutions at the various sampling times compared to the initial time (0 hr)

Drug and PN solutions	Differences[a] in turbidity (FTU) between various sampling times and initial time					
	2 hr	4 hr	8 hr	12 hr	24 hr	48 hr
Cefazolin						
-D5W	0.03	0.06	0	0	0.05	0.02
-TPN	0.02	0.02	0.01	0.16	0.16	0.18
-PPN	0.04	0.07	0.06	0.08	0.09	0.14
Cefoxitin						
-D5W	0	0.07	0.09	0.17	0.06	0.08
-TPN	0.05	0.07	0.06	0.15	0.10	0.12
-PPN	0.05	0.05	0.03	0.02	0	0.32
Cefotaxime						
-D5W	0	0.07	0.08	0.10	0.18	0.30
-TPN	0.02	0.04	0.03	0.01	0.04	4.12
-PPN	0.02	0	0.02	0.02	0.02	13.79

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Table 19 (continued)

Drug and PN solutions	Differences[a] in turbidity (FTU) between various sampling times and initial time					
	2 hr	4 hr	8 hr	12 hr	24 hr	48 hr
Ceftazidime						
-D5W	0.03	0.04	0.07	0.09	0.10	0.11
-TPN	0.01	0.02	0.03	0.12	0.11	0.11
-PPN	0.06	0.08	0.12	0.09	0.10	0.09
Ceftriaxone						
-D5W	0.01	0.03	0	0.02	0.04	0.03
-TPN	0.22	0.26	0.31	0.30	0.43	0.35
-PPN	0.01	0.05	0.02	3.46	8.66	20.53

[a] Differences between the mean values representing in absolute value

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Conversely, cefotaxime in combination with TPN solution had an increase in degree of turbidity from 0.20±0.03 FTU at the beginning to 4.32±0.72 FTU at 48 hours. Cefotaxime in combination with PPN solution showed an increase in degree of initial turbidity from 0.39±0.09 FTU to 14.18±0.47 FTU at 48 hours. Such a dramatic increase in turbidity was also observed in ceftriaxone in combination with PPN solution. The turbidity increased from the initial value of 0.79±0.05 FTU to 4.25±0.91, 9.45±1.86, and 21.32±7.75 FTU at 12, 24, and 48 hours, respectively. The differences in turbidity of cefotaxime and ceftriaxone in PN solutions were more than 0.5 FTU compared to drug in dextrose solution. Such differences were greater depending on the time intervals after mixing. It could be defined as evidence of incompatibility of cefotaxime and ceftriaxone in PN solutions. These findings were similar to the visual observation of incompatibility of cefotaxime and ceftriaxone.

It was mentioned here that some researchers previously reported the lowest turbidity consistently visible to the unaided eye was 6 to 7 FTU (Trissel and Bready, 1992). However, in the present study, the turbidity found in cefotaxime and ceftriaxone combined with PN solutions were visible if FTU values higher than 4. Hence no turbidimetric evidences of physical incompatibility were recorded when the values obtained were less than 4 FTU.

In the present study, cefazolin, cefoxitin, and ceftazidime were physically compatible with both PN solutions for 48 hours at room temperature. However, cefotaxime and ceftriaxone exhibited incompatibility with TPN and PPN solutions. Surprisingly, for ceftriaxone, the incompatibility with PPN solution was much higher than with TPN solution. It was noted that TPN studied containing 4% amino acids and 25% dextrose and PPN containing 2.5% amino acids and 10% dextrose. From the result, it was possible that the type of drug, compositions of PN solution, contact time of drug and PN solution influencing on the compatibility.

Some researchers have found the visual incompatibility of cefazolin with central-line PN solutions. The central-line formulas contained 4.25% amino acids, 25% dextrose, electrolytes, and multivitamins (Trissel et al., 1997). Cefazolin showed small amount of precipitate formed immediately after admixing with central-line PN solution (Trissel et al., 1997). However, the result was in contrast to the study of Baptista and Lawrence (1985) who found that cefazolin and cefoxitin at concentration of 20 mg/ml

were visually compatible with total nutrient admixtures containing 5% amino acids, 20% dextrose, 3% lipid emulsion, and electrolytes, observed at 0, 1, and 4 hours after mixing.

In addition, Veltri and Lee (1996) reported that cefotaxime and ceftazidime at concentration of 60 mg/ml were compatible with the peripheral-line and the central-line PN solutions. The central-line formula contained 3% amino acids, 20% dextrose and electrolytes and the peripheral-line formula contained 2% amino acids, 10% dextrose, and electrolytes. Observations were recorded at the time at initial mixing, 1 and 2 hours after mixing.

In 1999, the physical compatibility study of drugs during simulated Y-site injection into 3-in-1 parenteral nutrition admixtures has been reported that cefazolin 20 mg/ml, cefoxitin 20 mg/ml, cefotaxime 20 mg/ml, ceftazidime 40 mg/ml, and ceftriaxone 20 mg/ml were physically compatible with 3-in-1 parenteral nutrition admixtures for 4 hours at 23 $^{\circ}$C (Trissel et al., 1999). The parenteral nutrition admixtures studied includede formula for peripheral-line infusion containing 3% amino acids, 5% dextrose, and electrolytes; formula for central-line infusion consisting of 4.9% amino acids, 20% dextrose, and electrolytes; and formula for bone marrow transplant patients containing 6% amino acids, 11% dextrose, and electrolytes (Trissel et al., 1999). The previous compatibility studies were, however, mostly performed less than 4 hours after mixing and only a few drug concentrations have been tested.

There are many factors influencing on compatibility of drugs with parenteral nutrient solution. Differences in drug concentrations, nutrient formulations, temperature, contact times, and acidity of the solution may all play a role in the disparities (Trissel et al., 1997). Hence, the possibility of differing compatibility results from greater or lesser drug concentrations should be kept in mind.

It would be bear in mind that physical or visual compatibility data may serve as guidelines for the practitioner in preparing admixtures. However, it is usual to be a complete indication for compatibility of drug and parenteral nutrient solution. An investigation of the chemical stability of these mixtures would provide more information to ensure the acceptability of particular drug admixtures.

2. Determination of chemical incompatibility by pH measurement

Chemical incompatibility involves the irreversible degradation of component such that the chemical integrity and potency of the active ingredient are no longer within the specified limits (Manning and Washington, 1992). The pH of solution is the important factors that influence the decomposition rate of some drugs.

The pH values of commonly PN solutions are ranging from 5.0 to 8.0 (Percy and Rho, 1993). The pH of the PN solution is determined mainly by the concentration and titratable acidity of the amino acids used (Manning and Washington, 1992).

In this study, the mean pH values of freshly prepared TPN and PPN solutions were 6.57±0.06 and 6.87±0.06, respectively. The mean pH values of TPN and PPN solutions after 24 hours at room temperature were 6.50±0.05 and 6.83±0.06, respectively. The values were slightly changed to 6.43±0.06 for TPN and 6.80±0.00 for PPN after storage for 48 hours.

The values of pH of cephalosporins in 5% dextrose injection alone and in combination with PN solutions are shown in Tables 20. The pH values of some cephalosporins in 5% dextrose injection alone tended to increase during the observation period. The initial pH values of cefazolin (5.40), cefoxitin (5.20) and ceftriaxone (6.60) slightly increased to 6.30, 7.12±0.07, and 7.20, respectively after 48 hours of mixing. In contrast, the pH values of cefotaxime tended to slightly decrease with time and the pH values of ceftazidime seemed to be stable throughout the experimental period.

The pH values of cephalosporins in 5% dextrose injection in combination with PN solutions were found to be slightly higher than in dextrose solutions and were in the range of 6-7. No maximal obvious changes in the pH values were found during the observation period. In some cases, the pH values of solutions studied demonstrated statistically significant differences from the initial value, however the pH of the solutions were still in the same range, 5-7 for drugs in dextrose solution and 6-7 for drugs in dextrose solution with PN solutions added.

Table 20. The pH values of cephalosporins in 5% dextrose injection alone and in combination with PN solutions

Drug and PN solutions	pH values at various sampling times(mean±SD, n=6)						
	0 hr	2 hr	4 hr	8 hr	12 hr	24 hr	48 hr
Cefazolin							
-D5W	5.40±0.00	5.70±0.00*	6.00±0.00*	6.10±0.00*	6.20±0.00*	6.30±0.00*	6.30±0.00*
-TPN	6.38±0.04	6.47±0.05*	6.50±0.00*	6.60±0.00*	6.60±0.00*	6.50±0.00*	6.45±0.05
-PPN	6.75±0.05	6.75±0.05	6.72±0.04	6.68±0.04	6.67±0.05	6.65±0.05	6.58±0.04*
Cefoxitin							
-D5W	5.20±0.00	5.70±0.00*	6.15±0.08*	6.23±0.05*	6.60±0.00*	7.03±0.05*	7.12±0.08*
-TPN	6.58±0.04	6.70±0.00*	6.70±0.00*	6.80±0.00*	6.70±0.00*	6.60±0.00	6.55±0.05
-PPN	6.67±0.05	6.70±0.00	6.72±0.04	6.82±0.04*	6.88±0.04*	6.87±0.05*	6.80±0.00*
Cefotaxime							
-D5W	5.30±0.00	5.20±0.00*	4.95±0.05*	5.00±0.00*	4.83±0.05*	4.70±0.00*	4.67±0.05*
-TPN	6.60±0.00	6.50±0.00*	6.50±0.00*	6.48±0.04*	6.45±0.05*	6.30±0.00*	6.05±0.05*
-PPN	6.70±0.00	6.67±0.05	6.67±0.05	6.62±0.04	6.62±0.07	6.52±0.04*	6.10±0.00*

Table 20 (continued)

Drug and PN solutions	pH values after mixing time (mean±SD, n=6)						
	0 hr	2 hr	4 hr	8 hr	12 hr	24 hr	48 hr
Ceftazidime							
-D5W	6.80±0.00	6.70±0.00*	6.70±0.00*	6.77±0.05	6.73±0.05	6.73±0.05	6.70±0.00*
-TPN	6.45±0.05	6.60±0.00*	6.60±0.00*	6.70±0.00*	6.60±0.00*	6.63±0.05*	6.70±0.00*
-PPN	6.85±0.05	6.88±0.04	6.87±0.05	6.98±0.04*	7.00±0.00*	6.97±0.05*	6.93±0.05
Ceftriaxone							
-D5W	6.60±0.00	6.70±0.00*	6.73±0.05*	6.83±0.05*	7.00±0.00*	7.10±0.00*	7.20±0.00*
-TPN	6.63±0.05	6.60±0.00	6.70±0.00	6.65±0.05	6.70±0.00	6.83±0.08*	6.92±0.10*
-PPN	6.75±0.08	6.78±0.10	6.87±0.05	6.88±0.04	6.88±0.04	6.90±0.06	6.95±0.08*

* Significant changes from baseline (0 hr), $p < 0.05$

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From results of physical incompatibility, cefotaxime and ceftriaxone were showed some incompatibilities with PN solutions. However, the pH values of cefotaxime in combination with PN solutions were slightly decreased throughout the observation period while the pH values of ceftriaxone in combination with PN solutions were slightly increased throughout the observation period. The changes in pH values in the present study were unable to clearly indicate any incompatibility of drugs and PN solutions investigated.

The TPN studied containing 4% amino acids and 25% dextrose and PPN containing 2.5% amino acids and 10% dextrose. However, the pH values of these solutions were not markedly different and the final pH values when PN solutions added in drug solutions were also similar. There are also other factors influencing the compatibility of drug-PN combination solutions, namely, the drug concentration and properties. The final outcome will be a result of a multifactorial interaction (Allwood and Kearney, 1998).

The factors influencing the final pH of the mixture and thus the drug stability (Allwood and Kearney, 1998) are (1) The commercial source of the amino acid infusion. Amino acid infusions from different manufacturers can vary in pH between around approximately 5.0 and 7.4. In addition, each amino acid mixture will vary in buffering capacity. (2) The final concentration of amino acid. This will depend on amino acid concentration in the final mixture, which results in altering the buffering capacity. Increasing the final amino acid concentration enhances buffering capacity and vice versa. (3) The final concentration of glucose. Although glucose infusions are acidity but the buffering capacity of the amino acid infusion and phosphate additive will predominate as pH regulator.

Most of cephalosporins have pH values ranging from 4.5 to 7.5. Cefazolin sodium solutions are relatively stable at pH 4.5 to 8.5. Rapid hydrolysis of the drug occurs at pH above 8.5, and at pH below pH 4.5, precipitation of the insoluble free acid may occur. Cefotaxime sodium in aqueous solutions is stable at pH 5 to 7. Cefotaxime sodium should not be diluted in solutions with pH greater than 7.5. Cefoxitin sodium in aqueous solution is stable at pH 4 to 8. At pH less than 4, precipitation of the free acid may occur. Above pH 8, hydrolysis of the β-lactam group may result. Ceftazidime in aqueous solution is stable at pH 5 to 8. Ceftriaxone sodium in solution is

stable in range of 6-8 and maximum stable at pH 2.5 to 4.5 and 7.2 (The Board of Directors of the American Society of Health-System Pharmacists, 2002). Hence, there were no effects of pH on the stability of drugs in combination with PN solutions as the pH of the solutions were in the range of 6-7.

In addition, the solubility of weak acid drugs are known to correlate with pH and pK_a. For a weak acid, the solubility of drugs is high in solution which pH higher than pK_a about 2 units, due to an increase in ionized form of drug (Newton, 1978; Lund, 1994). Cephalosporins as a weak acid drug have pK_a between 2 to 4 (The Board of Directors of the American Society of Health-System Pharmacists, 2002). The pH values of solution studied were higher than pK_a of cephalosporins for at least 2 units, so, it could not theoretically describe any effect of pH on the incompatibility of drugs in combination with PN solution.

Finally, even the changes in pH were observed during the observation period. However, all pH values were not appeared to influence on compatibility in any of the admixtures studied and no chemical incompatibility was indicated by pH measurement in present study.

3. Stability of drug in PN solution

The drug stability was determined by high-performance liquid chromatography analysis. The HPLC condition defined UV detector wavelength at 254 nm. This wavelength of absorbances was in agreement with those obtained by UV spectrophotometry which was in a range of 240-280 nm. The drug concentrations in solutions were calculated from a regression line generated by least squares analysis from the calibration curves according to the following equations: $y = 72.46x + 0.4191$ for cefazolin and $y = 87.366x + 5.3666$ for ceftazidime; where y = peak area, x = drug concentration (mg/ml) (Figures 3 and 4). The retention times of cefazolin and ceftazidime in 5% dextrose solution and PN solutions were approximately 3 to 4 minutes. The validations of HPLC assay for cefazolin and ceftazidime are shown in Appendix C.

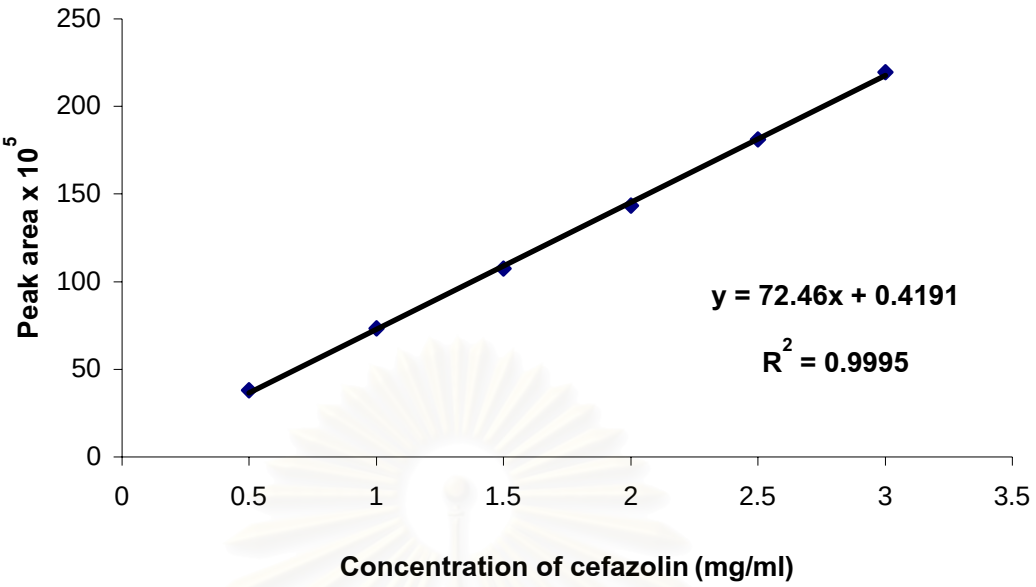

Figure 3. Calibration curve of cefazolin in 5% dextrose solution

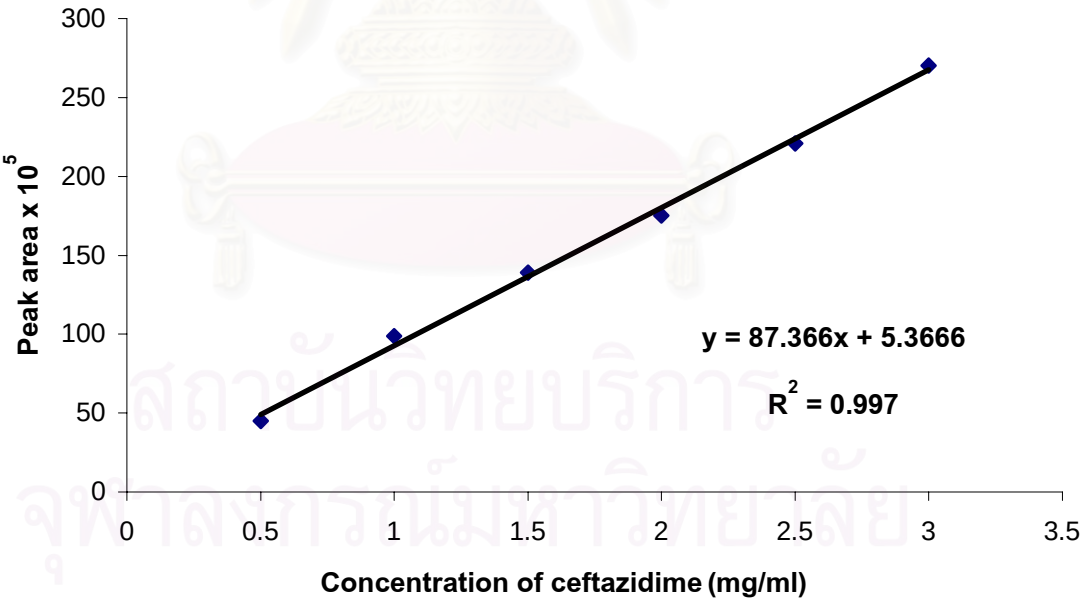

Figure 4. Calibration curve of ceftazidime in 5% dextrose solution

Table 21. Concentrations (mg/ml) and percentages of drug remaining of cefazolin in different solutions at various sampling times

Solutions	Concentration (% remaining) of cefazolin (mean±SD, n=3)					
	0 hr	2 hr	4 hr	8 hr	12 hr	24 hr
D5W	2.049 ± 0.019 (100)	2.008 ± 0.021 (97.97)	1.964 ± 0.013* (95.87)	1.946 ± 0.003* (94.99)	1.934 ± 0.002* (94.41)	1.930 ± 0.001* (94.22)
TPN	2.059 ± 0.030 (100)	1.998 ± 0.020* (97.05)	1.981 ± 0.001* (96.21)	1.963 ± 0.013* (95.33)	1.948 ± 0.002* (94.62)	1.919 ± 0.016* (93.23)
PPN	2.062 ± 0.014 (100)	2.026 ± 0.004* (98.26)	1.963 ± 0.009* (95.25)	1.939 ± 0.010* (94.09)	1.924 ± 0.007* (93.36)	1.905 ± 0.007* (92.43)

* Significant changes from baseline (0 hr), $p < 0.05$

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Table 22. Concetrations (mg/ml) and percentages of drug remaining of ceftazidime in different solutions at various sampling times

Solutions	Concentration (% remaining) of ceftazidime (mean±SD, n=3)					
	0 hr	2 hr	4 hr	8 hr	12 hr	24 hr
D5W	1.902 ± 0.001 (100)	1.882 ± 0.014 (98.98)	1.811 ± 0.004* (95.33)	1.761 ± 0.010* (93.39)	1.735 ± 0.007* (91.86)	1.643 ± 0.007* (91.07)
TPN	1.903 ± 0.008 (100)	1.882 ± 0.002 (98.94)	1.799 ± 0.007* (94.77)	1.764 ± 0.009* (92.93)	1.704 ± 0.007* (89.91)	1.579 ± 0.019* (83.52)
PPN	1.896 ± 0.008 (100)	1.873 ± 0.010 (98.84)	1.786 ± 0.010* (94.40)	1.725 ± 0.009* (91.26)	1.665 ± 0.010* (88.22)	1.504 ± 0.008* (80.01)

* Significant changes from baseline (0 hr), $p < 0.05$

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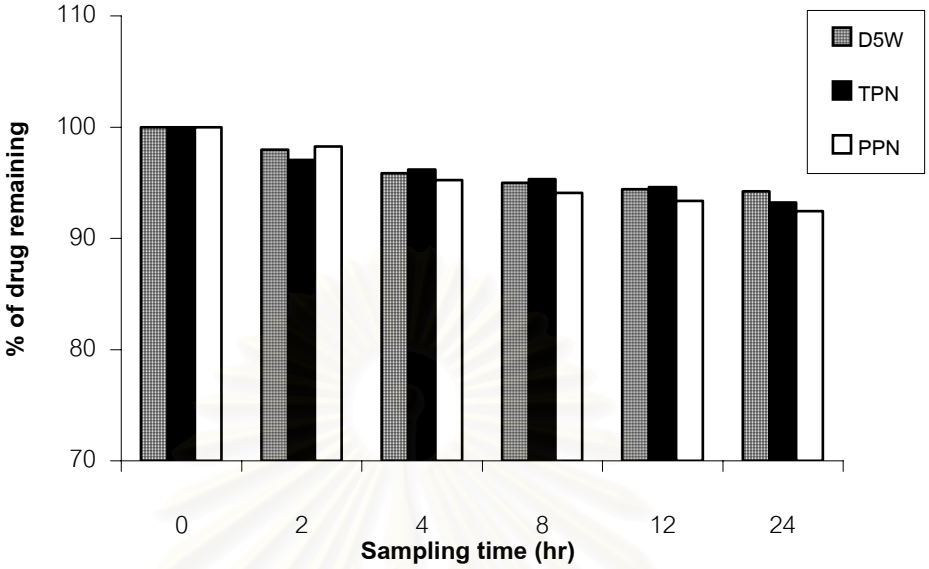

Figure 5. Stability of cefazolin in different solutions at various sampling times

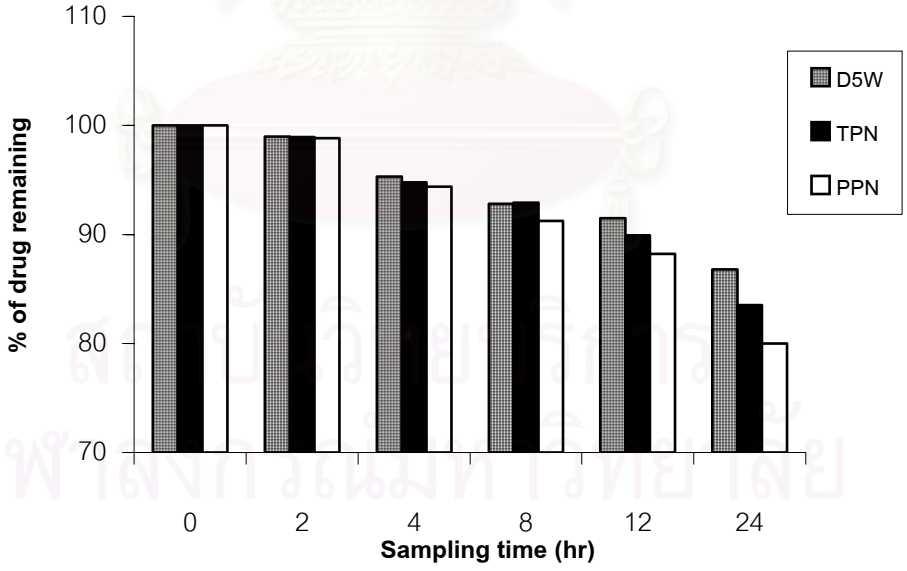

Figure 6. Stability of ceftazidime in different solutions at various sampling times

The concentrations of cefazolin and ceftazidime in 5% dextrose solution (D5W) at the various sampling times are shown in Tables 26 and 27, respectively. The percentages of the drug remaining of cefazolin and ceftazidime at the subsequent time intervals are shown in Tables 28 and 29, respectively. It was noted that the percentage of drug recovery at initial time was considered to be 100%. After 24 hours, the concentration of cefazolin was 94.22 $\pm$ 0.05%, 93.23 $\pm$ 0.76% and 92.43 $\pm$ 0.32% of the initial concentration in D5W, TPN and PPN, respectively. Consequently, cefazolin was stable for 24 hours in D5W and both PN solutions, TPN and PPN, as the percent recovery was not less than 90%.

Similarly, ceftazidime was stable for only 8 hours in TPN and PPN. After 12 hours, the remaining amounts of ceftazidime were 89.91 $\pm$ 0.36% and 88.22 $\pm$ 0.50% of the initial concentration in TPN and PPN, respectively. Moreover, after 24 hours, the drug stability was further decreased and only 83.52 $\pm$ 0.97% and 80.01 $\pm$ 0.42% of the initial concentration were remained in TPN and PPN, respectively. In contrast, ceftazidime in D5W was stable throughout the experimental period as the drug remaining was higher than 90% even the concentrations of drug seemed to decrease with time. There were also statistically significant differences between the concentrations of the drugs at the beginning time (0 hr) and the other sampling times.

The stability of cefazolin and ceftazidime in different solutions are also illustrated in Figures 5 and 6. From these findings the stability of the drugs in various solutions was different depending upon the types of drug and the compositions of PN solutions.

The stability result was in agreement with physical incompatibility studies in that cefazolin solutions alone and combination with PN solutions were physically compatible throughout 48 hours at room temperature. Similarly, the amount of cefazolin remaining at 24 hours in all solutions was more than 90% of initial concentration. Although cefazolin was stable for a day, the color changes were observed within at 24 hours in all solutions tested.

In contrary to cefazolin, ceftazidime was physically compatible with PN solutions for 48 hours at room temperature, however, it was stable in PN solutions for only 8 hours. While color changes of ceftazidime were observed at 12, 4, and 8 hours in D5W, TPN, and PPN solutions, respectively. In previous study, the color changes seem to correlate with the degradation of drugs (Zaccardelli et al., 1990). The findings from the present study might suggest that the change in color was not always indicated the degradation or the loss of therapeutic activity of drugs. The finding was similar to the work of Trissel (1980).

The stability of cefazolin sodium (500 mg/ml) in commonly used intravenous solutions has been previously reported to be stable for one week at either 5 or 25 $^{\circ}$C. However, it is recommended that solutions of cefazolin sodium should be discarded after 24 hours storage at 25 $^{\circ}$C in order to minimize the color, pH change as well as the potential for the growth of microorganism (Bornstein et al., 1974).

The stability of ceftazidime in normal saline and dextrose solution was recently studied by Walker and Dranitsaris (1988). After the study period of a month, the pH did not change in either normal saline or dextrose solution. However, the color change gradually became a darken yellow and the HPLC analysis showed a dramatic loss in concentration over the study period. Ceftazidime at a concentration of 40 mg/ml in either normal saline or dextrose in water retained 90% of the initial concentration for only 24 hours at room temperature.

In addition, Wade et al. (1991) studied the stability of ceftazidime under condition simulating administration via a Y-injection site. Three PN solutions containing 25% dextrose with 0, 2.5%, and 5% amino acids were used. They found that solutions containing ceftazidime at a concentration of 20 or 40 mg/ml may be coadministered with standard PN solutions, via a Y-injection site. Alternatively, ceftazidime may be added directly to containers of PN solution if infusion time is less than 12 hours for a final drug concentration of 6 mg/ml or less than 6 hours for a concentration of 1 mg/ml; these solutions may be stored at 4 $^{\circ}$C for up to three days. These findings were in agreement with the results obtained here.

It was mentioned that in the present study the drugs were not protected from light owing to the lack of light sensitivity of drugs. However, the effect of temperature, however, on decomposition of drug was reported (Walker and Dranitsaris, 1988; Stile, Tu, and Allen, 1989). The degradation products of cefazolin and ceftazidime were observed upon increasing the temperature to 45 $^{\circ}$C for 72 hours (figures 2B and 5B in Appendix C). Hence, the direct sunlight and high temperature upon storage should be avoided in order to prolong the shelf-life of drugs.

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CHAPTER V

CONCLUSIONS

There are many factors that influence on compatibility and stability of drugs and PN solution. This present study focused on compatibility of two types of PN solutions typically used in Ramathibodi Hospital with cephalosporins, namely, cefazolin (Fazolin®), cefoxitin (Cefxitin®), cefotaxime (Claraxim®), ceftazidime (Cef-4®), and ceftriaxone (Cef-3®). Stability of cefazolin and ceftazidime in PN solutions was also determined by HPLC analysis. The experiment simulated the Y-site administration by using the volume ratio of drug solution to PN solution of 1:1 and the final concentration of drug was 10 mg/ml. The following conclusions were obtained from the study.

Physical incompatibility, determined by visual observation and measurement of degree of turbidity, indicated that solutions of cefazolin, cefoxitin, and ceftazidime were free from visible particulate matter, haze, and gas evolution. They were physically compatible with PN soluion prepared for 48 hours at room temperature. Conversely, solutions of cefotaxime and ceftriaxone showed visible particulate matter and haze. All of the cephalosporin solutions presented some color changes which seemed to enhance with the contact time. The formazine turbidity units were markedly increased in cefotaxime in combination with TPN and PPN solutions and ceftriaxone in combination with PPN solution.

The changes in pH values could not indicate the chemical incompatibility of drugs and PN solutions because the values were in the range of 6-7 which presented no effect on drug stability. There were no obvious trended of the pH values over the sampling time for all of cephalosporin-PN combination solutions although the values were significantly differences.

The HPLC analysis was certified that cefazolin remained stable for 24 hours at room temperature when combined with PN solutions and ceftazidime, however, in combination with either TPN or PPN solutions were stable for approximately 8 hours at room temperature.

From the physical incompatibility results, cefotaxime and ceftriaxone showed some degree of physically incompatible with PN solution tested and should be administered through a separate line in order to avoid the potential for incompatibilities. Cefazolin, cefoxitin and ceftazidime were undoubtely coadministered with PN solutions via Y-injection sites. The continuous infusion of ceftazidime-PN solutions for a long time interval should be avoid in order to certain that the drug concentration given has reached the therapeutic dose.

In addition, only physical compatibility data were different to quarantee the proper use of drug in combination with PN solutions. For examples, The color change of drugs was not always an indication of degradation or loss of therapeutic activity of drug.

From the overall results suggested that in practical all of cephalosporins used in this study may be coadministered with PN solutions via Y-injection sites because they were illustrated physical incompatibility for at least 8 hours after mixing. In general, the contact time between two or more solutions administered through a Y-injection site tends to be short, often in the range of 15 to 30 minutes and generally not more than 60 minutes.

There were some factors which affected drug and PN compatibility including type of drug, composition of PN solution, contact time between drug and nutrient solution. The coadministration of drugs and PN solutions should never be undertaken without sufficient compatibility and stability data.

The limitation of the study was that only compatibility and chemical stability were addressed. The pharmacological activity of the drugs in combination with PN solutions was not assessed. Patient who needs the PN solutions which are substantially modified from the solutions used in this study as well as the variations in drug concentrations, could potentially affect any compatibilities and stability of drug. Future studies are needed to address the unresolved issues.

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APPENDICES

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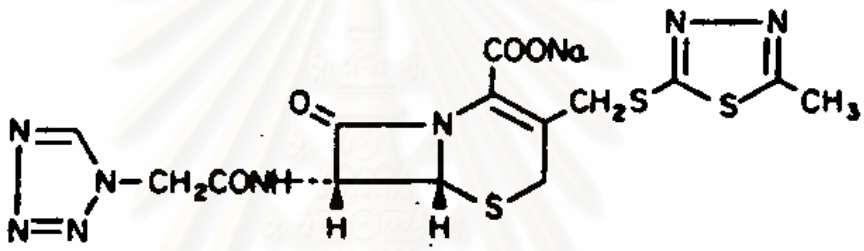
APPENDIX A

CEPHALOSPORINS

(Florey, 1975, 1982, 1990)

Cefazolin

Chemical name	3-[[(5-Methyl-1, 3, 4-thiadiazol-2-yl)thio] methyl] 8-oxo-7-[2 (1H-tetrazol-1-yl) acetomido]-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid
Structure	$C_{14}H_{14}N_8O_4S_3$

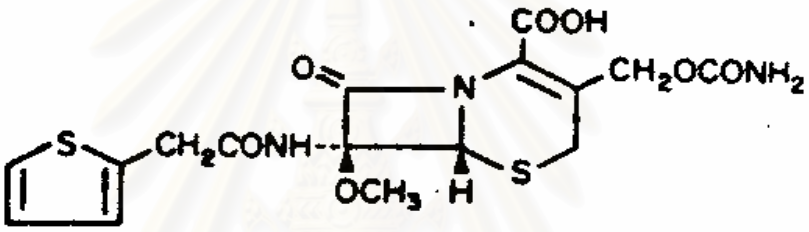


MW	454.52
Appearance	White to slightly off white, odorless.
Solubility	1.1 mg/ml in water, 1.7 mg/ml in methanol and 0.02 mg/ml in chloroform at room temperature ($25^{\circ}C \pm 1^{\circ}C$).
pK_a	2.15, and 2.05
pH	Between 4.5 and 7.0
Administration	Cefazolin sodium is administered by IV injection or infusion or by deep IM injection. The drug has also been administered intraperitoneally in dialysis solutions.
Dosage	The usual dosage of cefazolin is 250 mg every 8 hours to 1.5 g every 6 hours, depending on the severity of the infection and the susceptibility of the causative organism. In severe, life-threatening infections, up to 12 g daily may be required.

Stability	Prior to reconstitution, powders in their original containers are stable for up to 24 months. After reconstitution, solutions retain their potency for 24 hours at room temperature or for 10 days if refrigerated.

Cefoxitin

Chemical name	3-[[(Aminocarbonyl) oxy] methyl]-7-methoxy-8-oxo-7 [(2-thienylacetyl) amino]-5—thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid, sodium salt
Structure	$C_{16}H_{16}N_3NaO_7S_2$



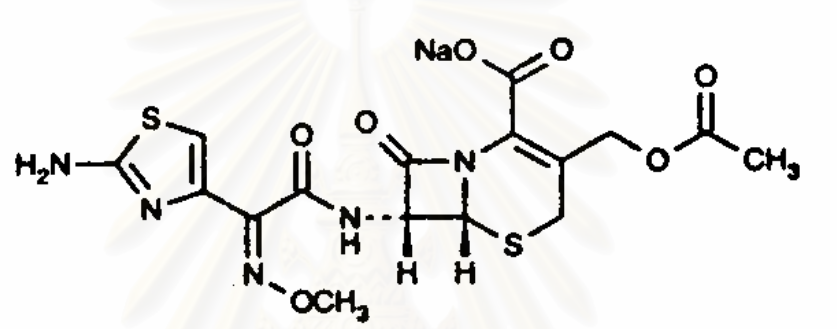
MW	449.44
Appearance	White to off-white granules or powder having a slight characteristic odor.
Solubility	Very soluble in water, sparingly soluble in methanol and dimethylformamide, slightly soluble in ethanol and insoluble in ether, chloroform, acetone aromatic and aliphatic hydrocarbons.
pH	Between 4.5 and 8.0
Administration	Cefoxitin sodium is administered by IV injection infusion. The drug also has been administered by IM injection.
Dosage	The usual adult dosage of cefoxitin is 1-2 g every 6-8 hours, depending on the severity of the infection and the susceptibility of the causative organism. In severe, life-threatening infections, up to 12 g daily may be required.
Stability	The solution stability of sodium cefoxitin was also studied after constitution with frequently used IV and IM additives. Stability in these systems was essentially the same as that observed for

unbuffered solutions. In these studies, sodium cefoxitin was shown to maintain potency in solution for at least 30 days at 5°C and for 30 weeks when stored in the frozen state.

Cefotaxime

Chemical name (6R-trans)-3-[(Acetyloxy) methyl]-7-[[(2-amino-4-thiazolyl) (methoxy-imino) acyl] amino]-8-oxo-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid monosodium salt

Structure $C_{16}H_{16}N_5O_7S_2Na$



MW 477.23

Appearance White to creamy white crystalline powder, odorless and has a salty taste at the beginning, followed by bitterness.

Solubility Freely soluble in water (0.5 g soluble in 5 ml), slightly soluble in alcohol (absolute, 95%), insoluble in chloroform.

pH The pH of a 10% aqueous solution is 4.5 to 6.5.

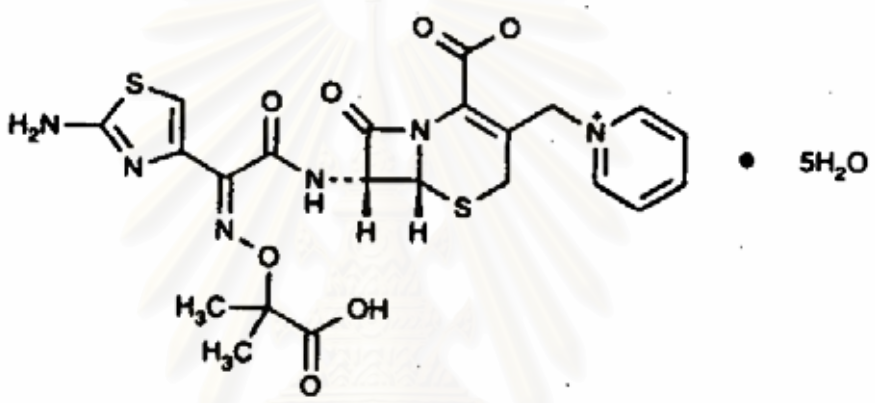
Administration Cefotaxime sodium is administered IV or deep IM injection. The drug should be given IV rather than IM in patients with septicemia, bactericemia, peritonitis,meningitis, or life-threatening infections.

Dosage The usual adult dosage of cefotaxime for uncomplicated infections is 1 g IM or IV every 12 hours. Moderate to severe infections usually respond to 1-2 g IM or IV every 8 hours. Severe or life-threatening infections may require 2 g IV every 4 hours.

Stability	The extemporaneously prepared solutions are stable in their containers for 24 hours at room temperature, 10 days when refrigerated at 5 °C or less, or at least 13 weeks when frozen.

Ceftazidime

Chemical name	1-[[(6R,7R) -7-(2-Amino-4-thiazoyl) glyoxyl-amido]-2-carboxy-8-oxo-5-thia-1-azabicyclo [4.2.0] —oct-2-en-3-yl] methyl] pyridinium hydroxide, inner salt, 7^2 (Z)-[*o*-(1-carboxy-1-methyl-ethyl)oxime]
Structure	$C_{22}H_{22}N_6O_7S_2 \bullet 5H_2O$



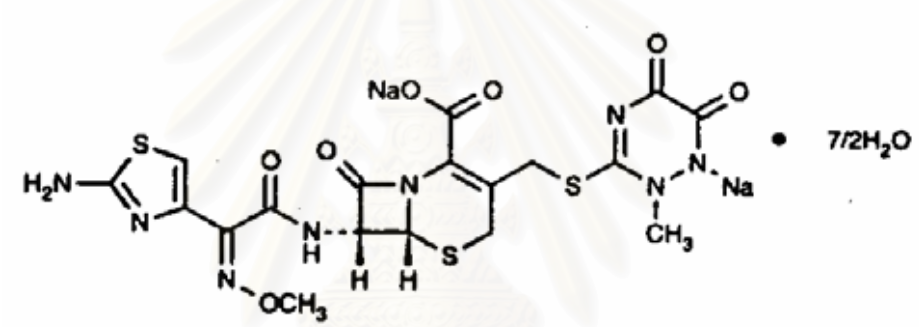
MW	546.30
Appearance	White to off-white powder.
Solubility	5 mg/ml in water and less than 1 mg/ml in alcohol.
pK_a	1.9, 2.7 and 4.1
pH	Between 5 and 7.5.
Administration	Ceftazidime is administered by intermittent IV injection or infusion or by deep IM injection. Ceftazidime sodium has been administered intraperitoneally in dialysis solution.
Dosage	The usual adult dosage of ceftazidime for the treatment of most infections caused by susceptible organisms is 1 g given IV or IM every 8 or 12 hours, in severe or life-threatening infections dosage is 2g every 8 hours. The maximum dosage of ceftazidime is 6 g daily.
Stability	Drug for injection is essentially stable in the dry state and can be stored at room temperature, but should be protected from light.

When reconstituted with water for injections loss of potency occurs slowly and it is recommended that it should be used within 6 hours if stored at room temperature and 24 hours if in refrigerator.

Ceftriaxone

Chemical name 5-Thia-1-azabicyclo [4.2.0] oct-2-ene-carboxylic acid, 7-[[(2-amino 4-thiazolyl) (methoxyimino)acetyl]amino]-8-oxo-3-[(1,2,5,6-tetrahydro-2-methyl-5,6-dioxo-1,2,4-triazin-3-yl)thio]methyl]-, disodium salt, [6R [6α, 7β (Z)]]-, hydrate (2:7)

Structure $C_{18}H_{16}N_8O_7S_3 \cdot 3\,\frac{1}{2}\,H_2O$



MW 661.61

Appearance White to yellowish-orange crystalline powder.

Solubility 400 mg/ml in water and 1 mg/ml in alcohol at 25 °C.

pK_a 3, 3.2 and 4.1

pH Between 6.0 and 8.0

Administration Cetriaxone sodium usually is administered by IV infusion or deep IM injection.

Dosage The usual adult dosage of ceftriaxone for treatment of most infections caused by susceptible organisms (except meningitis) is 1-2 g given once daily or in equally divided doses twice daily, depending on the type and severity of the infection. The maximum adult dosage is 4 g daily.

Stability Ceftriaxone sodium solutions containing 10-40 mg/ml are stable in glass or PVC containers for 3 days at room temperature or 10 days when refrigerated at 4 °C.

APPENDIX B

Concentrations of chemical for PN preparation

Commercial product	Concentration per ml
10% Amino acid	Amino acid 0.1 g
50% Dextrose	Dextrose 0.5 g
5% Dextrose	Dextrose 0.05 g
3% Sodium chloride	Sodium 0.5 mEq
	Chloride 0.5 mEq
8.71% Dipotassium phosphate	Potassium 1 mEq
	Phosphate 0.5 mmole (1 mEq)
29.4% Potassium acetate	Potassium 3 mEq
	Acetate 3 mEq
10% Calcium gluconate	Calcium 0.25 mmole (0.5 mEq)
50% Magnesium sulfate	Magnesium 4 mEq

Millimole (mM) = weight (mg) / molecular weight

Milliequivalent (mEq) = mM x valency of dissociated species

$$\text{Volume requirement of stock solution (ml)} = \frac{\text{Concentration (mEq or mM) per liter in PN solution} \times \text{Total volume of PN solution (L)}}{\text{Concentration (mEq or mM) per milliliter of stock solution}}$$

Composition of amino acid solution (Amiparen-10®)

Amino acids	Composition in 100 ml
L-Leucine	1.400 g
L-Isoleucine	0.800 g
L-Valine	0.800 g
L-Lysine Acetate	1.480 g
L-Threonine	0.570 g
L-Tryptophan	0.200 g
L-Methionine	0.390 g
L-Phenylalanine	0.700 g
L-Cysteine	0.100 g
L-Tyrosine	0.050 g
L-Arginine	1.050 g
L-Histidine	0.500 g
L-Alanine	0.800 g
L-Proline	0.500 g
L-Serine	0.300 g
Aminoacetic acid	0.590 g
L-Aspartic acid	0.100 g
L-Glutamic acid	0.100 g
Essential amino acids	29.55 g
Nonessential amino acids	20.45 g
Total amino acids	50 g
Branched chain amino acids	30 g/L
Sodium	2 mEq/L
Acetate	120 mEq/L
Total Nitrogen	8 g
Kcal / L	400
Osmolarity	960 mOsmol / L

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APPENDIX C

VALIDATION OF THE HPLC ANALYSIS

Validation for the quantitative determination of cefazolin by HPLC

1. Accuracy

These experiments were conducted to verify that the methods used for cefazolin analysis in PN solutions were sufficiently accurate and precise. Three sets of each concentration were prepared and the test result was calculated as percentage of analytical recovery (Table 1B).

$$\text{Accuracy (\%CV)} = \frac{SD}{\text{Mean}} \times 100$$

Where SD = Standard deviation of samples for each concentration

Mean = Mean experimental condition

Coefficient of variation within 2% was considered as acceptable (Synder, Kirkland, and Glajoh, 1997). The mean percent analytical recovery was high, 100.71±1.26% with low %CV (coefficient of variation), 1.25%, which indicated that HPLC method was accurate for quantitative analysis of cefazolin.

2. Precision

The precision of an analytical method is usually expressed as the standard deviation of relative standard deviation (coefficient of variation). Table 2B illustrates the data of within run precision, a measure of either degree of reproducibility or repeatability of the analysis of three sets of calibration curve in the same day, and Table 3B illustrates the data of between run precision determined by comparing three sets of calibration curve performed on different days. All coefficients of variation values were in range of 0.1329-2.4072. This indicated that the HPLC method used were precise for quantitative of cefazolin. The %CV of approximately 1 to 2% was acceptable. Some errors (such as sample preparation technique etc.) can have an effect on precision (Synder, Kirkland, and Glajoh, 1997).

Table 1B. Accuracy data of cefazolin

Expected concentration (mg/ml)	Analytical concentration (mg/ml)	% Recovery
1	1.0129	101.29
	1.0153	101.53
	1.0221	102.21
2	1.9909	99.54
	1.9903	99.51
	1.9688	98.44
3	3.0220	100.73
	3.0089	101.59
	3.0477	101.59
		Mean= 100.71
		SD= 1.26
		%CV= 1.25

Table 2B. Within run precision data of cefazolin

Concentration (mg/ml)	Peak area			Mean	SD	%CV
	n_1	n_2	n_3			
0.5	37.6821	38.0993	37.1211	37.6342	0.4908	1.3042
1.0	73.3529	74.8017	73.6344	73.9297	0.7682	1.0391
1.5	107.0908	107.6357	108.1801	107.6355	0.5446	0.5060
2.0	142.9195	143.6357	144.1195	143.5582	0.6037	0.4206
2.5	180.9378	181.5123	182.6344	181.6948	0.8629	0.4749
3.0	221.3957	220.6276	219.9886	220.6706	0.7045	0.3193

Table 3B. Between run precision data of cefazolin

Concentration (mg/ml)	Peak area			Mean	SD	%CV
	Day 1	Day 2	Day 3			
0.5	38.9378	37.1801	38.5298	38.2159	0.9199	2.4072
1.0	73.0968	74.1592	73.1149	73.4570	0.6082	0.8280
1.5	107.4150	107.6774	107.4479	107.5134	0.1429	0.1329
2.0	143.1868	142.0993	144.9378	143.4080	1.4321	0.9986
2.5	182.0773	180.4712	181.8017	181.4501	0.8588	0.4733
3.0	221.2527	218.9935	220.3529	220.1997	1.1373	0.5165

3. Specificity

The specificity was performed under the chromatographic conditions selected, the peaks of other components in the sample must not interfere with the peak of analyte. Under the condition of experiment, the typical chromatograms of cefazolin were eluted at 3-4 minutes. The chromatograms of standard solution are shown in Figure 1B (A-F). Figure 2B showed the chromatogram of cefazolin solution after 72-hour storage at 45 $^{\circ}$C, the condition which induces degradation. The chromatogram was evaluated by comparing with those of the standard solutions. It showed some distinct peaks assumed to be peaks of degradation products which did not interfere with the peak of drug.

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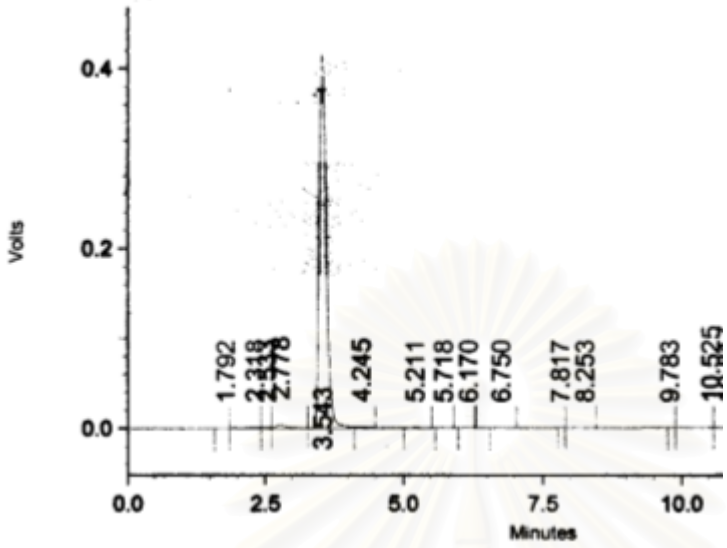

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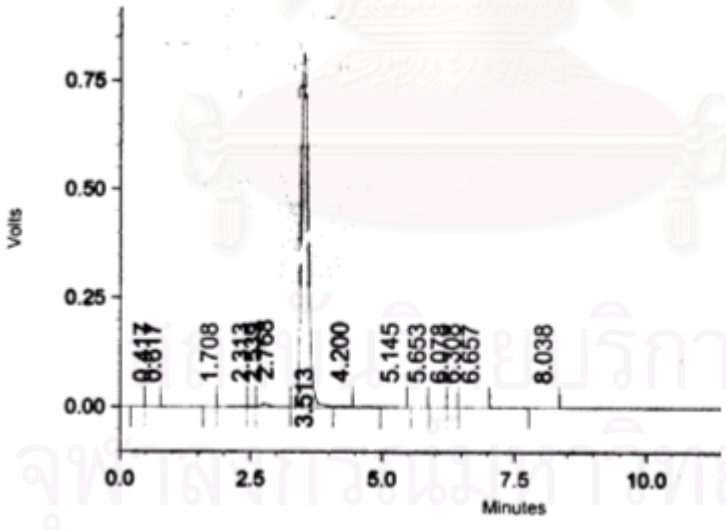

B

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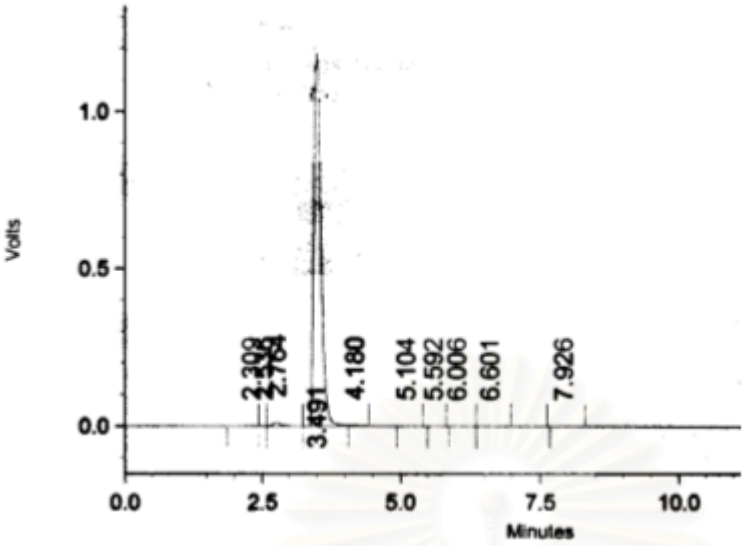

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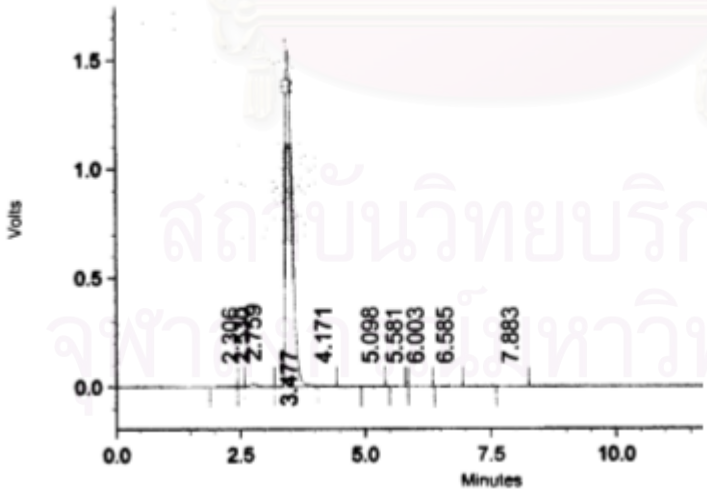

D

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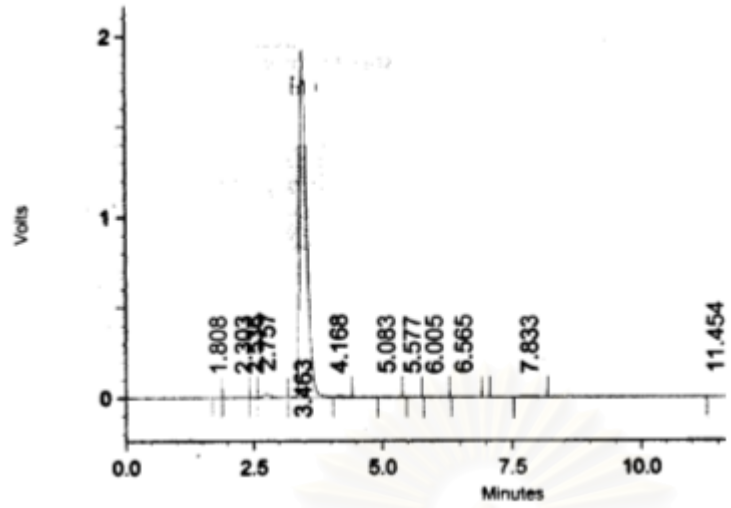

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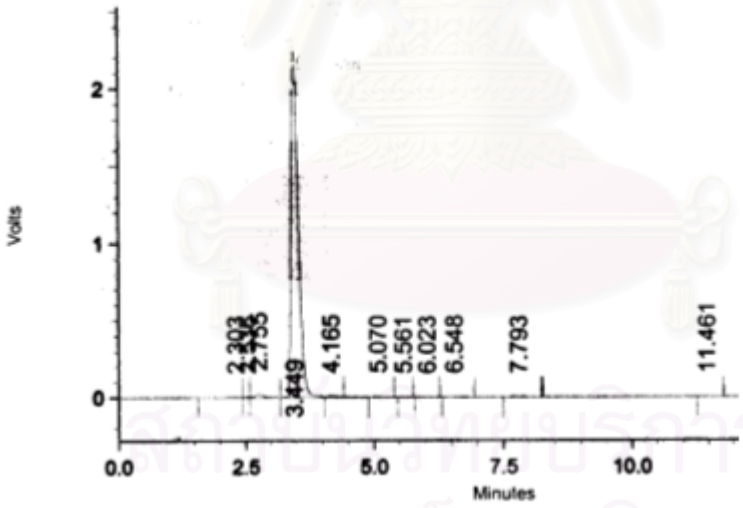

F

Figure 1B HPLC chromatograms of standard solutions of cefazolin at various concentrations [0.5 mg/ml (A), 1.0 mg/ml (B), 1.5 mg/ml(C), 2.0 mg/ml (D), 2.5 mg/ml (E), and 3.0 mg/ml (F)]

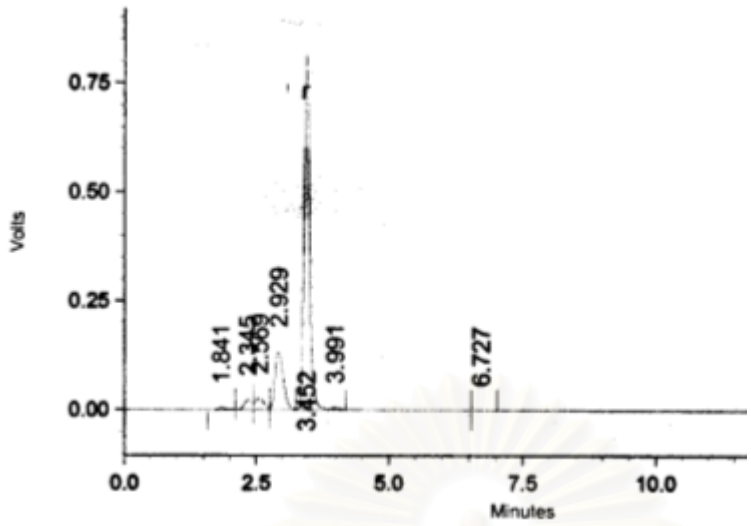

Figure 2B. HPLC chromatogram of cefazolin solution after storage for 72 hours at 45° C

4. Linearity

The linearity is usually expressed in terms of the variance around the slope of the regression line calculated according to an established mathematical relationship from test results obtained by the analysis of samples with varying concentrations. Data for the calibration curve of cefazolin are presented in Table 4B. Figure 3B shows the relationship between peak areas and cefazolin concentrations which is linear with coefficient of determination of 0.9995. These results indicated that the HPLC method was acceptable for quantitative analysis of cefazolin solutions in the range studied.

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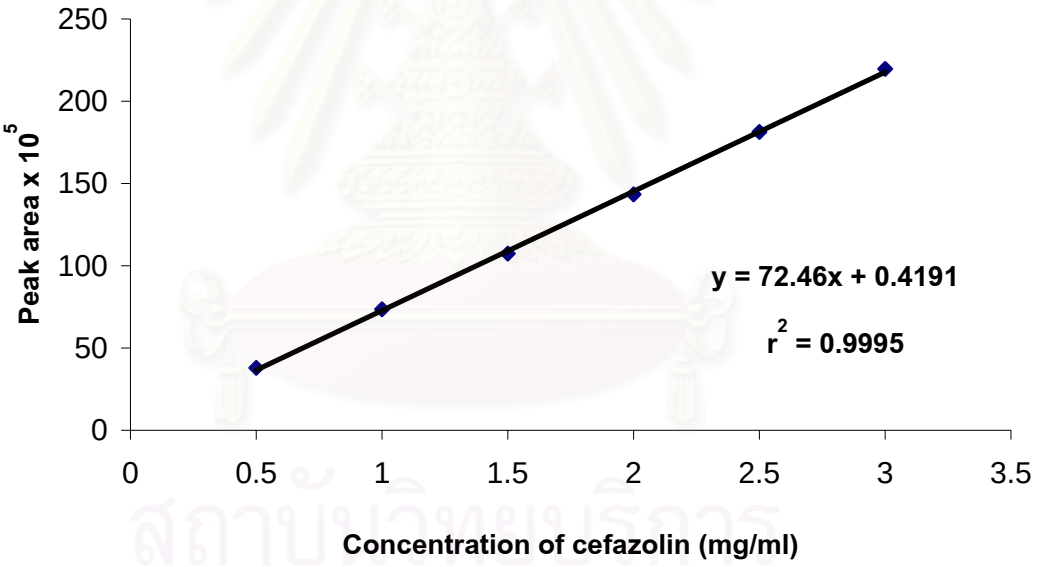
Table 4B. Data for calibration curve of standard solutions of cefazolin

Actual concentration (mg/ml)	Peak area ($x10^5$)	Analytical concentration (mg/ml)	% Recovery
0.5	37.9886	0.5185	103.69
1.0	73.4711	1.0082	100.82
1.5	107.4150	1.4766	98.44
2.0	143.4789	1.9743	98.72
2.5	181.3130	2.4965	99.86
3.0	219.6821	3.0260	100.87



$y = 72.46x + 0.4191$

$r^2 = 0.9995$

Where y = Peak area

x = Cefazolin concentration (mg/ml)

Figure 3B. A representation of calibration curve of standard solutions of cefazolin

Validation for the quantitative determination of ceftazidime by HPLC

1. Accuracy

Accuracy data of ceftazidime is shown in Table 5B. The mean percent analytical recovery was 102.26±3.68% with %CV of 3.68. Although accuracy within 2% of actual values is required, accuracy within 10% of actual value is still achievable. There may be some errors in any part of HPLC method can have effect on accuracy such as improper data handling because the reference standard materials are not certified standard (Synder, Kirkland, and Glajoh, 1997). These results indicated that HPLC method was achievable for quantitative analysis of ceftazidime.

Table 5B. Accuracy data of ceftazidime

Expected concentration (mg/ml)	Analytical concentration (mg/ml)	% Recovery
1	1.0608	106.08
	1.0784	107.84
	1.0695	106.95
2	1.9911	99.55
	1.9700	98.50
	1.9698	98.49
3	3.0422	101.41
	3.0245	100.82
	3.0212	100.71
		Mean= 102.26
		SD= 3.68
		%CV= 3.60

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2. Precision

Tables 6B and 7B illustrate the data of within run precision and between run precision of ceftazidime, respectively. This indicated that the HPLC method used were precise for quantitative of ceftazidime.

Table 6B. Within run precision data

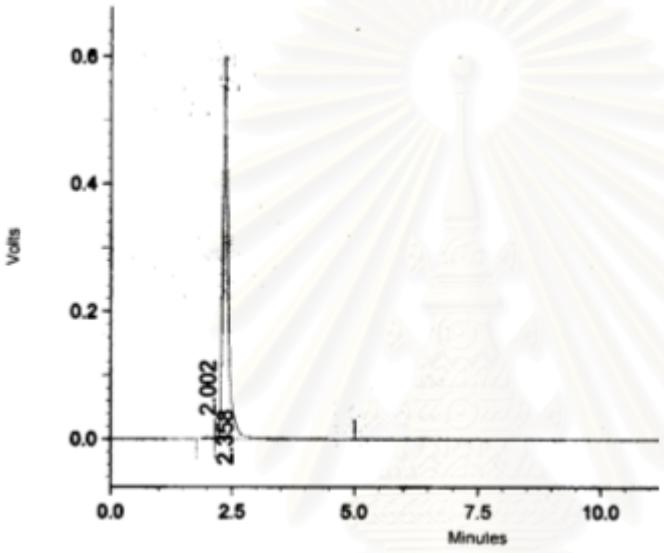
Concentration (mg/ml)	Peak area			Mean	SD	%CV
	n_1	n_2	n_3			
0.5	45.5786	44.8039	44.3142	44.8989	0.6375	1.4199
1.0	98.7970	98.8144	99.6042	99.0719	0.4611	0.4654
1.5	139.3142	138.8242	139.5848	139.2411	0.3855	0.2769
2.0	176.3141	175.1390	174.8242	175.4258	0.7853	0.4476
2.5	220.1390	221.0880	220.5854	220.6014	0.4748	0.2152
3.0	271.1648	269.8656	269.8660	270.2988	0.7499	0.2775

Table 7B. Between run precision data

Concentration (mg/ml)	Peak area			Mean	SD	%CV
	Day 1	Day 2	Day 3			
0.5	44.0455	46.1648	45.5786	45.2630	1.0943	2.4177
1.0	98.8656	99.0122	99.3232	99.0670	0.2337	0.2359
1.5	139.5641	138.5788	137.9963	138.7131	0.7925	0.5713
2.0	176.0025	174.8894	175.4597	175.4505	0.5566	0.3172
2.5	221.3145	220.8277	220.8144	220.9855	0.2850	0.1289
3.0	270.8662	271.6995	269.4569	270.6742	1.1336	0.4188

3. Specificity

The typical chromatograms of ceftazidime were eluted at 2-4 minutes. The chromatograms of standard solution of ceftazidime are shown in Figure 4B (A-F). Figure 5B shows chromatogram of ceftazidime after 72-hour storage at 45 °C.



A

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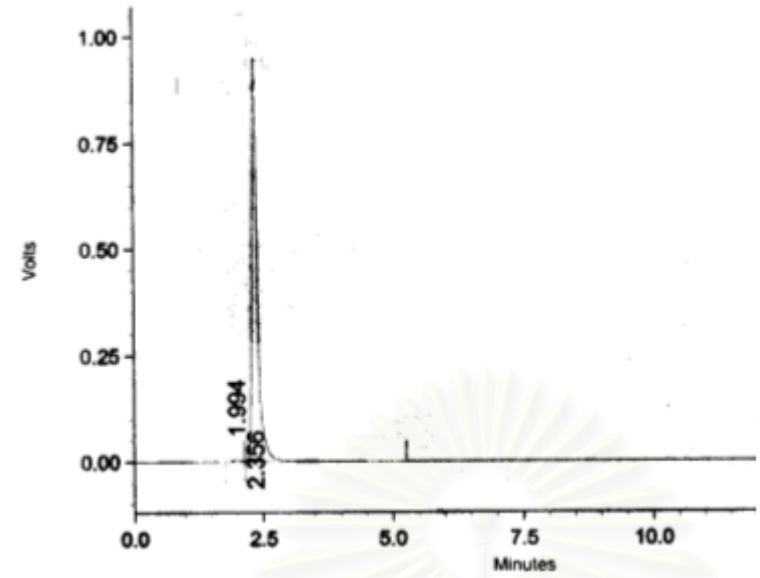

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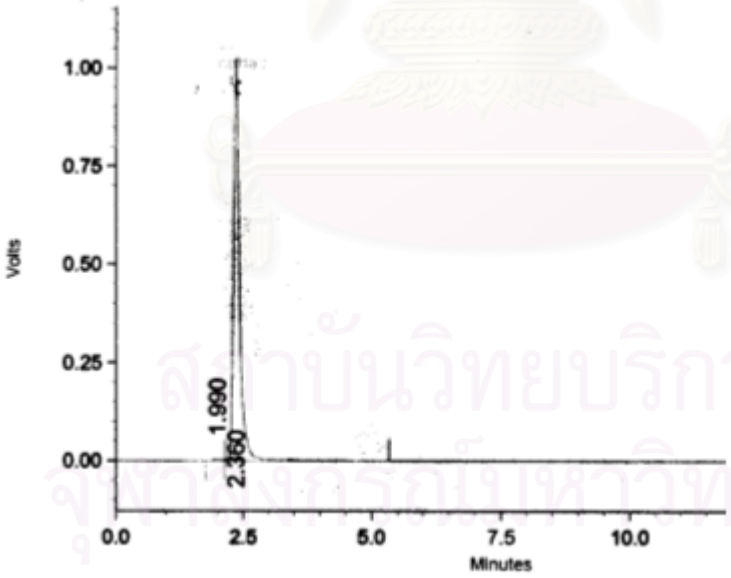

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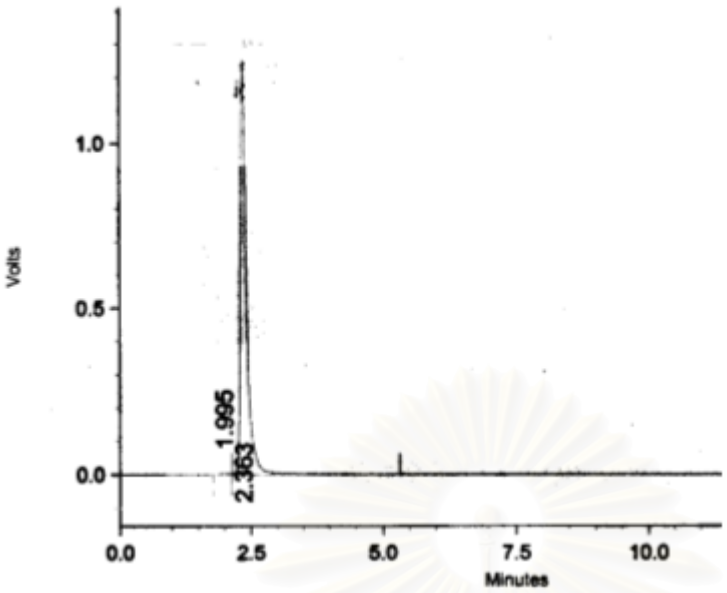

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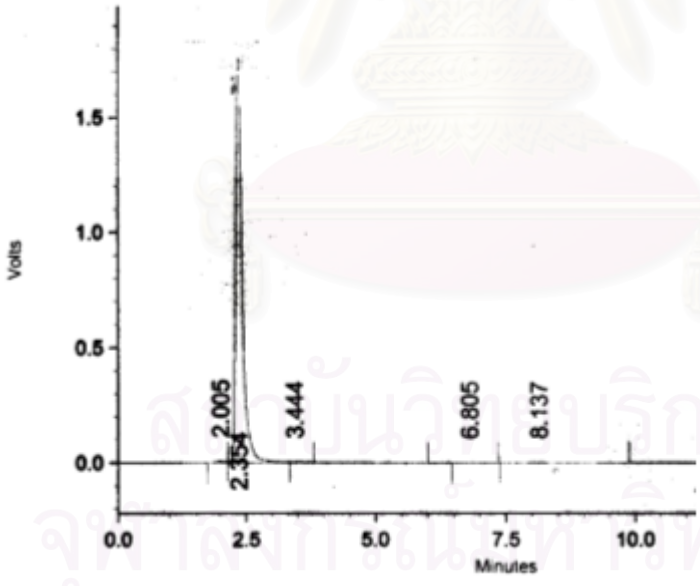

E

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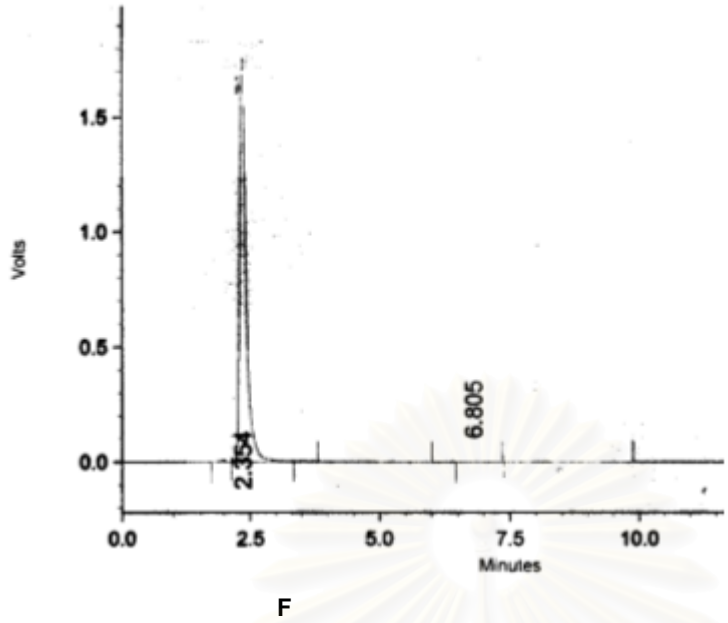

F

Figure 4B. HPLC chromatograms of standard solutions of ceftazidime at various concentrations [0.5 mg/ml (A), 1.0 mg/ml (B), 1.5 mg/ml(C), 2.0 mg/ml (D), 2.5 mg/ml (E), and 3.0 mg/ml (F)]

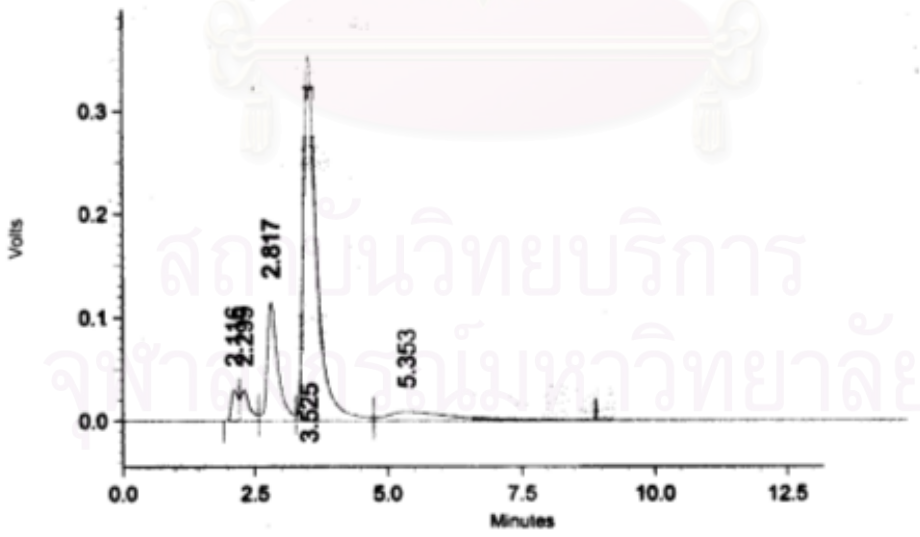

Figure 5B. HPLC chromatogram of ceftazidime solution after storage for 72 hours at 45°C

4. Linearity

Figure 6B shows the relationship between peak areas and ceftazidime concentrations which is linear with coefficient of determination of 0.997. These results indicated that the HPLC method was acceptable for quantitative analysis of ceftazidime solutions in the range studied.

Table 8B. Data for calibration curve of standard solutions of ceftazidime

Actual concentration (mg/ml)	Peak area ($x10^5$)	Analytical concentration (mg/ml)	% Recovery
0.5	45.0456	0.4542	90.84
1.0	98.8144	1.0696	106.96
1.5	139.1175	1.5309	102.06
2.0	175.3174	1.9453	97.26
2.5	220.9368	2.4674	98.70
3.0	270.3142	3.0326	101.09

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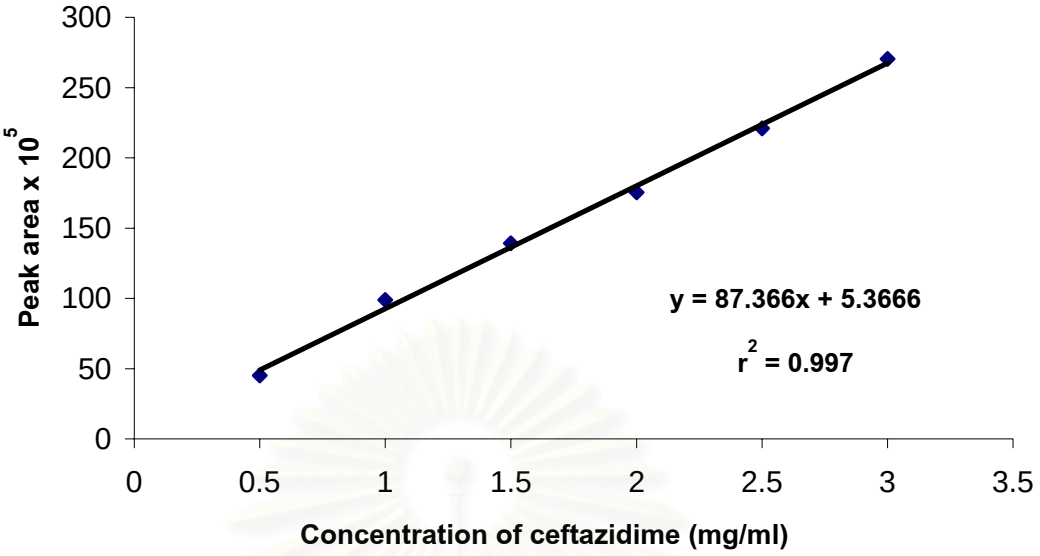

$y = 87.366x + 5.3666$

$r^2 = 0.997$

Where y = Peak area

x = Ceftazidime concentration (mg/ml)

Figure 6B. A representation of calibration curve of standard solutions of ceftazidime

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APPENDIX D

The degree of turbidity of cephalosporins at the various sampling times

a) Cefazolin in 5% dextrose injection

Time (h)	Degree of turbidity (FTU)						Mean	SD
0	0.26	0.26	0.24	0.24	0.25	0.25	0.25	0.01
2	0.23	0.23	0.24	0.24	0.24	0.23	0.24	0.01
4	0.20	0.20	0.21	0.20	0.22	0.20	0.21	0.01
8	0.26	0.26	0.26	0.25	0.25	0.26	0.26	0.01
12	0.26	0.26	0.25	0.25	0.25	0.25	0.25	0.01
24	0.21	0.21	0.21	0.20	0.20	0.21	0.21	0.01
48	0.28	0.28	0.27	0.27	0.27	0.28	0.28	0.01

b) Cefoxitin in 5% dextrose injection

Time (h)	Degree of turbidity (FTU)						Mean	SD
0	0.69	0.69	0.69	0.68	0.68	0.68	0.69	0.01
2	0.69	0.69	0.69	0.68	0.68	0.69	0.69	0.01
4	0.62	0.62	0.62	0.61	0.61	0.62	0.62	0.01
8	0.60	0.60	0.59	0.60	0.59	0.60	0.60	0.01
12	0.52	0.52	0.53	0.51	0.52	0.51	0.52	0.01
24	0.75	0.75	0.74	0.75	0.74	0.75	0.75	0.01
48	0.77	0.77	0.77	0.78	0.77	0.78	0.77	0.01

c) Cefotaxime in 5%dextrose injection

Time (h)	Degree of turbidity (FTU)						Mean	SD
0	1.06	1.06	1.06	1.05	1.07	1.05	1.06	0.01
2	1.06	1.06	1.05	1.04	1.06	1.06	1.06	0.01
4	0.99	0.99	0.99	1.00	0.99	0.99	0.99	0.01
8	0.98	0.99	0.98	0.99	0.98	0.98	0.98	0.01
12	0.96	0.96	0.96	0.97	0.95	0.95	0.96	0.01
24	0.88	0.88	0.89	0.89	0.88	0.87	0.88	0.01
48	0.76	0.76	0.76	0.75	0.75	0.76	0.76	0.01

d) Ceftazidime in 5%dextrose injection

Time (h)	Degree of turbidity (FTU)						Mean	SD
0	0.20	0.19	0.21	0.20	0.19	0.21	0.20	0.01
2	0.18	0.16	0.16	0.18	0.16	0.16	0.17	0.01
4	0.18	0.15	0.16	0.15	0.18	0.16	0.16	0.01
8	0.12	0.13	0.14	0.12	0.13	0.14	0.13	0.01
12	0.12	0.11	0.10	0.12	0.11	0.10	0.11	0.01
24	0.10	0.10	0.11	0.10	0.10	0.11	0.10	0.01
48	0.09	0.10	0.09	0.09	0.10	0.09	0.09	0.01

e) Ceftriaxone in 5% dextrose injection

Time (h)	Degree of turbidity (FTU)						Mean	SD
0	0.36	0.36	0.35	0.35	0.36	0.35	0.35	0.01
2	0.35	0.35	0.36	0.35	0.35	0.35	0.35	0.01
4	0.39	0.39	0.38	0.40	0.39	0.39	0.39	0.01
8	0.36	0.35	0.36	0.36	0.36	0.36	0.36	0.01
12	0.33	0.34	0.33	0.35	0.33	0.33	0.34	0.01
24	0.40	0.40	0.39	0.40	0.39	0.40	0.40	0.01
48	0.39	0.39	0.38	0.38	0.39	0.39	0.39	0.01

f) Cefazolin in 5% dextrose injection in combination with TPN solution

Time (h)	Degree of turbidity (FTU)						Mean	SD
0	0.22	0.18	0.19	0.24	0.13	0.16	0.19	0.04
2	0.18	0.17	0.16	0.21	0.12	0.19	0.17	0.03
4	0.18	0.08	0.19	0.24	0.13	0.19	0.17	0.06
8	0.22	0.14	0.20	0.23	0.12	0.17	0.18	0.04
12	0.08	0.04	0.03	0.03	0.00	0.02	0.03	0.03
24	0.06	0.05	0.03	0.02	0.01	0.00	0.03	0.02
48	0.03	0.02	0.00	0.00	0.00	0.00	0.01	0.01

g) Cefoxitin in 5% dextrose injection in combination with TPN solution

Time (h)	Degree of turbidity (FTU)						Mean	SD
0	0.61	0.63	0.59	0.61	0.66	0.65	0.63	0.03
2	0.62	0.59	0.57	0.59	0.59	0.55	0.59	0.02
4	0.55	0.58	0.55	0.54	0.57	0.58	0.56	0.02
8	0.59	0.58	0.55	0.56	0.60	0.59	0.58	0.02
12	0.67	0.65	0.70	0.89	0.88	0.90	0.78	0.12
24	0.62	0.65	0.64	0.83	0.83	0.80	0.73	0.10
48	0.67	0.65	0.70	0.83	0.83	0.80	0.75	0.08

h) Cefotaxime in 5% dextrose injection in combination with TPN solution

Time (h)	Degree of turbidity (FTU)						Mean	SD
0	0.26	0.22	0.21	0.18	0.18	0.17	0.20	0.03
2	0.20	0.20	0.20	0.15	0.14	0.18	0.18	0.03
4	0.21	0.19	0.18	0.13	0.12	0.12	0.16	0.04
8	0.21	0.20	0.20	0.13	0.13	0.14	0.17	0.04
12	0.24	0.25	0.23	0.14	0.15	0.15	0.19	0.05
24	0.22	0.20	0.21	0.11	0.12	0.12	0.16	0.05
48	3.80	3.65	3.64	4.83	4.70	5.31	4.32	0.72

i) Ceftazidime in 5% dextrose injection in combination with TPN solution

Time (h)	Degree of turbidity (FTU)						Mean	SD
0	0.24	0.31	0.30	0.30	0.31	0.33	0.30	0.03
2	0.25	0.33	0.29	0.30	0.31	0.29	0.30	0.03
4	0.26	0.29	0.25	0.30	0.31	0.30	0.29	0.02
8	0.23	0.19	0.29	0.32	0.30	0.31	0.27	0.05
12	0.15	0.15	0.18	0.23	0.18	0.20	0.18	0.03
24	0.14	0.15	0.22	0.21	0.21	0.20	0.19	0.03
48	0.15	0.15	0.16	0.24	0.23	0.23	0.19	0.04

j) Ceftriaxone in 5% dextrose injection in combination with TPN solution

Time (h)	Degree of turbidity (FTU)						Mean	SD
0	1.05	1.40	1.28	1.46	1.48	1.46	1.36	0.17
2	0.91	0.92	1.04	1.33	1.31	1.31	1.14	0.20
4	0.91	0.89	0.90	1.29	1.30	1.31	1.10	0.22
8	0.87	0.88	0.87	1.22	1.23	1.24	1.05	0.19
12	0.89	0.88	0.87	1.24	1.24	1.24	1.06	0.20
24	0.81	0.82	0.83	1.03	1.05	1.04	0.93	0.12
48	0.97	1.07	0.90	1.07	1.09	0.98	1.01	0.08

k) Cefazolin in 5% dextrose injection in combination with PPN solution

Time (h)	Degree of turbidity (FTU)						Mean	SD
0	0.31	0.28	0.31	0.34	0.31	0.30	0.31	0.02
2	0.26	0.25	0.25	0.28	0.28	0.28	0.27	0.02
4	0.22	0.23	0.22	0.26	0.25	0.25	0.24	0.02
8	0.26	0.22	0.22	0.28	0.27	0.26	0.25	0.03
12	0.21	0.20	0.20	0.27	0.26	0.26	0.23	0.03
24	0.22	0.19	0.19	0.25	0.25	0.25	0.23	0.03
48	0.17	0.15	0.14	0.19	0.19	0.15	0.17	0.02

l) Cefoxitin in 5% dextrose injection in combination with PPN solution

Time (h)	Degree of turbidity (FTU)						Mean	SD
0	0.55	0.60	0.51	0.54	0.53	0.52	0.54	0.03
2	0.50	0.50	0.50	0.49	0.48	0.49	0.49	0.01
4	0.49	0.50	0.50	0.49	0.48	0.49	0.49	0.01
8	0.51	0.54	0.52	0.49	0.49	0.49	0.51	0.02
12	0.53	0.52	0.53	0.51	0.51	0.51	0.52	0.01
24	0.53	0.54	0.54	0.53	0.51	0.56	0.54	0.02
48	0.84	0.95	0.92	0.84	0.83	0.83	0.87	0.05

m) Cefotaxime in 5% dextrose injection in combination with PPN solution

Time (h)	Degree of turbidity (FTU)						Mean	SD
0	0.32	0.32	0.30	0.49	0.46	0.46	0.39	0.09
2	0.33	0.31	0.42	0.46	0.46	0.47	0.41	0.07
4	0.29	0.42	0.31	0.44	0.43	0.44	0.39	0.07
8	0.28	0.29	0.30	0.45	0.45	0.46	0.37	0.09
12	0.28	0.27	0.32	0.45	0.46	0.46	0.37	0.09
24	0.30	0.27	0.27	0.45	0.45	0.46	0.37	0.09
48	14.58	13.82	13.69	13.99	14.09	14.90	14.18	0.47

n) Ceftazidime in 5% dextrose injection in combination with PPN solution

Time (h)	Degree of turbidity (FTU)						Mean	SD
0	0.15	0.16	0.18	0.16	0.14	0.14	0.16	0.02
2	0.13	0.08	0.19	0.06	0.08	0.06	0.10	0.05
4	0.13	0.05	0.15	0.07	0.05	0.04	0.08	0.05
8	0.06	0.06	0.07	0.02	0.02	0.03	0.04	0.02
12	0.08	0.08	0.08	0.05	0.04	0.06	0.07	0.02
24	0.07	0.08	0.08	0.05	0.04	0.04	0.06	0.02
48	0.21	0.35	0.15	0.19	0.25	0.33	0.25	0.08

o) Ceftriaxone in 5% dextrose injection in combination with PPN solution

Time (h)	Degree of turbidity (FTU)						Mean	SD
0	0.81	0.83	0.85	0.73	0.73	0.80	0.79	0.05
2	0.85	0.82	0.84	0.73	0.72	0.84	0.80	0.06
4	0.80	0.79	0.80	0.64	0.64	0.77	0.74	0.08
8	0.91	0.79	0.81	0.66	0.75	0.71	0.77	0.09
12	4.55	3.19	4.62	3.42	5.69	4.02	4.25	0.91
24	7.77	10.29	11.90	8.79	10.81	7.11	9.44	1.86
48	10.41	27.74	22.26	20.82	15.25	31.45	21.32	7.76

The pH values of cephalosporins at the various sampling times

a) Cefazolin in 5% dextrose injection

Time (h)	pH						Mean	SD
0	5.4	5.4	5.4	5.4	5.4	5.4	5.4	0
2	5.7	5.7	5.7	5.7	5.7	5.7	5.7	0
4	6.0	6.0	6.0	6.0	6.0	6.0	6.0	0
8	6.1	6.1	6.1	6.1	6.1	6.1	6.1	0
12	6.2	6.2	6.2	6.2	6.2	6.2	6.2	0
24	6.3	6.3	6.3	6.3	6.3	6.3	6.3	0
48	6.3	6.3	6.3	6.3	6.3	6.3	6.3	0

b) Cefoxitin in 5% dextrose injection

Time (h)	pH						Mean	SD
0	5.2	5.2	5.2	5.2	5.2	5.2	5.2	0
2	5.7	5.7	5.7	5.7	5.7	5.7	5.7	0
4	6.0	6.2	6.2	6.1	6.2	6.2	6.15	0.08
8	6.2	6.2	6.3	6.2	6.2	6.3	6.23	0.05
12	6.6	6.6	6.6	6.6	6.6	6.6	6.6	0
24	7.0	7.1	7.0	7.0	7.1	7.0	7.03	0.05
48	7.1	7.1	7.2	7.1	7.2	7.0	7.12	0.08

c) Cefotaxime in 5% dextrose injection

Time (h)	pH						Mean	SD
0	5.3	5.3	5.3	5.3	5.3	5.3	5.3	0
2	5.2	5.2	5.2	5.2	5.2	5.2	5.2	0
4	5.0	5.0	4.9	5.0	4.9	4.9	4.95	0.05
8	5.0	5.0	5.0	5.0	5.0	5.0	5.0	0
12	4.9	4.8	4.8	4.9	4.8	4.8	4.83	0.05
24	4.7	4.7	4.7	4.7	4.7	4.7	4.7	0
48	4.7	4.7	4.6	4.7	4.7	4.6	4.67	0.05

d) Ceftazidime in 5% dextrose injection

Time (h)	pH						Mean	SD
0	6.8	6.8	6.8	6.8	6.8	6.8	6.8	0
2	6.7	6.7	6.7	6.7	6.7	6.7	6.7	0
4	6.7	6.7	6.7	6.7	6.7	6.7	6.7	0
8	6.8	6.7	6.8	6.8	6.7	6.8	6.77	0.05
12	6.8	6.7	6.7	6.8	6.7	6.7	6.73	0.05
24	6.7	6.8	6.7	6.8	6.7	6.7	6.73	0.05
48	6.7	6.7	6.7	6.7	6.7	6.7	6.7	0

e) Ceftriaxone in 5% dextrose injection

Time (h)	pH						Mean	SD
0	6.6	6.6	6.6	6.6	6.6	6.6	6.6	0
2	6.7	6.7	6.7	6.7	6.7	6.7	6.7	0
4	6.7	6.8	6.7	6.8	6.7	6.7	6.73	0.05
8	6.8	6.9	6.8	6.9	6.8	6.8	6.83	0.05
12	7.0	7.0	7.0	7.0	7.0	7.0	7.0	0
24	7.1	7.1	7.1	7.1	7.1	7.1	7.1	0
48	7.2	7.2	7.2	7.2	7.2	7.2	7.2	0

f) Cefazolin in 5% dextrose injection in combination with TPN solution

Time (h)	pH						Mean	SD
0	6.3	6.4	6.4	6.4	6.4	6.4	6.38	0.04
2	6.4	6.4	6.5	6.5	6.5	6.5	6.47	0.05
4	6.5	6.5	6.5	6.5	6.5	6.5	6.5	0
8	6.6	6.6	6.6	6.6	6.6	6.6	6.6	0
12	6.6	6.6	6.6	6.6	6.6	6.6	6.6	0
24	6.5	6.5	6.5	6.5	6.5	6.5	6.5	0
48	6.5	6.5	6.5	6.4	6.4	6.4	6.45	0.05

g) Cefoxitin in 5% dextrose injection in combination with TPN solution

Time (h)	pH						Mean	SD
0	6.5	6.6	6.6	6.6	6.6	6.6	6.58	0.04
2	6.7	6.7	6.7	6.7	6.7	6.7	6.7	0
4	6.7	6.7	6.7	6.7	6.7	6.7	6.7	0
8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	0
12	6.7	6.7	6.7	6.7	6.7	6.7	6.7	0
24	6.6	6.6	6.6	6.6	6.6	6.6	6.6	0
48	6.6	6.6	6.6	6.5	6.5	6.5	6.55	0.05

h) Cefotaxime in 5% dextrose injection in combination with TPN solution

Time (h)	pH						Mean	SD
0	6.6	6.6	6.6	6.6	6.6	6.6	6.6	0
2	6.5	6.5	6.5	6.5	6.5	6.5	6.5	0
4	6.5	6.5	6.5	6.5	6.5	6.5	6.5	0
8	6.5	6.5	6.5	6.5	6.5	6.4	6.48	0.04
12	6.4	6.4	6.4	6.5	6.5	6.5	6.45	0.05
24	6.3	6.3	6.3	6.3	6.3	6.3	6.3	0
48	6.0	6.0	6.0	6.1	6.1	6.1	6.05	0.05

i) Ceftazidime in 5% dextrose injection in combination with TPN solution

Time (h)	pH						Mean	SD
0	6.4	6.4	6.4	6.5	6.5	6.5	6.45	0.05
2	6.6	6.6	6.6	6.6	6.6	6.6	6.6	0
4	6.6	6.6	6.6	6.6	6.6	6.6	6.6	0
8	6.7	6.7	6.7	6.7	6.7	6.7	6.7	0
12	6.6	6.6	6.6	6.6	6.6	6.6	6.6	0
24	6.6	6.6	6.6	6.6	6.7	6.7	6.63	0.05
48	6.7	6.7	6.7	6.7	6.7	6.7	6.7	0

j) Ceftriaxone in 5% dextrose injection in combination with TPN solution

Time (h)	pH						Mean	SD
0	6.6	6.6	6.6	6.6	6.7	6.7	6.63	0.05
2	6.6	6.6	6.6	6.6	6.6	6.6	6.6	0
4	6.7	6.7	6.7	6.7	6.7	6.7	6.7	0
8	6.6	6.6	6.6	6.7	6.7	6.7	6.65	0.05
12	6.7	6.7	6.7	6.7	6.7	6.7	6.7	0
24	6.9	6.9	6.9	6.7	6.8	6.8	6.83	0.08
48	6.9	6.8	6.9	6.9	6.9	7.0	6.92	0.10

k) Cefazolin in 5% dextrose injection in combination with PPN solution

Time (h)	pH						Mean	SD
0	6.7	6.7	6.7	6.8	6.8	6.8	6.75	0.05
2	6.7	6.7	6.7	6.8	6.8	6.8	6.75	0.05
4	6.7	6.7	6.7	6.7	6.7	6.8	6.72	0.04
8	6.7	6.7	6.7	6.7	6.6	6.7	6.68	0.04
12	6.7	6.7	6.7	6.6	6.6	6.7	6.67	0.05
24	6.7	6.7	6.7	6.6	6.6	6.6	6.65	0.05
48	6.6	6.6	6.6	6.6	6.6	6.5	6.58	0.04

l) Cefoxitin in 5% dextrose injection in combination with PPN solution

Time (h)	pH						Mean	SD
0	6.7	6.7	6.7	6.7	6.6	6.6	6.67	0.05
2	6.7	6.7	6.7	6.7	6.7	6.7	6.7	0
4	6.8	6.7	6.7	6.7	6.7	6.7	6.72	0.04
8	6.8	6.8	6.8	6.9	6.8	6.8	6.82	0.04
12	6.9	6.9	6.9	6.9	6.8	6.9	6.88	0.04
24	6.9	6.9	6.9	6.9	6.8	6.8	6.87	0.05
48	6.8	6.8	6.8	6.8	6.8	6.8	6.8	0

m) Cefotaxime in 5% dextrose injection in combination with PPN solution

Time (h)	pH						Mean	SD
0	6.7	6.7	6.7	6.7	6.7	6.7	6.7	0
2	6.6	6.7	6.6	6.7	6.7	6.7	6.67	0.05
4	6.6	6.6	6.7	6.7	6.7	6.7	6.67	0.05
8	6.6	6.6	6.6	6.6	6.7	6.6	6.62	0.04
12	6.7	6.6	6.6	6.5	6.6	6.7	6.62	0.07
24	6.6	6.5	6.5	6.5	6.5	6.5	6.52	0.04
48	6.1	6.1	6.1	6.1	6.1	6.1	6.1	0

n) Ceftazidime in 5% dextrose injection in combination with PPN solution

Time (h)	pH						Mean	SD
0	6.8	6.8	6.8	6.9	6.9	6.9	6.85	0.05
2	6.9	6.8	6.9	6.9	6.9	6.9	6.88	0.04
4	6.9	6.9	6.9	6.8	6.8	6.9	6.87	0.05
8	6.9	7.0	7.0	7.0	7.0	7.0	6.98	0.04
12	7.0	7.0	7.0	7.0	7.0	7.0	7.0	0
24	7.0	6.9	6.9	7.0	7.0	7.0	6.97	0.05
48	6.9	6.9	6.9	6.9	7.0	7.0	6.93	0.05

o) Ceftriaxone in 5% dextrose injection in combination with PPN solution

Time (h)	pH						Mean	SD
0	6.6	6.8	6.8	6.8	6.8	6.7	6.75	0.08
2	6.6	6.9	6.8	6.8	6.8	6.8	6.78	0.10
4	6.8	6.9	6.9	6.9	6.9	6.8	6.87	0.05
8	6.9	6.9	6.9	6.9	6.9	6.8	6.88	0.04
12	6.9	6.9	6.9	6.9	6.9	6.8	6.88	0.04
24	7	6.9	6.9	6.9	6.9	6.8	6.9	0.06
48	7.1	7	6.9	6.9	6.9	6.9	6.95	0.08

Peak areas of cefazolin at the various sampling times

a) Cefazolin in 5% dextrose injection

Time (h)	Peak area ($x10^5$)			Mean	SD
0	150.1458	147.4530	149.1416	148.9135	1.3608
2	144.3694	145.8659	147.4530	145.8961	1.5419
4	141.9547	143.8659	142.4816	142.7674	0.9871
8	141.5099	141.2089	141.6569	141.4586	0.2283
12	140.5005	140.5099	140.7712	140.5939	0.1536
24	140.3160	140.2275	140.3694	140.3043	0.7117

b) Cefazolin in 5% dextrose injection in combination with TPN solution

Time (h)	Peak area ($x10^5$)			Mean	SD
0	150.8898	147.1293	150.8537	149.6243	2.1607
2	146.7729	144.5850	144.2751	145.2110	1.3615
4	143.9017	144.0003	143.9427	143.9482	0.0496
8	143.0123	143.3682	141.5296	142.6367	0.9751
12	141.4756	141.5296	141.7100	141.5718	0.12274
24	140.5064	138.2561	139.7371	139.4999	1.1437

c) Cefazolin in 5% dextrose injection in combination with PPN solution

Time (h)	Peak area ($x10^5$)			Mean	SD
0	150.8305	149.7336	148.8537	149.8059	0.9904
2	147.1168	146.9442	147.5299	147.1969	0.3009
4	141.9556	142.7752	143.3206	142.6838	0.6871
8	140.1281	141.5104	141.2326	140.9571	0.7312
12	140.3236	139.9922	139.2643	139.8600	0.5419
24	139.0184	138.2012	138.1656	138.4617	0.4824

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Peak areas of ceftazidime at the various sampling times

a) Ceftazidime in 5% dextrose injection

Time (h)	Peak area ($x10^5$)			Mean	SD
0	171.6146	171.6112	171.4546	171.5601	0.0914
2	170.9712	169.9876	168.4625	169.8071	1.2641
4	163.4722	163.9349	163.2525	163.5532	0.3483
8	158.4601	160.2211	158.9591	159.2134	0.9076
12	156.2716	156.9333	157.5674	156.9241	0.6479
24	149.3631	149.2090	148.1495	148.9072	0.6607

b) Ceftazidime in 5% dextrose injection in combination with TPN solution

Time (h)	Peak area ($x10^5$)			Mean	SD
0	172.4280	171.3168	171.0231	171.5893	0.7411
2	169.5367	169.8413	169.9376	169.7719	0.2093
4	163.2958	162.1584	162.3816	162.6119	0.6027
8	158.5619	159.7023	160.1096	159.4579	0.8023
12	154.5944	154.6812	153.5664	154.2807	0.6201
24	142.3695	145.2396	142.3180	143.3090	1.6721

c) Ceftazidime in 5% dextrose injection in combination with PPN solution

Time (h)	Peak area ($x10^5$)			Mean	SD
0	171.7361	170.8926	170.2750	170.9679	0.7335
2	168.1478	169.9284	168.9032	168.9931	0.8937
4	162.7749	160.3450	161.0652	161.3950	1.2481
8	156.8471	156.0301	155.2157	156.0310	0.8157
12	150.0417	151.7499	150.7186	150.8367	0.8602
24	136.3240	137.6182	136.4520	136.7981	0.7132

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