한국임상약학회지 제11권 제2호
Kor. J. Clin. Pharm., Vol. 11, No. 2. 2001

Stability of Paclitaxel and Vancomycin in 5% Dextrose Injection, 0.9% Sodium Chloride Injection and Hartman's Solution during Simulated Y-Site Administration

Jin Pil Burm

Chosun Nursing College, Kwangju 501-140, Korea

Paclitaxel과 vancomycin을 5% 포도당주사액, 0.9% 염화나트륨주사액 또는 하트만용액과 함께 Y-Site 장치를 써서 환자에게 주입할 때 두 약물의 안정성에 관하여 연구하였다. Paclitaxel 0.3 mg/ml 및 1.2 mg/ml과 vancomycin 1 mg/ml, 5 mg/ml 및 10 mg/ml을 각각 1 : 1로 혼합한 후 0, 1, 2, 4, 12시간 시점에서 두 약물의 농도를 HPLC로 분석하였다. 방해물질에 의한 분석오차를 줄이기 위해 분석법을 여러상태에서 확인하였으며, 각 농도에서 3차례씩 실험하였고 각 샘플은 2차례 반복하여 HPLC로 분석하였다. 분석전에 각 시료의 투명도, 색의 변화, 침전상태 및 pH를 검사하였다. Paclitaxel 0.3 mg/ml 및 1.2 mg/ml와 vancomycin 1 mg/ml, 5 mg/ml 및 10 mg/ml를 각각 혼합하였을 때 12시간 동안 안정하였으며 주사액의 혼탁이나 색의 변화 및 침전은 나타나지 않았으며 pH도 변하지 않았다.

□ Key Words–Stability, Paclitaxel, Vancomycin, Y-Site Administration

Severely ill patients often require extensive multiple intravenous drug therapy during their treatment; those in intensive care may receive as many as 20 medications,[1] making management of i.v. administration and access a challenge.

Paclitaxel is one of the most active new agents introduced into cancer therapy recently.[2,3] The drug is most commonly administered as a continuous infusion over 24 hours every three weeks. In clinical trials, the drug should be prepared in glass bottles and administered through tubing of material other than polyvinylchloride (PVC) because of the evidence that the plasticizer, diethylhexyl phthalate, was extracted from the PVC tubing and containers.[4-7] With the recent FDA approval of paclitaxel for the treatment of ovarian cancer,[8] many questions concerning the compatibility and stability of paclitaxel in a variety of containers and with various drugs need to be addressed.

Vancomycin is active against many Gram-positive bacteria, including penicillinase-producing Staphylococci.[9] Vancomycin has been increasingly used as an antimicrobial agent in patients with cancer.[10,11]

Patients treated with paclitaxel may receive vancomycin against the infection associated with antineoplastic therapy. Since vancomycin may be given as a continuous infusion, consideration of compatibility becomes necessary upon concomitant administration. Waugh et al.[7] reported on the stability, compatibility and plasticizer extraction of paclitaxel when paclitaxel was diluted by various solutions and stored in various containers. Trissel et al.[12,13] reported turbidimetric assessment of the stability of paclitaxel when the drug was mixed with other drugs. The stability of paclitaxel in the presence of fluconazole during simulated Y-site administration was also investigated.[14]

The stability of vancomycin was reported in peritoneal dialysis solutions,[15,16] plastic syringes,[17] a total parenteral nutrition solution,[18] 5% dextrose and 0.9% sodium chloride injections.[19,20] In a review of the literature, we found no studies analyzing the compatibility and stability of paclitaxel with vancomycin.

Thus, the purpose of this study is to evaluate the compatibility and stability of paclitaxel and vacomycin in 5% dextrose injection, 0.9% sodium chloride injection and Hartman's solution during simulatedY-site adminis-

교신저자: 범진필
501-140 광주광역시 동구 서석동 280
조선간호대학
TEL. 062-231-7361, FAX. 062-2232-9072
E-mail. jpburm@venus.cnc.ac.kr

tration at clinically relevant concentrations.

Materials and Methods

Materials

Paclitaxel (lot L2F35A) was kindly provided by Bristol-Myers Squibb Co., and vancomycin (as the hydrochloride) was kindly provided by Lilly Co.. 5% dextrose injection, 0.9% sodium chloride injection and Hartman's solution were purchased from Baxter Healthcare Corporation. All other chemicals were reagent grade.

Preparation of solutions

Two stock solutions of paclitaxel 0.3 mg/ml and 1.2 mg/ml were prepared by diluting 2.5 and 10 ml of paclitaxel respectively with 50 ml of 5% dextrose injection, 0.9% sodium chloride injection and Hartman's solution in glass bottles.

Three stock solutions of vancomycin 1, 5 and 10 mg/ml were prepared by diluting 500 mg vial of vancomycin respectively with 500 ml, 100 ml and 50 ml of 5% dextrose injection, 0.9% sodium chloride injection and Hartman's solution in glass bottles. Allen et al.[21] and Allen and Stiles[22] demonstrated that secondary admixtures injected through a Y-injection port mix with the primary i.v. fluid in a 1 : 1 ratio. To simulate this condition for high and low concentrations of each drug, 2 ml of paclitaxel stock solution was mixed with 2 ml of vancomycin stock solution. Separate admixtures were prepared for the assay of each drug.

Samples were removed at room temperature at time zero, one, two, four and twelve hours for immediate assay. All solutions were prepared in triplicate, and each drug was assayed in duplicate. At the time of sampling assay and before any dilution, each sample was visually inspected for clarity, color and precipitation. The pH was also determined.

High-performance liquid chromatographic assays

The paclitaxel HPLC assay was modified from the method of Longnecker et al.[23] The vancomycin HPLC assay was modified from the method of Favetta et al.[24] The mobile phases were filtered through a Sartorius 0.45 micrometer nylon filter and degassed under vacuum in an ultrasonic bath. A Hitachi Intelligent Pump delivered the mobile phase at the flow rate (1 ml/min) appropriate for each drug analysis as listed in Table 1. The column used for paclitaxel was a 4.6 mm×25 cm adsorbosphere packed with C_{18} 5 μm particle size while the column for vancomycin was a 4.6 mm×25 cm octadecyl column. A Hitachi UV-VIS Detector was set at wavelengths listed in Table 1. Injections were made using a Hitachi autosampler. paclitaxel 1.2 mg/ml samples were diluted 1 : 4 and 20 μl of the resulting solution injected. Vancomycin 1, 5 and 10 mg/ml samples were diluted 1 : 2, 1 : 10 and 1 : 20 and 20 μl injected. Chromatographic data were recorded on a Hitachi Chromato-Integrator and the peak area was used for quantitation. The various concentrations were determined by comparing the peak area with the standard curve. A standard curve was determined daily using five standard concentrations. In addition, a quality control sample and blank 5% dextrose injection, 0.9% sodium chloride injection and Hartman's solution were run daily. The standard curves had ranges of 40-200 μg/ml (200, 150, 100, 60 and 40 μg/ml) for paclitaxel, and 100-400 μg/ml (400, 300, 200 and 100 μg/ml)

Table 1. High-performance liquid chromatographic conditions

Drug	Column	Mobile phase	Detection wavelength (nm)	Retention time (min)	CV(%)[a]	
					Interday	Intraday
Paclitaxel	C_{18} column	Acetonitrile: 12.5 mM ammonium phosphate (60 : 40 v/v), pH adjusted to pH 4.5 with 1 N hydrochloric acid	227	10.6	3	4
Vancomycin	Octadecyl column	Acetonitrile: sodium phosphate buffer (12 : 88 v/v), pH adjusted to 7.0 with 1 N NaOH solution	254	9.4	4	6

[a]CV: Coefficient of variation (%).

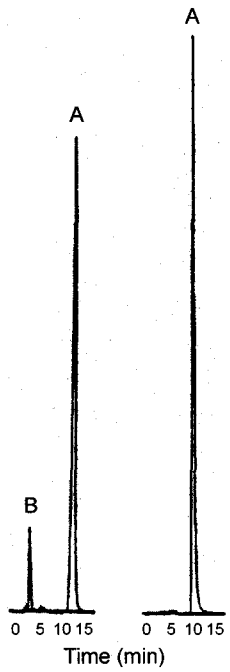

Fig. 1. Chromatogram of paclitaxel (peak A) and vancomycin (peak B) under a paclitaxel assay condition (left). Chromatogram of vancomycin (peak A) under a vancomycin assay condition (right).

for vancomycin. Paclitaxel standard solutions were made by dissolving paclitaxel in methanol and diluting them with 60% acetonitrile. All solutions were kept refrigerated at –4°C when not in use to avoid evaporation of the organic solvent. Vancomycin standard solutions were prepared in 5% dextrose injection, 0.9% sodium chloride injection and Hartman's solution. Standard curves in the linear analytical concentration range for each drug were constructed for calibration. The correlation coefficient of each curve was higher than 0.999. Detection limit was defined below 100 ng/ml and 1 mg/ml respectively for paclitaxel and vancomycin. The intraday and interday coefficients of variation were <5% for each of the standard solutions.

Validation of assay

The chromatographic measurement of paclitaxel was established by chromatographic separation of paclitaxel from its preservatives (Cremophor and dehydrated alcohol) from vancomycin (Fig. 1). The stability indicating nature of the assays was established by forcible degradation of the paclitaxel 200 μg/ml and vancomycin 400 μg/ml solutions. Samples were exposed to 1 N HCl or 1 N NaOH for 5 hours at 60°C, 3% hydrogen peroxide for 17 hours at room temperature, and ultraviolet light and 1 N HCl for 22 hours. All degradation products of paclitaxel and vancomycin did not interfere with the intact drug in the assay.

Analysis of data

The initial concentration was defined as 100% and subsequent sample concentrations were expressed as percentage of initial concentration. Stability was defined as greater than 90% remaining of the post-admixture drug concentration.

Table 2. Stability of paclitaxel and vancomycin in 5% dextrose injection during simulated Y-site administration

Drug combination	Initial concentration (mg/ml)[a,b]	% of Initial concentration remaining[b]			
		1 hr	2 hr	4 hr	12 hr
Paclitaxel 0.3 mg/ml	0.144±0.003	99.3±1.7	100.1±2.8	99.6±1.9	97.4±2.5
and vancomycin 1 mg/ml	0.518±0.012	100.1±1.2	99.2±2.1	98.4±1.7	96.3±2.2
Paclitaxel 0.3 mg/ml	0.162±0.004	99.6±1.8	99.7±0.9	98.9±0.7	96.2±2.4
and vancomycin 5 mg/ml	2.582±0.055	99.0±2.1	98.2±2.6	98.4±1.8	98.3±1.6
Paclitaxel 0.3 mg/ml	0.152±0.002	99.7±0.9	99.5±1.2	99.3±0.9	95.3±2.7
and vancomycin 10 mg/ml	5.144±0.121	100.5±1.7	99.4±0.6	100.6±1.7	94.5±1.8
Paclitaxel 1.2 mg/ml	0.654±0.026	100.3±1.8	101.6±1.4	99.5±1.4	96.9±2.0
and vancomycin 1 mg/ml	0.577±0.029	98.3±0.9	99.7±1.5	98.6±2.1	96.7±1.8
Paclitaxel 1.2 mg/ml	0.655±0.014	99.4±1.8	99.6±1.2	97.8±1.7	97.2±2.0
and vancomycin 5 mg/ml	2.446±0.039	101.4±1.9	97.9±2.9	96.8±1.8	98.2±1.8
Paclitaxel 1.2 mg/ml	0.646±0.020	99.4±0.8	99.6±0.9	99.7±1.8	98.7±1.8
and vancomycin 10 mg/ml	5.614±0.075	101.2±1.8	98.0±0.9	99.1±1.9	97.4±2.6

[a]After 1 : 1 dilution with two drugs. [b]Mean ± S.D., n=6

Results and Discussion

Paclitaxel in concentrations of 0.3 and 1.2 mg/ml was stable when mixed with concentrations of vancomycin 1, 5 and 10 mg/ml for twelve hours. Specifically, paclitaxel 0.3 mg/ml in 5% dextrose injection maintained a mean relative concentration of at least 94.5% (see Table 2) with vancomycin 10 mg/ml which retained at least 95.3%. At the 0.9% sodium chloride injection, vancomycin 5 mg/ml retained at least 95.4% (See Table 3) with paclitaxel 0.3 mg/ml and paclitaxel 1.2 mg/ml retained at least 95.5% (See Table 3) with vancomycin 1 mg/ml. At the Hartman's solution, vancomycin 10 mg/ml retained at least 95.6% (See Table 4) with paclitaxel 1.2 mg/ml. In terms of visual changes, no precipitates, color changes, or haziness appeared in any admixture for the twelve hours of inspection. The pH changes were minor with the greatest magnitude being a decrease of pH 0.61 units for the combination of paclitaxel 0.3 mg/ml and vancomycin 1 mg/ml in 5% dextrose injection. The pH measurements did not have a particular trend in any direction over time.

In this study, I would present general guidelines for avoiding common flaws in stability and compatibility studies of injectable drugs.[25,26] First, completely describe the materials, test conditions and methods. The drugs

Table 3. Stability of paclitaxel and vancomycin in 0.9% sodium chloride injection during simulated Y-site administration

Drug combination	Initial concentration (mg/ml)[a,b]	% of Initial concentration remaining[b]			
		1 hr	2 hr	4 hr	12 hr
Paclitaxel 0.3 mg/ml	0.146±0.005	98.5±1.8	99.8±2.1	97.9±2.1	96.6±2.9
and vancomycin 1 mg/ml	0.545±0.011	99.4±2.0	98.6±1.7	97.6±3.1	97.3±1.8
Paclitaxel 0.3 mg/ml	0.164±0.004	98.5±1.1	98.4±1.2	97.5±0.9	97.6±2.4
and vancomycin 5 mg/ml	2.597±0.030	98.2±2.2	96.5±1.9	97.9±2.9	95.4±2.4
Paclitaxel 0.3 mg/ml	0.159±0.003	99.6±1.5	101.6±1.8	98.2±1.0	96.2±2.7
and vancomycin 10 mg/ml	5.162±0.092	101.1±2.9	98.4±2.9	98.6±1.8	97.8±2.4
Paclitaxel 1.2 mg/ml	0.658±0.014	101.2±1.7	98.5±2.9	98.4±2.1	95.5±1.2
and vancomycin 1 mg/ml	0.523±0.011	97.3±1.3	98.7±2.5	96.6±2.9	96.7±2.4
Paclitaxel 1.2 mg/ml	0.651±0.010	97.6±1.8	98.3±1.7	96.2±1.8	96.3±2.8
and vancomycin 5 mg/ml	2.641±0.388	98.7±1.4	97.5±1.2	97.8±1.1	97.5±2.5
Paclitaxel 1.2 mg/ml	0.644±0.017	100.5±1.2	99.5±1.0	97.8±1.1	97.4±2.1
and vancomycin 10 mg/ml	5.578±0.108	99.9±2.4	98.8±2.1	98.8±1.1	96.1±3.3

[a]After 1 : 1 dilution with two drugs. [b]Mean ± S.D., n = 6.

Table 4. Stability of paclitaxel and vancomycin in Hartman's solution during simulated Y-site administration

Drug combination	Initial concentration (mg/ml)[a,b]	% of Initial concentration remainingb			
		1 hr	2 hr	4 hr	12 hr
Paclitaxel 0.3 mg/ml	0.156±0.004	96.7±1.8	95.7±2.1	97.5±2.1	97.2±1.9
and vancomycin 1 mg/ml	0.547±0.012	98.2±2.0	97.2±1.7	96.5±3.1	98.1±1.8
Paclitaxel 0.3 mg/ml	0.147±0.003	99.9±1.1	99.4±1.2	98.2±0.9	98.1±2.4
and vancomycin 5 mg/ml	2.512±0.036	99.9±2.2	97.1±1.9	98.9±1.9	96.6±3.4
Paclitaxel 0.3 mg/m	0.149±0.002	98.2±1.5	100.1±1.8	99.2±1.0	97.4±1.7
and vancomycin 10 mg/ml	5.123±0.127	100.7±2.9	97.9±2.9	99.8±1.8	98.1±2.4
Paclitaxel 1.2 mg/ml	0.621±0.014	99.8±1.7	99.2±2.9	97.0±2.1	95.9±2.2
and vancomycin 1 mg/ml	0.575±0.008	98.6±1.3	99.4±2.5	96.7±1.9	97.2±1.4
Paclitaxel 1.2 mg/ml	0.659±0.014	98.5±1.8	99.4±1.7	97.9±2.8	95.7±2.8
and vancomycin 5 mg/ml	2.612±0.037	99.9±1.4	97.1±1.2	98.6±1.0	96.0±1.5
Paclitaxel 1.2 mg/ml	0.644±0.009	101.8±1.2	97.8±1.0	97.5±1.1	98.0±3.1
and vancomycin 10 mg/ml	5.974±0.117	98.9±2.4	99.8±2.1	97.8±1.1	95.6±3.3

[a]After 1 : 1 dilution with two drugs. [b]Mean ± S.D., n = 6.

Table 5. pH of 5% dextrose injection, 0.9% sodium chloride injection and Hartman's solution containing both of paclitaxel and vancomycin

Drug combination	pH in 5% dextrose injectiona			pH in 0.9% sodium chloride injection[a]			pH in Hartman's solution[a]		
	Initial	4 hr	12 hr	Initial	4 hr	12 hr	Initial	4 hr	12 hr
Paclitaxel 0.3 mg/ml and vancomycin 1 mg/ml	6.89±0.11	6.77±0.18	6.28±0.15	6.45±0.12	6.59±0.15	6.67±0.13	7.12±0.12	7.14±0.17	7.02±0.11
Paclitaxel 0.3 mg/ml and vancomycin 1 mg/ml	6.67±0.08	6.54±0.09	6.59±0.11	6.76±0.09	6.64±0.11	6.49±0.05	7.02±0.10	6.99±0.18	6.88±0.04
Paclitaxel 1.2 mg/ml and vancomycin 10 mg/ml	6.34±0.18	6.24±0.08	6.28±0.04	6.49±0.18	6.57±0.08	6.33±0.13	6.98±0.08	9.78±0.02	6.72±0.09
Paclitaxel 1.2 mg/ml and vancomycin 10 mg/ml	6.23±0.10	6.21±0.11	6.30±0.09	6.54±0.08	6.48±0.19	6.37±0.14	6.85±0.11	6.71±0.09	6.70±0.13

[a]Mean ± S.D., n=6

and other materials used in the testing should be completely described including sources and quantities or concentrations. Similar products from different suppliers may have different formulations that can affect results. Varying the concentrations tested may also alter results. All conditions of a test should be included and thoroughly described. Some variables that are frequently unmentioned include the actual temperature, presence or absence of light and container materials. In addition, the analytical methods used should be described in detail and basic items such as pH, color and clarity determined should be described. The materials, test conditions and methods should be described sufficiently well to permit replication of the study. Second, use a stability-indicating assay. The most common flaw is the failure to use an analytical method that has been demonstrated to be stability-indicating.[27] It is incumbent on researchers to demonstrate that the methods they are using will detect and separate the intact drug in the presence of its decomposition products and other drugs and components. Third, perform an analytical determination at the outset. A time-zero determination of drug concentration is essential. Without such a determination of initial concentration, there is no definitely known starting point. Fourth, use replicate assays at adequate and appropriate intervals. Initially and at all test intervals, multiple assays of mutiple test solutions should be performed. Performing several determinations on replicate test solutions at each interval will help to increase confidence in the accuracy of the results obtained by minimizing the effects of assay variability and human error. As a general rule, duplicate assay of three replicate test solutions are considered a minimum. Finally, make the conclusions fit the results. Conclusions should be only as definite as all relevant facts permit. And also conclusion should take into account all of the data. If these problems are avoided at the outset in the design of the study and through project completion and writing of the paper, much wasted effort will be eliminated and higher quality papers on drug stability and compatibility will result.

In summary, paclitaxel at concentrations of 0.3 and 1.2 mg/ml may be administered through a Y-injection port along with vancomycin of 1, 5 and 10 mg/ml in 5% dextrose injection, 0.9% sodium chloride injection and Hartman's solution for periods of at least twelve hours at room temperature.

Acknowledgement

This work was supported by a grant from Chosun Nursing College.

References

1) Gundlach CA, Faulkner TP, Souney PF. Drug usage patterns in the ICU: Profile of a major metropolitan hospital and comparison with other ICUs. Hosp Formul 1991; 1: 132-36
2) Wall ME, Wani MC. Antineoplastic agents from plants. Ann Rev Pharmacol 1977; 17: 117-32
3) Wani MC, Taylor HL, Wall ME. Plant antitumor agents. VI. The isolation and structure of paclitaxel, a novel antileukemic antitumor agent from Taxus brevifolia. J Am Chem Soc 1971; 93; 2325-27
4) Moorhatch P, Chiou WL. Interaction between drugs and plastic intravenous fluid bags. Part II: Leaching of chemicals from bags containing various solvent media. Am J Hosp Pharm 1974; 31: 149-52
5) Rowinsky EK, Cazenzve LA, Donehower RC. Pacli-

taxel: a novel investigational antineoplastic agent. J Natl Cancer Inst 1990; 82: 1247-53
6) Venkataramanan R, Burkart GJ, Ptachcinski RJ. Leaching of diethylhexyl Phthalate from polyvinyl chloride bags into intravenous cyclosporine solutions. Am J Hsop Pharm 1981; 43: 2800-2
7) Waugh WN, Trissel LA, Stella VJ. Stability, compatibility and plasticizer extraction of paclitaxel (NSC-125973) injection diluted in infusion solutions and stored in various containers. Am Hosp Phar 1991; 48: 1520-24
8) Donehower RC, Rowinsky EK, Grochow LB. Phase I trial of paclitaxel in patients with advanced cancer. Cancer Treat Rep 1987; 71: 1171-77
9) Krogstad DJ, Moellering RC, Greenblatt DJ. Single-dose kinetics of intravenous vancomycin. J Clin Pharmacol 1980; 20: 197-201
10) Van der Auwera P, Aoun M, Meunier F. Randomized study of vancomycin versus teicoplanin for the treatment of gram-positive bacterial infections in immunocompromised hosts. Antimicrob Agents Chemother 1991; 35: 451-457
11) EORTC and the National Cancer Institute of Canada. Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. J Infect Dis 1991; 163: 951-958
12) Trissel LA, Bready BB. Turbidimetric assessment of the compatibility of the paclitaxel with selected other drugs during simulated Y-site injection. Am J Hosp Pharm 1992; 49: 1716-19
13) Trissel LA, Martinez JF. Turbidimetric assessment of the compatibility of paclitaxel with 42 other drugs during simulated Y-site injection. Am J Hosp Pharm 1993; 50: 300-4
14) Burm JP, Choi JS, Gill MA. Stability of paclitaxel and fluconazole during simulated Y-site administration. Am J Hosp Pharm 1994; 51: 2704-6
15) Stamatakis MK, Leader WG, Tracy TS. Stability of high-dose vancomycin and ceftazidime in peritoneal dialysis solutions. Am J Health Syst Pharm 1999; 56: 246-248
16) Vaughan LM, Poon CY. Stability of ceftazidime and vancomycin alone and in combination in heparinized and nonheparinized peritoneal dialysis solution. Ann Pharmacother 1994; 28: 572-576
17) Wood MJ, Lund R, Beavan M. Stability of vancomycin in plastic syringes measured by high-performance liquid chromatography. J Clin Pharm Ther 1995; 20: 319-325
18) Schilling CG, Watson DM, McCoy HG. Stability and delivery of vancomycin hydrochloride when admixed in a total parenteral nutrition solution. JPEN J Parenter Enteral Nutr 1989; 13: 63-64
19) Nahata MC, Miller MA, Durrell DE. Stability of vancomycin hydrochloride in various concentrations of dextrose injection. Am J Hosp Pharm 1987; 44: 802-804
20) Das Gupta V, Stewart KR, Nohria S. Stability of vancomycin hydrochloride in 5% dextrose and 0.9% sodium chloride injections. Am J Hosp Pharm 1986; 43: 1729-1731
21) Allen LV, Levinson RS, Phisutsinthop D. Compatibility of various admixtures with secondary additives at Y injection sites of intravenous administration sets. Am J Hosp Pharm 1992; 34: 939-43
22) Allen LV, Stiles ML. Compatibility of various admixtures with secondary additives at Y injection sites of intravenous administration sets. Part 2. Am J Hosp Pharm 1981; 38: 380-81
23) Longnecker SM. Donehower RC, Cates AE. High performance liquid chromatographic assay for paclitaxel in human plasma and urine and pharmacokinetics in a phase I trial. Cancer Treat Rep 1987; 71: 53-9
24) Favetta P, Guitto J, Bleyzac N, Dufresne C, Bureau J. New sensitive assay of vancomycin in human plasma using high-performance liquid chromatography and electrochemical detection. J Chromatogr B Biomed Sci 2001; 25: 377-382
25) Connors KA. Amidon GL, Stella VJ. Chemical stability of pharmaceuticals: a handbook for pharmacists, 2nd ed, John Wiley, New York 1986: 34-8
26) Trissel LA. Hadbook on injectable drugs, 4th ed, American Society of Hospital Pharmacists, Bethesda 1986: 129-32
27) Trissel LA, Flora KP. Stsbility studies: five year later. Am J Hosp Pharm 1988; 45: 1569-71