Compatibility and stability of ceftriaxone sodium with peritoneal dialysis solution

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Abstract

Drug compatibility and stability with the diluents is important expected therapeutic outcome. The administration of incompatible and unstable antibiotics admixtures is associated with several life threatening clinical situations. For the treatment of peritonitis or peritoneal infection, antibiotics are delivered at the site through peritoneal dialysis solution. Therefore, the investigation of compatibility and stability of antibiotic with peritoneal dialysis is imperative. To address this matter, the present study is aimed to determine the compatibility and stability of ceftriaxone sodium in isotonic and hypertonic peritoneal dialysis solutions. For such purposes, a spectroscopic method was developed and validated for the determination of ceftriaxone sodium in the presence of peritoneal dialysis solutions. Then the compatibility and stability of the antibiotic in both the peritoneal dialysis solutions at 4°C, 25°C and 40°C for 48 h using three concentrations of the drug such as 250 mg/L, 500 mg/L and 1000 mg/L. The aliquots were drawn from the admixtures at regular intervals and analyzed to determine the drug contents using UV spectrophotometry. The results of the study showed that the drug was stable for 10 days at 4°C, 28 h at 25°C and 8 h at 40°C in both the peritoneal dialysis solutions. The drug was found to be following the 1st order degradation at all the three temperatures. It is concluded from results of the present study that ceftriaxone sodium is compatible and stable with isotonic and hypertonic peritoneal dialysis solutions.

Introduction

CFX-Na is a crystalline, white hygroscopic powder and has a good water solubility. It is slightly soluble in ethanol and in methanol it shows sparingly solubility. The pH of 1% aqueous solution is approximately 6.7. It is optimum to store it under 25°C and should be shielded from light. It is recommended that the reconstituted solutions must be used immediately after preparation but they are stable for up to 24 h when stored in the refrigerator. The present study aimed to investigate compatibility and stability of ceftriaxone sodium and PD solutions at three different temperatures. To develop and validate UV spectroscopic method for the determination of ceftriaxone sodium in PD solutions. Compatibility and stability of the antibiotic and PD solutions.

Materials and methods
Preparation of admixtures

Three sample solutions were made by dissolving the quantity of CFX-Na equivalent to 25 mg, 50 mg and 100 mg in 100 ml isotonic PD solution. Similarly three sample solutions were also made by dissolving the quantity of CFX-Na equivalent to 25 mg, 50 mg and 100 mg in 100 ml hypertonic PD solution.

Processing of admixtures : The solutions of each concentration in isotonic PD solution were stored at three different temperatures such as 4°C, 25°C and 40°C for 48 h. Similarly, the solutions of each concentration in hypertonic PD solutions were

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stored at three different temperatures such as 4°C, 25°C and 40°C for 48 h. The physicochemical changes like color changes, precipitation, turbidity and clarity of the solutions were observed for 48 h at regular intervals.

Analysis of aliquots : One hundred micro liters aliquots were withdrawn at 0 (premixing), 15, 30, 45, 60, 120, 360, 720, 1440 and 2880 minutes and diluted up to 10 ml with isotonic PD solution. Same procedure was repeated for dilution with hypertonic PD solution, for the solutions which were formed in hypertonic PD solution. Then the aliquots of CFX-Na were analyzed by using spectrophotometer at ë $_{max}$ of 276nm. All readings were taken in triplicate by using isotonic PD solution as a blank for the solutions which were made in isotonic PD solution. Similarly, hypertonic PD solution was used as a blank for the solutions which were made in hypertonic PD solution.

Evaluation of chemical kinetic parameters
Order of the reaction : Chemical kinetics of the reaction were determined by graphic method as zero, first and second order [1]. Graphs were plotted for zero order, first order and second order kinetics for each of the solution stored at 4°C, 25°C and 40°C. The correlation coefficient of each of the graph at each temperature was evaluated and order of the chemical reaction with the best linearity was taken. The reaction rate constant (K) for zero order kinetic was calculated at each temperature from slope of the curve of % concentration remaining after 48h versus time, for first order by logarithm of % concentration remaining versus time and for second order by inverse of the concentration remaining (1/C) versus time [2].

Activation energy (Ea) : Activation energy (Ea), the energy required to move a molecule from initial state to the transitional state or the minimum energy needed for the reaction to occur. Rate constant K was used to ascertain Ea by taking natural logarithm (ln K) or logarithm (log K) on y-axis and reciprocal of absolute temperature (1/T) in Kelvin on x-axis (Pugh *et al.,* 2002). It can be calculated from the slope of the straight line of the plot (-Ea/2.303 R or Ea/R) [2].

Frequency Factor (A) : It is also called the pre-exponential factor or the steric factor. It determines factors like frequency of collision and their orientation. It can be calculated from the intercept (log A or ln A) taken from the plot of ln K versus 1/T [2]. Then Arrhenius equation was used to determine the reaction rate constant for each of the solution of CFX-Na in isotonic and hypertonic PD solutions stored at 4°C (277.15 K), 25°C (298.15) and 40°C (313.15 K).

Results and discussion
Physical changes of the CFX-Na in PD solutions : Different parameters were assessed during physical study like color changes, precipitation, clarity of solution and turbidity. No physical changes were observed in the solutions of CFX-Na in isotonic PD solution as well as in hypertonic PD solution, which were stored at 4°C, 25°C and 40°C for the time period of 48 h. Parameters for physical study like color changes, precipitation, clarity of solution and turbidity were assessed at all the three temperatures. No color change was observed in the solutions of CFX-Na in isotonic as well as in hypertonic PD solution, even after the storage time of 48 h at all the three temperatures i.e., 4°C, 25°C and 40°C. No precipitation was seen in the solutions of CFX-Na in isotonic PD solution neither in the solutions of CFX-Na in hypertonic PD solutions after keeping the solutions in storage upto 48 h at all the three temperatures. Solutions of CFX-Na in both PD solutions were crystal clear and no turbidity was found at all three temperatures during complete physical study of 48 h.

Degradation kinetics of admixtures at different temperatures : Compatibility and stability of CFX-Na with isotonic PD solution and CFX-Na with hypertonic PD solution was also studied by investigating their order of reactions at all three temperatures and the curve with the best linearity was taken as order of reaction. The graphs of percentage degradation versus time in minutes of all the three concentrations in isotonic PD solution

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Table 1- Parameters for physical changes observed during stability study

Color changes			
Drug Sample	4°C	25°C	40°C
CFX-Na in isotonic PD solution	No change	No change	No change
CFX-Na in hypertonic PD solution	No change	No change	No change
Precipitation observed			
CFX-Na in isotonic PD solution	Absent	Absent	Absent
CFX-Na in hypertonic PD solution	Absent	Absent	Absent
Clarity test			
CFX-Na in isotonic PD solution	Clear	Clear	Clear
CFX-Na in hypertonic PD solution	Clear	Clear	Clear
Turbidity observed			
CFX-Na in isotonic PD solution	No turbidity	No turbidity	No turbidity
CFX-Na in hypertonic PD solution	No turbidity	No turbidity	No turbidity

are shown in the Figure 3.1, 3.2 and 3.3 respectively.
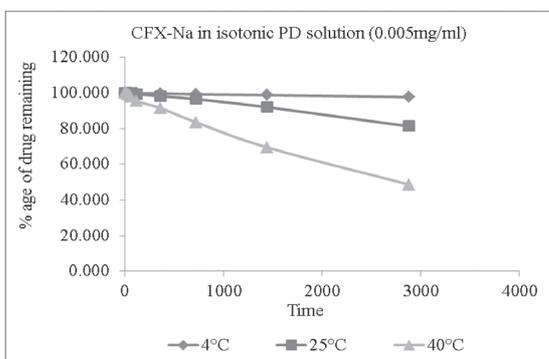
Fig. 1: % age of remaining CFX-Na in isotonic PD solution at concentration of 0.0025 mg/ml
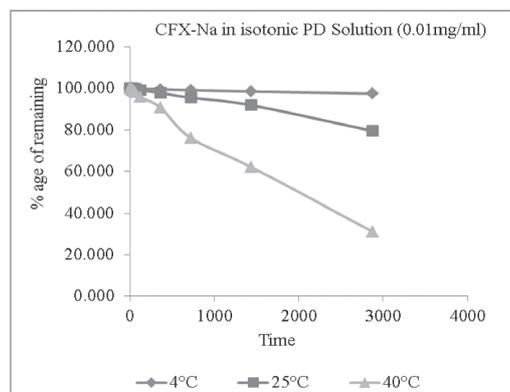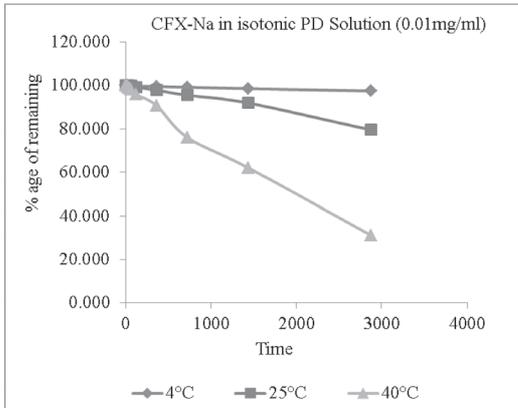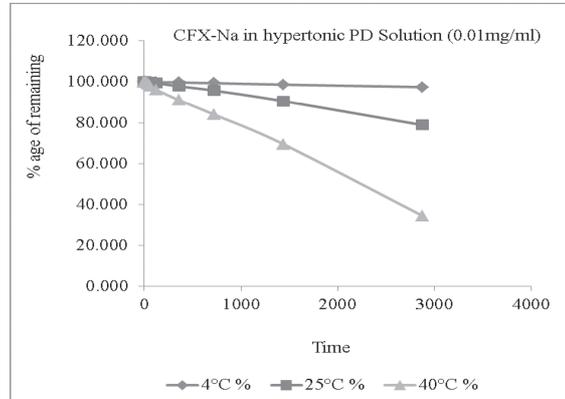

Figure 2: % age of remaining CFX-Na in isotonic PD solution at concentration of 0.005 mg/ml
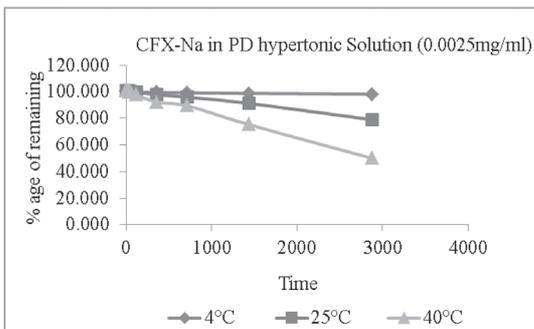
The above curves indicate that the drug is more stable at lower temperature than higher temperature. Drug is most stable at 4°C and it is least stable at 40°C. The degradation curves of CFX-Na in the hypertonic PD solution at the same three temperatures and concentrations are shown in the Figures 3.4, 3.5 and 3.6 respectively.
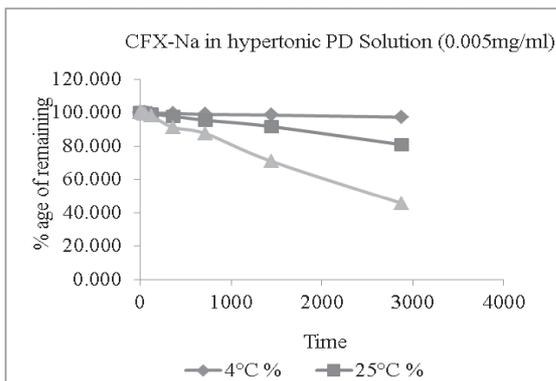
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Fig. 3: % age of remaining CFX-Na in isotonic PD solution at concentration of 0.01mg/ml

Fig. 4: % age of remaining CFX-Na in hypertonic PD solution at concentration of 0.0025 mg/ml

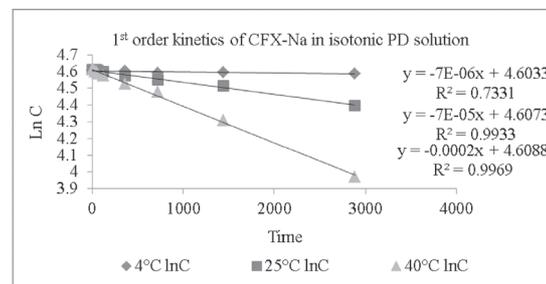**Fig. 5:** % age of remaining CFX-Na in hypertonic PD solution at concentration of 0.005 mg/ml

Fig. 6: % age of remaining CFX-Na in hypertonic PD solution at concentration of 0.01 mg/ml
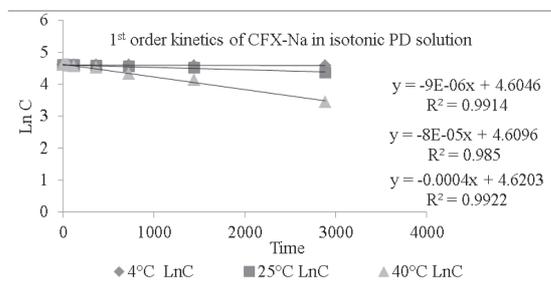
The study conducted in hypertonic PD solution also showed similar results as shown for the isotonic PD solution. The rate of degradation was maximum at temperature 40°C and was found to be minimum at temperature 4°C. The graphs of reaction order in isotonic PD solution at three temperatures are shown in Figure 3.7. 3.8 and 3.9 respectively.
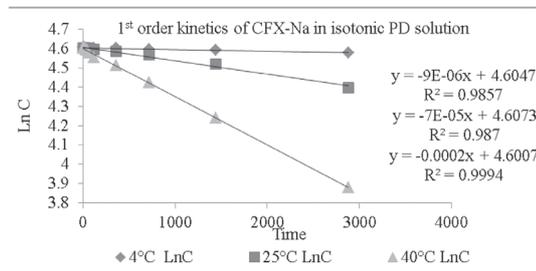
Fig. 7: 1st order degradation kinetics of CFX-Na in isotonic PD solution at 0.0025 mg/ml concentration.

Fig. 8: 1st order degradation kinetics of CFX-Na isotonic PD solution at 0.005 mg/ml concentration.

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Fig. 9: 1st order degradation kinetics of CFX-Na isotonic PD solution at 0.01 mg/ml concentration.

It can be seen from the graph of order of reaction that the value of correlation coefficient is almost approaching to '1' in all the curves. So it can be concluded that drug degradation follows 1st order kinetics at all the three concentrations i.e., 0.0025 mg/ml, 0.005 mg/ml and 0.01 mg/ml in isotonic PD solution. The slope of the degradation curve was minimum at 4°C and maximum at 40°C so the degradation was minimum at 4°C and maximum at 40°C. The graphs of 1st order reaction in hypertonic PD solution are shown in figures 3.10, 3.11 and 3.12.

The above graphs show that the degradation follows 1st order kinetics at all three temperatures in hypertonic PD solution. The concentration has no effect on the order of reaction and the degradation followed 1st order kinetics at all three concentrations.
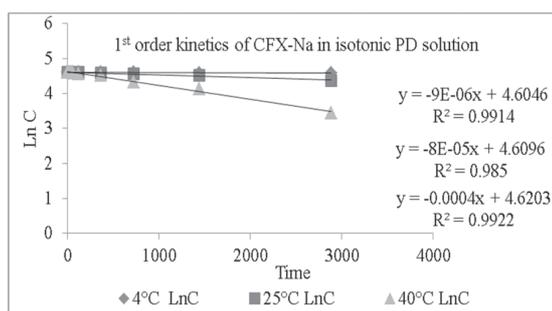
Arrhenius plots : Effect of temperature on rate of reaction was studied by taking Arrhenius plots of degradation rates. It was proved from the results of order of reaction because the reaction order was independent of the concentration of drug, so the Arrhenius plot was taken only for a single concentration of drug i.e., 0.0025 mg/ml. The reaction velocity or degradation rate constant (K) of the CFX-Na in peritoneal PD solutions at a concentration of 0.0025 mg/ml was taken from the slope of their curves of logarithm of concentration remaining (LnC) versus time. Rate constant of CFX-Na degradation was determined

by extrapolating the graphs of (LnK) versus inverse of temperature (1/T Kelvin^{-1}). Results of plots in isotonic and hypertonic PD solution are shown in figure 3.13 and 3.14 respectively.
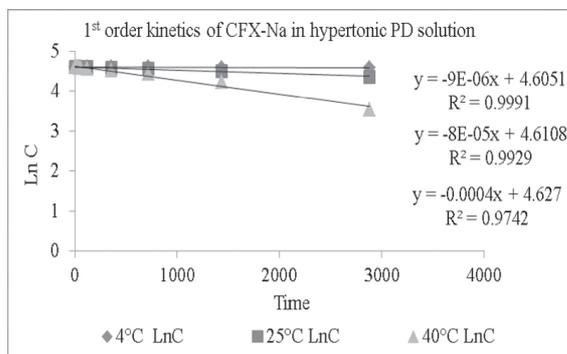
Activation energy (Ea) for each combination was calculated by multiplying slope of the straight line of the respective Arrhenius plot with gas constant (R= 8.314 KJ mol^{-1}) whereas pre-exponential factor or frequency factor (A) was calculated from the intercept of the curves. Degradation rate constant (K), activation energy (Ea) and frequency factor (A) of above stated combinations are presented in Table 3.2.
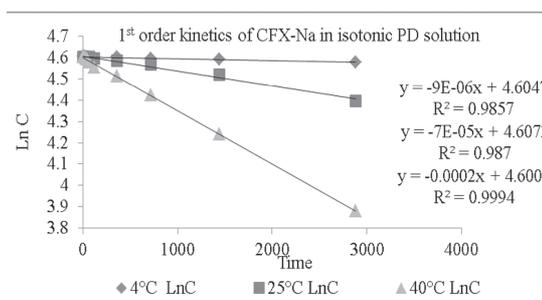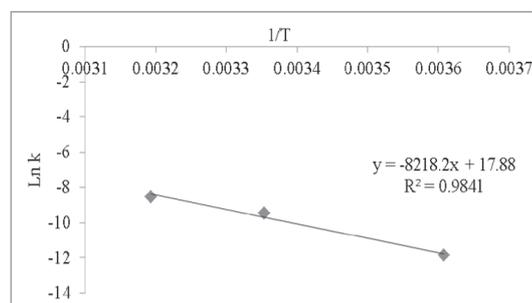

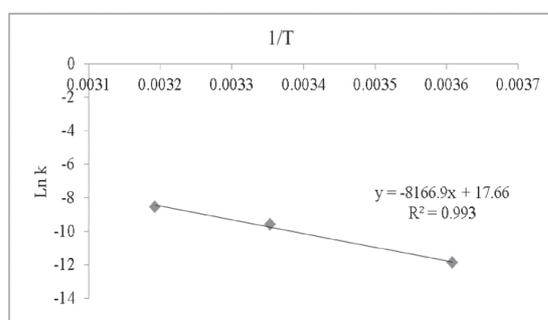**Fig. 10:** 1st order degradation kinetics of CFX-Na in hypertonic PD solution at 0.0025 mg/ml concentration.

Fig. 11: 1st order degradation kinetics of CFX-Na in hypertonic PD solution at 0.005 mg/ml concentration.

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Fig. 12: 1st order degradation kinetics of CFX-Na in hypertonic PD solution at 0.01 mg/ml concentration.

Fig. 13: Arrhenius plot of CFX-Na (0.0025 mg/ml) in isotonic PD solution

The above mentioned results show that the value of degradation rate constant (K) is maximum at 40°C and minimum at 4°C, so the rate of degradation is maximum at 40°C. The value of 'K'

Fig. 14: Arrhenius plot of CFX-Na (0.0025 mg/ml) in hypertonic PD solution.

is slightly greater in the hypertonic PD solution. It means the degradation rate is slightly faster in hypertonic PD solution than in the isotonic PD solution. The frequency factor 'A' is also greater in hypertonic PD solution. The shelf life of the CFX-Na in isotonic and hypertonic PD solutions was calculated and showed in Table 3.3.

The results shown in Table 3.3 indicate that as the temperature increases, the shelf life of CTX-Na decreases. The results also indicate that the drug showed a slightly lesser shelf life in hypertonic PD solution than in the isotonic PD solution. The shelf life of drug was almost 10 days in isotonic PD solution and 9.5 days in hypertonic PD solution at 4°C. At 25°C, the drug remained stable for almost 30 h in isotonic and for 28 h in hypertonic PD solution. Least shelf life was shown at 40°C where the drug remained stable for only about 8 h

Table 2: Rate constant (K), activation energy (Ea) and frequency factor (A) of all the combinations stored at 4°C, 25°C and 40°C for 48 h

Name of drug	K4°C	K25°C	K40°C	Ea (KJ mol⁻¹)	A (S⁻¹)
CFX-Na in isotonic PD solution	0.0000074	0.000059	0.00022	67.89961	46734817.4
CFX-Nain hypertonic PD solution	0.0000077	0.0000625	0.000233	68.32611	58235168.5

Ceftriaxone sodium (CFX-Na); PD (Peritoneal dialysis)

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Table 3: Shelf life of CFX-Na in isotonic and hypertonic PD solutions stored at 4°C, 25°C and 40°C for 48 h

Name of drug	Shelf Life (h) 4°C	Shelf Life (h)25°C	Shelf Life (h)40°C
CFX-Na in isotonic PD solution	236.49	29.66	7.95
CFX-Na in hypertonic PD solution	227.3	28.0	7.5

Ceftriaxone sodium (CFX-Na); PD (Peritoneal dialysis)

and 7.5 h in isotonic and hypertonic PD solution respectively. It was found in recent result that ceftriaxone disodum was more stable in water than isotonic solution [3].

Conclusion

Ceftriaxone sodium is a commonly used antibiotic for the prevention of peritonitis in patients of peritoneal dialysis. In most of the times, the drug is mixed with the dialyzing fluid at the time of administration, but if the admixture of drug and dialyzing fluid is required to be stored for some time, this solution must have to remain stable during that storage time. The present stability study of CFX-Na in isotonic and hypertonic PD solution has shown that as the temperature is increased, the drug degradation becomes faster. The degradation products are also soluble in the PD solutions so there is no precipitation or coloration produced in the admixtures after storage for 48 h. Moreover, the drug did not show any suspended particle with the passage of time. The increased degradation of drug is attributable to the increased kinetic energy of the molecules. Due to increased kinetic energy, molecular collision is increased. As the reaction rate is directly proportional to the collision of reactant molecules with one another. So, the degradation rate is also increased at increased temperature. The degradation rate was also greater in the hypertonic PD solution and can also be justified from the frequency factor obtained from the Arrhenius plots. The frequency factor was found to be greater in hypertonic PD solution. Due to the greater rate of degradation, the drug showed shorter shelf life at increased temperature. So, if the admixture is to be administered in a warm environment, it should be used immediately after mixing the CFX-Na in peritoneal dialysis solution. If storage is necessary, it must be stored in refrigerator at 4°C, at which the drug is stable for almost 10 days. The drug degradation follows 1st order kinetics at 0°C, 25°C and 40°C in both types of PD solutions. It means the increase in concentration does not affect the drug degradation rate, but effect of temperature is dominant and the rate of degradation is very slow at 4°C. Overall, it can be suggested by this study that the ceftriaxone sodium is compatible with peritoneal dialysis solutions.

Reference:

[1] Murphy, B., C. Murphy & B. J. Hathaway (1997) A Working Method Approach for Introductory Physical Chemistry Calculations. Royal Society of Chemistry: London, pp. 115-7

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