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ORIGINAL ARTICLE

Long-term stability of temocillin in dextrose 5% and in sodium chloride 0.9% polyolefin bags at $5 \pm 3^\circ\text{C}$ after freeze-thaw treatment

Stabilité à long terme de la temocilline dans une solution de glucose à 5% ou de chlorure sodique à 0,9% stockée dans une poche de polyoléfine après congélation, décongélation par micro-ondes et stockage final à $5 \pm 3^\circ\text{C}$

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Summary

Introduction. — The aim of this study was to investigate the stability of a mixture of temocillin 20 mg/ml in 5% dextrose and in 0.9% sodium chloride polyolefin bags after freezing, microwave thawing and long-term storage at $5 \pm 3^\circ\text{C}$.

Methods. — The stability of ten polyolefin bags containing 20 mg/ml of temocillin, five bags in 5% dextrose and five bags in 0.9% sodium chloride, prepared under aseptic conditions was studied after freezing for 1 month at -20°C , thawing in a microwave oven with a validated cycle, and stored at $5 \pm 3^\circ\text{C}$. Over 30 days, temocillin concentrations were measured by high-pressure liquid chromatography. Visual inspections, microscope observation, spectrophotometric measurements and pH measurements were also performed.

Results and discussion. — No precipitation occurred in the preparations but minor colour change was observed. No microaggregate was observed with optical microscopy or revealed by a change of absorbance. Based on a shelf life of 95% residual potency, temocillin

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MOTS CLÉS

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infusions were stable at least 11 days in 5% dextrose and 14 days in 0.9% sodium chloride after freezing and microwave thawing (corresponding at the period where 95% lower confidence limit of the concentration-time profile remained superior to 95% of the initial concentration). During this period, the pH values of drug solutions have been observed to decrease without affecting chromatographic parameters.

Conclusion. – Within these limits, temocillin in 5% dextrose and in 0.9% sodium chloride infusions may be prepared and frozen in advance by a centralized intravenous admixture service then thawed before use in clinical units.

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Résumé

Objectifs. – L'objectif de cette étude est d'évaluer la stabilité d'un mélange de temocilline à 20 mg/mL dans une solution de glucose 5% (G5) et de chlorure sodique 0,9% (S) contenu dans des poches de polyoléfine.

Méthode. – La stabilité de dix poches contenant 20 mg/mL de temocilline, cinq poches dans du G5 et cinq poches dans du S a été étudiée après congélation d'un mois à -20°C , décongélation par micro-ondes suivant un cycle validé et stockage à $5 \pm 3^{\circ}\text{C}$. Les concentrations de temocilline ont été mesurées par méthode chromatographique à haute performance et détection spectrophotométrique UV à 235 nm. Des examens macroscopique, microscopique et spectrophotométrique des solutions ainsi qu'une mesure de pH ont été réalisés.

Résultats. – Aucune précipitation ni augmentation de l'absorbance n'ont été observées. L'examen microscopique n'a pas mis en évidence de micro-agrégats. Seule une légère modification de la coloration est apparue. Les préparations de temocilline sont stables pendant au moins 11 jours dans du G5 et au moins 14 jours dans du S après congélation et décongélation par micro-ondes, période durant laquelle la limite inférieure de l'intervalle de confiance à 95% est restée supérieure à 95% de la concentration initiale. Durant cette période, les valeurs de pH ont diminué sans affecter les paramètres chromatographiques.

Conclusion. – Dans ces conditions, la temocilline dans du G5 ou du S peut être préparée et congelée à l'avance dans une unité centrale de reconstitution d'injectables, puis être décongelée par micro-ondes pour être utilisée.

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Introduction

Temocillin (6- α -methoxy-ticarclillin)[1] is a narrow spectrum β -lactam with useful activity against *Enterobacteriaceae* and a remarkable resistance to most β -lactamases [2–4], including ESBLs, AmpC [5,6] and carbapenemases [7]. It presents a particular interest in septicæmia, urinary tract infection and lower respiratory tract infections caused by these organisms as long as Gram-positive and *P. aeruginosa* can be excluded, because it allows decreasing the pressure exerted by carbapenems in this environment. This stability of β -lactamase results from a decreased accessibility of water molecules to the β -lactam ring thanks to the presence and orientation of the 6- α -methoxy moiety [4]. Not surprisingly, this also confers an improved chemical stability to temocillin when present in aqueous solutions. Thus, one study showed that temocillin remains stable in concentrated solutions at 37°C for more than 24 h, which facilitates its use by continuous infusion in the hospital setting [8]. Another more recent study, showed that temocillin also remains stable when stored in elastomeric pumps for up to 3 weeks at 4°C followed by warming to room temperature for 24 h, corresponding to a typical use for outpatient antibiotic therapy by continuous infusion [9]. In the present study, we evaluated the stability of temocillin as a freeze-thaw preparation for large-scale use in hospitals or in other situations

where a centralized intravenous additive service (CIVAS) is advantageous. Freeze-thaw treatment, indeed, extends the long-term storage of infusion solutions [10] while thawing in microwave oven allows for their rapid use when needed [11–24].

As previously described [12–24], several therapeutic infusions can be prepared in this way, which has several potential benefits including reduction in medication errors, better safety control, and high assurance of sterility and standardization of drug concentration [25].

Materials and methods**Solution preparations**

One commercially available vial of temocillin (Negaban[®] 2 g, Eumédica, Bruxelles, Belgium, lot L114552) was solubilized in 12.5 ml of water for injection (Braun, Diegem, Belgium, lot 8504A192) and added in a vertical laminar-airflow hood to 100 ml polyefin bags (co-extruded layers of polyethylene, polyamide, polypropylene) containing 5% dextrose injection or 0.9% sodium chloride (NaCl) injection (Viaflo, Baxter, Lessines, Belgium, 09L04G60 for dextrose and lot 09L03G61 for NaCl) to produce solutions containing approximately 20 mg/ml of temocillin [26].

Assay solutions

Ten microliter of each assay solution diluted 1 to 40 in water were injected into the chromatograph. The injection of an identical volume of standard solution was used to calibrate the system. Results were automatically calculated by interpolation of single-level calibration curve (linear through zero), performed with Empower 2 software using peak areas versus standard concentrations.

Standard solutions

Each working day, 500 mg of temocillin is weighted and added to 25 ml of water to obtain a solution of 20 mg/ml, which was used for the preparation of standard and quality control solutions.

This solution was then diluted in purified water to prepare three standard temocillin solutions (1.50 mg/ml, 0.75 mg/ml and 0.25 mg/ml).

Quality control solutions

Quality control solutions of 0.125 mg/ml, 0.5 mg/ml and 1.0 mg/ml were also used at each day of the test after dilution in purified water of the 20 mg/ml temocillin solution.

Chromatographic apparatus and conditions

The high-pressure liquid chromatographic system (Alliance, model 2690, Waters Association, Milford, MA, USA) was used with a DAD detector (model 996, Waters Association, Milford, MA, USA) and a data acquisition and processing module (Empower 2 Software, Waters Association, Milford, MA, USA).

A reversed phase column C18 was used (Grom-Sil 80 ODS-7pH, 4 μ m 150 mm \times 4 mm, Grace ref GSOD7040851504, Alltech associates, Lokeren, Belgium).

The mobile phase was constituted of 15% acetonitrile (ref C03C11X, Lab-Scan, Sowinskiego, Poland) and 85% 0.01 M ammonium acetate (ref 1.01116.0500, Merck, Darmstadt, Germany) at pH=4 with acetic acid (ref RH-014, Romil Chemicals Limited, Loughborough, Leics).

The flow rate was set at 1.0 ml/min, the column temperature at 30 °C, the wavelength (DAD detector) at 235 nm.

pH determination

The pH of the solutions was measured with a pH-meter (Inolab WTW Weilheim, Germany) equipped with a glass electrode (Biotrode Hamilton Bonaduz, Switzerland) calibrated with two standard solutions at pH 4 and pH 7 (CertiPur, Merck, Darmstadt, Germany).

Validation of high-pressure liquid chromatographic method

Precision

For the within-day and the between-day variation, three levels of control solutions respectively 0.25 mg/ml, 0.5 mg/ml,

1 mg/ml and 0.125 mg/ml, 0.5 mg/ml, 1 mg/ml were undertaken to calculate these variations.

Linearity of analytical response

Linearity was evaluated by six dilutions of temocillin (the first concentration was 1.50 mg/ml and the last is 0.125 mg/ml) injected in duplicate.

Stability indication

The stability indicating capability of the chromatographic method was assessed using decomposed solutions of temocillin.

We prepared at different pH, one solution of temocillin: initial solution (pH 7.01) acidic solution (pH 2.68) obtained by adding HCL 12 M (Merck, Darmstadt, Germany) and alkaline solution (pH 12.33) obtained by adding NaOH 5 M (Merck, Darmstadt, Germany).

One microliter of each solution was degraded by heating at 100 °C during 60 minutes. Ten microliter of these solutions, after dilution 1 on 40, was injected in the HPLC system before and after heating.

Stability study

Each polyolefin bag containing 2 g/100 ml of temocillin (5 in 5% dextrose and 5 in 0.15 M NaCl, were prepared before freezing at -20 °C. After 1 month, these bags were thawed in a microwave oven (NND998 C/W, 230 V, 2450 MHz, 800 W, Panasonic, Saint-Denis, France) by a standardized and validated cycle, as described in a previous publication [12].

The five bags were hung to a carousel thawed for 13 minutes with an output power of 270 W then stirred and thawed again for seven minutes, allowing us to obtain a remaining ice volume between 1 and 8 cm³.

These bags were agitated and stored at 5 \pm 3 °C for 30 days. At day 0, 2, 3, 4, 7, 9, 11, 16, 18, 21, 23, 25, 28 and 30, 2 ml of solution from each bag were withdraw using 5 ml polypropylene plastic syringes (Terumo, Haasrode, Belgium) and placed in separated glass tubes.

Aliquots were visually and microscopically inspected, and their spectrophotometric absorbance and pH measured. The concentrations of temocillin, after dilution 1 on 40 of each solution with purified water was determined in triplicate by HPLC.

High-pressure liquid chromatographic assay: statistical analysis

Data were expressed as mean \pm standard deviation. Drug concentrations and pH were followed as a function of time and slopes of regression lines were compared. As recommended by the US Food and Drug Administration, the drug solution were considered stable as long as the 95% one-sided lower confidence limit of the estimated common regression line of the concentration-time profile remained above 90% [27] or 95% of the initial concentration when any signs of physical instability exist as recently recommended [28].

Results and discussion

Validation of high-pressure liquid chromatographic method

Linear-regression analysis of peak area yielded a determination coefficient $r^2 > 0.999$ in the range of 0.125 to 1.50 mg/ml.

The day variations ranged from 1.75% to 3.96%: 3.96%, 3.03% and 1.75% for the within-day variations at the 0.25, 0.50 and 1.00 mg/ml concentrations, 3.18%, 1.89% and 2.34% for the between-day variations at the 0.125, 0.50 and 1.00 mg/ml concentrations respectively.

Quality control results show a good reliability of the analytical method during the study with a mean \pm SD of 40.98 ± 0.96 mg/ml, 19.90 ± 0.38 mg/ml, 5.09 ± 0.16 mg/ml for the high, medium and low-level quality control respectively ($n = 16$).

Degraded samples of temocillin were assayed to confirm separation of the parent molecule from its degradation products. In all cases, the peak of the decomposition products were adequately separated from native products except little additional peaks appearing after strong alkaline and heating degradation conditions which were never observed during the stability period. The photodiode array detection confirmed the purity of temocillin peaks by spectral comparison (Fig. 1).

Chemical stability of temocillin

No precipitation was observed in the solution during the storage at $5 \pm 3^\circ\text{C}$ for 30 days by visual, microscope and spectrophotometric analysis, the colour of the solution nevertheless varying from light to dark yellow. Any additional chromatographic peaks didn't appear over the whole study period.

There was significant change in the pH values of stored solutions, varying from 6.65 ± 0.21 before freezing to 5.91 ± 0.01 for temocillin in 5% dextrose and from 6.0 ± 0.13 to 5.81 ± 0.01 for temocillin in 0.9% NaCl after 30 days at $5 \pm 3^\circ\text{C}$. These changes did not affect chromatographic parameter (retention time) and were not clinically significant, the solutions remaining in the acceptable range for perfusion ($4 \leq \text{pH} \leq 10$), probably due to blood buffer capacity [29]. Concentrations of temocillin admixtures during storage expressed as percentage of the initial dosage are shown in the Table 1.

The slopes of the five regression lines of drug concentration according to time did not differ significantly between bags for temocillin in NaCl and in dextrose. The slope of the common estimates regression line differed significantly from zero ($P < 0.001$). The 95% one-sided lower confidence limit remaining greater than 95% of the initial concentration during 11 and 14 days for dextrose and NaCl respectively.

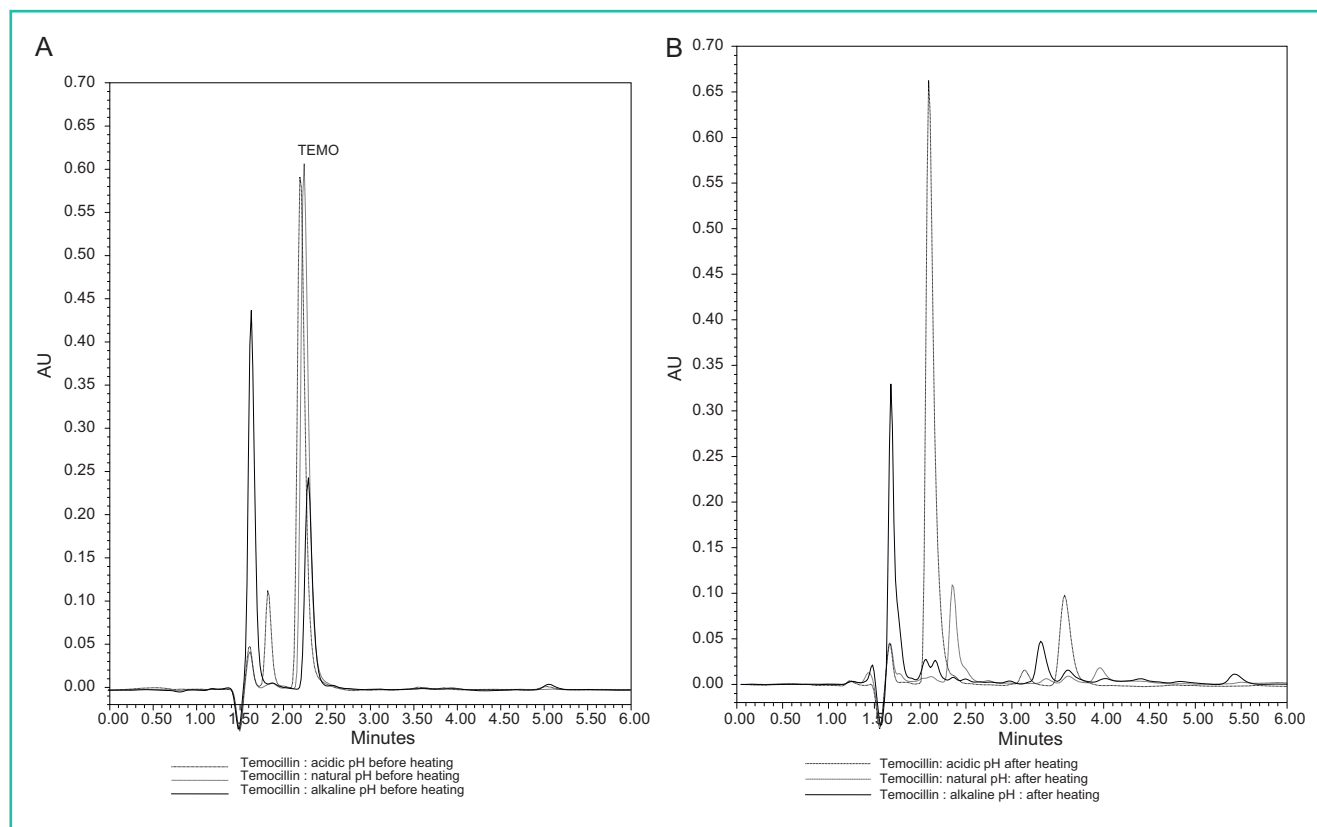


Figure 1. Chromatograms showing degradation test at different pH, before and after heating for temocillin. A. Different pH (natural, alkaline and acidic) before heating. B. Different pH (natural, alkaline and acidic) after heating.
Chromatogrammes des tests de dégradation de la temocilline à différentes valeurs de pH, avant et après chauffage. A. Différentes valeurs de pH (neutre, alcalin et acide) avant chauffage. B. Différentes valeurs de pH (neutre, alcalin et acide) après chauffage.

Table 1 Stability of temocillin 20 mg/ml in 5% dextrose and in 0.9% sodium chloride polyolefin bags.
Stabilité de la temocilline 20 mg/mL dans une solution de glucose à 5% et de chlorure sodique à 0,9% stockée dans une poche de polyoléfine.

Storage time 5 ± 3 °C (days)	Temocillin in 5% dextrose			Temocillin in 0.9% sodium chloride		
	Mean concentration (mg/ml) n = 5	95% lower confidence limit of mean %	pH mean ± SD	Mean concentration (mg/ml) n = 5	95% lower confidence limit of mean %	pH mean ± SD
Initial	20.93		6.65 ± 0.02	21.11		6.55 ± 0.01
0	21.30	99.68	6.59 ± 0.02	21.74	100.06	6.49 ± 0.01
1	21.25	99.31	6.53 ± 0.02	21.13	99.74	6.43 ± 0.01
2	20.90	98.94	6.51 ± 0.02	21.27	99.41	6.38 ± 0.02
3	20.43	98.56	6.42 ± 0.01	20.80	99.09	6.32 ± 0.01
4	20.02	98.19	6.39 ± 0.01	20.40	98.76	6.30 ± 0.02
7	20.19	97.04	6.28 ± 0.02	20.57	97.754	6.19 ± 0.01
9	20.33	96.27	6.22 ± 0.02	20.69	97.07	6.13 ± 0.01
11	20.11	95.48	6.15 ± 0.01	20.52	96.36	6.06 ± 0.01
14	19.68	94.26	6.10 ± 0.02	20.01	95.26	6.00 ± 0.01
16	20.00	93.43	6.08 ± 0.02	20.33	94.50	5.97 ± 0.01
18	19.38	92.58	6.04 ± 0.01	20.18	93.73	5.95 ± 0.01
21	19.40	91.29	6.01 ± 0.01	19.65	92.53	5.91 ± 0.01
23	19.29	90.42	5.98 ± 0.02	19.88	91.73	5.89 ± 0.01
25	18.96	89.54	5.94 ± 0.01	19.82	90.92	5.84 ± 0.01
30	18.09	87.34	5.91 ± 0.01	18.22	88.87	5.81 ± 0.01

Chemical stability was evaluated but the microbiological aspects were not investigated.

After the preparation and dispensing of parenteral nutrition mixtures and anticancer drugs [30], the preparation of adjuvant treatments by a CIVAS contributes to the global management of treatment by providing ready-to-use injectable drugs with acceptable physico-chemical and bacteriological quality and by relieving nursing staff from the tasks of infusion preparation [31,32].

Conclusion

The solution of 20 mg/ml of temocillin is chemically stable 11 days in 5% dextrose and 14 days in 0.9% NaCl when stored in polyolefin bags at 5 ± 3 °C after having been kept frozen for up to 30 days and subjected to microwave thawing. This mode of preparation appears, therefore, suitable for centralized pharmacy services, which could be of significant benefit to patients and of help to the nursing staff.

A minor decrease of pH was observed without an interference with the stability of these bags.

Advance preparation of temocillin infusion may be considered and added to the range of drugs reconstituted by a CIVAS [12–24].

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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