First of all, we would like to thank the review committee of the journal for their pertinent comments on this work. If you agree, we changed the title and the main document without the term “time-dependent antibiotics” when we listed the number of antibiotics studied. Indeed, vancomycin is a time-dependent but also a concentration-dependant antibiotic. Using only the term "time dependent" when listing the antibiotics studied (including vanomycin) can lead to confusion.

Comments and suggestions for authors : 1

1. We modify the abstract with the addition of the analytical techniques used.

2. We have corrected this error.

3. We added a section in the introduction to present analytical techniques used.

   “To study the physico-chemical stability of a drug, the determination of the active ingredient must be carried out using a separative analytical method, in order to be able to separate the active substance from its degradation products. To perform these stability studies, we used High-Performance Liquid Chromatography (HPLC) [16].”

4. LOD values were calculated and included in Table 1.

5. The standard curves were constructed from plots of peak area versus concentration. The linearity of each method was evaluated with five concentrations (line 265-267). We have decided not to specify, in the main document, the five concentrations analyzed for each standard range of each analysis method. If you consider it important, it is possible to add these information.

6. We added chromatograms in the main document (figure 1).

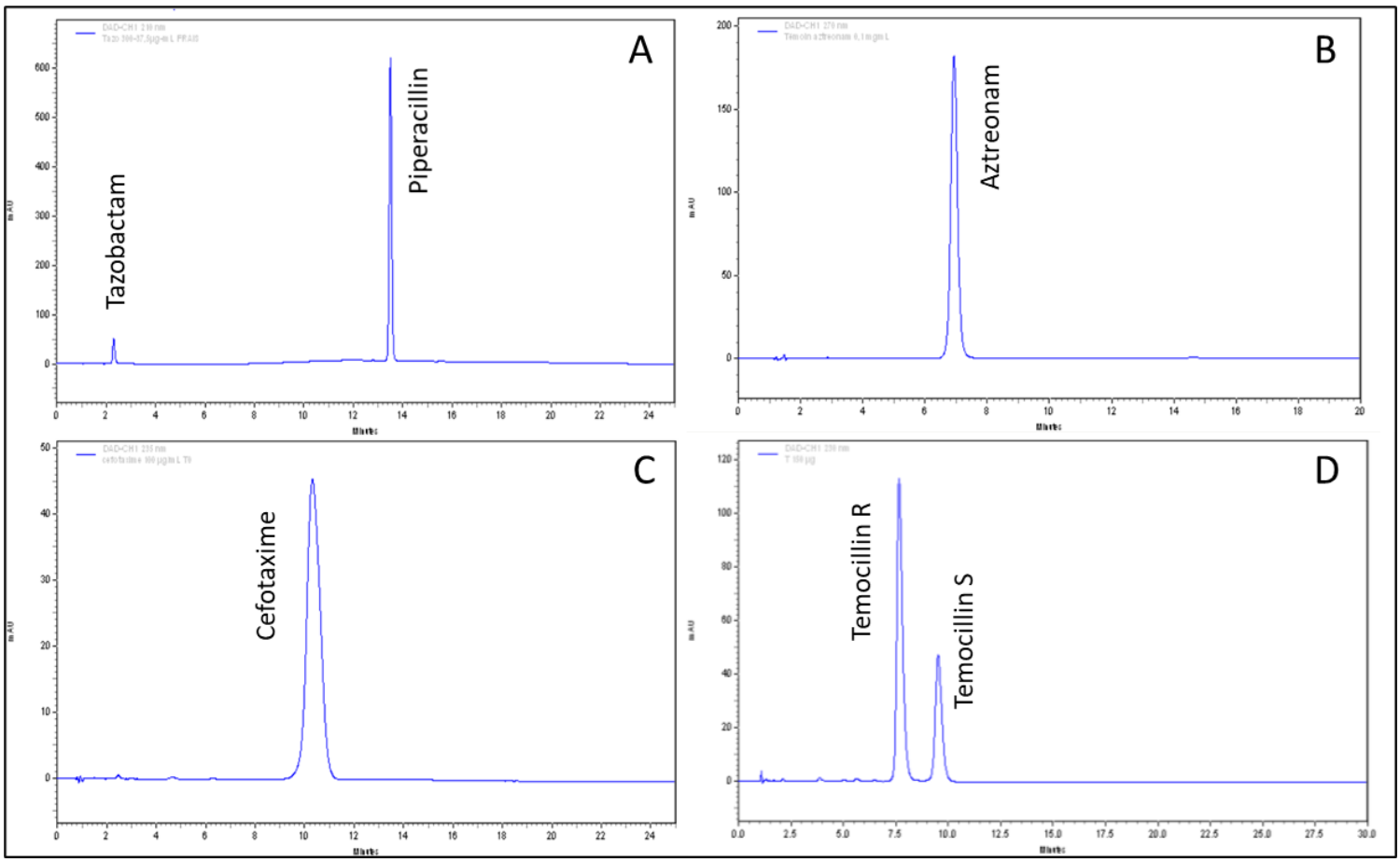

Figure 1: Examples of chromatograms of piperacillin/tazobactam (300/37.5 µg/mL) (A); aztreonam (100 µg/mL) (B); cefotaxime (100 µg/mL) (C) and temocillin R and S (150 µg/mL) (D), obtained immediately after reconstitution in Normal Saline solution.

7. For each stability study, the selectivity of the analytical method was validated by carrying out analyzes of the solvents and excipients without the molecule of interest, either Normal Saline, Water for injection or Dextrose 5%.
   For solutions prepared in D5W, we investigated a possible interference with 5-hydroxymethylfurfural (5-HMF, the main degradation product of dextrose). Finally, in order to prove that our methods were stability indicating, forced degradations were performed to avoid any interaction between our peak of interest and the formation of degradation products, according to the recommendations of ICH guidelines.

8. We modified.

9. We modified.

10. Water for chromatography was obtained from a reverse osmosis system (Millipore Iberica, Madrid, Spain), with a resistivity < 15 MΩ.cm.

11. We wanted to carry out our stability studies as close as possible to real practice. For the syringes, the storage conditions were carried out in a room (with windows) without protection against light, at a temperature of between 20-25°C, to be in the same conditions as in the ICUs.

    For the diffusers (details on the section “Choice of temperature” in the discussion), a storage temperature at 37°C was chosen , which can be considered as a worst condition, in order to be able to conclude more easily for our studies.

    The influence of light could not be studied in the diffusers, as these containers were placed in a climatic chamber at 37°C. Although, in most cases, the diffusers are worn under the patient's clothing, it is necessary to protect them from light if they are worn on top.

    Humidity**:** The influence of humidity has not been evaluated in our studies. Indeed, the ICH guidelines recommend a residual humidity rate close to 60%. Our containers, polypropylene syringes and polyisoprene elastomer devices, are hermetic containers, so humidity has little influence on this type of administration. The impact of humidity is more crucial for solid oral forms as tablets or capsules.

    Time: We analysed for a maximum of 48 hours to allow a continuous infusion.

12. We have studied each molecule with an adapted analytical method. For some molecules with a similar chemical structure, we have chosen close analytical methods.

13. For four analytical methods (cefiderocol, ceftazidime/avibactam, cefotaxime and piperacillin/tazobactam), a gradient elution mode was used. We added the details of these different gradients in the table 6 to be synthetic.

14. We modified.

15. We modified the conclusion.

16. We adjusted the references with requirements of the journal.