PHYSICAL-CHEMICAL STABILITY OF DOCETAXEL CONCENTRATED SOLUTION DURING ONE MONTH

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Introduction:
Docetaxel is an antineoplastic agent widely used in combination with others cytotoxic agents in many cancers (breast cancer, non small cell lung cancer, prostate cancer...). Today, this costly cytotoxic agent is marketed by different pharmaceutical companies (In France : Accord Healthcare Limited, Actavis Group PTC, Aventis Pharma, EG Labo, Fresenius Kabi Oncology Plc, Hospira Pharma, Sandoz and Teva Pharma) who suggest to discard it just after the first sampling, making it a very costly procedure.

Objectives:
The aim of this study is to determine the physical-chemical stability of docetaxel stock solution after the first sampling in the vial in order to fix a shelf life to the solution, and finally, to reduce costs without reducing healthcare quality.

Material and method:
The study was conducted in accordance with guidelines for the practical stability study of anticancer drugs established by an European consensus (a) and by two societies GERFAC (Evaluation and Research Group on Protection in Controlled Atmospher) and SFPC (French Society of Clinical Pharmacy) (b).

The physical-chemical stability was assessed on 3 different vials of docetaxel (Taxotere® 20mg/mL). On day 0, 2, 4 and 30 triplicate samples of each vial of docetaxel were assayed by high performance liquid chromatography (HPLC) method with UV detection at 230nm (method validated following ICH guidelines).

Docetaxel concentration at day 0 was considered as 100% and docetaxel concentration in following days samples greater than 90% were considered stable. A degradation of 20% of the reference concentration was obtained by an addition of a quantity of NaOH 0,01N in order to produce and observe primary degradation products. On each vial and at different days, docetaxel UV absorption spectra between 200 and 600 nm, pH, color change by a visual inspection were compared with reference at D=0, and finally a turbidimetry method at 350, 410 and 530nm was used to evaluate visible and subvisible particles formation.

(b) Sautou V, et al. Methodological guidelines for stability studies of hospital pharmaceutical preparations, First edition, October 2013, 74p

Results:

Fig 1: Exemple of 2 docetaxel solutions chromatograms at 230 nm : in grey D0 and blue D30. All chromatograms (D0, D2, D4 and D30) were strictly similar to the reference solution.

<table>
<thead>
<tr>
<th>Vial 1</th>
<th>Vial 2</th>
<th>Vial 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wavelength</td>
<td>350nm</td>
<td>410nm</td>
</tr>
<tr>
<td>Day 0</td>
<td>0,0203</td>
<td>0,0033</td>
</tr>
<tr>
<td>Day 2</td>
<td>0,0203</td>
<td>0,0034</td>
</tr>
<tr>
<td>Day 4</td>
<td>0,0204</td>
<td>0,0032</td>
</tr>
<tr>
<td>Day 30</td>
<td>0,0202</td>
<td>0,0032</td>
</tr>
</tbody>
</table>

Fig 2: Average and standard deviation of the docetaxel concentration for triplicate sample at each day

All relative concentrations were in the range (90-110%) of the initial concentration

Fig 3: Evaluation of visible and subvisible particles formation at 3 wavelengths (310, 410 and 530nm) for 3 different vials (1, 2 and 3). Absorption of docetaxel solutions concentrated at 0,4mg/mL were measured at 350, 410 and 530nm.

There is no difference in solution absorptions, indicated that there is no particle formation in these solutions.

According to these results, we have not detect drug lost, modification of spectral properties, visible or subvisible particles formation, apparition of primary degradation drug product. Anymore, during the study period, no color change or pH modification were observed.

Conclusion:
Under storage temperature between 20 to 25°C during 30 days, docetaxel solution at 20mg/mL was seen to be stable. The sterility of the solution was not tested because the handling environment (Iso 5) was strictly controlled and operator validations are regularly checked.