Analyse critique d'une étude de stabilité physico-chimique publiée

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Vincent Lebreton*, Blandine Bourcier, Karine Cosson, Frédéric Lagarce, Laurence Spiesser-Robelet and Sandy Vrignaud

New liquid oral formulations of hydroxychloroquine: a physicochemical stability study

Stability of Extemporaneously Compounded Suspensions of Trimethoprim and Sulfamethoxazole in Amber Plastic Bottles and Amber Plastic Syringes

Isabelle St-Jean, M Mihaela Friciu, Anaëlle Monfort, Jessica MacMahon, Jean-Marc Forest, Scott Walker, and Grégoire Leclair

Can J Hosp Pharm. 2021;74(4):327-33

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pharmaceutics

Article

Stability of Ophthalmic Atropine Solutions for Child Myopia Control

Baptiste Berton [1], Philip Chennell [2,*], Mouloud Yessaad [1], Yassine Bouattour [2], Mireille Jouannet [1], Mathieu Wasiak [1] and Valérie Sautou [2]

Physicochemical stability of cefiderocol, a no
siderophore cephalosporin, in syringes at 62
for continuous administration in intensive ca

Guillaume Loeuille,[1] Jean Vigneron,[1,2] Elise D'Huart,[1,2] Alexandre Charmillon,[3] Béatrice Demoré[1,4]

OBJECTIFS

- Points forts et faibles d’un article portant sur une étude de stabilité physico-chimique
- Extrapolation possible des données à sa propre pratique

Exemple de fiche d'analyse d'un article de stabilité

ANALYSE DES ETUDES DE STABILITE

Référence : .....
Lecteur : .....
Date : .....

Proposition : Accepté / Refusé
BUT DE L'ETUDE :
.....
.....

STABILITE PHYSIQUE :

EXAMEN VISUEL				EXAMEN SUBVISUEL			
Méthode			**Résultats**	**Méthodes**			**Résultats**
Précipité	oui □	non □		Turbidimétrie	oui □	non □	
Changement couleur	oui □	non □		Comptage particulaire	oui □	non □	
Dégagement gazeux	oui □	non □		Analyse microscopique	oui □	non □	

STABILITE CHIMIQUE :

METHODE				RESULTATS		
Méthode séparative	oui □	non □	Si oui, laquelle :	Résultats avec x% de la [] à T0	90% □	95% □
Description conditions	oui □	non □		Expression chiffrée des résultats	oui □	non □
Validation de la méthode analytique				Résultats CV <5%	oui □	non □
Stability-indicating	oui □	non □		Cohérence globale	oui □	non □
Gamme-étalon	oui □	non □	Nb de point :	**Commentaires sur la validation de méthode**		
Répétabilité CV<5%	oui □	non □				
Fidélité intermédiaire CV<5%	oui □	non □				
Etalon interne	oui □	non □				

AUTRES :

pH	oui □	non □	**Commentaires** :
Osmolalité	oui □	non □	**Commentaires** :
Stabilité microbiologique	oui □	non □	**Commentaires** :

STABILITE DE LA MOLECULE EN SOLUTION

CONTENANT	SOLVANT	[]	CONDITIONS de CONSERVATION	DUREE de STABILITE

STABILITE DE LA MOLECULE EN MELANGE

CONTENANT	SOLVANT	MOLECULE(S) UTILISEE(S) en MELANGE		CONDITIONS de CONSERVATION	DUREE de STABILITE
		DCI	[]		

BUT DE L'ARTICLE

Molécule(s) étudiée(s)	▪ Quel type de sel (morphine chlorhydrate, sulfate ?) ▪ Molécule « classique » ? Protéine ? Anticorps ? 
Concentration(s)	▪ Une seule concentration ? Plage de concentrations ? ▪ Concentrations adaptées à la pratique ?
Solvant(s)	▪ NaCl 0,9% ? G5% ? EPPI ?
Contenant(s)	▪ Seringue ? Poche en polyoléfine, PVC ? ▪ Flacon verre ? ▪ Diffuseurs en polyisoprène? Silicone ?
Condition(s) de conservation	▪ 2-8°C ? 20-25°C ? -20°C ? ▪ A la lumière ou non ?
Durée de l'étude Intérêts en pratique	▪ USI : courte durée ▪ Préparation à l'avance : longue durée
Auteurs	▪ Industriels ? ▪ Equipe de recherche hospitalière ? Universitaire?

USI : Unité de soins intensifs
NaCl 0,9% : chlorure de sodium 0,9% ; G5% : glucose 5% ; EPPI : eau PPI

BUT DE L'ARTICLE - *Exemples*

DE GRUYTER Pharm. Technol. Hosp. Pharm. 2018; aop

Marie Godet, Joanna Simar, Mélanie Closset, Jean-Daniel Hecq*, Maximilien Braibant, Laura Soumoy, Patricia Gillet, Jacques Jamart, Benoît Bihin and Laurence Galanti

Stability of Concentrated Solution of Vancomycin Hydrochloride in Syringes for Intensive Care Units

https://doi.org/10.1515/pthp-2017-0031
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Abstract

Background: Vancomycin is increasingly administrated by continuous infusion. But the treatment of patient in intensive care need restricted volume to prevent fluid overload. The aim of the study was to evaluate the physical and chemical stability of solutions of a high concentration of vancomycin hydrochloride in 5% glucose or 0.9% NaCl.
Methods: Eight syringes of 50 mL, containing 41.66 mg/mL of vancomycin hydrochloride four syringes in 5% glucose and four in 0.9% NaCl were prepared and stored at ambient temperature during 48 h. Immediately after preparation and during 48 h, vancomycin hydrochloride concentrations were measured by a high-performance liquid chromatography (HPLC). Spectrophotometric absorbance at different wavelengths, pH measurement and microscopic observations were also performed.
Results: All solutions were physico-chemically stable during the whole period storage at ambient temperature: no color change, turbidity, precipitation or opacity, no significant pH variations or optic densities were observed in the solutions. Any crystals were seen by microscopic analysis. Solutions are considered chemically stable as the lower limit of the 95% unilateral confidence interval on the mean remained above 90% of the initial concentration for at least 48 h.
Conclusions: Solutions of vancomycin hydrochloride 41.66 mg/mL in syringe of 5% glucose or 0.9% NaCl are physically and chemically stable for at least 48 h when stored in syringes at ambient temperature.

Keywords: vancomycin infusions, concentrated solutions, high performance liquid chromatography, physicochemical stability, syringe, intensive care units

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Introduction

Vancomycin, a glycopeptide antibiotic, is often used as antibiotherapy for hospitalized patients (1). The most common usage of vancomycin is to treat methicillin-resistant Staphylococcus aureus and epidermidis infections (2, 3) and for patients who are allergic to penicillin and cephalosporin. A temporary association with aminoglycoside or rifampicin can be used to obtain a synergic effect in case of endocardite (3).

Vancomycin is increasingly administrated by continuous infusions (4). As reported in the literature, the infusions of vancomycin (2.5 g/250 mL) can be prepared by the centralized intravenous admixture service (CIVAS) (5–7) of the Pharmacy, according to the stability of the solutions (8–21).

Vancomycin could also be infused by syringe, particularly in intensive care to reduce the perfusion volume. Some data are available about this containers showing that the syringes of low dose vancomycin can be stored at 4 °C for 6 months (12) or at least 84 days (19) and once brought to 25 °C it must be used within 48 h (12). Nevertheless, the stability of high concentrated solutions are not often investigated. Allen and Stiles (7) demonstrated a stability for 96 h at room temperature for a 40 mg/mL vancomycin while Barbault et al., a stability of vancomycin eye drops at 50 mg/mL for 15 days.

Furthemore, the production of vancomycin (GSK) was stopped requiring the use of another supplier (Mylan). The stability of this new vancomycin was studied at 12.5 mg/ml but not at higher concentrations such as 40 mg/mL.

The aim of the study is to determine the physical and chemical stability of a higher concentration of vancomycin hydrochloride (Mylan) (41.66 mg/mL) in 5% glucose or 0.9% NaCl solutions.

Molécule étudiée	▪ Vancomycine chlorhydrate
Contenant	▪ Seringue
Intérêts en pratique	▪ USI

BUT DE L'ARTICLE - *Exemples*

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Contenant	▪ Seringue
Intérêts en pratique	▪ USI
Condition(s) de conservation	▪ 20-25°C ▪ *A la lumière ou non : non précisé dans l'introduction ou l'abstract*
Durée de l'étude de stabilité	▪ USI : courte durée : 48 heures

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Durée de l'étude de stabilité	▪ USI : courte durée : 48 heures
Concentration	▪ 41,66 mg/mL
Solvants	▪ NaCl 0,9% ou G5%

MATÉRIELS UTILISÉS

Produit(s) utilisé(s)	▪ Princeps ? Génériques ?: attention aux excipients *Exemple* : Etoposide TEVA vs Etoposide MYLAN
Contenant(s)	▪ Seringue ? ▪ Poche en polyoléfine, PVC ? ▪ Flacon verre ? ▪ Diffuseurs en polyisoprène ? Silicone ?

PVC-bags >> PO bags
~~**PO bags >>PVC bags**~~

➡ EXTRAPOLATION ???

Exemple :

Materials and methods

Solution preparation

Commercially-available vancomycin hydrochloride solutions (Vancomycine® 1 g Mylan, Hoeillart, Belgium lot B2173) were prepared in a vertical laminar-airflow hood with sterile water-for-injection (Baxter, Lessines, Belgium, lot 14IO2T1E) as recommended by the manufacturers. These solutions were added to polypropylene syringes (Terumo, Haasrode, Belgium; lot 1412283) containing glucose 5 % (Baxter, Lessines, Belgium, lot15A14E46) or NaCl 0.9 % (Baxter, Lessines, Belgium, lot14L01660) to obtain a final volume of 48 mL and then a 41.66 mg/mL concentration solution. The syringes were stored at ambient temperature, without protection from light.

Produit utilisé	▪ Vancomycine® MYLAN 1 g
Contenant(s)	▪ Seringue en polypropylène

STABILITE PHYSIQUE : méthodes ?

Examen visuel	▪ Observation à l'œil nu de l'apparition d'un précipité, changement de couleur, dégagement gazeux
Examen subvisuel	▪ Comptage particulaire ▪ Microscope optique ▪ Turbidimétrie

Exemple 1 :

Physical stability

Visual compatibility was defined as the absence of particulate formation, haze, precipitation, color change and gas evolution (23). At each time of the study, various tests were conducted to detect any particle contamination: visual and microscopical inspection and optical density measurements. The samples were then visually inspected with unaided eye, in front of a black and white background, the pellet obtained after centrifugation at 3000 rpm for 8 min was observed with a microscope 10 × (Carl Zeiss, Germany), looking for crystals.

The potential presence of subvisible particles was investigated by spectrophotometry. The optical densities were then measured by a spectrophotometer (Genesys 10 UV, Spectronic Unican) at 350 nm, 410 nm and 550 nm (24).

Examen visuel	✓
Examen subvisuel	▪ Microscope optique ▪ Turbidimétrie

STABILITE PHYSIQUE : méthodes ?

Examen visuel	▪ Observation à l'œil nu de l'apparition d'un précipité, changement de couleur, dégagement gazeux
Examen subvisuel	▪ Comptage particulaire ▪ Microscope optique ▪ Turbidimétrie

Exemple 2:

Original research

Physicochemical stability of cefiderocol, a novel siderophore cephalosporin, in syringes at 62.5 mg/mL for continuous administration in intensive care units

Guillaume Loeuille,[1] Jean Vigneron,[1,2] Elise D'Huart,[1,2] Alexandre Charmillon,[3] Béatrice Demoré[1,4]

conference.[13] Physical stability was also assessed by performing a particulate contamination test (Particle counter; PAMAS SVSS) at the beginning and end of the study. According to the criteria of the European Pharmacopoeia, preparations of a volume < 100 mL comply with the particulate contamination test if the number of particles measured does not exceed 6000 particles of ≥ 10 µm per container and 600 particles of ≥ 25 µm per container.[14] These criteria are used for polypropylene syringes which have a volume less than 100 mL.

Examen subvisuel	▪ Comptage particulaire

STABILITE CHIMIQUE

Choix de la méthode analytique : dépend du type de molécule

- Méthode séparative ?
- Description des conditions analytiques

Choix du détecteur

Exemple :

Chromatographic conditions

As previously described (20), an Alliance Waters high-performance liquid chromatographic (Alliance, model 2695, Waters Association, Milford, MA, USA) system was used with a DAD detector (model 996, Waters Association) and a data acquisition and processing module (Empower 2 Software, Waters Association, Milford, MA, USA).

A reversed phase column was used with associated guard column (Prevail C18 5 µm 150 mm × 4.6 mm, ref 99209 with Prevail guard column C18 7.5 mm × 4.6 mm, ref 99286, Alltech associates, Deerfield IL 60015).

The mobile phase was constituted of 15 % acetonitrile (ref C03C11X, Lab-scan Ltd, Dublin, Ireland) and 85 % KH_2PO_4 buffer (pH 3.00; 0.025 M) (KH_2PO_4, ref 1.04873.1000, Merck, Darmstadt, Germany and H_3PO_4, ref 10G090501, VWR International, Fontenay-sous-Bois, France).

The flow rate was set at 1 mL/min, the column temperature at 35 °C, the Wavelenght (DAD detector) at 210 nm.

☑ **Méthode analytique** : CLHP

- Méthode séparative
- Description des conditions analytiques

Phase stationnaire : C18 5 µm 150 mm x 4,6 mmm
Phase mobile : 15 % acétonitrile/ 85% tampon phosphate
Débit : 1 mL/min
Température de la colonne : 35°C

☑ **Détecteur :** Barrette de diodes (DAD) à 210 nm

☒ Manquants : volume d'injection, temps d'analyse

STABILITE CHIMIQUE

Choix de la méthode analytique : dépend du type de molécule

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MATERIELS ET METHODE

Choix de la méthode analytique : dépend du type de molécule

- Méthode séparative ?
- Description des conditions analytiques

Choix du détecteur

Stability of stock and diluted rituximab

YANG ZHANG, LEE C. VERMEULEN, AND JILL M. KOLESAR

Purpose. The stability of two rituximab preparations stored in polyvinyl chloride (PVC) bags at 4 °C for up to 14 days was investigated.

Methods. Two types of test samples were prepared: (1) 10 mL of rituximab solution (10 mg/mL) drawn directly from the original manufacturer's vial and injected into sterile glass vials and (2) 3 mL of rituximab 10 mg/mL mixed with 17 mL of 0.9% sodium chloride injection and injected into sterile PVC bags. Samples were analyzed immediately after preparation and after storage at 4 °C for 3, 7, and 14 days. Rituximab activity at the designated time points was measured using a validated enzyme-linked immunosorbent assay (ELISA) method. Chemical stability was defined as the retention of ≥85% of the drug's initial activity. Physical stability was evaluated through visual inspection for color changes or precipitate formation under normal laboratory lighting.

Results. The results of ELISA testing (with spectrophotometric absorbance assessment) indicated that the percentage of initial rituximab activity retained was over 85% for both test preparations under the storage conditions evaluated; no changes in color or turbidity were observed in any of the test samples. These findings suggest that extending the expiration dating of both stock and diluted rituximab solutions beyond the manufacturer-specified limit of 24 hours is feasible.

Conclusion. Rituximab 10 mg/mL undiluted in glass vials and 1.5 mg/mL diluted in 0.9% sodium chloride injection in PVC bags are stable at 4 °C for up to 14 days.

Am J Health-Syst Pharm. 2013; 70:436-8

STABILITE CHIMIQUE

Validation de la méthode analytique

- **Linéarité** : gamme étalon en 5 points (ICH Q2) avec R (coefficient de corrélation) proche de 1

Exemple :

Validation of high-pressure liquid chromatographic method (22)

Precision

Two control solutions of 10 and 40 mg/mL of vancomycin hydrochloride were undertaken in triplicate to calculate the within (n = 10) and between (n = 9) day reproducibility.

Linearity of analytical response

Linearity was evaluated by 7 dilutions of the solution (2.5, 5, 10, 20, 30, 40, and 50 mg/mL of vancomycin hydrochloride) injected in triplicate.

STABILITE CHIMIQUE

Validation de la méthode analytique

- Précision : répétabilité (3 x 3 ou 1 x 6) et précision intermédiaire

Exemple :

Validation of high-pressure liquid chromatographic method (22)

Precision

Two control solutions of 10 and 40 mg/mL of vancomycin hydrochloride were undertaken in triplicate to calculate the within (n = 10) and between (n = 9) day reproducibility.

Linearity of analytical response

Linearity was evaluated by 7 dilutions of the solution (2.5, 5, 10, 20, 30, 40, and 50 mg/mL of vancomycin hydrochloride) injected in triplicate.

STABILITE CHIMIQUE

Validation de la méthode analytique

☐ Capacité à indiquer la stabilité *(stability-indicating capability) :*

→ **Dégradation d'environ 20 % de la molécule d'intérêt**

Exemple :

Stability indication

The stability indicating capability of the chromatographic method was assessed using decomposed solutions of drugs. Degraded samples of vancomycin hydrochloride were then assayed to confirm separation of the parent antibiotic from its degradation products. Vancomycin solutions at natural pH (3.72), alkaline pH (11.54) by adding NaOH 5 M (Merck, Darmstadt, Germany), and acidic pH (1.60) by adding HCl 12 M (Merck, Darmstad, Germany) were heating at 100 °C during 30 and 60 min. Ten µL of these solutions was injected in the HPLC system before and after heating.

☑ Dégradation alcaline + chaleur : NaOH 5 M (100 °C 30-60 min)
Dégradation acide : HCl 12 M : (100 °C 30-60 min)

☒ Absence de dégradation oxydative et photolytique

STABILITE CHIMIQUE

Validation de la méthode analytique

- ☐ Spécificité

Exemple :

Original article

Physicochemical stability of etoposide diluted at range concentrations between 0.38 and 1.75 mg/mL in polyolefin bags

Elise D'Huart,[1] Jean Vigneron,[1] Pauline Lider,[1] Béatrice Demoré[1,2]

demonstrate the specificity of the method and the absence of interaction between etoposide and its excipients, a solution for each excipient of etoposide (polysorbate 80, polyethylene glycol 300, benzyl alcohol, citric acid) was realised and analysed by HPLC.

AUTRES METHODES

- ☐ pH
- ☐ Stabilité microbiologique
- ☐ Osmolalité
- ☐ Autre : odeur , viscosité, remise en suspension (forme buvable)
- ☐ Si anticorps : activité biologique

Exemples :

DE GRUYTER Pharm. Technol. Hosp. Pharm. 2018; aop

Marie Godet, Joanna Simar, Mélanie Closset, Jean-Daniel Hecq*, Maximilien Braibant, Laura Soumoy, Patricia Gillet, Jacques Jamart, Benoît Bihin and Laurence Galanti

Stability of Concentrated Solution of Vancomycin Hydrochloride in Syringes for Intensive Care Units

The pH of the solutions were measured with a pH-meter (Inolab WTW Weilhein, Germany) equipped with a glass electrode (Biotrode Hamilton Bonaduz, Switzerland) calibrated with two standard solutions at pH4 and pH7 (CertiPur, Merck, Darmstadt, Germany).

Stability of extemporaneously compounded temozolomide 10 mg/mL suspensions in Oral Mix SF® in glass and plastic bottles and plastic syringes

Karen Lingertat-Walsh[1], JoEllen Weilnau[2], M Petrea Cober[3], Andrew Ostrenga[4], Betsy Poon[5], Sales Pacita[1], Shirley Law[6], L Lee Dupuis[1,7,8] and Scott E Walker[6,8]

a magnifying glass. Samples were shaken manually to evaluate re-suspendability and portions were poured into a separate container to evaluate consistency and pourability. Only suspensions of reasonable physical stabililty (i.e. acceptable consistency, pourability, re-suspendability, no caking or clumping. and little or no precipitate or crystal formation) were to be chosen for further testing.

STABILITE PHYSIQUE

DE GRUYTER Pharm. Technol. Hosp. Pharm. 2018; aop

Marie Godet, Joanna Simar, Mélanie Closset, Jean-Daniel Hecq*, Maximilien Braibant, Laura Soumoy, Patricia Gillet, Jacques Jamart, Benoît Bihin and Laurence Galanti

Stability of Concentrated Solution of Vancomycin Hydrochloride in Syringes for Intensive Care Units

Physical stability

All solutions were physically stable during the whole period storage at ambient temperature: no color change, turbidity, precipitation or opacity, no significant variation

Original research

Physicochemical stability of cefiderocol, a novel siderophore cephalosporin, in syringes at 62.5 mg/mL for continuous administration in intensive care units

Guillaume Loeuille,[1] Jean Vigneron,[1,2] Elise D'Huart,[1,2] Alexandre Charmillon,[3] Béatrice Demoré[1,4]

Physical stability

After reconstitution and preparation of the polypropylene syringes the solutions were clear and colourless. Throughout the study no physical changes were detected, either the formation of gas or precipitate, or the detection of a colour change.

Particle counting was performed on a syringe of cefiderocol diluted in NS and D5W exposed to light with analysis at T0 and T12 hours. This average count is related to the initial syringe volume of 48 mL. For the syringe diluted in NS, 352 particles ≥10 µm and 16 particles ≥25 µm were counted on average after reconstitution. After 12 hours, 896 particles ≥10 µm and 48 particles ≥25 µm had been counted. For the syringe diluted in D5W, 256 particles ≥10 µm and 32 particles ≥25 µm were counted on average after reconstitution. After 12 hours, 1312 particles ≥10 µm and 16 particles ≥25 µm had been counted. The particle count was in accordance with the standards set by the European Pharmacopoeia.

STABILITE CHIMIQUE

Validation de la méthode analytique

☐ Linéarité : R^2 proche de 1

DE GRUYTER Pharm. Technol. Hosp. Pharm. 2018; aop

Marie Godet, Joanna Simar, Mélanie Closset, Jean-Daniel Hecq*, Maximilien Braibant, Laura Soumoy, Patricia Gillet, Jacques Jamart, Benoît Bihin and Laurence Galanti

Stability of Concentrated Solution of Vancomycin Hydrochloride in Syringes for Intensive Care Units

Results

Validation of the method

Linear-regression analysis of peak area yielded a determination coefficient $r^2 > 0.999$ in the range of 2.5 mg/mL to 50 mg/mL.

Original research

Physicochemical stability of cefiderocol, a novel siderophore cephalosporin, in syringes at 62.5 mg/mL for continuous administration in intensive care units

Guillaume Loeuille,[1] Jean Vigneron,[1,2] Elise D'Huart,[1,2] Alexandre Charmillon,[3] Béatrice Demoré[1,4]

The results of the calibration study highlight the homogeneity of the variance (Cochran's test: $C_{exp}=0.424 < C_{th(5\%;\ 3;\ 5)}=0.684$). Linearity was demonstrated for cefiderocol with an R^2 of >0.9999. ANOVA (non-linearity) demonstrated the

STABILITE CHIMIQUE

Validation de la méthode analytique

☐ Précision :

DE GRUYTER Pharm. Technol. Hosp. Pharm. 2018; aop

Marie Godet, Joanna Simar, Mélanie Closset, Jean-Daniel Hecq*, Maximilien Braibant, Laura Soumoy, Patricia Gillet, Jacques Jamart, Benoît Bihin and Laurence Galanti

Stability of Concentrated Solution of Vancomycin Hydrochloride in Syringes for Intensive Care Units

Validation of the method

The within and between-day repoducibilities realized on two concentrations (40 mg/mL and 10 mg/mL) are shown in Table 1 and could be considered as acceptable.

Table 1: Precision of the assay.

		Within-day variation (n – 10)	Between-day variation (n – 9)
40 mg/mL	Mean (mg/mL)	41.14	39.61
	SD (mg/mL)	0.98	0.9
	CV (%)	2.4	2.3
10 mg/mL	Mean (mg/mL)	10.26	10.60
	SD (mg/mL)	0.20	0.29
	CV (%)	2.0	2.8

STABILITE CHIMIQUE

Validation de la méthode analytique

☐ Capacité à indiquer la stabilité *(stability-indicating capability)*

ORIGINAL RESEARCH

Physicochemical Stability of Vancomycin at High Concentrations in Polypropylene Syringes

Élise d'Huart, Jean Vigneron, Alexandre Charmillon, Igor Clarot, and Béatrice Demoré

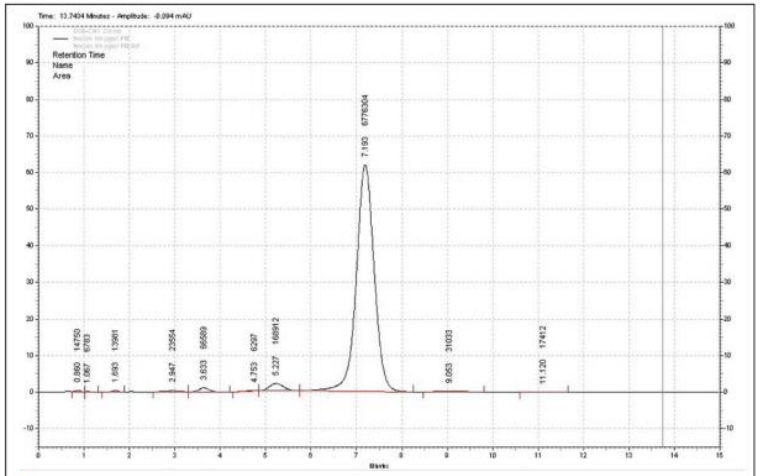

Figure 1. Chromatogram of vancomycin 100 µg/mL without degradation.

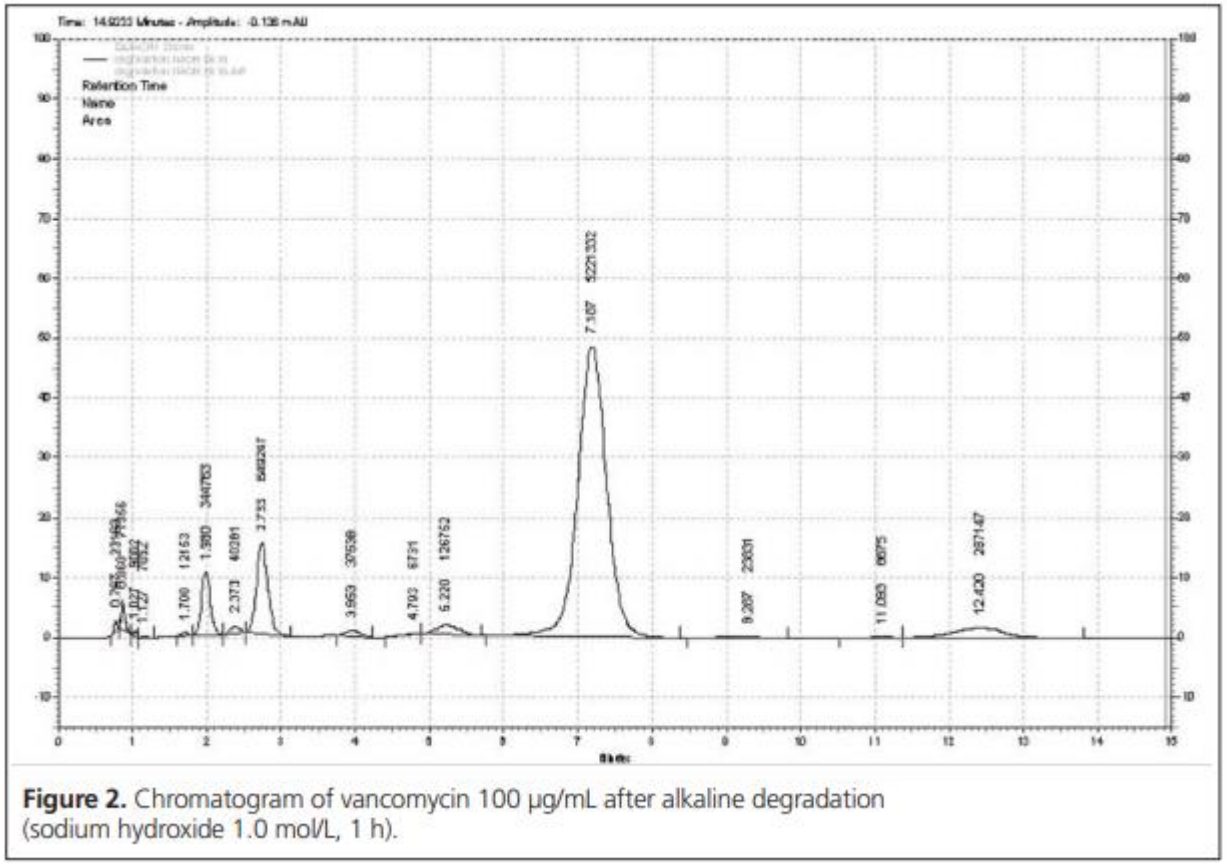

Figure 2. Chromatogram of vancomycin 100 µg/mL after alkaline degradation (sodium hydroxide 1.0 mol/L, 1 h).

STABILITE CHIMIQUE

Validation de la méthode analytique

☐ Capacité à indiquer la stabilité *(stability-indicating capability)*

Stability of extemporaneously compounded temozolomide 10 mg/mL suspensions in Oral Mix SF® in glass and plastic bottles and plastic syringes

Karen Lingertat-Walsh[1], JoEllen Weilnau[2], M Petrea Cober[3], Andrew Ostrenga[4], Betsy Poon[5], Sales Pacita[1], Shirley Law[6], L Lee Dupuis[1,7,8] and Scott E Walker[6,8]

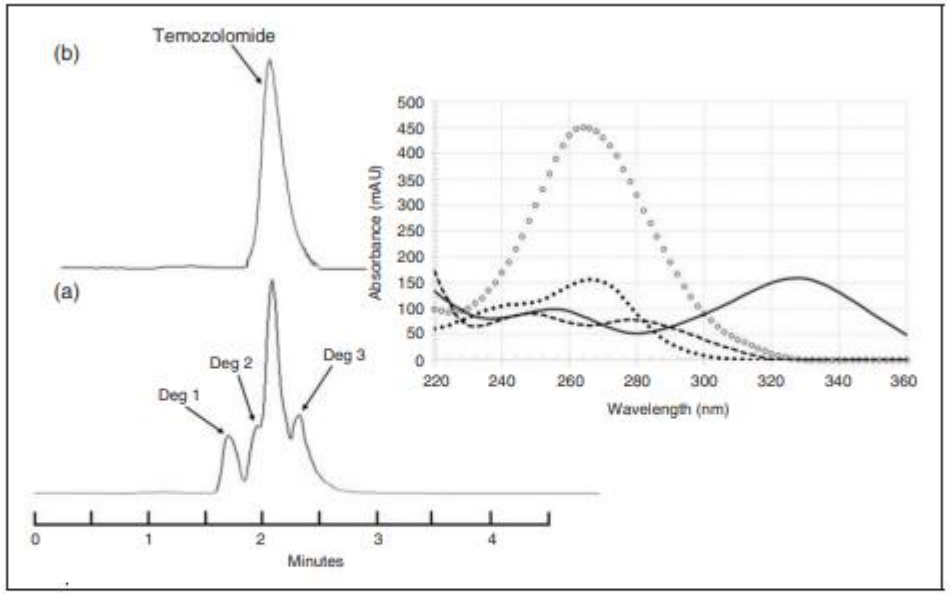

Figure 2. Chromatogram (a) represents a 5 mg/mL solution of temozolomide in water sample after 240 min of incubation at 40°C when 20.4% of initial temozolomide remains. In chromatogram (a) column effluent is monitored at 250 nm and three degradation products are evident at 1.75, 2.0, and 2.4 min, eluting closely to temozolomide at 2.15 min. UV spectra for all found compounds are shown on the right. Temozolomide is the solid line with a relative maxima at 330 nm. Degradation product 1 is represented by the dashed line, degradation product 2 is represented by the open circles, and degradation product 3 is represented by the solid (closed) circles. It is important to note that none of the three degradation products overlaps at the measurable absorption of 330 nm. Chromatogram (b) represents the same 5 mg/mL solution of temozolomide in water after 240 min of incubation at 40°C when 20.4% of initial temozolomide remains when the column effluent is monitored at 330 nm. Since degradation products do not absorb at this wavelength, there is no interference with temozolomide quantification.

STABILITE CHIMIQUE

Validation de la méthode analytique

☐ Capacité à indiquer la stabilité *(stability-indicating capability)*

PEER REVIEWED

Stability of Sotalol Hydrochloride in Extemporaneously Prepared Oral Suspension Formulations

Abstract

The physical, chemical, and microbial stabilities of extemporaneously compounded oral liquid formulations of sotalol hydrochloride were studied. Sotalol hydrochloride oral liquid suspensions (5 mg/mL) were prepared from commercially available tablets (Betapace) in a 1:1 mixture of Ora-Plus:Ora-Sweet, a 1:1 mixture of Ora-Plus:Ora-Sweet SF, and a 1:2.4 mixture of simple syrup:methylcellulose vehicle. Six batches of each formulation were prepared; three were stored at refrigerated temperature (2° to 8°C) and three at room temperature (20° to 25°C). Samples were collected from each batch weekly for 6 weeks, and again at 12 weeks. Samples were analyzed by means of a high-performance liquid chromatographic method, and the concentrations obtained were

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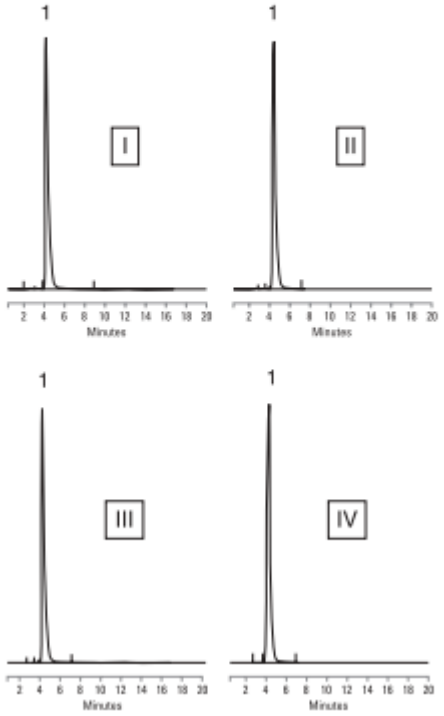
Int J Pharm Compound 2005, 9, 5: 402-404

Figure 1. Sample chromatograms of sotalol HCl (peak 1) control solution (I) and after exposure to the following conditions: 1 N hydrochloric acid (pH 2.02) for 2 hours (II), 1 N sodium hydroxide (pH 12.0) for 2 hours (III), and heated to 90°C for 2 hours (IV). The concentration of sotalol HCl was 100 µg/mL.



An HPLC method was developed in the laboratory for measuring sotalol HCl concentrations. In a series of preliminary studies, the effects of heat, acid, and base on the stability of sotalol HCl solution were studied. As shown in Figure 1, no interfering peaks were observed, and the resultant chromatograms showed only the peak of the drug. This indicates that the method is valid under the conditions studied. Likewise, the different vehicles used to prepare the suspension formulations did not interfere with the HPLC assay (data not shown).

STABILITE CHIMIQUE

Validation de la méthode analytique

☐ Capacité à indiquer la stabilité *(stability-indicating capability)*

Compatibility of tramadol hydrochloride injection with selected drugs and solutions

NORAH O. ABANMY, IMAN Y. ZAGHLOUL, AND MAHASEN A. RADWAN

Am J Health-Syst Pharm. 2005; 62:1299-302

The HPLC method was validated as stability indicating by accelerated decomposition of tramadol.[7] Tramadol 5 µg/mL was stable for at least four weeks when stored at 4, 25, and 50 °C. In addition, tramadol was stable at extreme pH conditions. No tramadol decomposition products were observed in any chromatogram during the validation.

STABILITE CHIMIQUE

- ☐ Résultats avec +/- 10% de la concentration initiale
- ☐ Expression chiffrée des résultats
- ☐ Résultats avec CV <5%
- ☐ Cohérence globale

Original research

Physicochemical stability of cefiderocol, a novel siderophore cephalosporin, in syringes at 62.5 mg/mL for continuous administration in intensive care units

Guillaume Loeuille,[1] Jean Vigneron,[1,2] Elise D'Huart,[1,2] Alexandre Charmillon,[3] Béatrice Demoré[1,4]

Table 2 Chemical stability of cefiderocol diluted in 0.9% sodium chloride (NS) or in dextrose 5% in water (D5W)

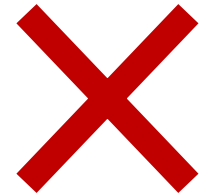
Concentration (mg/mL)	Solvent	Light exposure	Syringe	Concentration at T0 hours (mg/mL)	Time: % of initial concentration of cefiderocol (mean±SD)*			
					T0 hours	T12 hours	T24 hours	T48 hours
62.5	NS	No	S1	61.3	100%±1.11%	95.43%±0.60%	92.80%±0.66%	85.56%±1.43%
			S2	61.1	100%±0.36%	95.52%±0.90%	93.28%±0.13%	86.04%±0.60%
			S3	60.7	100%±0.18%	96.71%±0.17%	94.82%±0.16%	89.37%±0.12%
62.5	D5W	No	S1	60.4	100%±0.27%	97.28%±0.17%	93.49%±0.13%	87.39%±0.10%
			S2	61.5	100%±0.40%	95.09%±0.16%	91.79%±0.15%	87.41%±0.18%
			S3	60.4	100%±0.19%	97.10%±0.12%	92.51%±0.18%	87.87%±1.28%
62.5	NS	Yes	S1	62.2	100%±0.30%	93.15%±0.97%	89.94%±1.28%	82.93%±1.69%
			S2	61.9	100%±0.31%	93.16%±1.83%	91.84%±0.39%	87.16%±1.31%
			S3	60.5	100%±0.20%	96.25%±0.13%	93.00%±0.03%	86.98%±0.32%
62.5	D5W	Yes	S1	61.0	100%±0.13%	96.15%±0.17%	92.86%±0.06%	85.36%±0.13%
			S2	59.1	100%±0.08%	97.87%±0.01%	94.41%±0.11%	88.91%±0.09%
			S3	59.7	100%±0.13%	98.02%±0.37%	94.82%±0.01%	87.05%±0.06%

*Samples tested in triplicate at all time points.
D5W, dextrose 5% in water; NS, normal saline.;

Loeuille G, *et al*. *Eur J Hosp Pharm* 2021;**0**:1–6. doi:10.1136/ejhpharm-2021-002935 5

STABILITE CHIMIQUE

- ☐ Résultats avec +/- 10% de la concentration initiale
- ☐ Expression chiffrée des résultats
- ☐ Résultats avec CV <5%
- ☐ Cohérence globale



Original article

Physicochemical stability of cabazitaxel containing premix solution and diluted infusion solutions

Kirsten C Spindeldreier, Judith Thiesen, Irene Krämer

EJHP 2015; 22: 260-266.

Table 2 Stability of cabazitaxel diluted infusion solutions (0.1 and 0.26 mg/mL) in 0.9% NaCl in polypropylene/polyethylene containers under different storage conditions

Nominal cabazitaxel concentration and vehicle		0.1 mg/mL 0.9% NaCl infusion solution				0.26 mg/mL 0.9% NaCl infusion solution			
Storage temperature		25°C		2–8°C		25°C		2–8°C	
	Test solution		Visible particulate matter (yes +, no –)		Visible particulate matter (yes +, no –)		Visible articulate matter (yes +, no –)		Visible particulate matter (yes + no –)
Initial measured concentration (mg/mL)	1	0.1±0.5	–	0.1±1.1	–	0.3±1.9	–	0.3±0.6	–
	2	0.1±3.2	–	0.1±4.7*	–	0.3±8.5	–	0.3±3.1*	–
	3	0.1±1.2	–	0.1±3.9	–	0.3±1.0	–	0.3±1.4	–
Remaining concentrations expressed as percentage rate[5] of the initial concentration ±RSD, mean of triplicate assays of 3 test solutions (n=3 if not otherwise indicated)									
12 h	1	97.6±4.0	–	109.2±5.5	–	99.5±0.3	–	(119.5±0.8)	–
	2	101.4±5.9	–	93.7±6.6	–	99.0±0.6	–	(111.2±1.8)	–
	3	102.4±2.4	–	101.3±3.0	–	103.9±8.0	–	98.9±1.2	–
24 h	1	101.3±0.5	–	99.4±0.6	–	(116.7±12.3)	–	100.7±0.3	–
	2	102.1±1.0	–	97.9±1.6	–	98.5±1.9	–	103.9±2.2	–
	3	101.7±0.4	–	102.9±1.2	–	(128.6±14.6)	–	(122.9±2.2)	–
48 h	1	107.5±12.4	–	98.6±1.7	–	(115.7±20.8)	–	(111.0±22.0)	–
	2	100.4±1.9	–	94.6±2.0	–	106.1±14.6	–	95.3±3.6	–
	3	105.1±5.8	–	101.4±1.4	–	(121.8±30.4)	–	(115.4±24.0)	–
72 h	1	(112.7±14.9)	–	102.5±1.2	–	102.7±4.5	–	103.2±0.7	–
	2	98.0±1.5	–	105.9±18.6	–	99.1±3.3	–	100.8±0.4	–
	3	103.1±6.0	–	103.6±10.0	–	101.2±1.6	–	108.1±1.3	–
120 h	1	99.8±0.9	–	100.1±0.4	–	97.2±2.9	–	100.5±1.8	–
	2	102.9±0.3	–	98.4±0.4	–	98.1±2.1	–	101.6±1.8	–
	3	101.5±0.2	–	100.9±0.2	–	103.0±6.5	–	(124.1±18.0)	–
7 days	1	97.6±1.2	–	98.2±0.7	–	99.9±1.2	–	106.4±2.9	–
	2	102.5±1.2	–	96.5±0.3	–	96.6±2.1	–	98.4±3.5	–
	3	100.5±0.4	–	100.9±0.9	–	100.4±1.9	–	101.9±1.0	–

STABILITE CHIMIQUE

- ☐ Résultats avec +/- 10% de la concentration initiale
- ☐ Expression chiffrée des résultats
- ☐ Résultats avec CV <5%
- ☐ Cohérence globale

STABILITY OF CALCIUM FOLINATE (TEVA) IN CONCENTRATE AFTER RE-USE AND IN DILUTE INFUSIONS IN 0.9% NaCl IN POLYETHYLENE BAGS

AGNIESZKA KARBOWNIK*, EDYTA SZAŁEK, HANNA URJASZ, MALWINA KĄDZIOŁKA and EDMUND GRZEŚKOWIAK

Department of Clinical Pharmacy and Biopharmacy, Faculty of Pharmacy, Karol Marcinkowski University of Medical Sciences, Św. Marii Magdaleny 14, 61-861 Poznań, Poland

Table 2. Calcium folinate (%) at different sampling times in concentrate, stored at refrigerator temperature (2-8°C) and room temperature (15-25°C) for *Leucovorin Ca Teva*® 100 mg/10 mL.

Temp.	Percentage of initial concentration at indicated time (day)									
	0	1	2	3	7	14	22	28	30	34
2-8°C										
Mean	100.0	100.21	100.00	99.99	100.04	100.09	100.10	100.09	100.12	86.96
SD	0.0	0.14	0.09	0.15	0.42	0.06	0.22	0.17	0.09	5.32
n	3	3	3	3	3	3	3	3	3	3
Visual apperance	pass	pass	pass	pass	pass	pass	pass	pass	pass	pass
15-25°C										
Mean	100.0	99.92	99.80	99.89	100.03	100.09	99.98	100.04	100.00	88.38
SD	0.0	0.29	0.56	0.41	0.08	0.06	0.07	0.14	0.12	8.29
n	3	3	3	3	3	3	3	3	3	3
Visual apperance	pass	pass	pass	pass	pass	pass	pass	pass	pass	pass

Autre exemple ①

ABSTRACT

Ursodiol is used in the treatment and prevention of certain types of gallstones and for patients with primary biliary cirrhosis. Ursodiol is marketed for this purpose by Watson Pharma, Inc. as ACTIGALL, by Axcan Scandipharm Inc. as URSO 250 and URSO Forte, and by a number of generic manufacturers. Ursodiol is available as capsules of varying strengths. The need for other dose-form options for those patients who cannot take capsules has led compounding pharmacies to seek other alternatives, namely oral solutions and suspensions. Additionally, some patients are unable to tolerate suspending agents containing alcohol or sorbitol. The objective of this study was to determine the stability of ursodiol in SyrSpend SF Cherry Flavored which does not contain sorbitol or alcohol. The studied sample was compounded into a 30-mcg/mL suspension and stored in a low-actinic plastic bottle at temperatures between 2°C and 8°C. Six samples were assayed at each time point out

Preparation of Ursodiol Suspension Samples

The ursodiol suspension was prepared by adding 3.32 g of ursodiol to a 4-oz low actinic cylindrical prescription bottle. Four 25-mL aliquots of SyrSpend SF Cherry Flavored were added to the bottle and stirred vigorously following each addition. Another 10 mL of SyrSpend SF Cherry Flavored was added to bring the volume to 110 mL and stirred until a homogeneous preparation was achieved. The contents were stored at *USP*-controlled refrigerated temperature (2°C to 8°C) for the stability study.

Autre exemple ②

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Research Article

Pharmaceutical Sciences

CHEMICAL STABILITY OF BORTEZOMIB SOLUTIONS IN ORIGINAL MANUFACTURER VIALS

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[1]Corresponding author: E-mail address: fsanchezr@uma.es

Table 1. Mean concentration and stability of unused reconstituted bortezomib in manufacturer vials stored at 4°C in the dark

Study day	Concentration of bortezomib (mean ± SD, ng mL^{-1})	Percent of bortezomib remaining)
Day 0	122.38 ± 0.99	97.90
Day 1	110.23 ± 1.24	88.18
Day 2	120.13 ± 0.84	96.10
Day 3	116.16 ± 0.80	92.93
Day 4	111.11 ± 2.21	88.89
Day 7	119.49 ± 2.05	95.59
Day 9	118.50 ± 1.89	94.80
Day 14	118. 00 ± 2.10	94.40
Day 22	117.94 ± 2.25	94.35
Day 30	122.68 ± 1. 15	98.14

Stabilité microbiologique

DE GRUYTER Pharm Technol Hosp Pharm 2020; 20200001

Guideline

Sylvie Crauste-Manciet*, Irene Krämer, Frederic Lagarce, Valerie Sautou, Alison Beaney, Julian Smith, V'Iain Fenton-May, Jean-Daniel Hecq, Farshid Sadeghipour and Paul Le Brun

GERPAC Consensus Conference – Guidance on the Assignment of Microbiological Shelf-life for Hospital Pharmacy Aseptic Preparations

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Abstract: All dosage forms prepared in hospital pharmacies should be labelled with an appropriate shelf-life. This shelf-life should be validated taking chemical, physical and microbiological data into consideration. This guidance focuses on parenteral aseptically prepared products, as they are high-risk preparations. The risk is exacerbated by a requirement for longer shelf lives for reasons of economy and efficiency. The scope of this guidance includes individual patient preparations, preparations prepared in series (same type of preparation being repeatedly prepared) and batch preparations prepared from the same initial bulk admixture.

Keywords: shelf-life, microbiological, consensus, guidance

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Introduction and scope

All dosage forms prepared in hospital pharmacies should be labelled with an appropriate shelf-life. This shelf-life should be validated taking chemical, physical and microbiological data into consideration.

This guidance focuses on parenteral aseptically prepared products, as they are high-risk preparations. The risk is exacerbated by a requirement for longer shelf lives for reasons of economy and efficiency. The scope of this guidance includes individual patient preparations, preparations prepared in series (same type of preparation being repeatedly prepared) and batch preparations prepared from the same initial bulk admixture.

Background considerations

In the monograph on Pharmaceutical Preparations (Ph. Eur. 9.0/2619), the European Pharmacopoeia (Ph. Eur.) states: "Health care professionals involved in unlicensed preparations have a duty of care to the patient receiving these preparations: a risk assessment is required to determine the extent and significance of testing."

Based on this risk assessment, the person responsible for the preparation must ensure that the pharmaceutical preparation is fit for purpose throughout its shelf life. Storage conditions and shelf lives must be justified based on physicochemical and microbiological stability. Published experimental data may be available to support the shelf life assigned to a preparation. In the absence of data, professional judgement is required. Numerous publications regarding the physicochemical stability of ready-to-use and ready-to-

Conclusion

- **Comprendre le but de l'étude**
- **Stabilité chimique** :
  - Point critique : la validation de la méthode analytique, notamment la capacité à indiquer la stabilité
  - Résultats :
    - T0 à 100 %
    - Cohérence globale
    - CV < 5%
- **Stabilité physique** : ne pas oublier l'examen subvisuel
- **Conclusion en accord avec les résultats**

Merci pour votre attention