Welcome to the STABILIS users for this Twenty-first Newsletter!

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Test your knowledge on stability

**A new language in Stabilis**

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The analytical pharmacology laboratory - Institut Régional du Cancer (ICM) - Montpellier

**Statistics**
Answer to the test
Test your knowledge on stability!

Which of the following solutions will precipitate in the refrigerator?

- Fluorouracile 50 mg/ml
- Mitoxantrone 2 mg/mL
- Cytarabine 50 mg/ml
- Cisplatine 0.5 mg/mL
- Ganciclovir 10 mg/mL

See the answer on the last page

New language in Stabilis!

Welcome to the Bulgarian language!

After the Arabic language, announced in the previous newsletter, we are pleased to inform you of a new language, the 26th language in Stabilis.
News from the 18th EAHP Congress, Paris, France, March 2013

The 18th Congress of the European Association of Hospital Pharmacists (EAHP) took place in Paris, France. The congress attracted more than 2000 participants. The weather was unusually cold with heavy snow that disrupted the first day of the conference.

More than 600 posters were presented. Around 20 posters were on the topic of stability of drugs, we have selected several of them about the stability of injectable drugs, of oral solutions, capsules and gels.

Stability of injectable drugs

Extended chemical-physical stability of 25 mg/mL azacitidine suspension. Galloni C. from the hospital of Brescia, Italy.
In this study, the authors have demonstrated that a suspension prepared with water for injection at 4°C is stable for 48 hours (stability defined with a concentration not less than 95% of the initial concentration). The results are in accordance with the previous studies selected for Stabilis.

Long-term stability of indomethacin 0.2 mg/mL ready-to-use solution for intravenous use. Moudry R et al. From the Kantonsspital Graubunden, Switzerland
Indomethacin 1 mg is used in premature infants to close the patent ductus arteriosus. Liometacen®, containing 50 mg sterile indomethacin (as meglumin salt), was reconstituted with 2 mL water for injection and then diluted with 250 mL 0.9% NaCl to a final indomethacin concentration of 0.2 mg/mL. The solution was stored in glass vials. The stability testing revealed that the solutions retained at least 95% of their initial indomethacin concentration when they were stored at room temperature for 12 days or at 2-8°C for 23 days. Indomethacin solutions may be prepared in advance and stocked for at least 18 months at -20°C. After thawing they can be kept at room temperature for 7 days or alternatively at 2-8°C for 14 days.

Physico-chemical stability of ready-to-administer epinephrine injection solutions 20 µg/mL. Heb RM et al. from the University medical center, Mainz, Germany.
Epinephrine bulk solution 20 µg/mL was prepared aseptically by diluting Suprarenin 25 mg/mL Sanofi-Aventis with 5% glucose infusion solution in empty infusion bags (PP/PE). The solutions were stored in BD perfusion syringes in the refrigerator protected from light. A two months stability was demonstrated.

Results of a systematic long-term stability study for ready-to-use injectable drugs produced by a centralized intravenous admixture service. Hecq JD. University hospital of MontGodinne, Belgium.
In this poster, Jean Daniel Hecq presented his long-term stability studies after storage at -20°C. 25 drugs have been studied (10 antiinfectives, 4 anesthesics, 2 propulsives, 2 detoxifying agents for antineoplastic treatment and 7 with other properties). For each drug, long-term stability varied from 11 days to 70 days. The freeze-thaw treatment by microwave may extend the stability and allow batch-scale production of intravenous drugs.

Stability of frozen ceftazidime solution in polypropylene syringes for intravitreal injection Vigneron J, Daul A et al. From the University Hospital of Vandoeuvre, France.
A 20 mg/mL ceftazidime solution in 0.9% sodium chloride was stored in polypropylene syringes at -20°C. After 3 months the concentration was over 95% of the initial concentration and the concentration of the degradation products was less than 2%. This allows the batch preparation in advance and the immediate availability of the syringes to treat patients.
Stability study of **ganciclovir** in 0.9% sodium chloride in different types of containers: optimization of resources. Tomasello C et al. University of Turin, Italy. This stability study confirmed the previous stability studies with a 3 week stability for the solutions at 4.55 and 0.8 mg/mL in normal saline in two different kind of bags (Viaflo® and Ecoflac® 100 mL).

**Stability of oral solutions**

Evaluation of the chemical and physical stability of **sodium dichloroacetate**, an orphan drug for rare metabolic diseases. Cascone V et al. From the University of Messina, Italy.

Sodium dichloroacetate is used in the treatment of rare diseases with congenital defects of a pyruvate-dehydrogenase comex (PDHC). The stability of a solution at 100 mg/mL was investigated by UV spectrometry. Samples kept at 4°C were stable for 60 days and those kept at room temperature were stable for 30 days.

Liquid oral formulations of **propranolol hydrochloride** for the treatment of infantile haemangiomas. Horak P et al. From the University hospital of Prague, Czech Republic.

A solution of propranolol 2mg/mL was prepared from the substance. The authors have used citric acid or citrate-phosphate buffer to achieve the optimum stability of propranolol and simple syrup to mask the bitter taste of the active ingredient. Sodium benzoate was used as preservative. The solutions in glass bottle were stored at room temperature and in the refrigerator for 180 days. The formulation was stable at both temperatures for 6 months.

Development of an **hydrochlorothiazide** 0.5 mg/mL oral solution for children. YY Li from the Royal Dutch Pharmacists Association, Scientific Institute of Dutch Pharmacists, Den Haag, The Netherlands.

The authors have developed a formulation of a hydrochlorothiazide 0.5 mg/mL with an optimised solubility, taste and stability. A shelf life of 6 months was established. This new formulation has been published in the Dutch formulary.

**Stability of capsules**


Sildenafil, a phosphodiesterase V inhibitor, is used in paediatrics to treat pulmonary arterial hypertension. Capsules of 1 mg, 5 mg and 10 mg (of sildenafil base) were prepared with sildenafil citrate and corn starch. Samples were kept at room temperature in transparent blister packs sealed with aluminium. A stability of ten weeks has been demonstrated.

**Stability of gels**

Topical **morphine** gels for painful wounds. Mateus D et al. From the University hospital of Lisboa, Portugal.

The authors have developed two physicochemically and microbiologically stable gels; a more viscous formulation and a fluid formulation for spraying. Organoleptic characteristics, pH, viscosity, morphine hydrochloride and preservative content were assessed. Sterility tests, microbiological control and preservative efficacy were studied according to the European Pharmacopoeia. The preparations remain sterile and stable for 60 days.
The following abstracts were presented during the 18th Dubai International Pharmaceuticals & Technologies Conference & Exhibition:

1. **Stability indicating validated HPLC method for determination of Febuxostat in drug substance and marketed formulation**

   The objective of the study was the development and validation of a RP-HPLC method for the determination of Febuxostat and separation from its degradation products. Febuxostat was susceptible to alkali and acid hydrolysis, and stable under the oxidation, thermal, neutral and sunlight degradation. The drug was separated on a Hypersil BDS C18 (150 x 4.6 mm i.d. 5 µ) column, acetonitrile in sodium acetate (10 mM, pH 4) (50:50 v/v) as mobile phase. The PDA detector was set at 315 nm. The method was found to be linear over the concentration range 0.5 / 40 µg/ml. The LOD and LOQ were found to be 0.02 µg/ml and 0.16 µg/ml respectively.

2. **Stability indicating validated RP-HPLC method for simultaneous determination of lamivudine, zidovudine and abacavir sulphate in drug substance and marketed formulation**

   The objective of the study was the development and validation of a RP-HPLC method for the simultaneous determination of lamivudine, zidovudine and abacavir sulphate. The optimized chromatographic condition was obtained on PDA detector with Waters Xterra C18 (250 x 4.6 mm, 5 µ) column. Mobile phase being 10 mM ammonium acetate buffer and acetonitrile with gradient run for 12 minutes at 1 ml/min flow rate. Column temperature maintained at 250°c and detection wavelength was set at 265 nm. The method was found to be linear over the concentration range 1.5 / 150 µg/ml for lamivudine and 3.0 / 300 µg/ml for zidovudine and abacavir sulphate. The LOD of the method was found to be 0.013 µg/ml, 0.070 µg/ml and 0.030 µg/ml. The LOQ of the method was found to be 0.044 µg/ml, 0.230 µg/ml and 0.102 µg/ml for lamivudine, zidovudine and abacavir sulphate respectively.
New Monograph

Levofolinate disodium
Levofolinate disodium 1.6 or 3.8mg/ml in 0.9% sodium chloride injection or 5% glucose injection, stored in glass vials, was stable for 72 hours under controlled ambient conditions. 
MEDAC France 2011

New references from international publications

Butorphanol and Droperidol
Admixtures of butorphanol tartrate 0.08 mg/ml and droperidol 0.05 mg/ml in 0.9% sodium chloride injection were stable for at least 15 days when stored in PVC bags or glass bottles at 4°C and 25°C and protected from light. 
Am J Health-Syst Pharm 2013 ; 70:515-519

Diltiazem
Diltiazem hydrochloride diluted to 1 mg/ml in 5% dextrose injection was stable for 30 days when stored at -20°C, 2-6°C and 22-25°C.

Epinephrine
The ready-to-administer epinephrine injection solution 20 µg/ml, aseptically prepared by diluting the marketed injection concentrate with 5% glucose infusion solution in 50 ml light protected plastic syringes, is stable under refrigerated conditions for at least 6 months.
EAHP Congress Paris 2013

Morphine hydrochloride
The chemical and physical stability studies of diluted morphine solutions have shown that solutions of morphine hydrochloride diluted in 0.9% sodium chloride at a concentration of 0.33 mg/ml in polypropylene syringes were stable up to two years when syringes are kept away from light at 5°C or at 22°C.
Pharmaceut Anal Acta 2013 ; 4: 205

New references of incompatibility

- Ketorolac trometamol and cyclizine lactate
  (Anaesthesia 2001 ; 56: 494-495)

- Epinephrine and sodium bicarbonate
  (Anaesthesia 2000 ; 55, 9: 853-858)

- Thiopental with suxamethonium, atracurium, vecuronium or rocuronium
  (J R Soc Med Sh Rep 2011 ; 2: 58)

- Sugammadex with amiodarone, dobutamine or protamine hydrochloride
  (Rev Bras Anestesiol 2013 ; 63, 1: 163-166)

- Vancomycin with temocillin, piperacillin/tazobactam, ceftazidime, imipenem, cefepime, flucloxacillin, propofol, valproic acid, phenytoin, theophyllin, methylprednisolone, furosemide
  (AFPHB Congress 2013)

- Oxaliplatin and 0.9% sodium chloride infusion
  (Pharm Res 2004 ; 21, 5: 891-894)

- Piritramide with cefuroxime or cefazolin
  (Ann Pharmacotherapy 2013 ; 47:426-427)

- Micafungin and levofloxacin
  (Am J Health-Syst Pharm 2012 ; 69:2130)

- Naloxone with ciclosporine, diazepam, indomethacin, lorazepam, nitroglycerin, pantoprazole, phenytoine or thiopental
  (Pharmactuel 2013 ; 46, 1 : 16-21)

- Total parenteral nutrient solution with amiodarone, phenobarbital, pentobarbital, rifampicine
  (Am J Health-Syst Pharm 2013 ;70:520-524)

Updated data from the manufacturers

Stability studies have shown that solutions of Amphotericin B liposomal at a concentration of 4 mg/ml was stable for 24 hours at room temperature in glass vials or for 7 days at 4°C in glass vials or polyethylene syringes.
Diluted solutions at the concentration of 0.2 to 2 mg/ml in 5% dextrose infusion were stable 72 hours at room temperature or 7 days at 2-8°C. Amphotericin B liposomal is incompatible with 0.9% sodium chloride injection.
Gilead Science (France) 2013
New documents in Infostab website  www.infostab.fr
See in « Publications » and « Stability and compatibility ». 

Stability of frozen ceftazidime in polypropylene syringes for intravitreal injection 
Pharmacie – CHU Nancy – Hôpital Brabois, allée du Morvan, 54511 Vandoeuvre-les-Nancy
j.vigneron@chu-nancy.fr
Poster presented during “EAHP” congress, Paris, France, March 2013

2. Franz B(1), Maywald D (2), Knoth H (2) 
Zytostatikahaltige orale Liquida in der Pädiatrie – Entwicklung, Herstellung und Analytik einer Trofosfamid-Orallösung 
(1) Menarini von Heyden GmbH, Dresden 
(2) Klinik-Apotheke des Universitätsklinikums Dresden

3. Hecq J.D, Hospital Pharmacist, Doctor in Pharmaceutical Sciences 
31 years litterature review 
Cliniques Universitaires UCL Mont-Godinne, Yvoir, Belgium
Poster presented during the annual meeting of the Belgian Association of French speaking hospital pharmacists, Brus- sels, March 2013

Evaluation of the physical stability of a mixture of Clorazepate and Alizapride in Dextrose 5% polyolefin bag at room temperature 
CHU UCL Mont-Godinne, Dinant
Poster presented during the annual meeting of the Belgian Association of French-speaking hospital pharmacists, La Hulpe, Belgium, March 2013

5. Hecq J.D, Godet M, Jamart J, Galanti L. 
Results of a systematic long-term stability study for ready-to-use injectable drugs produced by a centralized intravenous admixture service 
Drug Stability Research Group, University Hospital of Mont-Godinne, Yvoir, Belgium
Poster presented during “EAHP” congress, Paris, France, March 2013

6. Raverdi V.1, Ampe E.1, Hecq J.-D.2 and Tulkens P.1 
Stability and compatibility of Vancomycin for administration by continuous infusion 
1. Pharmacologie cellulaire et moléculaire et Centre de Pharmacie Clinique, Louvain Drug Research Institute, Université Catholique de Lou- vain, Brussels, Belgium 
2. Département de Pharmacie, CHU Mont-Go- dinne, Yvoir, Belgium 
Poster presented during the annual meeting of the Belgian Association of French-speaking hospital pharmacists, La Hulpe, Belgium, March 2013

7. Trittler R., Hecklinger J., Hug M. J. 
Aliquotierte Levosimendanlösungen – stabil ? 
Apotheke des Universitätsklinikums Freiburg, Hugstetter Strasse 55, 79106 Freiburg
Poster presented during the ADKA congress, Dresden, Germany, May 2013
Our laboratory is a mixed team represented by the University Montpellier 1 and the ICM hospital.

Our research program is presently centered around four domains: Drug stability and quality control, new cancer drug assessment, drug delivery pharmacokinetics (particularly therapeutic drug monitoring), and pharmacogenetics. We are more particularly investigating developments on breast cancer, colorectal cancer, prostate cancer and cutaneous malignant melanoma.

Our lab facilities included several high-performance liquid chromatography (HPLC) systems (UV and diode array detectors), ultra HPLC, liquid chromatography and mass spectrometry (electrospray ionization source), ultraviolet spectrophotometer, Elisa microplate reader, Real-Time PCR systems (LightCycler® 480), and capillary electrophoresis sequencing system (Applied Biosystems 3730xl DNA Sequencer), and a cell culture platform.

The laboratory employed 3.5 pharmacists, two Master 2 student, and a full time technician. In an attempt to improve quality, an analytical method using an UV/visible spectrometer (Multiplex ®) was developed that quantitatively and qualitatively verified preparations of anticancer chemotherapies formulated in the hospital (43000 a year). The implementation of a systematic control allows to secure the circuit of the preparations of chemotherapy and to improve the system of quality assurance for a real time pharmaceutical authorization use.

Concerning Drug stability, our group has recently determined the stability of ready-to use temsirolimus and eribulin infusion solutions under different storage conditions for the daily practice but also docetaxel, analgesic association, irinotecan ...

We are strongly implicated in SFPO (French Society of Oncology Pharmacists) stability-oriented activities such as the European consensus on guidelines to perform stability studies of anticancer drugs (published in Annales Pharmaceutiques Françaises 2011, 69: 221-231)

Dr Frederic Pinguet PharmD; PhD
Head of department of Pharmacy and pharmacology
ICM: Institut Régional du Cancer
208 rue des Apothicaires
34298 Montpellier
The Stabilis website frequentation has stabilized over the last months, with nearly 14,000 visits.

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For this Newsletter issue, North Africa will be highlighted: Algeria, Tunisia and Egypt are on the podium. Let’s imagine that the visits from this area will increase following the recently added translation in Arabic: many thanks to our Egyptian colleague Sherif Kamal!

The proportion of English users is still rising, with 10.6% of visits. We welcome our colleagues from Arabic countries and Bulgaria, whose visits are also increasing in their recently added language.
Answer to the test

- Fluorouracile 50 mg/ml
- Mitoxantrone 2 mg/ml
- Cytarabine 50 mg/ml
- Cisplatine 0.5 mg/mL
- Ganciclovir 10 mg/mL

The solubility generally decreases with temperature which causes the precipitation above a threshold concentration. Fluorouracile 50 mg/ml and mitoxantrone 2 mg/ml are the concentrations of the commercial vials which have to be stored at room temperature to avoid the crystallisation. Ganciclovir 10 mg/ml is the reconstituted solution which must not be stored in the refrigerator.

There are no problems with cytarabine at this concentration and cisplatiné is just under the limit value which is 0.6 mg/ml.