SUMMARY

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Answer to the crosswords
Stabilis crosswords: Anticancer drugs

Horizontal
1. Only my phosphate salt does not precipitate between 0.4 mg/l and 10 mg/l
6. Is more stable in NaCl 3%
7. Antibiotic extracted from *Streptomyces* and unstable in dextrose 5%
9. Busulfan’s excipient which can precipitate in presence of polycarbonate
13. Very unstable drug used to treat myelodysplasia
14. Used to treat bladder cancer and unstable under pH 6
16. His chemical structure is in equilibrium between lactone and carboxylate depending on the pH (used in the treatment of colon cancer)

Vertical
2. Excipient used to dissolve, docetaxel or temsirolimus
3. I become liquid above 31°C
4. Very sensitive to light - in the regimen ABVD
5. I’m used in R-DHАОx regimen and chloride ions influence my stability
8. Excipient used to dissolve paclitaxel
9. Concept to prepare cytotoxic drugs in advance
10. It can precipitate the 5-fluorouracile
11. An orange precipitate appear if I’m used in sodium chloride
12. Alternative to DEHP (abbreviation)
15. Should not be sent to wards by pneumatic system without removing air from the IV bag
News from the SFPO Congress

From October 16 to 18, 2015, the French Society of Oncology Pharmacy Congress was held in Nantes, France. 212 posters and 12 oral communications were presented for more than 400 participants. The scientific committee has noted their very good level and relevance. Eight posters and two oral communications concerned stability and compatibility.

When Dr Frédéric Pinguet, president of the SFPO, declares open the Congress!

Oral communication and posters presented

Incompatibility of busulfan with a tuberculin Luer lock syringes: a case report
This poster was a case report about a change in the manufacturing process of a busulfan low dose syringe. Busulfan was mixed with 0.9% sodium chloride via a Rapid Fill® system. Instead of using a 2 mL polypropylene syringe, the technician used a 1 mL tuberculin Luer Lock syringe to be more precise. However, 1ml tuberculin Luer Lock syringes are made of polycarbonate which are in incompatible with dimethylacetamide, the excipient of busulfan. The incompatibility is well known and is indicated in the manufacturer’s recommandation on the website of Becton Dickinson but the information « polycarbonate » is not written on the package of the syringe. This incompatibility resulted in a precipitate in the mixture.

Loboda C, Arnoux A-L, May I, Vigneron J. Department of Pharmacy - University Hospital of Nancy, France.
This poster received the second price of the poster session.

The stability of temozolomide oral suspension was established at +4°C and protected from light by a UV-HPLC validated method for 35 days and for the concentrations 10 and 20 mg/mL and for 21 days for the concentration 30 mg/mL. The impact of temperature excursion (24 hours at “room temperature”) was evaluated without any influence on the stability. The suspensions were prepared with the commercial vehicle Syrstand® developed for children who can’t swallow capsules.


The coffee break: ideal to share experience and talk about stability!

Ganciclovir (0.5 and 2 mg/mL) in ethylenevinyl acetate (EVA) bags was stable for one year, even if temperature deviation occurs (three excursions of 24 hours and one for one week at 25°C). Chemical, physical and microbiological stability were performed by many methods: HPLC stability indicating method, osmolality, visual examination, particle counting, pH measurement, endotoxin assay and sterility assay.


Azacitidine is commonly administered by subcutaneous injection but intravenous infusion can also be considered. Three solutions (1.4 mg/mL, 2.0 mg/mL and 2.4 mg/mL) were prepared after reconstitution with 10 mL of refrigerated sterile water then dilution in refrigerated NaCl 0.9% polyolefin bags. The stability of these solutions was established at +4°C for three hours by a stability-indicating HPLC-UV method, turbidity and osmolality study (only one hour in the Summary of Product Characteristics).

C. Balouzet, C. Chanat, M. Jobard, ML. Brandely-Piat, F. Chast. Department of clinical pharmacy, University Hospital Paris, France.
Influence of mechanical (stirring) and thermal (freezing/thawing cycles) stress on Cetuximab and Rituximab was studied by several specific methods for proteins study: UV spectrophotometry, turbidity, dynamic light scattering (DLS), IR spectroscopy. For Cetuximab, turbidity and DLS show that agitation reduces stability and oligomers appear. After freezing at -20°C, no aggregation was detected by UV. For Rituximab, DDL shows that oligomers appear only after stirring for 24 hours. The secondary structures of Cetuximab and Rituximab seems to be destabilized after freezing (-20°C and -80°C for Rituximab, -20°C for Cetuximab).

W. Akrout, V. Vieillard, A. Astier, M. Paul.
Pharmacy, Henri Mondor Hospital, Creteil, France

Stability of Bevacizumab solution (4 mg/mL) doesn’t reduce if prepared with Baxa Repeater® pump ! Turbidity, dynamic light scattering (DLS), UV spectrometry, and size exclusion chromatography (SEC) were performed: no aggregation was detected. SEC shows that AUC of bevacizumab is equal to 98 % of total AUC regardless of speed flitting. The Baxa Repeater® pump doesn’t lead aggregation.

C. Sauzay, M. Moine, V. Vieillard, N. Jourdan, A. Astier, M. Paul.
Pharmacy, Henri Mondor Hospital, Creteil, France

A Reward for the new function in Stabilis®: the level of evidence!

The first price for the best thesis was awarded to Dr Pauline Lider for the new function “level of evidence” on Stabilis® by CHUGAI and SFPO.

News from
The third SMPO Congress

The third congress of the Moroccan Society of Oncology Pharmacists (SMPO) held in Marrakech, Morocco, 18-19 September 2015.

Marrakech is a town situated in the center of Morocco and is a highly touristic destination. The Jemaa el-Fna is a square and market place in Marrakesh’s medina quarter.

More than 100 participants attended the congress and 55 posters were presented.

The INFOSTAB association was present with a presentation « The interest of the long-term stability studies in oncology » by Jean Vigneron. A session was dedicated to the biosimilars and generics medications and a session was about the current status of oncology in different African countries.

Klaus Meier, president of the European Society of Oncology Pharmacy and Pr Alain Astier , Vice president were present. This Congress was the opportunity to develop cooperations between European and North African countries.

Pr Bouchra Meddah, president of SMPO, during the opening session.

For more informations, please, visit the website of the SMPO : http://www.smpo.org
News from the SNPHPU Congress

The Congress of SNPHPU («Convergence Santé»), one of the French Society of Hospital Pharmacists was organized in Tours, France, September 2015.

Four posters have been presented on the topic of stability. Two posters have been included in the section «New documents on Infostab website». The two posters are in French.

The first one is about the development of a stability indicating method for spiramycin and the second one about a stability study of a mixture of fluorouracil, oxaliplatine and irinotecan for hyperthermic intraperitoneal chemotherapy.

The mixture was studied during 2 hours. Oxaliplatin and fluorouracil were stable for one hour (>10% degradation) but irinotecan degraded rapidly (less than 10% after 20 minutes). This instability is due to the alkaline pH created by the addition of fluorouracil. Irinotecan is in equilibrium between a carboxylate form and a lactone form depending on the pH value and the best stability is with an acidic pH. The formulation has to be changed to lower the pH value before being evaluated in clinical practice.

Twentieth birthday of the «Drug Stability Research Group» (DSRG)

On Wednesday 9th October 2015, Pr Jean-Daniel Hecq from the University Hospital of Mont-Godinne, Belgium organized a meeting dedicated to the stability of injectable drugs for the 20th birthday of the DSRG created in 1996.

The DSRG has published numerous stability studies mainly for long-term stability of antibiotics but also on the stability of antalgic, antiemetics etc.

They have considerably contributed to extend the freeze-thaw technique with microwave oven and have published retrospective articles on these topics.

Since 1996, they have published 42 articles, 57 posters and 8 oral communications on the stability of injectable drugs and the group receive 4 prices and awards. Pr Hecq publishes every year his database on stability and compatibility of injectable drugs as a CDROM. This project is supported by Baxter company.

For more information on this database, please contact Pr Hecq: jean-daniel.hecq@mont.ucl.ac.be

The topic of the meeting was «How to improve the Centralized Intravenous Additive Service (CIVAS)»

Several oral communication were presented during the meeting:
Interest of long-term stability studies for the organisation of CIVAS by Jean Vigneron

A review of the long term stability studies was presented with the stability data in different fields like antibiotics with the possibility of the batch preparation and storage at -20°C, anesthesiology, ophthalmology and oncology/hematology with the possibility to develop the Dose Banding. The evolution towards the automation was evoked with different tools like IV Station from Health Robotics, Pharmahelp® or Apotheca® from Loccioni.

The importance of the stability studies for the daily practice performed by the teams in hospital pharmacies was emphasized. The necessity to maintain this research activity in hospital pharmacies was evoked, every action in favor of this development should be encouraged as the number of stability studies has decreased over the past years as Lawrence Trissel writes in his articles (Int J Pharm Compound 2012; 16, 1: 54-56)

In this context, the Masterclass « Stability studies in oncology » organized every year by the French Society of Oncology Pharmacy is in favor of this development.

Then, the statistical approach of the stability studies was presented by Pr Jamart and B Bihin.

New monographs

Artesunate (Artesun®, Malacef®)

Artesunate is part of the artemisinin group of drugs that treat malaria. It is a semi-synthetic derivative of artemisinin that is water-soluble and may therefore be given by injection.

![Chemical structure of artemisinin](image)

Artesunate is found to be stable in 0.9% sodium chloride at 9°C, 23°C and 36°C for 60, 10 and 4 hours respectively.  

New references from international publications

Epinephrine

Diluted epinephrine solution stored at room temperature or at 2-8°C is chemically stable and sterile for 24 weeks.  

Magnesium sulfate

Magnesium sulfate infusions diluted in lactated Ringer’s solution in polyolefin bags to a final concentration of 10% is stable for 30 days at room (22°C to 25°C), refrigerated (2°C to 6°C), and frozen (-20°C) temperatures.  

Norepinephrine

Solutions of Norepinephrine 100 µg/ml diluted in 0.9% sodium chloride and stored in polypropylene syringes were chemically stable for at least 7 days at 2-8°C, stored in the dark.  
Krankenhauspharmazie 2012; 33: 427-431.
Telavancin
Telavancin IV infusion solutions in 5% dextrose solution or 0.9% sodium chloride solution in both PVC and PVC-free IV bags were stable for at least 32 days when stored at -20°C without light.
*Hosp Pharm 2015; 50, 7: 609-614*

Vancomycine
Premixed vancomycin-icodextrin PD solutions, whether stored refrigerated or at room temperature, were found to be stable for up to 7 days.

New references of incompatibility
- Incompatibility of Vancomycine with sodium citrate (*Am J Health-Syst Pharm 2010; 67: 1195-1198*).
- Incompatibility of Aciclovir with solutions of amifostine, amsacrine, aztreonam, diltiazem HCl, dobutamine HCl, dopamine HCl, fludarabine phosphate, foscarin sodium, idarubicin HCl, meropenem, morphine sulfate, ondansetron HCl, pethidine HCl, piperacillin sodium-tazobactam sodium, sargramostin (*Hospira 2009*).
- Incompatibility of Vancomycine with Gelatin (*Anaesthesia 2000 ; 55, 10: 1039-1040*).

Stability in SyrSpend

Stability Assessment of 10 Active Pharmaceutical Ingredients Compounded in SyrSpend
SF.Geiger C M, Sorenson B, Whaley P.

Feasibility of amlodipine besylate, chloroquine phosphate, dapsone, phenytoin, pyridoxine hydrochloride, sulfadiazine, sulfasalazine, tetracycline hydrochloride, trimethoprim and zonisamide in SyrSpend® SF PH4 oral suspensions.

Two articles have studied the stability of 20 molecules used in pediatrics and for which no specialty is marketed. Anderson O. Ferreira and al have studied amlodipine besylate 1.0 mg/mL, chloroquine phosphate, 15.0 mg/mL, dapsone, 2.0 mg/mL, phenytoin 15.0 mg/mL, pyridoxine hydrochloride 50.0 mg/mL, sulfadiazine 100.0 mg/mL, sulfasalazine 100.0 mg/mL, tetracycline hydrochloride 25.0 mg/mL, trimethoprim 10.0 mg/mL and zonisamide 10.0 mg/mL. Christine M. Geiger and al have studied amiodarone 4.9 mg/mL, furosemide 9.64 mg/mL, hydrocortisone hemisuccinate, and hydrocortisone sodium phosphate 2.05 mg/mL, nifedipine 4.12 mg/mL, phenobarbital 9.26 mg/mL and 8.98 mg/mL, prednisolone sodium 1.32 mg/mL and 1.4 mg/mL, ranitidine 14.49 mg/mL, simvastatin 1.11 mg/mL, spironolactone 25.79 mg/mL and 25.02 mg/mL. An oral suspension of each active pharmaceutical ingredient was compounded in plastic bottles at a specific concentration in SyrSpend SF PH4 or SyrSpend SF Alka. All suspensions were stored both at 2–8 °C and room temperature (20–25 °C).

The 10 commonly used active pharmaceutical ingredients tested by Anderson O. Ferreira and al, Spironolactone, Simvastatine, Nifedipine, Phenobarbital and Amiodarone were stable at least 90 days with regard to both the controlled temperatures. Furosemide is the least stable molecule with only 14 days stability at 2–8 °C. Both study have demonstrated the stability of a wide range of frequently used active pharmaceutical ingredients, tested in SyrSpend SF PH4 and SyrSpend SF Alka at different storage conditions.

Chemical and Functional Analysis of Hydroxyurea Oral Solutions.
Matthew M. Heeney, Matthew R. Whorton, Thad A. Howard, Christina A. Johnson, Russell E. Ware.

Since hydroxyurea is currently commercially available only in capsules, a liquid formulation of hydroxyurea is needed for young patients. Hydroxyurea oral solutions were prepared by dissolving the contents of the capsules in water (room temperature or mildly heated) with vigorous stirring, filtering excipients, and adding flavored syrup to a final concentration of 100 mg/mL. Chemical stability was determined by measuring the hydroxyurea concentration using a standardized analytical colorimetric analysis, while functional stability was determined by measuring the inhibition of Phytohemagglutinininduced T lymphocyte proliferation. Hydroxyurea oral solutions (100 mg/mL) prepared and maintained at room temperature have chemical and functional stability for 3 months.
Valacyclovir

Stability of valacyclovir hydrochloride in extemporaneously prepared oral liquids.
Fish DN, Vidaurri VA, Deeter RG.

The stability of valacyclovir hydrochloride in three commonly used syrups was studied. Triplette suspensions of valacyclovir (from caplets) in Ora-Sweet, Ora-Sweet SF, and Syrpalta syrups were extemporaneously compounded to yield a final concentration of valacyclovir 50 mg/mL (as the Hydrochloride salt). The nine suspensions were stored at 4 °C in amber glass bottles. Valacyclovir 50 mg/mL (as the hydrochloride salt) in three oral liquids stored in amber glass bottles at 4 °C was stable for at least 21 days when prepared with two of three syrups and for at least 35 days when prepared with the third syrup. All the liquids were free of microbial growth for at least 28 days.

Oxycodone and lidocaine

Stability indicating HPLC method for the estimation of oxycodone and lidocaine in rectal gel.
Markus G. Gebauer *, Anna F. McClure, Thean L. Vlahakis

An HPLC method for the quantification of oxycodone and lidocaine in a gel matrix is described. The method was applied to assess the stability of a gel containing oxycodone hydrochloride (0.3% w/w) and lidocaine (1.5% w/w). The gel was stored under refrigeration in ready-to-use syringes and under these conditions oxycodone and lidocaine were stable for at least 1 year. The gel is useful in the management of tenesmus in rectal cancer.

New documents on Infostab website
www.infostab.com
See in « Publications » and « Stability and compatibilities »

Clinical Pharmacy Department, General Surgery Department – Institut Gustave Roussy, Villejuif, FRANCE
Poster presented at the «Convergence Santé» Congress, Tours, France, September 2015

2. Stordeur F., Chanat C., Brandely ML., Chast F. A stability study of 25 mg/mL phenylephrine hydrochloride and 5 mg/mL tropicamide eye drops
Pharmacy unit, GHU Paris Centre, site Hôtel-Dieu, Paris, France
Poster presented at the GERPAC Congress, Hyères, France, October 2015

3. Loboda C, Lider P, Vigneron J. Incompatibilité du Busulfan avec des seringues de 1 mL Luer-Lock : à propos d’un cas
Department of Pharmacy, University Hospital of Nancy, France.
Poster presented at the SFPO Congress, Nantes, France, October 2015

4. Balouzet C., Chanat C., Jobard M., Brandely-Piat ML., Chast F. Stability of 25 mg/ml 5-azacitidine suspensions kept in frigde after freezing
Pharmacy unit, GHU Paris Centre, site Hôtel-Dieu, Paris, France
Oral communication presented at the GERPAC congress, Hyères, France, October 2015

5. Lam S., Sadou Yaye H., Kably B., Babiard M., Tilleul P. Evaluation de la stabilité intrinsèque de la spiramycine
Service Pharmacie, Groupe hospitalier Pitié-Salpêtrière, Paris
Poster presented at the «Convergence Santé» Congress, Tours, France, September 2015
6. Balouzet C., Chanat C., Jobard M., Brandely-Piat ML., Chast F.  
**Stabilité des poches d'azacitidine pour injec- 
tion intraveineuse (1,4 à 2,4 mg/mL) conservées à +4°C**  
*Service Pharmacie, Hôpitaux universitaires Paris Centre, site 
Hôtel-Dieu, Paris, France*  
Poster presented at the SFPO Congress, Nantes, 
France, October 2015

7. Akrout W, Vieillard V, Astier A, Paul M.  
**Influence d'un stress mécanique ou thermo- 
mique sur la stabilité du cetuximab**  
*Department of Pharmacy, University Hospital Henri Mondor, 
Créteil, France.*  
Poster presented at the SFPO Congress, Nantes, 
France, October 2015.

8. Akrout W, Vieillard V, Astier A, Paul M.  
**Stabilité physique des anticorps monoclo- 
naux sous conditions de stress : exemple du 
Rituximab**  
*Department of Pharmacy, University Hospital Henri Mondor, 
Créteil, France.*  
Poster presented at the SFPO Congress, Nantes, 
France, October 2015.

9. Sauzay C, Moine M, Vieillard V, Jourdan N, 
Astier A, Paul M.  
**Etude de stabilité de solution de bévacizumab 
réparties avec la pompe Baxa Reapea- 
ter.**  
*Department of Pharmacy, University Hospital Henri Mondor, 
Créteil, France.  
Department of Pharmacy, University Hospital Saint-Louis, 
Paris, France.*  
Poster presented at the SFPO Congress, Nantes, 
France, October 2015.
The number of users exceeded 250,000 in 2015 (until December 15th).

Country focus: Venezuela

The use of Stabilis has dramatically increased in Central and South America and especially in Venezuela where the increase reaches 107% in 2015 in comparison with 2014!

The main users are concentrated in the capital, Caracas.
Answers to the crosswords

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