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

SUMMARY

Test your knowledge on stability

**New Stabilis coming soon!**

First Masterclass «Stability studies in oncology»

SFPO and ESOP recommendations for the practical stability of anticancer drugs

News from congresses

News from the Synprefh Congress, Lyon, France

New monographs

Levosimendan, Tiapride, Romidepsin

New references from international publications

Adenosine, Bleomycin and lidocaine-epinephrine, Bortezomib, Cardioactive drugs, Daunorubicin, Dexmedetomidine, Doxorubicin-loaded drug-eluting beads (DC Bead®)

New documents on Infostab website

Statistics

Answer to the test
Test your knowledge on stability!

What kind of degradation process do you suggest for this molecule?

☐ Hydrolysis
☐ Epimerisation
☐ Oxidation
☐ Polymerisation
☐ Aggregation

See the answer on the last page

New Stabilis coming soon!

In a few weeks, Stabilis will give informations on the stability of non-injectable drugs! The stability of oral solutions or suspensions, eye drops, capsules, aerosol etc will be available. After clicking on the button «List of drugs» the user will open this new screen where he will choose the type of preparation to obtain stability datas. We will give you practical informations about the novelties in the next newsletter.
Masterclass «Stability study in Oncology» organized by the French Society of Hospital Pharmacists, Paris 13-14 June 2013

The masterclass « Stability studies in oncology » was organised by the French Society of Oncology Pharmacy (SFPO) in June 2013 in Paris, France.

17 pharmacists from French Hospitals attended the meeting which was supported by Merck Serono.

The objectives were :
- to give fundamentals about the chemistry of pharmaceutical
- to give the methodology to perform stability studies
- to develop critical thinking on stability studies published

Pr A Astier, Dr J Vigneron and Dr C Bardin have facilitated the meeting.

The fundamentals of the degradation process of « classical molecules » were presented in details with the hydrolysis, oxydation, isomerisation, polymerisation ... The Arhennius equation was presented.

The methodology of stability studies for classical molecules was presented with the physical (visual and subvisual evaluation) and chemical aspects.

The stability of proteines was developped by Pr Astier from the University Hospital of Creteil.

The main aspects of the ICH Guidelines were presented and the main lines of the «Guidelines for the practical stability studies of anticancer drugs: A European consensus conference» published in Ann Pharm Fr 2011, 69: 221-231.

At the end of the meeting, articles of stability studies were given to the participants for critical analysis. The interpretation of the results of stability studies were discussed.

The French Society of Oncology Pharmacists and the Infostab association thanks Merck Serono for their sponsoring.

A second Masterclass will be organized in 2014, always in Paris, in June. The date will be precised later.

SFPO and ESOP recommendations for the practical stability of anticancer drugs

The new recommendations for the practical stability of anticancer drugs have been published in Ann Pharm Fr. The previous data had been published in 2010.

In this updated article, new drugs have been included (asparaginase, azacitidine, bevacizumab, clofarabine, eribuline mesylate, folinate sodium, levofofinate calcium, nelarabine, rituximab, temsirolimus). Some drugs received new informations (cisplatine, docetaxel, fludarabine, vincristine). Three drugs no longer available on the market have been removed from the table : chlormethine, mitoguazone and pirarubicine.
The Congress of one of the French Society of Hospital Pharmacists (Synprefh) took place in Lyon, France. An interesting oral communication presented the stability of a mixture of bleomycine, lidocain and epinephrine in 0.9% sodium chloride for the treatment of keloids.

The stability study has been performed by the team of the Saint Louis Hospital from Paris: Michael Chaussard, Christelle Elias, Antoine Petit, Patrice Bellenger, Nathalie Jourdan, Pierre Faure, Nabil El Kateb. The study was presented by Dr Nabil El Kateb.

The authors have demonstrated that the solution containing 0.75 mg/mL Bleomycin, 3.5 mg/mL lidocain and 3.5 mg/mL epinephrine was stable for 3 days at 4°C and only one day at 22°C. In this mixture, bleomycin was the limiting compound for the stability.

### New monographs

#### Levosimendan

Levosimendan is a calcium sensitiser used in the management of acutely decompensated congestive heart failure. It is marketed under the trade name Simdax®. Levosimendan 2.5 mg/ml stored in polypropylene at 8°C is stable for 60 days.

*ADKA Congress, Dresden, Germany 2013*

#### Tiapride

Tiapride is a drug that selectively blocks D2 and D3 dopamine receptors in the brain. It is used to treat a variety of neurological and psychiatric disorders including dyskinesia, alcohol withdrawal syndrome, negative symptoms of psychosis, agitation and aggression in the elderly. Dilutions of tiapride in 0.9% sodium chloride and in 5% dextrose solution, at concentrations of 1 mg/ml and 2 mg/ml, in glass bottles and at room temperature were stable both physically and chemically during 48 hours.

*Farm Hosp 2013;37,1:10-14*

#### Romidepsin

Romidepsin (trade name Istodax®) is an anticancer agent used for the treatment of cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma (PTCL), in patients who have received at least one prior therapy. Romidepsin is a natural product obtained from the bacteria Chromobacterium violaceum, and works by blocking enzymes known as histone deacetylases and inducing apoptosis.

Each 10 mg single-use vial of romidepsin must be reconstituted with 2 ml of the supplied diluents. The reconstituted solution (5mg/ml) is chemically stable for at least 8 hours at room temperature. Before intravenous infusion, further dilute Romidepsin in 500 ml 0.9% sodium chloride injection. The diluted solution is compatible with polyvinyl chloride (PVC), ethylene vinyl acetate (EVA), polyethylene (PE) infusion bags as well as glass.

*Celgene Corporation 2013*
New references from international publications

Adenosine
Adenosine solutions of 10 and 50 µg/ml were stable for at least 14 days in 50 ml polyolefin infusion bags of 0.9% sodium chloride injection or 5% dextrose injection stored at controlled room temperature and refrigerated conditions.
*Hosp Pharm 2013 ; 48, 6: 484-488*

Bleomycin and lidocaine-epinephrine
Bleomycin diluted to 0.75 mg/ml in 0.9% sodium chloride injection was stable for 7 days when stored in polypropylene infusion bags at 4°C and 22°C, when protected from light. Diluted in association with lidocaine 3.5mg/ml and epinephrine 3.5 µg/ml, bleomycin was stable 1 day at 22°C and 3 days at 4°C.
*Hopipharm Congress, Lyon France, May 2013*

Bortezomib
Reconstituted bortezomib 2.5 mg/ml for subcutaneous administration was physically and chemically stable at least for 33 days in the original vial at room temperature and at 4°C at least for 23 days in syringe, both in the dark.

Cardioactive drugs
This study was undertaken to evaluate the physicochemical compatibility of five common associations of cardioactive drugs:
- Norephedrine is physicochemically compatible with dopamine and dobutamine
- Amiodarone is physically compatible with dobutamine and norephedrine
- Dobutamine is physicochemically compatible with sodium nitroprusside if the light-sensitive sodium nitroprusside is protected from light
*EJHP 2013 ; 20:110-116.*

Daunorubicin
Daunorubicin at different concentrations (0.4 to 3 mg/ml) was stable in polyolefin infusion bags, under different storage conditions (22 or 4°C, protected from light) during 14 days.
*J Pharm Biomed Anal 2013 ; 83 : 164-470*

Dexmedetomidine
Dexmedetomidine hydrochloride 4, 8, 12 and 20 µg/ml stored in PVC bags at 23+/−2°C was stable for 48 hours.
*Am J Health-Syst Pharm 2013 ; 70:1336-1341*

Doxorubicin-loaded drug-eluting beads (DC Bead®)
DC Bead® loaded with doxorubicin can be stored in a glass vial at 2-8°C for 14 days with no detrimental impact on the doxorubicin dose released and eluted from the beads and non increase in the level of chromatographic impurities.
*J Oncol Pharm Practice 2013 ; 19, 1: 65-74*

New reference of incompatibility

- Vancomycin and piperacillin/tazobactam : A combination of vancomycin 10 mg/ml and piperacillin/tazobactam 112.5 mg/ml demonstrated precipitation immediately upon mixing.
*Hosp Pharm 2013 ; 48, 1: 44-47*

New documents on Infostab website

[www.infostab.com](http://www.infostab.com)
See in « Publications » and « Stability and compatibilities »

Heeb R, Krämer I
Physicochemical stability of ready-to-administer epinephrine injection solutions 20 µg/mL, 50 mL.
*Pharmacy Department, Universität Medical Center, Mainz, Germany*
Poster presented during the last EAHP Congress in Paris, March 2013.
Statistics

English users’ proportion is still growing. French language represents now less than half of all users.

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Traffic on Stabilis website has been stable in 2013 so far, with at least 13,000 visits per month.

Country focus
This time Australia is under the spotlights, with the 5 most active cities on Stabilis website.
Answer to the test

- Hydrolysis
- Epimerisation
- Oxydation
- Polymerisation
- Aggregation

Drugs that are a derivative of carboxylic acid or contain functional groups based on this moiety like ester, amide, lactone, lactam, imide, carbamate are liable to undergo hydrolytic degradation. The molecule presented here is acetylsalicylic acid (aspirin). The hydrolysis is shown in the figure below.

See: web.uvic.ca/~pmarrs/chem463/463e35aspirinhydrolysis.pdf

For more informations about the chemical decomposition of drugs, read the very interesting book of Alexander T Florence and David Attwood «Physicochemical principles of Pharmacy» Fifth edition.