Welcome to the STABILIS users for this thirtieth Newsletter!

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ADKA Congress in the Congress Center
Rosengarten, Mannheim, Germany, May 2015

Test your knowledge on stability

News from congresses
News from the ADKA Congress May

Masterclass SFPO 2015

New monographs
Ceftazidime Avibactam (Aycaz®), Isavuconazonium (Cresemba®), Ceftolozane / Tazobactam (Zerbaxa®)

New references from international publications
Ampicillin – Amoxicillin, Antipseudomonal betalactams, Bevacizumab, Butorphanol / Ropivacaine, Colistine mesilate (Colistimethate), Cabazitaxel – Docetaxel, Cefuroxime, Chlorothiazide, Diphenhydramine / Lorazepam / Dexamethasone, Lenograstim, Meropenem, Micafungin, Oxaliplatin, Rituximab, Metronidazole, Metronidazole Benzoate, Prednisone, Quinapril, Sulfadiazine

New documents on Infostab website

Statistics
Focus on Sweden

Answer to the test
Test your knowledge on stability!

Across

3. His scale is logarithmic
7. His increase provokes the degradation of proteins
8. A common path of degradation for sulfur compounds
11. A common path of degradation for molecule containing an ester group
13. Interaction with the surface of a container
14. The separative method of choice for stability studies

Down

1. Ions involved in the stability of all platinum compound
2. Interaction with the matrix of a plastic container
4. The most frequent way of degradation of the proteins
5. Must be proven before using long-term stability data
6. Can extract plasticizers (abreviation)
9. Degradation due to the exposure to light
10. The most inert container
12. His Handbook is famous
News from the ADKA Congress

The annual Congress of the German Association of Hospital Pharmacists (ADKA) took place in Mannheim, Germany, May 2015.

Around 60 posters were presented. Two posters were about stability and compatibility and presented by the team of the Universitätlinikum Freiburg. These posters can be downloaded on Infostab (see this section in the newsletter).


The authors have studied the influence of dexamethasone on the stability of the mixture hydromorphone-metamizol. The conclusion was that Dexamethasone does not affect the stability of this mixture. (concentration measured by HPLC with mass detector)


The authors have studied the “leachables” and “extractables” from syringes of 5 manufacturers by UV spectroscopy after sampling of NaCl 0.9% or ethanol. The analysis was performed after 24, 48 hours and 3 months, the UV absorption at 270 nm increased even after sampling of NaCl 0.9% as a consequence of the presence of “leachables” and “extractables” substances. Big differences were seen between the 5 manufacturers (see the poster).

Thanks to Rainer Trittler for his collaboration for this newsletter.

Masterclass SFPO 2015

For the third consecutive year, the French Society of Hospital Pharmacists (SFPO) organised a two days Masterclass on the stability studies in Oncology. 25 hospital pharmacists from France, Morocco and Swiss have participated.

The content was updated with new articles for the always appreciated critical analysis of the articles of stability studies. This two day session has received for the first time, the labeling for continuous education of pharmacist.

The participants of the Masterclass 2015 with Dr Jean Vigneron, Pr Alain Astier and Dr Christophe Bardin.
New monographs

Ceftazidime Avibactam (Aycaz®)
AVYCAZ® combines ceftazidime, a cephalosporin with in vitro activity against certain Gram-negative and Gram-positive bacteria, and avibactam, a non-beta-lactam beta-lactamase inhibitor that inactivates certain key beta-lactamases and protects ceftazidime from degradation by these beta-lactamases.

Ceftazidime / Avibactam was approved by the FDA for treating complicated urinary tract and complicated intra-abdominal Infections caused by antibiotic resistant-pathogens, including those caused by multi-drug resistant gram-negative bacterial pathogens.

The reconstituted AVYCAZ® solutions, diluted with 0.9% sodium chloride injection or 5% dextrose injection or lactated Ringer’s injection, to achieve a total volume of 50 ml to 250 ml, were stable 12 hours when stored at room temperature in the infusion bags and up to 24 hours when stored under refrigeration (2-8°C).

Summary of Product Characteristics, Forrest Pharmaceuticals, 2015

Isavuconazonium (Cresemba®)
Isavuconazole is a triazole antifungal drug. Its prodrug, isavuconazonium sulfate (Cresemba®), is indicated for treatment of invasive aspergillosis or invasive mucormycosis.

The reconstituted solutions may be stored below 25°C for maximum 1 hour prior to preparation of patient infusion solution.

After dilution in 0.9% sodium chloride or 5% dextrose, the intravenous administration should be completed within 6 hours of dilution at room temperature. If this is not possible, immediately refrigerate (2-8°C) the infusion solution after dilution and complete the infusion within 24 hours.

Summary of Product Characteristics, Astellas, 2015

Ceftolozane / Tazobactam (Zerbaxa®)
Ceftolozane (Zerbaxa®) is a 5th generation cephalosporin antibiotic, developed for the treatment of infections with gram-negative bacteria that have become resistant to conventional antibiotics. Ceftolozane is combined with the β-lactamase inhibitor tazobactam, which protects ceftolozane from degradation.

Ceftolozane is indicated for the treatment of complicated urinary tract infections and complicated intra abdominal infections.

Reconstituted Zerbaxa® solution may be held for 1 hour prior to transfer and dilution in a suitable infusion bag.

Following dilution on the solution with 0.9% sodium chloride or 5% dextrose, Zerbaxa® is stable for 24 hours when stored at room temperature or 7 days when stored under refrigeration at 2-8°C.

Summary of Product Characteristics, Cubist Pharmaceuticals, 2014
New references from international publications

Stability of injectable drugs

**Alprostadil**
Preparations of Alprostadil 1.5 or 15 µg/ml diluted with 10% dextrose are stable for up to 48 hours when stored in polypropylene syringes at 28-32°C.

*Chavan E. Pharmacist Master, University of Genève 2014*

**Ampicillin – Amoxicillin**
Ampicillin and amoxicillin in different types of Peritoneal Dialysis solutions remained stable for at least 336 hours when stored at 4°C, 48 to 72 hours at 25°C and 24 hours at 37°C.

*Am J Health-Syst Pharm 2015; 72:13-14*

**Antipseudomonal betalactams**
E. Viane et al examined and compared the stability of parenteral antipseudomonal betalactams in concentrated solutions (aztreonam, piperacillin+/tazobactam, ceftazidime, cefpirome, cepapime) in view of their potential administration by continuous infusion with external pumps or with portable pumps.


**Bevacizumab**
K. Khalili et al examined the storage stability of compounded bevacizumab 25 mg/ml in polycarbonate and polypropylene syringes. No significant difference over a 6-month period was observed in the quality of bevacizumab repackaged into syringes when compared with freshly opened vial. The syringes are used for the treatment of macular degenerescence.

*Eye 2015; 29, 6: 820-827.*

**Butorphanol / Ropivacaine**
Butorphanol and ropivacaine in 0.9% sodium chloride injection are stable for at least 15 days when stored in polyolefin bags at 4°C and 25°C.

*EJHP 2015 ;22:7-11*

**Colistin mesilate (Colistimethate)**
The 0.8 mg/ml solution of Colistin mesilate with saline solution (0.9%) can be stored for up to 3 days at 4°C in an elastomeric pump.


**Cabazitaxel – Docetaxel**
Reconstituted cabazitaxel solutions (premix solutions) stored at 4°C were physicochemically stable for a minimum of 4 weeks. Diluted infusion solutions in PVC-free infusion bags (docetaxel concentration 0.30 mg/ml ; cabazitaxel concentration 0.15 mg/ml) were physicochemically stable for a minimum of 4 weeks, independently of storage temperature (4 or 25°C).

*EJHP 2014; 22:150-155*

**Cefuroxime**
Solutions of Cefuroxime 10 mg/ml diluted in 0.9% sodium chloride and stored in polypropylene syringes or polyolefine vials were chemically stable for at least 365 days at -20°C, 21 days at 5°C and 16 hours at 25°C, stored in the dark.


**Chlorothiazide**
When packaged in 1-ml polypropylene syringes and stored protected from light at refrigerated conditions, a solution of chlorothiazide sodium injection in water was stable for 6 days.

*Am J Health-Syst Pharm 2015 ; 72:1292-1297*

**Diphenhydramine / Lorazepam / Dexamethasone**
Diphenhydramine hydrochloride 4 mg/ml, lorazepam 0.16 mg/ml and dexamethasone sodium phosphate 0.27 mg/ml in 0.9% sodium chloride, stored in polypropylene syringes were compatible. Components retained greater than 95% of their original concentration over 48 hours when stored at room temperature.


**Lenograstim**
Lenograstim solution can be stored in the infusion device (elastomeric infusion system) for 14 days under sterile conditions at 4°C before delivery without loss of biological activity.


**Meropenem**
Meropenem solutions at concentrations of 4 and 10 mg/ml, diluted with 0.9% sodium chloride infusion and stored at controlled room temperature (25+/−3°C) in polyolefin bags, in the light or in the dark, were stable for at least 4 hours.

*Hosp Pharm 2015; 50, 4 : 296-303*
Micafungin
Micafungin diluted in 0.9% sodium chloride and stored in polypropylene syringes was chemically stable for at least 15 days at 25°C in the dark.
*Int J Pharm* 2015; 492 : 137-140.

Oxaliplatin
5 mg of Oxaliplatin was added to 50 ml of various carrier solutions at 42°C: 5% dextrose, 0.9% sodium chloride, Ringer lactate, Dianeal PD4 glucose 1.36% solution for peritoneal dialysis. Oxaliplatin solutions remained stable over 2-hour period in 5% dextrose, 30 min in Ringer lactate or Dianeal PD4 glucose 1.36% solution.

Rituximab
Rituximab (MAbThera SC DPS) was tested for compatibility with standard materials used for SC administration and during storage for up to 4 weeks at 2°C to 8°C and 24 hours at ambient temperature (30°C). The analytical results showed that relevant quality attributes of Rituximab were maintained during in-use stability in contact with the different test materials.

Metronidazole
Stability of Metronidazole Suspensions
Donnelly Ronald F, Ying James
*Int J Pharm Compound* 2015; 19, 3: 248-251

The objectives of this study were to develop concentrated metronidazole suspensions that are inexpensive and easy to prepare and determine the stability of these suspensions after storage in amber polyvinyl chloride bottles at room temperature (23°C) and under refrigeration (5°C). Metronidazole suspensions (50 mg/mL) were prepared from powder using Ora-Blend or simple syrup as the vehicles. Samples were assayed using a high-performance liquid chromatography method that had been validated as stability indicating. There was no apparent change in color or physical appearance. The pH values changed by less than 0.20 units over the 93 days. The stability of metronidazole suspensions compounded from United States Pharmacopeia powder using Ora-Blend or simple syrup and packaged in amber polyvinyl chloride bottles was determined to be 93 days when stored at either room temperature or under refrigeration.

Metronidazole Benzoate
Stability of Metronidazole Benzoate in SyrSpend SF One-Step Suspension System.
Vu N.T, Aloumanis V, Ben MJ, Kupiec T.C, Patterson E K, Radke J, Erickson M A III, Schneider G.
*Int J Pharm Compound* 2008; 12, 6: 558-564.

The objective of this study was to determine the stability of metronidazole benzoate suspension in SyrSpend SF One-Step Suspension System. The studied samples were packaged in 60-mL amber plastic prescription bottles, which were stored protected from light under controlled environmental conditions for a period of 360 days. Stability of metronidazole benzoate suspension in SyrSpend SF was assessed based on retention of initial color or appearance, pH of suspension, and recovery of metronidazole benzoate from the packaged product. Metronidazole benzoate in SyrSpend SF was stable for at least 1 year when stored protected from light at ambient condition (25°C/60% relative humidity). The shelf life for this product may be extended to 2 years when stored at refrigerated temperature.

Prednisone
Stability of prednisone in Oral mix suspending vehicle
Friciu M, Plourde K, Leclair G, Danopoulos P, Savji T.

The stability of prednisone (5 mg/ml) formulated as a suspension in Oral mix vehicle was evaluated. Suspensions were prepared from both pure active and commercial tablets utilizing two different container closures : amber glass bottle and polypropylene syringes. Formulations were stored at 5°C or 25°C and organoleptic properties, pH and concentration were evaluated at predetermined time points up to 90 days. Beyond use date was evaluated by statistical analysis of the overall degradation trend. Prednisone was stable for at least 90 days at 25°C.
Quinapril
The development and stability assessment of extemporaneous pediatric formulations of Accupril
Anita L. Freed, Steven B. Silbering, Kevin J. Kolodsick, David T. Rossi, Majid Mahjour, Carol A. Kingsmill


Quinapril is unstable in aqueous solution and therefore the development of a liquid formulation is a significant challenge. The authors have developed nine prototypes and their characteristics evaluated after 1 week under stressed conditions. The three formulations that most closely matched the stability criteria were chosen for a definitive stability study. A stability-indicating method was developed and validated for these studies. All three formulations met the following specifications when stored at 5°C for 6 weeks; Quinapril remained ≥90% intact and the two known degradants did not reach values ≥3.0% individually or ≥5.0% combined.

Sulfadiazine
Stability of sulfadiazine oral liquids prepared from tablets and powder.
Umma Pathmanathan, David Halgrain, Fouad Chiadmi, Joël Schlatter, Norbert Vermerie


Solutions of sulfadiazine 200 mg/mL were prepared from commercially available 500 mg tablets and powder in sterile water for irrigation. They were stored in amber glass bottles at 4°C and 23°C. Detectable change in odor was observed for the solutions stored at 23°C. The solution prepared from powder was stable 3 days stored at 4°C. Other formulations lost over 10% of the initial sulfadiazine concentration within 2 days.

New documents on Infostab website

www.infostab.com
See in « Publications » and « Stability and compatibilities »

Poster presented at the ADKA Congress Mannheim, Germany, May 2015

2. Trittler R., Hug MJ., Leachables – ein weltweites Problem *University Medical Center, Pharmacy, Freiburg, Germany*
Poster presented at the ADKA Congress Mannheim, Germany, May 2015

3. Trittler R. Leachables -Ein weltweites Problem ! *University Medical Center, Pharmacy, Freiburg, Germany*
Oral communication at the ADKA Congress Mannheim, Germany, May 2015
Statistics

Country focus
For this newsletter we highlight our Sweden colleagues: thank you all for your support to Stabilis.
Greetings to our friend Pr Per Hartwig Honoré.

Frequentation
As every summer our colleagues (and us !) have taken some holidays, which illustrates on the statistics.

Languages
Over the past 12 months the rank of Japanese language has much improved, reaching the 9th place!

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Answer to the test