# Hypromellose prolongs the dissolution of ketamine out of gelatine capsules

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## Objectives

The prolonged release of active pharmaceutical ingredients is widely used to achieve long lasting therapeutic effects combined with the patient's advantage to take his medication less often and reduce the possible risks of adverse effects. Most methods for retardation used in industrially manufactured dosage forms cannot be applied in case of individual preparations manufactured in pharmacies. The addition of a gelling agent such as hypromellose in capsule production could serve as promising possibility for small scale productions. Aim of this investigation was to compare the dissolution characteristics of capsules containing 20 mg Ketamine-HCl and either a mixture of lactose and hypromellose or lactose alone. As there is no clear recommendation considering the optimal lactose-hypromellose-ratio one established formulation was investigated.

## Material and Methods

Capsule composition:

| | Conventional | Prolonged release |
|---|---|---|
| Ketamine | 20 mg | 20 mg |
| Lactose-monohydrate | 330 mg | 85 mg |
| Hypromellose | - | 200 mg |

Placebo capsules with hypromellose + lactose and with lactose alone were used as a reference for quantification.

Dissolution was simulated in an experimental setup with 200ml 0.1M hydrochloric acid with stirring at a controlled temperature of 37±1°C. Depending on the capsule type and its dissolution profile samples were taken at defined intervals. Five dissolution tests on each capsule type were conducted.

Quantification is performed by UV/VIS spectrophotometry at 268nm. Dissolved placebo capsules containing lactose or lactose/hypromellose alone were used as reference. The method was validated regarding linearity, accuracy, precision and repeatability.

## Results and Discussion

Capsules containing Ketamine and lactose dissolve rapidly and liberate 100% of Ketamine within approximately 7 min. Those capsules containing hypromellose as well release only 70% active ingredient within 2 hours (figure 1). Within this period the release is almost linear. Full liberation is obtained in about 3 hours.

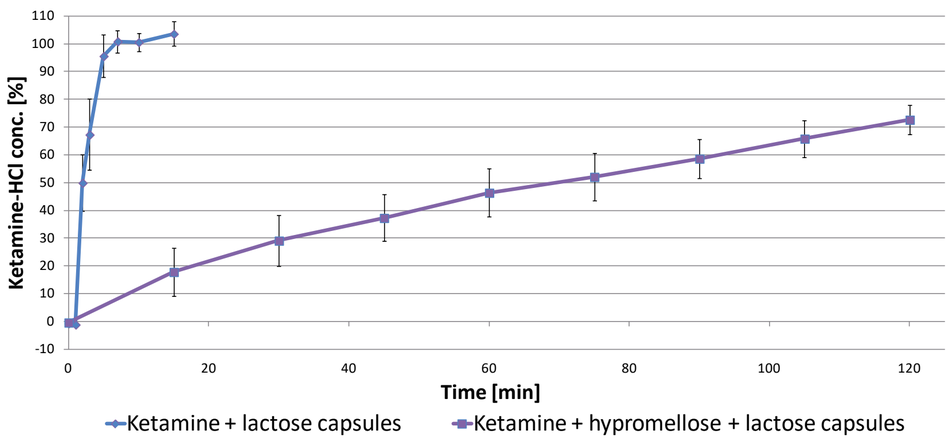


**Figure 1:** Dissolution profile of Ketamine-HCl out of gelatine capsules with the excipient hypromellose + lactose vs. the excipient lactose alone

This different behaviour can be explained by the different physical properties of lactose and hypromellose. Lactose serves as filling agent. Thus the content of the capsules containing only lactose as excipient is immediately released after dissolution of gelatine (figure 2). In contrast hypromellose is forming a gel when coming into contact with stomach fluid. Ketamine is released out of the gel primarily by diffusion. Consequently the dissolution of ketamine is significantly prolonged (figure 3).

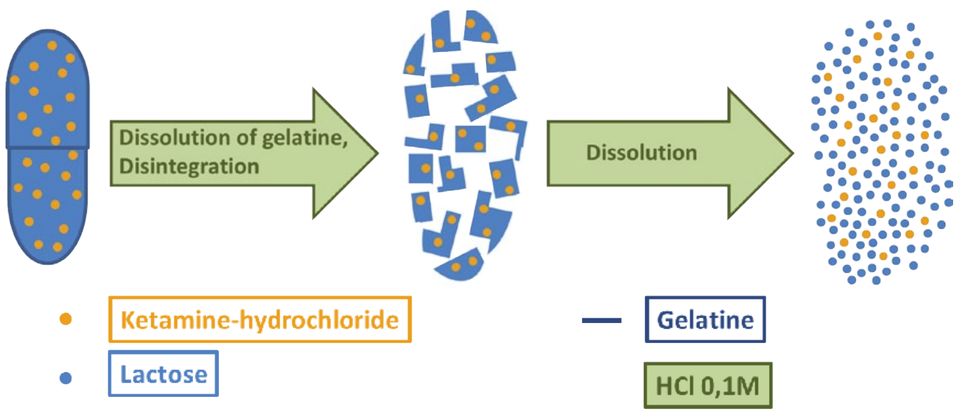


**Figure 2:** The disintegration and dissolution process is very fast, using lactose as excipient alone.

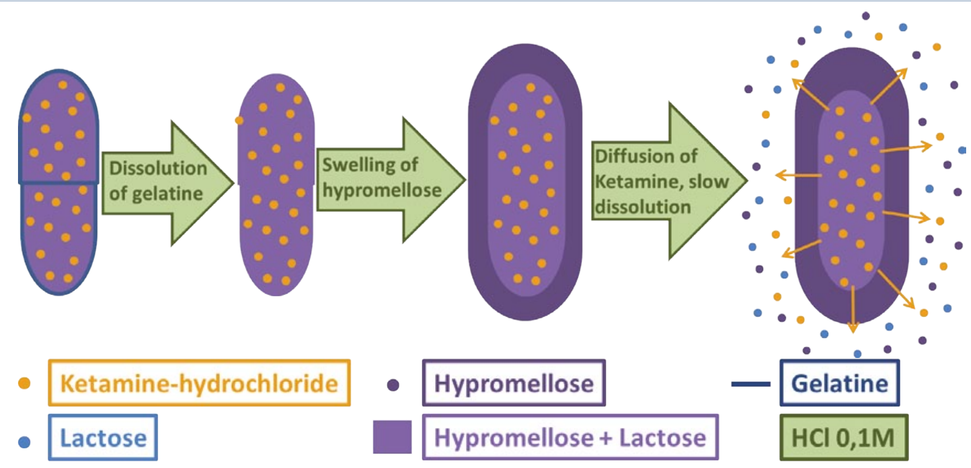


**Figure 3:** Hypromellose as additional excipient to lactose causes a swelling and therefore slow liberation of Ketamine-HCl.

## Conclusion

Hypromellose has an enormous effect on the liberation characteristics of a gelatine capsule when used as an excipient. It swells in aqueous solutions and prolongs the liberation of Ketamine out of the matrix and contributes to very a consistent release. Hypromellose is therefore a promising excipient for individual pharmaceutical preparations with prolonged release.

**References:**
Pharm. Eur. 8.4. (2014).
Hunnius; 7. Auflage. (1993). Berlin; New York: de Gruyter.; Pharm. Eur. 8.4. (2014).
J. Ermer, J. M. (2005). Method Validation in Pharmaceutical Analysis, 15-19. Weinheim: WILEY-VCH.;
Kromidas, S. (2000). Handbuch Validierung in der Analytik. Weinheim: WILEY-VCH.

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22nd Congress of the EAHP
22-24 March 2017, Cannes,
PP-003

# Stability study of Bortezomib (Velcade) with limit test for all degradation products

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## Background

Bortezomib (Velcade®) costs approx. 1000 € per vial and is available as a lyophilized powder, which must be reconstituted before administration. The resulting solution is stable for 8 hours according to the SPC, and leftovers therefore cannot be used on subsequent days. This imposes a significant economic loss on hospital budgets. Several studies have shown that the reconstituted drug is stable for > 24 hrs, but none of these have contained identification and quantification of the degradation products formed during storage.

## Materials and methods:

The analytical method was based on the work by Srinivasulu and colleagues (1). The storage conditions were 5 °C ± 3 °C, protected from light, and the study consisted of the following measurements: Assay, DPs and visual inspection. Measurements were conducted at 0, 1, 3, 7, 10 and 14 days with analysis of the same three vials of Bortezomib per timepoint. The acceptance criteria for the study were: Assay: 95,0 - 105.0 % of initial value, Bortezomib impurity E: < 3.0 %, other impurities: < 0,5 %, summarized other impurities: < 2,0 % and a clear and particle free liquid.

## Objective

To conduct a stability study of reconstituted Velcade 2,5 mg/mL in the manufacturer's vial , with identification and quantification of all degradation products.

## Results

### Identification of degradation products

The degradation pathway of Bortezomib (figure 1) was confirmed by stress tests and the identity of the degradation products was confirmed by comparison with litterature values and UPLC-MS analysis. Furthermore, the identity of Impurity E was confirmed by comparison with the synthesized compound. (table 1)

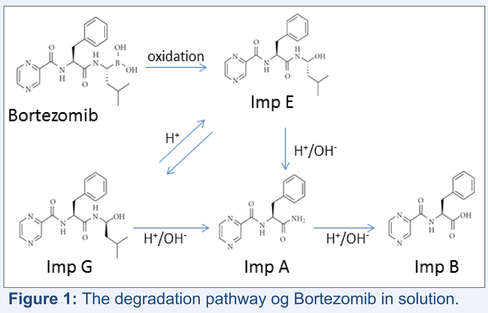


**Figure 1:** The degradation pathway og Bortezomib in solution.

**Table 1:** Comparison of retention times from literature (1), our study HPLC-UV method and confirmatory UPLC-UV-MS analysis. The theoretical and observed masses are shown.

| Imp ID | Retention times (min) | | | Masses (Da) | |
|---|---|---|---|---|---|
| | Litera-ture HPLC-UV[a] | Study HPLC-UV[a] | UPLC-UV-MS[b] | Theo-retical | Observed |
| A | 6,0 | 6,0 | 2,8 | 270,3 | 293,2 $[M + Na]^+$ |
| B | 11,7 | 11,7 | 3,4 | 271,3 | 272,14 $[M+H]^+$ |
| E | 22,5 | 22,8 | 4,4 | 356,4 | 379,2 $[M + Na]^+$ |
| G | 25,8 | 27,7 | 4,7 | 356,4 | 379,2 $[M + Na]^+$ |
| E synthetic | 22,5 | 22,8 | 4,4 | 356,4 | 379,2 $[M + Na]^+$ |

[a]As described in (1)

[b]Conducted on a Waters Aqcuity UPLC system with a QDA detector. Coloum: Aqcuity UPLC BEH 1.8µm, 2.1 x 100mm, mobile phase A: $H_2O$ w 0.1 % Formic acid, mobile phase B: acetonitrile with 0.1 % Formic acid. Flow: 0.6 mL/min, gradient: 0 min; 90 % A, 8 min; 25 % A. column temperatrure 35°C. MS cone voltage 15 V, probe temperature 600°C, capilary positive 0,8kV, mass range 80-450 Da.

### Stability study

A. Visual inspection:

- No change throughout study

B. Degradation products (figure 2)

- No increase in amount of known impurities
- Small increase in one unknown impurity, concentration below specification limit at t=14 days.

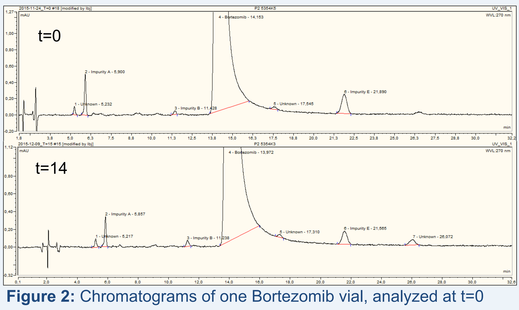


**Figure 2:** Chromatograms of one Bortezomib vial, analyzed at t=0 days and t=14 days .

C. Assay (figure 3)

- Large deviations due to sampling error caused by viscosity and low sample volume.
- 95% confidence interval of regression line >105.0 % after 13 days.

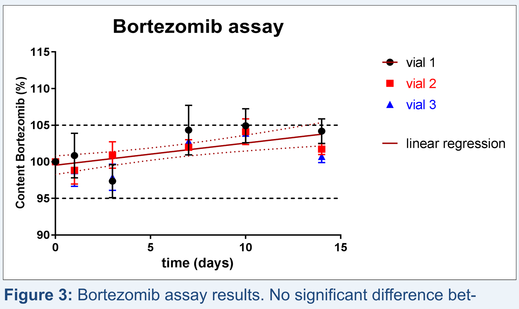


**Figure 3:** Bortezomib assay results. No significant difference between the slope (p=0,62) or the y-intercept (p=0.47) of the individual data series was found, and therefore the data was pooled. The resulting regression line is shown in brown, along with the 95 % confidence band of the line (dotted, brown lines)

The individual data points are shown as mean ± S.D. (3 replicates), and the black, dotted lines show the specification limits (95.0 — 105.0 %). The statistical analysis was performed using GraphPad Prism software (v. 7.0)

## Conclusion

Bortezomib (Velcade) 2,5 mg/mL is stable for at least 12 days for 5°C when stored in the manufacturer's vial.

**No conflict of interests**

**References:**

(1). Srinivasulu K, Naidu MN, Rajasekhar K, Veerender M, Suryanarayana MK. Development and Validation of a Stability Indicating LC Method for the Assay and Related Substances Determination of a Proteasome Inhibitor Bortezomib. Chromatography Research International. 2012;2012:Article ID 801720, 13 pages.

# Stability study of 10 mg/ml pediatric cyclosporine solution in olive oil

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## Background

Cyclosporine is an immunosuppressive drug known for its narrow therapeutic range (NTR). The only formulation available on the market offers a 100 mg/ml concentration. However, in our hospital, pediatric department regularly requires dosages as low as 4 mg that are difficult to prepare from the pharmaceutical specialty. This may lead to inaccurate doses that can have heavy clinical impact. In this context, we developed a 10 mg/ml cyclosporine formulation.

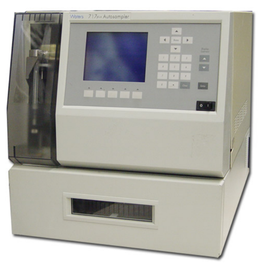
## Purpose

Determine the physico-chemical stability of 10 mg/ml cyclosporine solution in olive oil in order to fix a shelf life.

## Material and methods

- **Solution coumponding**: 3 batches
  - *European Pharmacopoeia compliant*

  - ➢ Cyclosporine (FAGRON)
  - ➢ Olive oil (COOPER)
  - ➢ Alpha-tocoferol 0,02% v/v (INRESA)
- **Analytic method validation**
  - ✓ Linearity: $R^2$ estimation, 3 standard curves
  - ✓ Accuracy: R%=(Cmeas./Ctheo.)x100
  - ✓ Repetability: intra-day variability
  - ✓ Intermediate precision: inter-day variability
  - ✓ Forced degradation by HCl, NaOH and $H_2O_2$
- **Analytic method caracteritics**

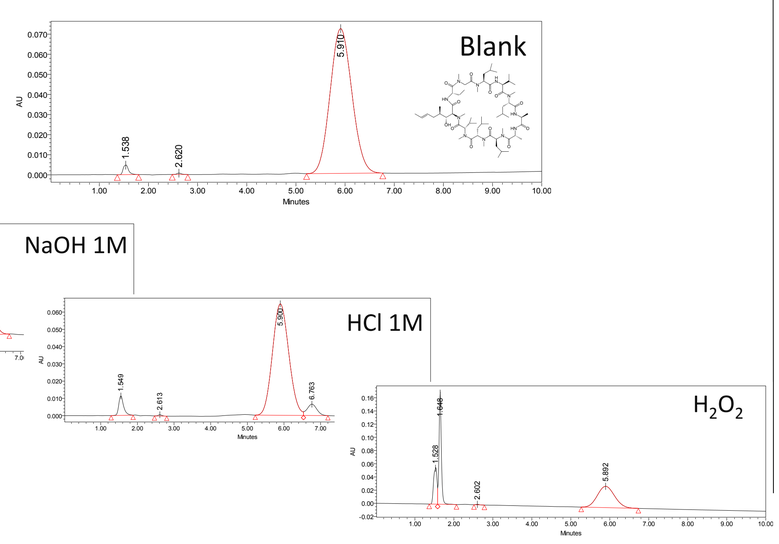


  - ➢ 717plus autosampler, 2487 UV detector, HPLC 515 pump, Empower® Software
  - ➢ Column: Waters C18 Xterra (150 x 4,6mm, 5µm)
  - ➢ Mobile phase: Acetonitrile/Water (70:30 v/v)
  - ➢ Flow rate: 1ml/min; λ=210nm
  - ➢ Thermostatic column oven: 60 ± 0,5°C

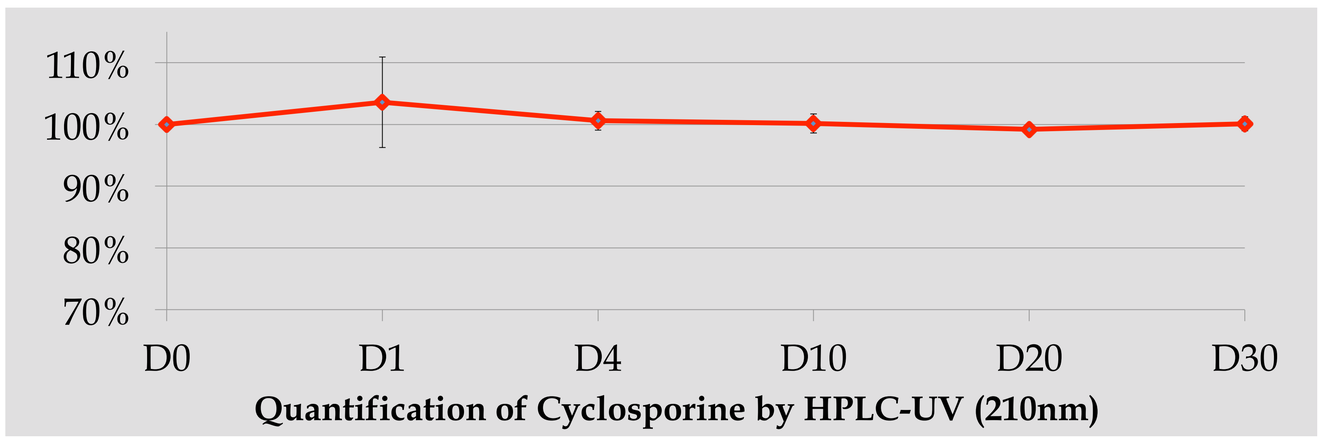
| Days | D0 | D1 | D4 | D10 | D20 | D30 |
|---|---|---|---|---|---|---|

## Results

- **Analytic method validation**
  - ✓ No matrix effect was observed
  - ✓ Linearity: $R^2$>0,99
  - ✓ Accuracy: R%=[99,2%; 98,3%; 99,8%]
  - ✓ Repetability: CV=[1,05%; 1,40%; 2,05%]
  - ✓ Intermediate precision: CV=1,5%
  - ✓ Forced degradation:

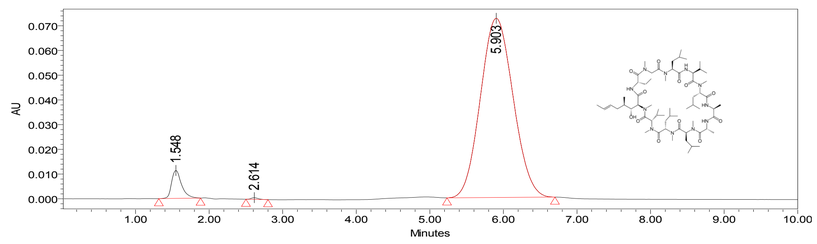



- **Stability study**
  - ✓ Cyclosporine concentration evolution over 30 days




**Quantification of Cyclosporine by HPLC-UV (210nm)**

  - ✓ No macroscopic alteration
  - ✓ No degradation products detected




## Conclusion

10 mg/mL cyclosporine oral solution in olive oil was stable for at least 30 days at room temperature and protected from light. Therefore we can set a shelf life of 30 days. This 10 mg/ml cyclosporine solution would provide an interesting alternative to the pharmaceutical specialty in order to administrate more accurate cyclosporine doses to pediatric patients.

22nd Congress of the EAHP, 22 – 24 March 2017, Cannes - France

**PP-014**

PP-029

# STABILITY OF FROZEN 1% VORICONAZOLE EYE DROPS IN GLASS AND IN INNOVATIVE CONTAINERS

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## Background

Voriconazole is effective on most keratitis causative fungi with an excellent transcorneal penetration.
Voriconazole eye drops (VED) specialities being unavailable in Europe, they are usually compounded in hospital pharmacies.

New eyedrops containers emerged on hospital market, e.g; High-Density-PolyEthylene bottles available in trays (CAT®), for which few stability data are available[1], or Novelia® bottles which innovative insert maintains sterility after opening (no stability data available).

## Purpose

To collect data on VED stability in 3 different containers in order to switch if necessary: Amber glass, HDPE bottles and Novelia® bottles stored frozen (-20°C) and refrigerated once thawed.

## Material and Methods

Voriconazole concentration was assessed using a stability-indicating HPLC-UV Diode-Array-Detector method (Ultimate 3000® Thermo Scientific, France).

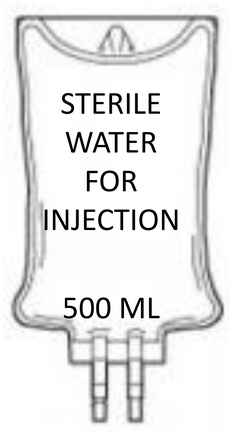
Racemization (impurity D-(2S,3R)-voriconazole) was detected by chiral HPLC (Waters 600®, Guyancourt, France)

European Pharmacopoeia 2.9.19 apparatus (light obscuration particle count test (APSS-2000, Particle measuring systems, Boulder, USA) was used for non visible particle count.

Containers were statistically compared using appropriate non parametric tests (α<5%).

**Compounding of Voriconazole eye drops at 10mg/mL (1%)**

Three batches of VED (10mL) were aseptically compounded and **stored at -20°C** in 3 different containers:
Amber glass (N = 32, Gravis®), HDPE bottles (N = 32, CAT®) and Novelia® bottles (N = 31,Nemera®)




Sterile water for injection (BAXTER®)


Vfend® (PFIZER®)

**Stability study led according to the GERPAC-SFPC stability studies guidelines**

D0 D1 D3 D7 D14 D21 D52 D85 D100

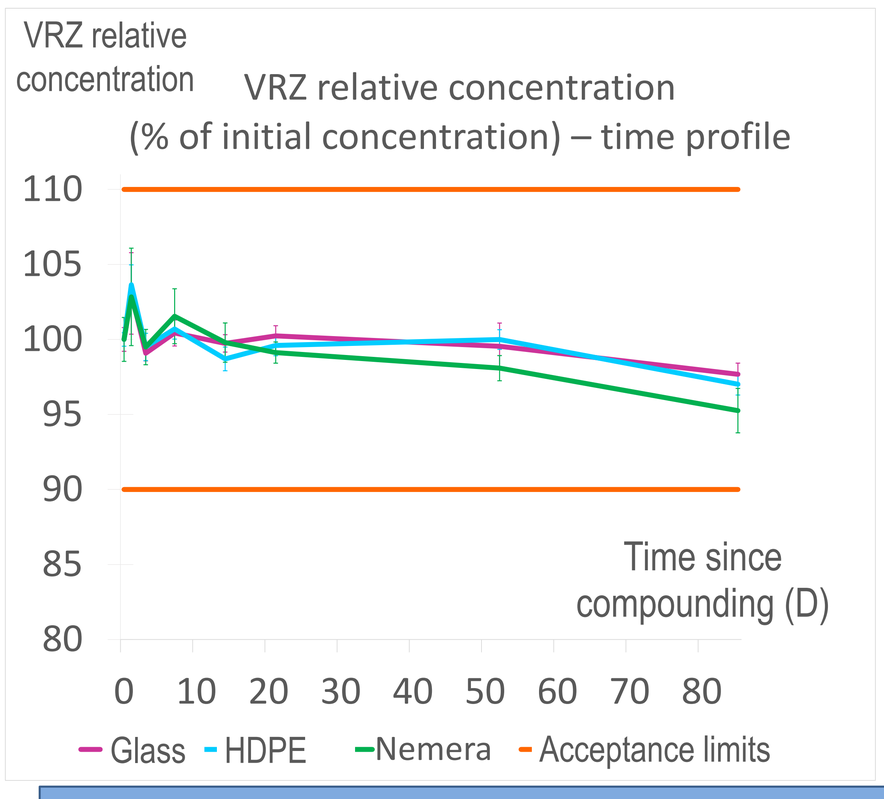
Frozen (-20°C) → 2-8°C

At each time point: Analyses performed in triplicates after thawing
- Visual aspect
- Voriconazole relative concentration (% of initial concentration)
- pH
- Osmolality

At D0 and D85:
- Signs of racemization (quantification of impurity D),
- Non-visible particles count for particle size ≥10µm and ≥25µm
- Sterility assay (performed in duplicate)

Parameters were measured :
- when stored for three months at -20°C,
- then thawed, after 15 days at +2-+8°C, comparing two thawing methods (2-8°C for 6 hours or 25°C for 2 hours)

## Results




| | D0 Amber glass | D85 Amber glass | D0 HDPE bottles | D85 HDPE bottles | D0 Nemera | D85 Nemera |
|---|---|---|---|---|---|---|
| Osmolality (mOsm/kg) | 533.3 | 533.2 | 530.4 | 522.2 | 532.5 | 517.5 |
| pH | 6.31 | 6.38 | 6.32 | 6.34 | 6.33 | 6.33 |
| Particles >10µm (particle/mL) | 8.93 | 70.27 | 25.33 | 11.73 | 34.13 | 24.73 |
| Particles>25µm (particle/mL) | 1 | 3.13 | 5.27 | 0.93 | 5.33 | 1.53 |

## Discussion

pH and osmolality remained stable (NS).
Sterility was preserved with no change in visual aspect.
Counts of ≥ 10µm particles remained inferior to 80 particles /mL.
About Voriconazole degradation products (unknown toxicity), areas increased by maximum 1.45 , remaining unquantifiable.
Impact of thawing method on stability was not evidenced.
Impurity D was not detected (LOD=0.3µg/mL) : no racemization was shown.

**During storage at -20°C:**
- Concentration was between 95.2 ± 1.4% and 103.6 ± 1.3% of initial concentration (Co) (Non significant (NS))

**Fifteen days after thawing:**
- Concentration was between 97.1 ± 1.6% and 98.6 ± 0.8% of Co (NS)

## Conclusion

**Voriconazole eye drops remained stable up to three months at -20°C and fifteen days after thawing (stored at 2-8°C).**
**No notable difference was evidenced between the three containers, allowing to chose the most suitable.**

[1] Amoros-Reboredo P. *et al*. Stability of frozen 1% voriconazole ophthalmic solution. Am J Health Syst Pharm (2015);72(6):479-82

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22nd Congress of the EAHP
March 22-24, 2017, Cannes

UNIVERSITÄTSmedizin. MAINZ
Pharmacy
Inga Ulmer, Claudia Mildner, Irene Krämer

# Feasibility of utilization and patient satisfaction with a nationwide standardized electronic medication plan

## Background

The loss of information about hospital patients' medication during admission and discharge implies a challenge for patients and healthcare providers. Taking the patients' drug history by a face-to-face interview is routinely done in the hospital but more reliable sources such as standardized medication plans are necessary to improve medication and patient safety.

Since October 2016, every patient in Germany taking 3 or more chronic medications is entitled to the nationwide standardized medication plan which is to be compiled by their general practitioner.

The medication plan provides information on the active ingredient (1), brand name of the medicinal product (2), dosage (3), dose frequency (4), medical indication (6) and how to apply the medication correctly (5).

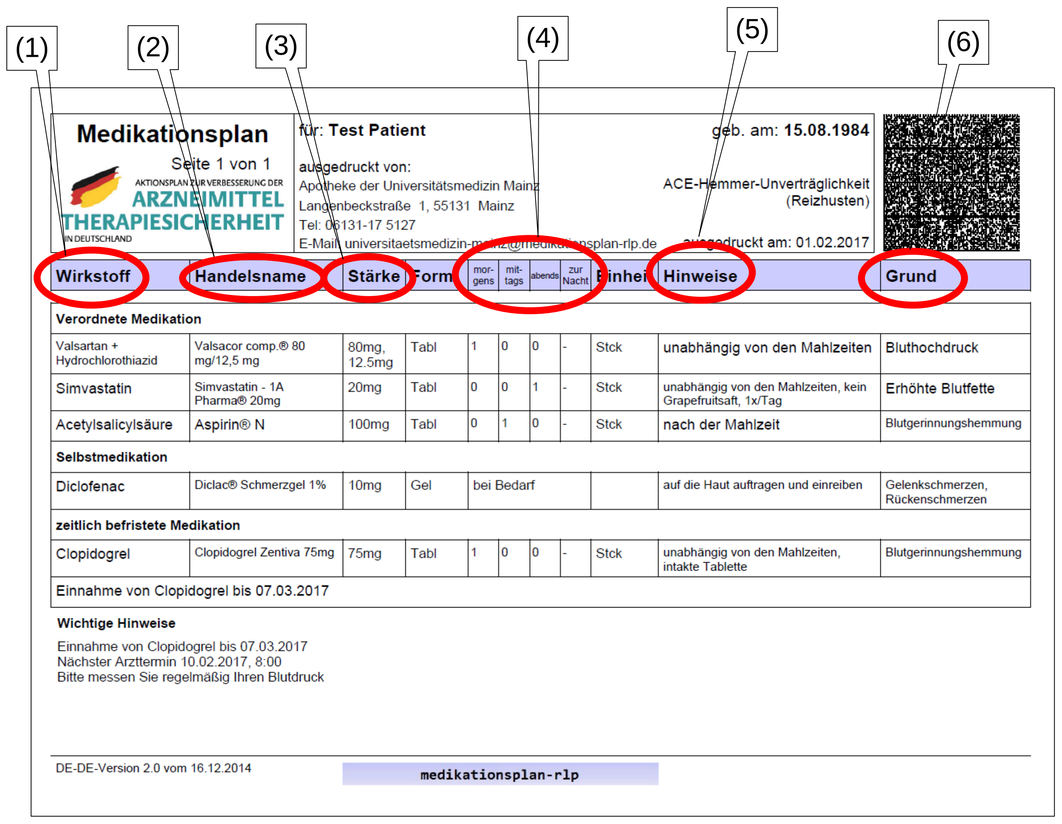


*Figure 1 German nationwide standardized medication plan*

## Purpose

The innovative, nationwide standardized electronic (e-) medication plan was evaluated in a pilot project regarding feasibility and usefulness for 600 patients in Rhineland-Palatinate, Germany. The primary physicians' and local pharmacists' utilization of the e-medication plan during the first 6 months after discharge and patients' and healthcare providers' satisfaction should be evaluated.

## Materials and methods

<u>During hospital stay</u>
- Study enrollment of patients in 5 hospitals in Rhineland-Palatinate, Germany
- Hospital pharmacist compiles medication plan in the web-based program especially set up for the project
- Medication reconciliation

<u>At discharge</u>
- Patient counselling concerning the drug therapy and medication plan
- Delivering the printed medication plan to the patient

<u>After discharge</u>
- For 6 months: routine update of the e-medication plans by local pharmacists and/or general practitioners & delivering printed version to the patients
- Interview concerning feasibility and satisfaction with the e-medication plan (written questionnaire):
  - Patients: 2 weeks and 6 months after discharge
  - Local pharmacists, physicians: 6 months after discharge

## Results

An interim analysis included interviews with 387 patients, 128 pharmacists and 55 general practitioners. The patient interviews two weeks after hospital discharge indicate that the broad majority of patients was satisfied with content and comprehensibility of the medication plan and has gained new information on indication or proper administration of their medicines.

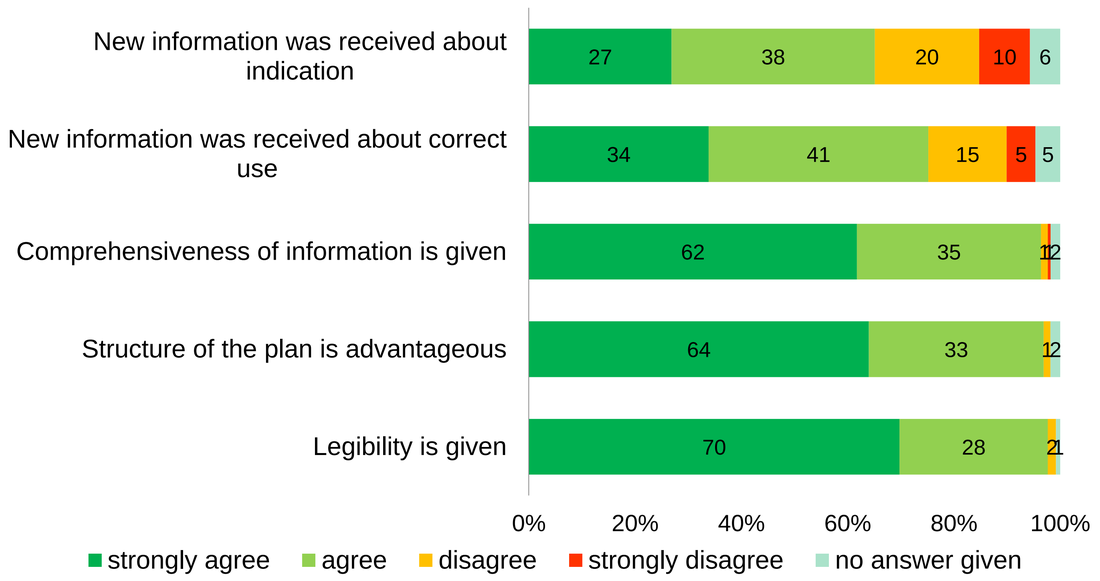


*Figure 2 Results of interviews with patients 2 weeks after hospital discharge (n=387)*

Pharmacists and physicians are mostly satisfied with this new tool to facilitate communication between pharmacists, doctors and patients.

## Conclusions

The utilization of the standardized e-medication plan is feasible in the inpatient and outpatient setting. Patients acknowledged the useful design and content of the medication plan and have a better understanding of their medication. Healthcare providers acknowledged the availability of comprehensive information about the patients' medication.