MEDINOXX

Quality and Sustainability

Contents

The **Safe** Medication Management

Throughout the development of our patented Medinoxx sealed cup system, special attention was given to the quality and pharmaceutical compliance of the product and its materials. This claim is supported by regular certification and testing done by the Central Laboratory of German Pharmacists (ZL).

For us, sustainability and environmental protection are just as important as the quality of our products. For this reason, we use long-lasting reusable resources and single-variety, easily recyclable materials.

Additionally, our competence pharmacies provide us with necessary feedback so that we can adapt our system to meet the ever-changing demands of modern pharmacies.

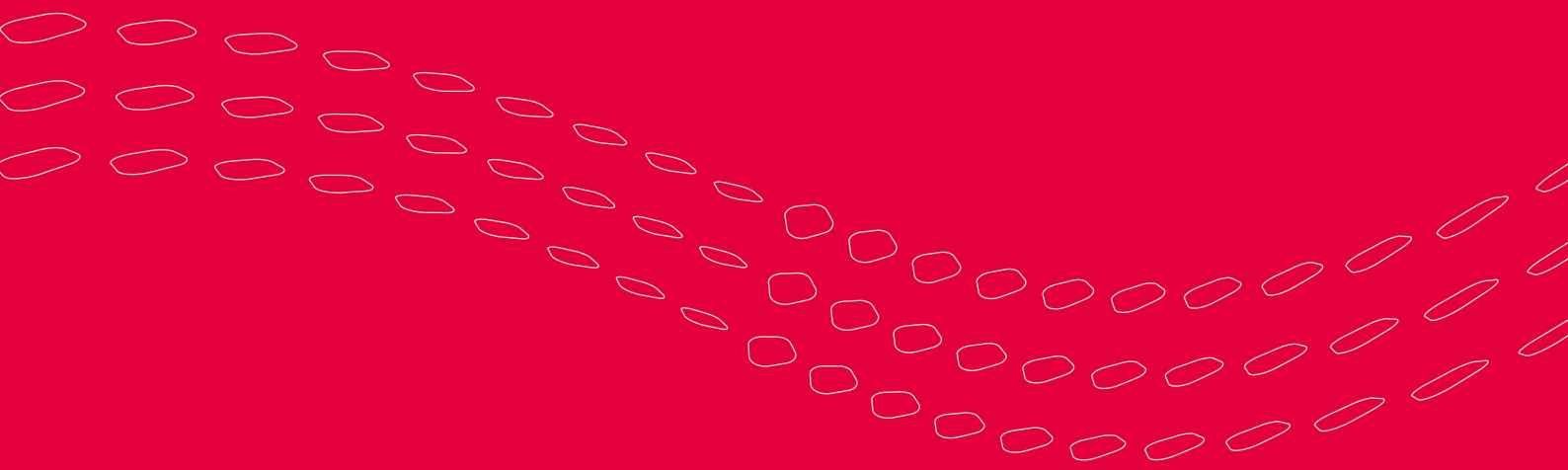
Münster Pharmacy, Titisee-Neustadt - Germany

Pharmacist
Dr. rer. nat. Michael Kunkel

“For us, quality comes first when managing medication for patients. The Medinoxx cup system works with tested and certified materials and it has an effective one-way distribution from the manufacturing pharmacy directly to the patient.“

ZL Short Report I

Stability of liquid and solid pharmaceuticals
Microbiological stability of liquids



Guaranteed stability of sealed solid pharmaceuticals over a period of 31 days

Guaranteed microbiological stability of sealed liquids over a period of 31 days

Short Report I

Assessing the pharmaceutical quality of the Medinoxx medication system

The Medinoxx medication system, being composed of a tray-cup system sealed with a foil, represents a newly developed blistering system for the patient-individualized dosing of tablets, capsules and for the first time also liquids.
On behalf of Medinoxx GmbH the Central Laboratory of German Pharmacists conducted a study on the pharmaceutical quality of this new blistering system in the time from February until August 2016.

In particular the study was dedicated to:

a) collect data on the stability of representative liquid as well as solid dosage forms

b) check the microbiological stability of exemplary liquid formulations

c) determine potential extractables under extreme conditions

1. Stability of blistered finished products

1.1 Stability of liquids in the blistering system

Liquid finished products containing melperone and pipamperone as active ingredients were blistered individually and stored under controlled conditions in a climate chamber at 25°C / 60 % RH for a total period of 31 days..

Table 1: Overview on the investigated products and the results obtained for content and pH

Product	Content			pH-value		
	t-zero [% of declaration]	t-10d [% of declaration]	t-31d [% of declaration]	t-zero	t-10d	t-31d
Pipamperon neuraxpharm®	99,4 ± 0,4	98,4 ± 0,4	101,2 ± 0,3	3,3	3,3	3,2
Pipamperon Hexal®	101,1 ± 0,3	100,7 ± 0,6	104,3 ± 0,4	2,9	3,0	2,9
Dipiperon®	102,2 ± 0,3	101,6 ± 0,2	104,6 ± 0,4	2,8	2,9	2,8
Melperon neuraxpharm forte®	102,3 ± 0,7	101,9 ± 0,2	102,6 ± 0,2	2,7	2,7	2,7
Melperon STADA®	102,9 ± 0,4	102,4 ± 0,8	104,8 ± 0,5	3,0	3,0	3,0
Melperon ratiopharm®	101,3 ± 1,7	102,1 ± 0,6	104,9 ± 0,1	3,4	3,0	3,0

Based on content and pH determination the physicochemical stability could be verified for all investigated liquid preparations over a period of 31 days.

1.2 Stability of solid finished products after simultaneous blistering

In addition the stability of three representative solid finished products was studied after simultaneous blistering in the tray-cup system. For this purpose ASS 100 mg HEXAL® tablets were simultaneously blistered with L-Thyroxin-Na ratiopharm® 100 µg tablets and Aciclovir ratiopharm® 200 mg tablets and stored under controlled conditions in a climate chamber at 25°C / 60 % RH for a total period of 31 days.

Table 2: Overview on the investigated products and the results obtained for content and mass uniformity

Product	Content		Mass uniformity			
	t-zero [% of declaration]	t-31d [% of declaration]	t-zero [mg]		t-10d	
L-Thyroxin-Na ratiopharm® 100 µg	82,2 ± 1,0	80,2 ± 1,2	Av. Min. Max	131,3 129,7 133,0 OK	Av. Min. Max.	134,4 132,0 136,1 OK
Aciclovir ratiopharm® 200 mg	99,5 ± 0,5	98,9 ± 0,7	Av. Min. Max.	504,3 500,2 509,6 OK	Av. Min. Max.	506,1 490,4 512,8 OK
ASS 100 mg Hexal®	101,6 ± 1,9 *	100,0 ± 1,4 *	Av. Min. Max.	158,0 152,9 165,3 OK	Av. Min. Max.	159,1 155,0 165,8 OK

* because of a laboratory mistake the content of ASS was determined separately in the frame of a repetitive analysis after renewed simultaneous blistering with L-Thyroxin-Na ratiopharm 100 µg and Aciclovir 100 mg Hexal

The determined contents and the proven mass uniformity for all investigated finished products clearly confirm the physicochemical stability of ASS mg Hexal® in case of simultaneous blistering with L-Thyroxin-Na ratiopharm® 100 µg and Aciclovir ratiopharm® 200 mg in the medication cup with foil seal over a period of 31 days and storage at room temperature (25 °C / 60 % RH).

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2. Microbiological stability of liquids in the blistering system

In order to investigate the microbiological stability of liquid drugs three representative liquid finished products with different active ingredients were individually blistered and stored under controlled conditions in the climate chamber at 25 °C / 60 % RH for a period of 31 days.

Assessing the pharmaceutical quality of the Medinoxx medication system

Table 3: Overview on the investigated products and the results obtained for the microbiological stability

Test parameter:	Results (t0, t10 and t31) TAMC	TYMC	specified microorganisms
Method: Ph. Eur. 8.6	2.6.12	2.6.12	101,2 ± 0,3
Specifications: Ph. Eur. 8.6, 5.1.4	10^2 CFU / ml ≙ 200 CFU / ml	10^1 CFU / ml ≙ 20 CFU / ml	**Escherichia coli:** absence / ml
Product			
Lactulose-Stada	< 2 CFU / ml	< 2 CFU / ml	absent
Lactulose ratiopharm	< 2 CFU / ml	< 2 CFU / ml	absent
Lactulose Saar	< 2 CFU / ml	< 2 CFU / ml	absent
Lactuflor	< 2 CFU / ml	< 2 CFU / ml	absent
Bifiteral	< 2 CFU / ml	< 2 CFU / ml	absent
Pipamperon neuraxpharm	< 2 CFU / ml	< 2 CFU / ml	absent
Pipamperon Hexal	< 2 CFU / ml	< 2 CFU / ml	absent
Dipiperon	< 2 CFU / ml	< 2 CFU / ml	absent
Melperon neuraxpharm forte	< 13 CFU / ml	< 5 CFU / ml	absent
Melneurin Hexal	< 13 CFU / ml	< 5 CFU / ml	absent
Melperon ratiopharm	< 13 CFU / ml	< 5 CFU / ml	absent

The above results verify the microbiological stability of all investigated liquid finished products over a period of 31 days.

18.02.2021
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Qualified Person

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ZL Short Report II

Stability of liquid Sodium Metamizole /
Novaminsulfon drops / dipyrone

Guaranteed stability of sealed Sodium Metamizole drops over a period of 31 days

Suitable for all liquid pharmaceuticals containing Sodium Metamizole

Short Report II

Assessing the pharmaceutical quality of blistered Novaminsulfon drops in Medinoxx medication system

ZL

1. Stability of blistered Novaminsulfon 500 mg Lichtenstein drops

The industrially manufactured liquid medicine „Novaminsulfon 500 mg Lichtenstein oral drops“ contains the analgesic metamizole sodium. Since this analgesic has a wide field of application and is often prescribed, the drops were blistered and stored under controlled conditions in a climate chamber at 25°C / 60 % RH for a total period of 30 days.

1.1 Examination of the content

Table 1: Overview on the results obtained for content

Product	Content		
	t-zero [% of declaration]	t-10d [% of declaration]	t-31d [% of declaration]
Novaminsulfon® 500 mg Lichtenstein oral drops	102,2 ± 5,6	99,8 ± 1,9	103,2 ± 3,8

Based on content the physicochemical stability could be verified for the industrially manufactured liquid medicine „Novaminsulfon 500 mg Lichtenstein oral drops“ over a period of 30 days.

1.2 Microbiological stability

Table 2: Overview on the results obtained for the microbiological stability (test parameters according to Ph. Eur. 9.3. 2.6.12 TAMC and TYMC (specification according to Ph. Eur. 9.3 5.1.4 TAMC 102 CFU / ml = 200 CFU / ml and TYMC 101 CFU / ml = 20 CFU / ml) and Ph. Eur. 9.3 2.6.13 absence of Escherichia coli (detection limit 10 CFU / ml))

Product	TAMC			TYMC			specified microorganisms: Escherichia coli
	t-zero	t-9d	t-30d	t-Null	t-9d	t-30d	t-zero, t-9d and t-30d
Novaminsulfon® 500 mg Lichtenstein oral drops	2 CFU/ml	< 2 CFU/ml	< 2 CFU/ml	8 CFU/ml	< 2 CFU/ml	< 2 CFU/ml	absent

The above results verify the microbiological stability of the liquid industrially manufacturing medicine „Novaminsulfon 500 mg Lichtenstein oral drops“ over a period of 30 days.

2. Conclusion

The above studies have clearly demonstrated the suitability of the Medinoxx medication system for the blistering of the industrially manufactured liquid medicine „Novaminsulfon 500 mg Lichtenstein oral drops“. It can be assumed that the medication system is likewise suitable for further liquid industrially manufacturing medicine with metamizole sodium as active substance present an the German market.

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ZL Short Report III

Extractables in Medi-Cups and Seals

No extractable substances with
alcohol based liquid medication

Short Report III

Extractables in Medi-Cups and Seals

The investigation focused on substances that can potentially be extracted from the Medi-Cups and the seals under extreme conditions. Under certain circumstances, these extractables can have a negative impact on the quality of the products blistered with seals in the Medi-Cups.

In order to analyse the identity and quantity of extractables from the blister packaging as comprehensively as possible, various methods were used to extract the substances, their subsequent chromatographic separation and detection.

- HS-GC/MS analytics – determination of volatile components
- GC-FID/MS analytics - determination of semi-volatile components
- HPLC-DAD/MS analytics – determination of non-volatile components

The following solvents with different polarity were tested for the extraction of substances from the Medi-Cups and the seal: 20 % (v/v) aqueous ethanol, isopropyl alcohol and n-hexane. The selected solvents isopropyl alcohol and n-hexane are suitable for the extraction of „non-volatile and less volatile substances". They reflect so-called „worst-case" conditions.

Design of the Extractables study at a glance

Material	Extraction solvent	Tray and seal Extraction conditions	Detection techniques
Tray and seal N=1	20 % (V/V) Ethanol in water	Static extraction in a bottle for 24 h at 40 °C	GC-MS/FID HPLC-DAD/MS (APCI, +/-)
	Isopropanol	Soxhlet extraction for 24 h	
	n-Hexan		
	none	Thermal Extraction for 1 h at 80 °C	HS-GC/MS

Conclusion:
Based on the results obtained, it cannot be assumed that substances can be extracted from the system when ethanolic solutions are bottled. Solvents such as hexane or isopropanol (e.g. for cleaning purposes in terms of reusability) should be excluded. The results of the study show that the seals are not resistant to these solvents.

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ZL Short Report IV

Microbiological contamination of Medi-Trays

Wearing gloves significantly reduces contamination

Acceptable levels of contamination can be achieved with 3-week cleaning intervals.

Short Report IV

Microbiological contamination of the Medi-Trays and cleaning advise

ZL

On behalf of Medinoxx, their Medi-Trays were tested for germ contamination in the Central Laboratory of German Pharmacists in order to clarify whether:

1. the disinfectants normally used to disinfect the Medi-Trays are sufficiently effective in the case of high microbiological contamination

2. the microbiological contamination of the Medi-Trays is so low after one week of use without intermediate cleaning or disinfection that the frequency of disinfection can be reduced to a minimum

Effectiveness of the disinfectants used

To clarify question 1, the two alcohol-based disinfectants Bacillol 30 Foam from Bode Chemie and MyClean DS without spray head from MalMed GmbH as well as the aldehyde-alcohol-free disinfectant DESTAsept SW sensitive from Dometra were tested in accordance with the germ carrier test of the Association for Applied Hygiene (VAH) without mechanical action (without wipe disinfection) on a Gram negative (Pseudomonas aeruginosa) and a Gram positive bacterium (Staphylcoccus aureus) as well as a yeast fungus (Candida albicans) with medical relevance.

The results show that when all three disinfectants were applied for 1 minute, the bacterial count was reduced by 5 and 4 log levels, respectively, as required by the VAH. In case of a contact time of 30 seconds Bacillol 30 Foam reduced the Staphylococcus aureus count by only 3 log levels. General adherence to a 1 min exposure time is therefore recommended.

Determination of microbiological contamination

To estimate the extent of contamination attributed to filling and dispensing of Medi-Trays by pharmacy and nursing staff and from patient use, swab samples were taken from eight locations on the Medi-Trays (six in the front and two in the back) where the highest risk of contamination was suspected. One nursing station of a clinic and three senior centres participated in the study.

Under conditions of no cleaning over the seven-week study period, the detected bioburden was relatively low. The greatest bioburden was detected in the front area of the Medi-Trays, which is frequently touched by hands during filling and dispensing. Mainly three types of germs were detected: Molds, aerobic spore formers and cocci. The number of cocci, which remained at a constant level during the study, was due to natural colonization of the skin and not wearing gloves or not disinfecting worn gloves. In contrast, the initially high contamination of spore formers decreased continuously from week to week, indicating a low survivability of spores on the Medi-Trays. The number of yeasts and molds, on the other hand, increased continuously and reached its maximum in week 7, which can be attributed to the missing cleaning.

Conclusion

Safe disinfection of the Medi-Trays according to the instructions of the disinfectant manufacturer is ensured.

Disinfection of hands and wearing of gloves when filling and placing the blisters is recommended to avoid contamination of the trays with cocci.

If cleaning is carried out in accordance with Medinoxx instructions, the cleaning interval can be extended to a period of three weeks on a risk-based basis.

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A recent study conducted by FiGuS GmbH (Research Institute for Health and System design) and HILSE:KONZEPT (Management and Communication Consulting) has shown that full inpatient care facilities can achieve significant cost reductions by working with packaged liquid drugs as well as solid pharmaceuticals.

Cost Savings by including **Liquid Medication**

Results of the Study

For this survey, six representative care homes were used. On average, 7.33 residents received liquid medication. In a month, the average amount of medication per patient was 16.59. This was due to some residents receiving up to 5 doses per day, while others received liquid medication only a few times per month. Overall, 44 residents received 730 single liquid doses in a period of 4 weeks.

The time for preparation and handing over was measured. In total, 695 minutes were required for the preparation of the medication. Another 1451 minutes were required for the delivery of the medication to the patient. Therefore, the overall time per manually delivered liquid medication was 3 minutes. Medinoxx offers the possibility to include all pharmaceuticals on the market and allows facilities to safe 3 minutes per dosage.

Economic Evaluation: Realising the Potential for High Savings

If we consider average care home and labour costs in Germany, the savings add up to €130 per patient. The final result is over €4500 in total savings per month in a representative care home with 60 residents.

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The Medinoxx Philosophy - **Environment and Sustainability**

Reduce. Reuse. Recycle. For a cleaner environment.

Environmental consciousness and sustainability are more than just a cooperate philosophy. For us, it is a personal matter.

For this reason, we are not simply limiting our environmental concerns to our products. We endeavour to act as environmentally friendly and responsible as possible in all areas.
The Medinoxx medication management system was developed according to this principle.

CLIMATE NEUTRAL
COMPANY
certified by Fokus Zukunft

Medinoxx is **Climate Neutral**

We are proud to be a certified climate neutral company and we acknowledge the responsibility that accompanies the use and recycling of raw materials.

Greenhouse gases and other pollutants affect the whole world. The most sensible way to cope with this is to focus on achieving the biggest positive impact while using the least resources and creating the least costs. By supporting projects in emerging markets and developing countries, we can contribute to improving their economic, ecological and social climates, therefore doing our part in fulfilling the United Nations sustainable development goals.

Emission trading is a vital tool for emerging markets to invest in new, green technologies in order to develop a sustainable and ecological economy. Therefore, Medinoxx has collected all the relevant information needed to determine the greenhouse emission of our company and services contribute. These are compensated by climate protection certificates, which are in turn used to fund innovative projects in Africa, South America, and Asia.

Why should we do that? Because we understood what was demonstrated conclusively by the World Climate Council: Avoiding greenhouse emission only costs about 0.6% of total annual reserves, while the costs of climate change, both financial and non-financial, will be significantly more detrimental if we continue as we have in the past.

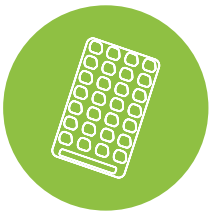
Medinoxx, Innsbruck

CEO Jens Häfner, B.A. (Hons)

„In the context of sustainability and environmental protection for the next generation, careful handling of raw materials is of particular importance. As far as is justifiable, in the context of medical safety, waste must be reduced or avoided altogether."

Reduce | **Re**use | **Re**cycle

Reduce: Modular System
Only use the number of Medi-Cups required. This way, you can save on costs and waste.



Reuse: Medi-Trays
Medinoxx sealed cups offer the first and only solution for reusable trays. Easy to recycle materials are used as necessary. In comparison to similar systems, Medinoxx is able to avoid up to 95% of plastic waste over a 3-year period.

Recycle: Medi-Cups
The patented Medi-Cup is made from single-variety materials which can be easily separated. Therefore, they can all be completely sorted and recycled in an easy and efficient way.

Certified Production
In the Medinoxx manufacturing plants, production is carried out exclusively in accordance with the standard for primary packaging materials DIN EN ISO 15378, which was developed from the QM systems ISO 9001 and GMP, and the guideline of the German Federal Chamber of Pharmacists "Testing and Storage of Primary Packaging Materials" in an environmentally friendly manner.

Modern Medication Management.

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