Short report 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. OK	131,3 129,7 133,0	Av. Min. Max. OK	134,4 132,0 136,1
Aciclovir ratiopharm® 200 mg	99,5 ± 0,5	98,9 ± 0,7	Av. Min. Max. OK	504,3 500,2 509,6	Av. Min. Max. OK	506,1 490,4 512,8
ASS 100 mg Hexal®	101,6 ± 1,9 *	100,0 ± 1,4 *	Av. Min. Max. OK	158,0 152,9 165,3	Av. Min. Max. OK	159,1 155,0 165,8

* 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).

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.

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

Test parameter:	**Results (t_0, t_{10} und t_{31})**		
	TAMC	**TYMC**	**specified microorganisms**
Method: Ph. Eur. 8.6	2.6.12	2.6.12	2.6.13
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
Lactuflor	< 2 CFU / ml	< 2 CFU / ml	absent
Lactulose Saar	< 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.

3. Extractables

“Extractables” represent potential “leachables” (reaction partners for the packaged drugs) and may thus exert an influence on product quality.
Based on that background it was additionally investigated which theoretically possible extractables may be extracted from the blistering system under extreme conditions.
In order to extensively analyse the identity and the quantity of extractable substances from the blister packaging, several analytical methods were applied for extraction and subsequent chromatographic separation and detection

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

For the extraction of substances from the cup and seal foil the following different solvents of different polarity were tested: 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 and reflect so-called “worst-case” conditions.

Table 4: Overview on the design of the extractable study

Cup and foil			
Material	Extraction solvent	Extraction conditions	Detection method
Cup and foil 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, +/-)
	isopropyl alcohol	Soxhlet extraction for 24 h	
	n-hexane		
	none	Thermical extraction for 1 h at 80 °C	HS-GC/MS

In the frame of this study extractable substances (and their concentrations) were detected, the risk of which associated with oral administration has to be evaluated or derived from available data / long term studies.

Based on the above results it is not expected that substances are extracted from the blistering package upon filling ethanolic solutions into the blistering system.

On the other hand solvents as hexane or isopropyl alcohol (applied e.g. for cleaning purposes in terms of reuse) should be excluded. As demonstrated by the present study the foils reveal not to be resistant to these solvents.

4. Conclusion

In general the present study revealed the suitability of the Medinoxx® medication system for blistering the solid as well as liquid medications tested above. Moreover no extractable substances are to be expected upon blistering alcoholic liquid drugs.