Examination of a new method for analysing identity and concentration of drugs in ready-to-use preparations – proof of concepts of the DrugLog® system

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Background and importance

The increasing awareness of the necessity of safety in drug therapyand at the same time immense skills shortages pose new challenges for hospital pharmacies. The number of ready-to-use preparations increase especially in high risk fields such as Oncology and Pediatric medicine. For the immediate quality control in accordance with the German and European Pharmacopoeia, there is a need for analytical methods which do not require large volumes for testing and which were safety and fast by processing accurate results. Pharmacolog (Upsala, Sweden) promotes the UV/Vis spectrometer DrugLog® **(figure 1)** with these features.

figure 1: DrugLog ®-System; (Pharmacolog, Sweden)

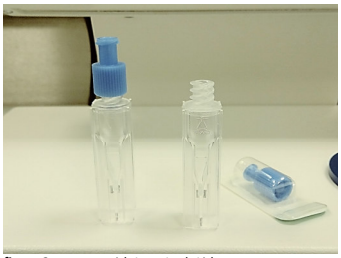

figure 2: cuvette with Luer-Lock-Lid

Aims and objectives

The aims of examining DrugLog® were to test the reliability and precision of the method as well as process optimization in the quality control department. As part of this, the sample extraction without further processing in terms of everyday usability and safety, especially in the analysis of cytostatic drugs was examined.

Material and methods

The drugs norepinephrine, midazolam, atropine and cytarabine were tested during the first step. Standard curves of each drug were created in the system **(table 1)**.
Samples of ready-to-use preparations (pre-filled syringes (pfs) and infusion-flasks (inf.fl)) were analysed without further processing with 0.5 ml sample volumes each in micro UV single-use cuvettes with a lid.
For preparations of cytarabine special cuvettes with Luer-Lock-lid were used **(figure 2)**.
The content as well as the identity of the drugs were determined simultaneously in the instrument.

Table 1: Overview of tested active ingredients

Active ingredient	Calibration-range	Ready-to-use-preparation
Noradrenalin	8 µg/mL – 120 µg/mL	Noradrenalin 0,01 mg/mL pfs Noradrenalin 0,1 mg/mL pfs
Midazolam	0,8 mg/mL – 2,2 mg/mL	Midazolam 1 mg/mL pfs
Atropin	20 µg/mL – 70 µg/mL	Atropin 0,05 mg/mL pfs
Cytarabin	0,2 mg/mL – 1,0 mg/mL	Cytarabin 200 mg/500 mL inf. fl

Comparison of methods

The method of the DrugLog® system was compared to the established UV-Vis-spectroscopy using the example of Midazolam **(table 2)**.

Table 2: Comparison of method and precision

	Evolution 201 (Thermo scientific)	DrugLog® (Pharmacolog)
Concentration (Midazolam)	0,005 mg/mL	1,0 mg/mL
Number of determination (n)	15	9
Average amount %	100,76	105,00
coefficient of variation (cv) %	1,015	0,635

Results

All tested substances could be analysed reliably with the new method, even atropine in the minimum concentration of 0.05 mg/mL with low UV absorption (not shown as figure).
The total time required for analyses was reduced by 50-75% compared to the established UV-Vis analysis depending on the analysed drug.
The cytostatic ingredient cytarabine could be analysed without cytotoxic contamination of staff or equipment.

Measurement of cytostatic ingredients (Cytarabine)

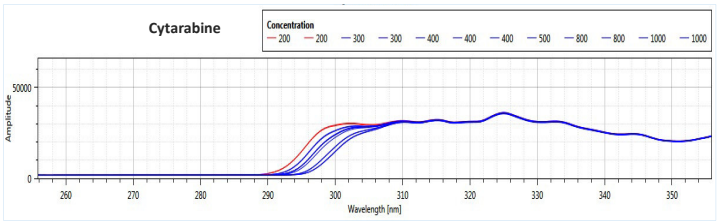

Fig. 3a: Cytarabine - Raw spectrum as transmission

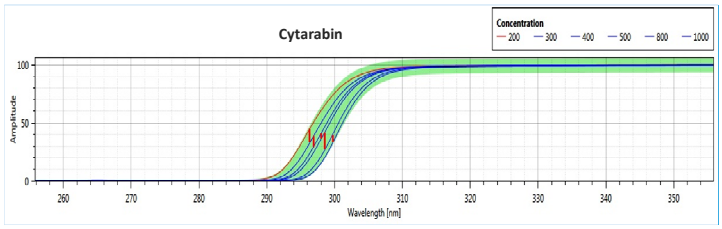

Fig. 3b: Cytarabine – margin of the standard-concentrations

Preparations in Infusionflask

To quantify cytarabine, the overfilling of the diluent is of particular importance **(Table 4).**

Diluent volume:
as specified by the manufacturer: 510 - 518 mL
Experimentally verified: 524 - 527 mL

Table 4: Cytarabine of quantification

Preparation	Concentration Labeled [µg/mL]	Measured value [µg/mL]	Amount found [%]	Amount found after volume correction [%]
A	395,3	373,4	94,5	95,9
B	384,3	371,8	96,8	98,3
C	393,4	379,0	96,3	97,8
Ø	391,0 µg/mL	374,7 µg/mL	95,9 %	97,3 %

Conclusion and relevance

DrugLog® simplifies processing, provides maximum work safety when dealing with cytotoxic drugs and ensures valid results for the tested drugs. Each drug requires a separate calibration. For substances without UV activity or very similar spectra, the methodology has limitations. Future investigation is planned in particular for the application in pediatric settings.

References:
- F. Feutry, A. Exquis, L. Falaschi: Evaluation of a new quality-control system for cytotoxics based on UV-visible spectrophotometry (DrugLog®); 18th GERPAC Conference,13th European GERPAC, Pharmaceutical Technology: Quality & Security, Octobre 7-9, 2015
- S. Kromidas: Validierung in der Analytik; 2. Auflage 2011; Wiley-VCH Verlag
- European Pharmacopeia; Edition 9.0

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