

Preparation and Quality Control of 3D printed Spironolactone Gel-Tablets for Paediatric Patients

¹Department of Pharmacy, University Medical Center of the Johannes Gutenberg University, Mainz, Germany

²Institute of Pharmaceutical and Biomedical Sciences, Johannes Gutenberg University, Staudingerweg 5, 55128 Mainz, Germany

Background and Importance

Spironolactone is widely used in paediatric patients with heart failure. 3D printing offers the opportunity to prepare single-dose tablets in pharmacies in patient-individual doses over a wide range. Advantages of 3D printed gel tablets include precise dosing, easy administration, improved palatability and easier swallowing, what is especially important for paediatric patients.

Aim and Objectives

Our aim was to develop and validate a stability-indicating HPLC method suitable for analyzing the content of 3D-printed spironolactone gel tablets. With the newly developed analytical method, the process of 3D-printing spironolactone gel-tablets with a wide range of drug load, was validated.

Materials and Methods

Spironolactone and polysorbate 80 (Caesar & Loretz GmbH) were mixed with Curablend® gel tablet excipient base (CSS; CurifyLabs Oy, Helsinki, Finland) by centrifugation at 2600 rpm for 10 minutes (see **Table 1**). The resulting printing ink was transferred into a syringe and placed in the 3D printer (CSS; CurifyLabs Oy, Finland,) where after 15 minutes of pre-heating it was printed at 41°C into PVC blisters (Gako Deutschland GmbH, Germany). On three different days, a batch (30 tablets) of 4 mg, 10 mg, and 20 mg spironolactone gel-tablets was prepared each. (see **Table 2 Figure 1**)

Table 1: Printing ink composition

Material	Proportion (m/m%)
Spironolactone	2
Polysorbate 80	2,6
Curablend	95.4

Table 2: Tablets printed for production validation

Spironolactone dose (mg)	Nominal weight per tablet (mg)	Number of printed tablets per day
4	200	30
10	500	30
20	1000	30



Figure 1: Spironolactone gel-tablets

Validation of the HPLC assay

Spironolactone (SP) CRS (EDQM) was dissolved in a 50:50 acetonitrile (Solstice Advanced Materials US, USA): water (Fisher Scientific GmbH, Germany) mixture to create a SP standard solution (SPSS). A seven-point calibration curve was established by injecting aliquots of 25, 40, 45, 50, 55, 60, 75 ppm SPSS in triplicate. Intra- and inter-day precision was determined by injecting 10 aliquots of 50 ppm SPSS in triplicate on 3 different days. Method accuracy was determined by percentage recovery of SP in 45, 50, and 55 ppm SPSS aliquots assayed on each day. Chromatographic conditions are shown in **Table 3**.

Content Uniformity of Spironolactone gel-tablets

10 tablets of each strength and batch were randomly chosen and dissolved each in 50:50 acetonitrile:water mixture by ultrasound sonification for 10 minutes at 40°C, diluted to a nominal concentration of 50 ppm spironolactone, filtered through a 0.22 µm RC syringe filter (Wicom Germany GmbH, Germany) into HPLC vials, and aliquots assayed in triplicate. Placebo tablets were assayed to exclude the possibility of overlapping peaks of spironolactone and excipients. The stability-indicating nature of the assay was proven by forced degradation studies.

Results

UV-HPLC Assay Validation

Linearity of the calibration curve was proven by **R² 0.9993**.

Intra and inter-day precision, as well as accuracy tests of the analytical method met the specifications set. Results are shown in **Table 4**.

Placebo tablets and forced degradation measurements did not show overlapping peaks with the spironolactone peak. (See **Figure 2**)

Table 4: HPLC assay validation. (RSD=relative standard deviation)

Parameter (Acceptance criterion)		Day1	Day2	Day3
Average spironolactone recovery (%) n=30		99.68%	98.84%	99.79%
Intraday precision (RSD) (RSD <2%), n=30		0.084%	0.116%	0.150%
Interday precision (RSD) (RSD <2%), n=30		0.4375%		
Accuracy (SP recovery 95-105%), n=9	45 ppm	100.11%	101.56%	100.94%
	50 ppm	98.97%	99.38%	99.73%
	55 ppm	98.23%	99.54%	97.62%

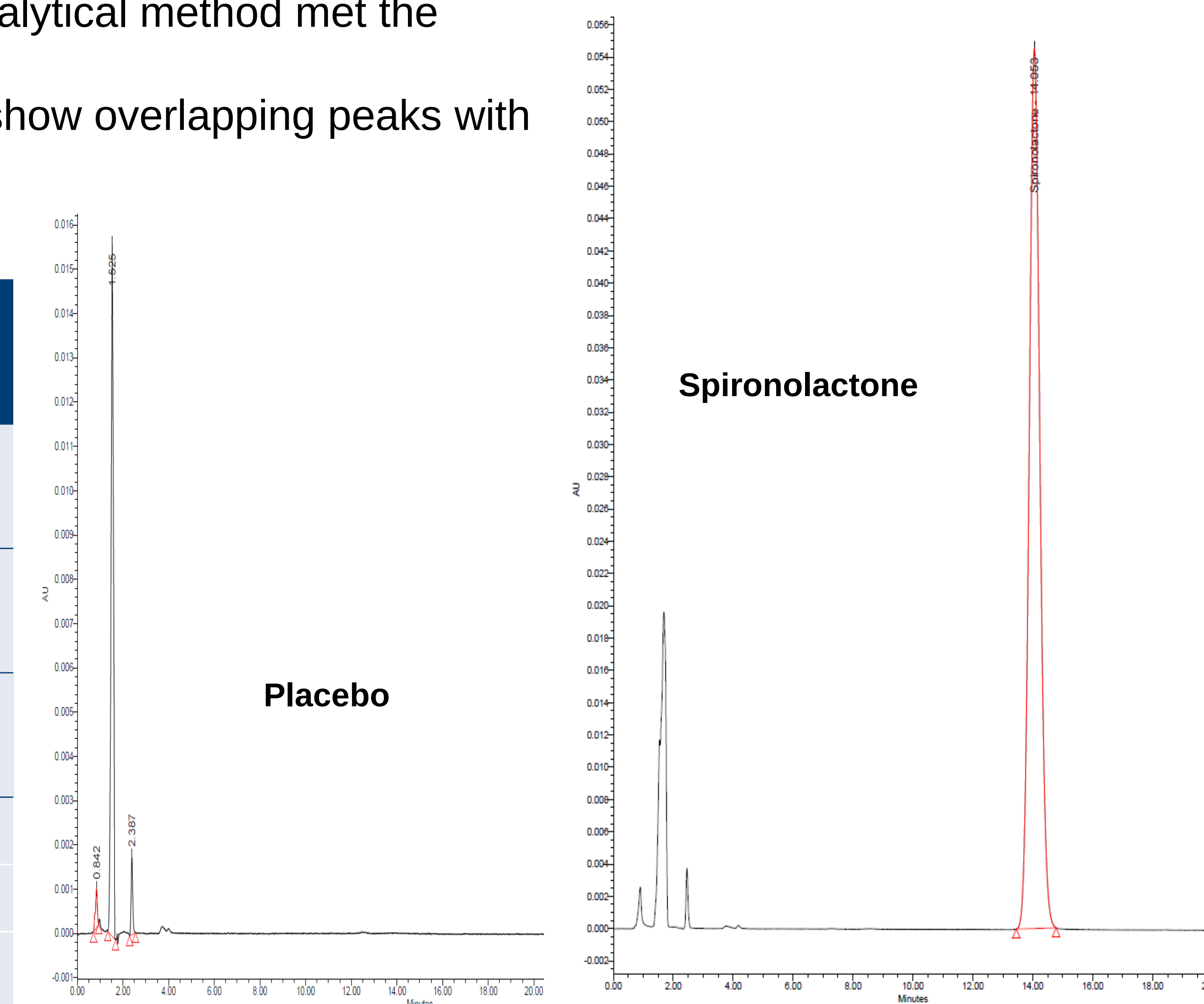


Figure 2: Chromatograms of placebo/spironolactone gel-tablets

Content uniformity of 3D-printed Spironolactone 4, 10, 20 mg Gel-tablets

All three batches of the three spironolactone doses met the specifications of Ph. Eur. 2.9.6. ‘Uniformity of content of single-dose preparations Test A and Ph. Eur. 2.9.40. ‘Uniformity of Dosage Units’ (see **Table 5**). According to the reports of the integrated scale in the 3D-printer, all gel-tablets met the specification of Ph. Eur. 2.9.5. ‘Uniformity of Mass of Single-Dose Preparations’.

Table 5: Content uniformity of spironolactone gel-tablets 4, 10, 20 mg, AV = acceptance value

Specification (Acceptance Value)	Day1			Day2			Day3		
Spironolactone dose (mg)	4	10	20	4	10	20	4	10	20
SP content (n=90) (Average % nominal content) (Ph. Eur. 2.9.6: 85-115%)	98.09	101.68	102.59	102.76	103.27	99.37	103.11	105.71	106.01
Content uniformity (n=90) (Ph. Eur. 2.9.40: AV<15)	2.78	3.26	5.45	8.46	5.16	2.94	7.33	11.59	12.85

Conclusion

A robust and reliable HPLC assay was developed and implemented to measure the content of spironolactone in 3D-printed spironolactone gel-tablets. Pharmacy preparation of 3D-printed spironolactone gel-tablets revealed to be precise, reliable, and reproducible. Further testing of other physico-chemical attributes and stability are subject of ongoing research.