Supporting Information

for

Diazepam quantification in street tablets using benchtop ^{1}H qNMR spectroscopy: Method validation and its application.

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Table S1. Results of the experiments conducted to confirm the purity of the diazepam certified reference standard[a] and TMSP-d_4[b].

Analyte	Mass of Analyte [mg]	Molar amount of Analyte [µmol]	Mass of maleic acid [mg]	Molar amount of maleic acid [µmol]	Mass fraction of Analyte in %, average of triplicates[c]
Diazepam	2.50	8.78	1.29	11.11	99.06
TMSP-d_4 (Sample 1)	12.78	74.19	37.20	320.5	98.21
TMSP-d_4 (Sample 2)	12.40	71.98	37.65	324.4	98.18

[a] To determine the purity of the diazepam certified reference standard, the stated amounts of diazepam and maleic acid (99.98% TraceCert®) were dissolved in 1 mL of CD_3OD, vortexed, and 600 µL of the resulting solution was transferred to an NMR tube. Obtained purity: 99.06%. [b] To determine the purity of TMSP-d_4, two samples with the stated respective amounts of TMSP-d_4 and maleic acid (99.98% TraceCert®) were dissolved in 1 mL of CD_3OD, vortexed, and 700 µL of the resulting solutions were transferred to NMR tubes. Obtained purity (average of two samples): 98.20%. [c] 60 MHz ^{1}H qNMR experiments run in triplicates using the following acquisition parameters: 40 ppm spectral width, 16,384 data points, 32 scans for diazepam/16 scans for TMSP-d_4, relaxation delay 60 s, 10 ppm spectral centre, 90° pulse angle, and automatic receiver gain.

Figure S1. Pictures of most common markings on pharmaceutical diazepam tablets.

Table S2. Accuracy and precision test results for the sample with low concentration, c(diazepam) = 2.5 mg/mL referencing the starting concentration of diazepam in CD_3OD and its actual concentration in the resulting NMR sample (calculated as 2.11 mg/mL). The results are reported for triplicate experiments (experiment 1, 2, 3) conducted in the morning and afternoon for five consecutive days.

Day	am/pm	Experiment 1 mass fraction of diazepam in %	Experiment 2 mass fraction of diazepam in %	Experiment 3 mass fraction of diazepam in %	Mass fraction of diazepam in %, average of triplicates
1	am	97.47	95.06	96.37	96.30
1	pm	96.03	99.90	96.51	97.48
2	am	94.05	101.17	94.42	96.55
2	pm	98.12	95.80	92.80	95.57
3	am	97.55	94.01	98.97	96.84
3	pm	95.00	98.01	96.99	96.67
4	am	93.16	95.26	93.98	94.13
4	pm	94.44	94.25	92.92	93.87
5[a]	am	97.11			97.11
5[a]	pm	93.90			93.90
Average inter/intra day results in wt%					95.84
Standard deviation					1.39
Precision (%RSD)					1.45
Expected mass fraction of diazepam in wt%					99.06
Accuracy in % (deviation from expected value)					-3.25

[a] Single experiment run on day five due to laboratory time restrictions.

Table S3. Accuracy and precision test results for the sample with medium concentration, c(diazepam) = 5 mg/mL referencing the starting concentration of diazepam in CD_3OD and its actual concentration in the resulting NMR sample (calculated as 4.23 mg/mL). The results are reported for triplicate experiments (experiment 1, 2, 3) conducted in the morning and afternoon for five consecutive days.

Day	am/pm	Experiment 1 mass fraction of diazepam in %	Experiment 2 mass fraction of diazepam in %	Experiment 3 mass fraction of diazepam in %	Mass fraction of diazepam in %, average of triplicates
1	am	93.49	96.37	96.11	95.32
1	pm	95.12	95.60	95.42	95.38
2	am	92.96	92.62	93.84	93.14
2	pm	95.65	94.80	95.64	95.36
3	am	94.46	94.96	95.50	94.97
3	pm	93.08	93.37	98.40	94.95
4	am	95.04	96.39	95.82	95.75
4	pm	94.33	95.54	94.16	94.68
5[a]	am	93.95			93.95
5[a]	pm	94.66			94.66
Average inter/intra day results in wt%					94.82
Standard deviation					0.77
Precision (%RSD)					0.82
Expected mass fraction of diazepam in wt%					99.06
Accuracy in % (deviation from expected value)					-4.28

[a] Single experiment run on day five due to laboratory time restrictions.

Table S4. Accuracy and precision test results for the sample with high concentration, c(diazepam) = 10 mg/mL referencing the starting concentration of diazepam in CD_3OD and its actual concentration in the resulting NMR sample (calculated as 8.57 mg/mL). The results are reported for triplicate experiments (experiment 1, 2, 3) conducted in the morning and afternoon for five consecutive days.

Day	am/pm	Experiment 1 mass fraction of diazepam in %	Experiment 2 mass fraction of diazepam in %	Experiment 3 mass fraction of diazepam in %	Mass fraction of diazepam in %, average of triplicates
1	am	95.47	95.91	96.19	95.86
1	pm	94.22	94.31	95.14	94.56
2	am	94.80	97.21	94.17	95.39
2	pm	96.01	95.77	97.70	96.49
3	am	92.97	94.93	92.77	93.56
3	pm	95.68	95.61	94.80	95.36
4	am	94.84	93.05	93.42	93.77
4	pm	94.02	96.20	94.18	94.80
5[a]	am	94.96			94.96
5[a]	pm	97.35			97.35
Average inter/intra day results in wt%					95.21
Standard deviation					1.16
Precision (%RSD)					1.22
Expected mass fraction of diazepam in wt%					99.06
Accuracy in % (deviation from expected value)					-3.89

[a] Single experiment run on day five due to laboratory time restrictions.

Table S5. Testing batch results (N = 100, including four analysed samples with no diazepam detected) showing the year, sample reference number, average diazepam concentration (average of triplicate experiments), tablet weight and diazepam dose for each samples.

Year	Sample Reference	Mass fraction of diazepam in %, average of triplicates	Total tablet weight [mg]	Diazepam content [mg]
2002	16866	0.40	169	0.68
2002	16867	1.40	170	2.38
2002	16816	3.01	170	5.12
2002	16850	0.41	173	0.71
2002	16995	1.49	174	2.59
2002	16851	1.32	175	2.31
2002	16852	3.83	175	6.70
2002	16994	0.60	178	1.07
2003	17579	3.39	173	5.86
2004	19434	1.32	171	2.26
2004	18921	1.43	173	2.47
2005	19942	0.55	168	0.92
2005	19943	1.63	171	2.79

Table S5 – continued. Testing batch results (N = 100, including four analysed samples withg no diazepam detected) showing the year, sample reference number, average diazepam concentration (average of triplicate runs), tablet weight and diazepam dose for each samples.

Year	Sample Reference	Mass fraction of diazepam in %, average of triplicates	Total tablet weight [mg]	Diazepam content [mg]
2005	19944	3.30	172	5.68
2006	21476	1.58	159	2.51
2006	21309	1.42	167	2.37
2006	21310	3.44	169	5.81
2006	21308	0.50	170	0.85
2006	21956	1.35	173	2.34
2006	21955	0.30	174	0.52
2006	21251	3.04	182	5.53
2006	21673	6.61	292	19.30
2007	28353	2.91	171	4.98
2007	23259	1.57	175	2.75
2007	23260	3.44	175	6.02
2007	23258	0.36	176	0.63
2007	13856	3.00	249	7.47
2008	24154	3.44	166	5.71
2008	24152	0.48	167	0.80
2008	24153	1.90	167	3.17
2008	23986	1.20	188	2.26
2008	24039	3.18	199	6.33
2009	29724	7.29	74	5.39
2009	17786	1.44	169	2.43
2009	17785	0.40	170	0.68
2009	17787	3.38	170	5.75
2009	29723	3.56	170	6.05
2010	26434	1.55	169	2.62
2010	26163	2.52	196	4.94
2011	27084	5.21	103	5.37
2011	27500	5.41	109	5.90
2011	27183	3.54	156	5.52
2011	27041	1.62	172	2.79
2011	25878	0.36	175	0.63
2011	25880	3.40	175	5.95
2011	25879	1.37	176	2.41
2011	27070	1.51	188	2.84
2011	27085	2.88	225	6.48

Table S5 – continued. Testing batch results (N = 100, including four analysed samples with no diazepam detected) showing the year, sample reference number, average diazepam concentration (average of triplicate runs), tablet weight and diazepam dose for each samples.

Year	Sample Reference	Mass fraction of diazepam in %, average of triplicates	Total tablet weight [mg]	Diazepam content [mg]
2012	16454	1.58	172	2.72
2013	29518	1.37	180	2.47
2014	30202	1.34	70	0.94
2014	30722	2.90	130	3.77
2014	30728	3.81	170	6.48
2014	30727	4.32	170	7.34
2014	30203	1.43	175	2.50
2014	30664	3.08	193	5.94
2014	30724	3.26	200	6.52
2014	30204	1.62	350	5.67
2015	31894	7.31	150	10.97
2015	31784	5.60	170	9.52
2015	31640	3.70	179	6.62
2016	32937	4.61	130	5.99
2016	32935	1.67	160	2.67
2016	32938	3.50	170	5.95
2016	32854	6.53	180	11.75
2017	33841	1.50	170	2.55
2017	33721	3.55	170	6.04
2017	33705	0.00	180	0.00
2017	33676	1.07	200	2.14
2018	34678	5.75	60	3.45
2018	34433	3.92	170	6.66
2018	34679	3.06	200	6.12
2019	35549	7.73	80	6.18
2019	19-1468	2.95	110	3.25
2019	35550	3.81	160	6.10
2019	19-1650	15.72	167	26.25
2019	19-1633	0.00	168	0.00
2019	19-1224G	8.60	169	14.53
2019	35447	1.41	170	2.40
2019	35197	3.06	170	5.20
2019	19-1149	4.66	173	8.06
2019	19-1630	10.76	175	18.83

Table S5 – continued. Testing batch results (N = 100, including four analysed samples with no diazepam detected) showing the year, sample reference number, average diazepam concentration (average of triplicate runs), tablet weight and diazepam dose for each samples.

Year	Sample Reference	Mass fraction of diazepam in %, average of triplicates	Total tablet weight [mg]	Diazepam content [mg]
2019	19-1434	6.81	196	13.35
2020	35993	9.04	80	7.23
2022	37970	4.47	170	7.60
2022	22-239	2.14	172	3.68
2022	22-240C	2.76	180	4.97
2022	22-046	0.00	190	0.00
2022	22-277	0.00	305	0.00
2023	38845	1.39	150	2.09
2023	23-699A	2.81	167	4.69
2023	23-453B	3.59	169	6.07
2023	38854	0.48	170	0.82
2023	38830	4.14	170	7.04
2023	23-869	3.37	172	5.80
2023	38512	0.72	180	1.30
2023	23-230	1.08	205	2.21