Supporting information

Development of a Sensitive Headspace Gas Chromatography−Mass Spectrometry Method for the Simultaneous Determination of Nitrosamines in Losartan Active Pharmaceutical Ingredients

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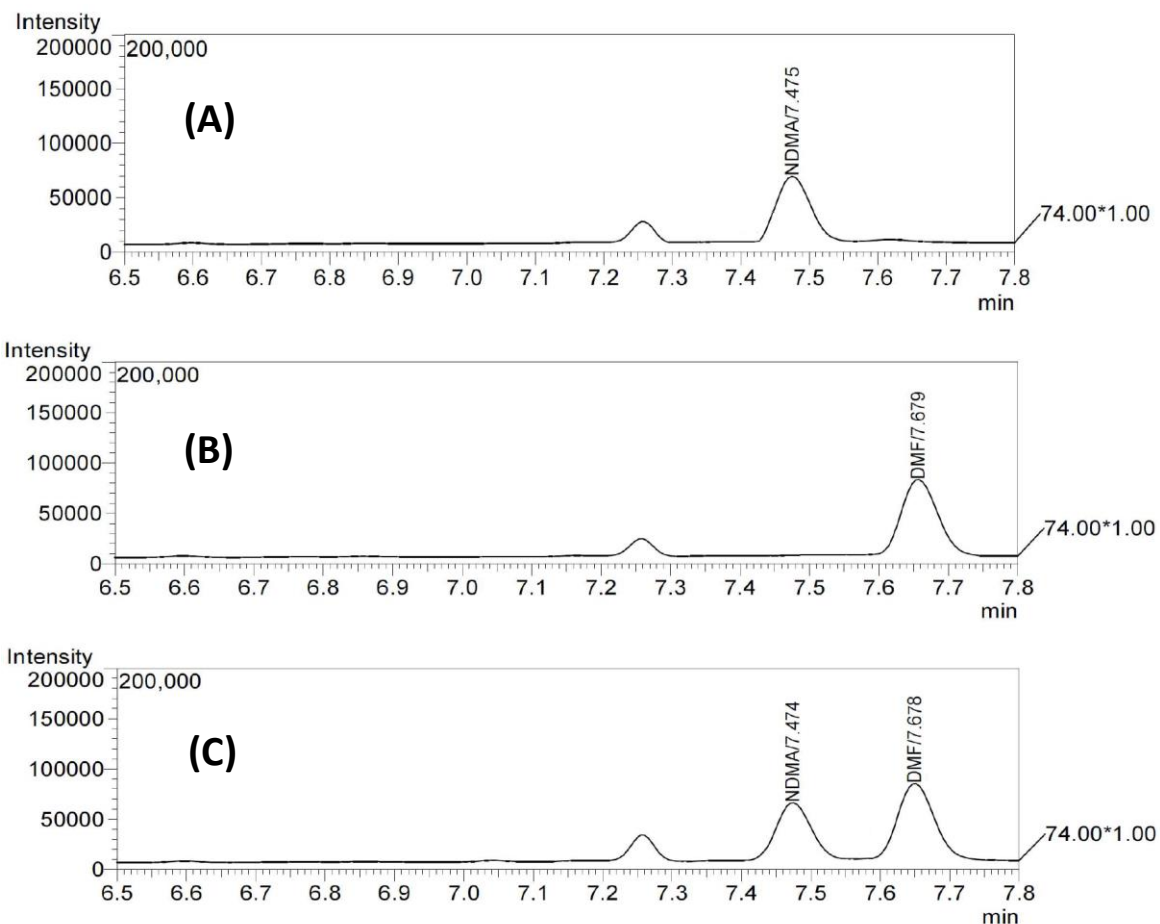*Corresponding author

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1. Method development

[MS] ID1 Compound Name:NDMA				
Title	Sample Name	Ret. Time	Area	Resolution
NDMA and DMF.qgd	DMF and NDMA	7.474	178274	---

[MS] ID2 Compound Name:DMF				
Title	Sample Name	Ret. Time	Area	Resolution
NDMA and DMF.qgd	DMF and NDMA	7.678	260868	2.26

Figure S1. The representative chromatograms of (a) spiked NDMA (*m/z* 74), (b) spiked DMF (^{15}N isotopic ion at *m/z* 74) and (c) co-spiked between NDMA and DMF in losartan

2. Robustness

Table S1. System suitability results under HS equilibration time (intra-variation of typical method: 15 min)

Injection no.	NDMA			NDEA			EIPNA			DIPNA		
	Peak area	RT	Tailing	Peak area	RT	Tailing	Peak area	RT	Tailing	Peak area	RT	Tailing
#1	140636	7.537	1.106	70612	8.171	1.135	35203	8.446	1.154	24355	8.646	1.317
#2	128975	7.537	1.106	66265	8.170	1.151	32720	8.447	1.143	22677	8.647	1.273
#3	129689	7.535	1.105	65754	8.169	1.135	32043	8.445	1.145	21965	8.646	1.241
#4	132265	7.536	1.103	68565	8.170	1.145	33557	8.446	1.152	22817	8.646	1.267
#5	131122	7.535	1.112	67767	8.168	1.159	33476	8.445	1.127	22380	8.645	1.268
Average	132537	7.536	1.106	67793	8.170	1.145	33400	8.446	1.144	22839	8.646	1.273
SD	4702.897	0.001	0.003	1938.796	0.001	0.010	1181.639	0.001	0.011	908.232	0.001	0.027
%CV	**3.55**	**0.01**	**0.30**	**2.86**	**0.01**	**0.91**	**3.54**	**0.01**	**0.93**	**3.98**	**0.01**	**2.16**

Table S2. System suitability results under HS equilibration time (intra-variation of 14 min)

Injection no.	NDMA			NDEA			EIPNA			DIPNA		
	Peak area	RT	Tailing	Peak area	RT	Tailing	Peak area	RT	Tailing	Peak area	RT	Tailing
#1	119970	7.534	1.097	60663	8.168	1.147	29054	8.442	1.164	20142	8.645	1.223
#2	134818	7.539	1.096	68957	8.171	1.160	34396	8.448	1.131	23445	8.649	1.216
#3	127253	7.537	1.094	64574	8.170	1.135	31738	8.445	1.158	21807	8.647	1.213
#4	132658	7.537	1.095	66586	8.171	1.126	33169	8.447	1.149	22813	8.649	1.183
#5	134538	7.540	1.105	69318	8.173	1.144	35076	8.448	1.166	23518	8.650	1.215
Average	129847	7.537	1.097	66020	8.171	1.142	32687	8.446	1.154	22345	8.648	1.210
SD	6302.817	0.002	0.004	3557.088	0.002	0.013	2395.810	0.003	0.014	1409.575	0.002	0.016
%CV	**4.85**	**0.03**	**0.40**	**5.39**	**0.02**	**1.12**	**7.33**	**0.03**	**1.24**	**6.31**	**0.02**	**1.29**

Table S3. System suitability results under HS equilibration time (intra-variation of 16 min)

Injection no.	NDMA			NDEA			EIPNA			DIPNA		
	Peak area	RT	Tailing	Peak area	RT	Tailing	Peak area	RT	Tailing	Peak area	RT	Tailing
#1	136310	7.538	1.100	68092	8.172	1.141	34293	8.448	1.124	23424	8.647	1.263
#2	134393	7.541	1.101	69253	8.174	1.140	34025	8.450	1.130	23567	8.651	1.271
#3	133069	7.539	1.099	67883	8.172	1.136	33698	8.449	1.135	23391	8.650	1.215
#4	136804	7.538	1.101	69572	8.171	1.149	33899	8.445	1.174	23293	8.646	1.268
#5	142334	7.539	1.101	72469	8.172	1.133	36004	8.449	1.131	24782	8.649	1.244
Average	136582	7.539	1.100	69454	8.172	1.140	34384	8.448	1.139	23691	8.649	1.252
SD	3547.593	0.001	0.001	1834.914	0.001	0.006	931.045	0.002	0.020	617.525	0.002	0.023
%CV	**2.60**	**0.02**	**0.08**	**2.64**	**0.01**	**0.53**	**2.71**	**0.02**	**1.76**	**2.61**	**0.02**	**1.86**

Table S4. System suitability results under transfer line temperature (intra-variation of Typical method: 250°C)

Injection no.	NDMA			NDEA			EIPNA			DIPNA		
	Peak area	RT	Tailing	Peak area	RT	Tailing	Peak area	RT	Tailing	Peak area	RT	Tailing
#1	130505	7.532	1.126	68342	8.166	1.151	34019	8.441	1.174	22763	8.642	1.268
#2	128563	7.532	1.115	66211	8.165	1.148	33529	8.440	1.185	22523	8.643	1.243
#3	121988	7.532	1.122	63913	8.166	1.154	32445	8.441	1.192	21427	8.643	1.241
#4	124316	7.533	1.132	65558	8.167	1.157	33548	8.442	1.216	21427	8.644	1.275
#5	129650	7.534	1.114	67920	8.168	1.156	34665	8.443	1.196	22582	8.645	1.277
Average	127004	7.533	1.122	66389	8.166	1.153	33641	8.441	1.193	22144	8.643	1.261
SD	3676.765	0.001	0.008	1803.538	0.001	0.004	812.876	0.001	0.016	660.837	0.001	0.017
%CV	**2.89**	**0.01**	**0.67**	**2.72**	**0.01**	**0.32**	**2.42**	**0.01**	**1.30**	**2.98**	**0.01**	**1.39**

Table S5. System suitability results under transfer line temperature (intra-variation of 245°C)

Injection no.	NDMA			NDEA			EIPNA			DIPNA		
	Peak area	RT	Tailing	Peak area	RT	Tailing	Peak area	RT	Tailing	Peak area	RT	Tailing
#1	127042	7.535	1.129	65466	8.168	1.149	33123	8.443	1.165	21415	8.645	1.245
#2	125627	7.535	1.125	64358	8.169	1.156	32807	8.444	1.188	21507	8.646	1.259
#3	124766	7.535	1.121	64329	8.168	1.141	32702	8.443	1.158	21132	8.644	1.265
#4	127934	7.536	1.129	66488	8.169	1.172	33336	8.445	1.187	22203	8.647	1.258
#5	125748	7.536	1.122	65250	8.169	1.166	32588	8.444	1.210	21952	8.646	1.275
Average	126223	7.535	1.125	65178	8.169	1.157	32911	8.444	1.182	21642	8.646	1.260
SD	1255.186	0.001	0.004	894.068	0.001	0.013	309.998	0.001	0.021	430.312	0.001	0.011
%CV	**0.99**	**0.01**	**0.33**	**1.37**	**0.01**	**1.08**	**0.94**	**0.01**	**1.75**	**1.99**	**0.01**	**0.87**

Table S6. System suitability results under transfer line temperature (intra-variation of 255°C)

Injection no.	NDMA			NDEA			EIPNA			DIPNA		
	Peak area	RT	Tailing	Peak area	RT	Tailing	Peak area	RT	Tailing	Peak area	RT	Tailing
#1	114794	7.537	1.114	59203	8.170	1.142	29732	8.444	1.189	19559	8.646	1.236
#2	113182	7.537	1.113	58708	8.170	1.136	29054	8.444	1.185	19116	8.645	1.235
#3	116510	7.536	1.116	59298	8.169	1.145	30375	8.444	1.179	20116	8.646	1.249
#4	132082	7.538	1.127	69710	8.171	1.188	34451	8.444	1.231	22914	8.646	1.336
#5	116531	7.536	1.128	61283	8.170	1.156	30941	8.443	1.229	20165	8.646	1.240
Average	118620	7.537	1.120	61640	8.170	1.153	30911	8.444	1.203	20374	8.646	1.259
SD	7652.640	0.001	0.007	4617.166	0.001	0.021	2101.088	0.000	0.025	1483.967	0.000	0.043
%CV	**6.45**	**0.01**	**0.65**	**7.49**	**0.01**	**1.79**	**6.80**	**0.01**	**2.10**	**7.28**	**0.01**	**3.44**

Table S7 System suitability results under HS equilibration time (inter-variation of 14-16 min)

| Variation of HS equilibration time	NDMA			NDEA			EIPNA			DIPNA		
	Peak area	RT	Tailing	Peak area	RT	Tailing	Peak area	RT	Tailing	Peak area	RT	Tailing
15 min	132537	7.536	1.106	67793	8.170	1.145	33400	8.446	1.144	22839	8.646	1.273
14 min	129847	7.537	1.097	66020	8.171	1.142	32687	8.446	1.154	22345	8.648	1.210
16 min	136582	7.539	1.100	69454	8.172	1.140	34384	8.448	1.139	23691	8.649	1.252
Average	132989	7.537	1.101	67756	8.171	1.142	33490	8.447	1.146	22958	8.648	1.245
SD	3390.141	0.002	0.005	1717.304	0.001	0.003	852.099	0.001	0.008	680.889	0.002	0.032
%CV	**2.55**	**0.02**	**0.42**	**2.53**	**0.01**	**0.22**	**2.54**	**0.01**	**0.67**	**2.97**	**0.02**	**2.58**

Table S8. System suitability results under transfer line temperature (inter-variation of 245-255°C)

Variation of Transfer line temperature	NDMA			NDEA			EIPNA			DIPNA		
	Peak area	RT	Tailing	Peak area	RT	Tailing	Peak area	RT	Tailing	Peak area	RT	Tailing
250 ˚C	127004	7.533	1.122	66389	8.166	1.153	33641	8.441	1.193	22144	8.643	1.261
245 ˚C	126223	7.535	1.125	65178	8.169	1.157	32911	8.444	1.182	21642	8.646	1.260
255 ˚C	118620	7.537	1.120	61640	8.170	1.153	30911	8.444	1.203	20374	8.646	1.259
Average	123949	7.535	1.122	64402	8.168	1.154	32488	8.443	1.193	21387	8.645	1.260
SD	4631.541	0.002	0.003	2467.690	0.002	0.002	1413.377	0.002	0.011	912.207	0.002	0.001
%CV	**3.74**	**0.03**	**0.22**	**3.83**	**0.03**	**0.20**	**4.35**	**0.02**	**0.88**	**4.27**	**0.02**	**0.08**
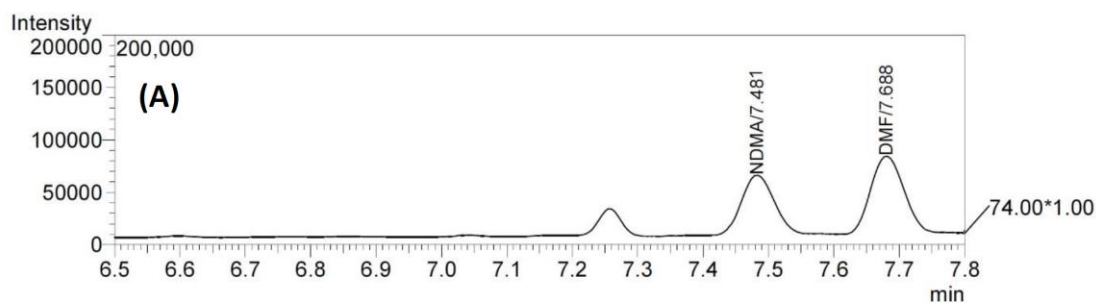
[MS] ID1 Compound Name:NDMA

Title	Sample Name	Ret. Time	Area	Resolution
NDMA and DMF.qgd	DMF and NDMA1.9	7.481	182280	---

[MS] ID2 Compound Name:DMF

Title	Sample Name	Ret. Time	Area	Resolution
NDMA and DMF.qgd	DMF and NDMA1.9	7.688	266828	2.28
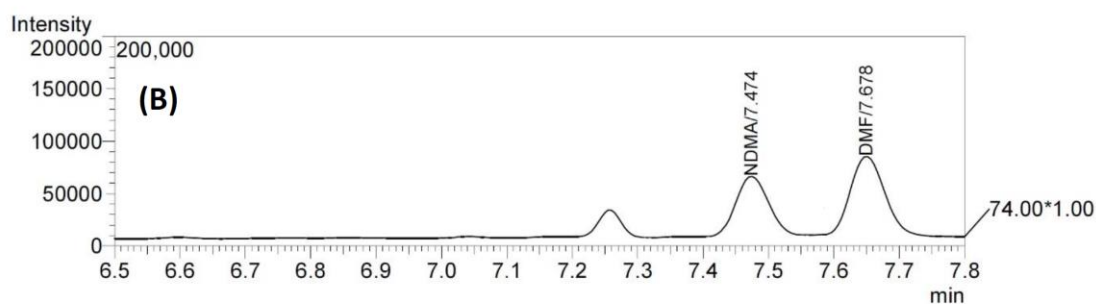
[MS] ID1 Compound Name:NDMA

Title	Sample Name	Ret. Time	Area	Resolution
NDMA and DMF.qgd	DMF and NDMA	7.474	178274	---

[MS] ID2 Compound Name:DMF

Title	Sample Name	Ret. Time	Area	Resolution
NDMA and DMF.qgd	DMF and NDMA	7.678	260868	2.26
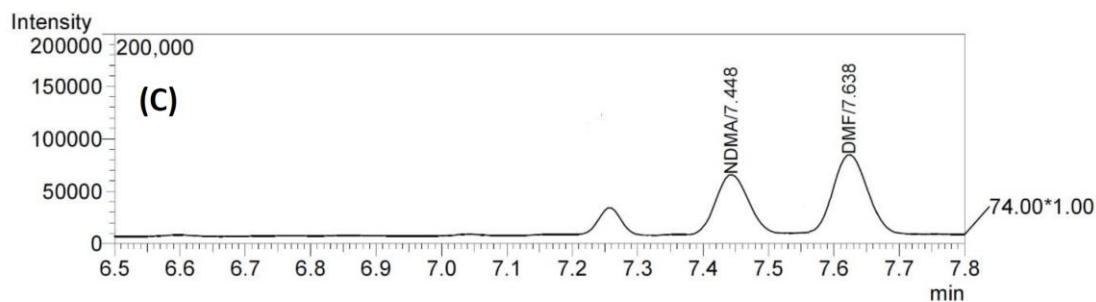
[MS] ID1 Compound Name:NDMA

Title	Sample Name	Ret. Time	Area	Resolution
NDMA and DMF.qgd	DMF and NDMA 2.1	7.448	178486	---

[MS] ID2 Compound Name:DMF

Title	Sample Name	Ret. Time	Area	Resolution
NDMA and DMF.qgd	DMF and NDMA 2.1	7.638	261273	2.21

Figure S2. The representative chromatograms of co-spiked between NDMA and DMF in losartan under the variations of flow rate at (a) 1.9 mL/min (b) 2.0 mL/min (method condition) (c) 2.1 mL/min.