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ORIGINAL ARTICLE / ÖZGÜN MAKALE

DETERMINATION OF *N*-NITROSODIMETHYL AMINE (NDMA) AND *N*-NITROSODIETHYL AMINE (NDEA) IN MEDICINES CONTAINING SARTAN AND ITS DERIVATIVES

SARTAN VE TÜREVLERİNİ İÇEREN İLAÇLARDA N-NİTROSODİMETİL AMİN (NDMA) VE N-NİTROSODİETİL AMİN (NDEA) TAYİNİ

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ABSTRACT

Objective: *In this study, it was aimed to determine the amounts of N-nitrosodimethyl amine (NDMA) and N-nitrosodiethyl amine (NDEA) in drugs containing sartan and its derivatives.*
Material and Method: *Medicines containing sartan and its derivatives as active ingredients such as valsartan, losartan, telmisartan, olmesartan, candesartan, irbesartan were purchased from pharmacies. NDMA and NDEA amounts of drugs were determined by headspace GC-MS.*
Result and Discussion: *The highest NDMA concentrations were found in drugs with losartan active ingredient (67.05±0.15mg kg^{-1}), and the highest NDEA concentrations were found in drugs with candesartan (22.48±0.06 mg kg^{-1}) and olmesartan (20.13 ± 0.06 mg kg^{-1}) active ingredient. The NDMA contents in each tablet were between $3.6x10^{-4}$- $1.7x10^{-2}$ mg and the NDEA contents were between $3.3x10^{-4}$ – $8.8x10^{-3}$ mg. The acceptable daily intake limits specified by the European Medicines Agency and the Food and Drug Administration are 96 ng/day for NDMA and 26.5 ng/day for NDEA. It was observed that the values obtained were above the acceptable intake limits even if one tablet was taken per day.*
Keywords: *Drug, headspace GC-MS, N-nitrosodiethyl amine (NDEA), N-nitrosodimethyl amine (NDMA), sartan*

ÖZ

Amaç: *Bu çalışmada, sartan ve türevlerini içeren ilaçların N-nitrosodimetil amin (NDMA) ve N-nitroso dietil amin (NDEA) miktarlarının belirlenmesi amaçlanmıştır.*
Gereç ve Yöntem: *Etken madde olarak valsartan, losartan, telmisartan, olmesartan, kandesartan, irbesartan gibi sartan ve türevlerini içeren ilaçlar eczanelerden satın alınmıştır. İlaçların NDMA ve NDEA miktarları headspace GC-MS ile belirlenmiştir.*
Sonuç ve Tartışma: *En yüksek NDMA konsantrasyonu losartan etken maddeli ilaçlarda (67.05 ± 0.15 mg kg^{-1}), en yüksek NDEA konsantrasyonu ise kandesartan (22.48±0.06 mg kg^{-1}) ve olmesartan (20.13 ± 0.06 mg kg^{-1}) etken maddeli ilaçlarda bulunmuştur. Her tabletteki NDMA içerikleri $3.6x10^{-4}$-$1.7x10^{-2}$ mg arasında, NDEA içerikleri ise $3.3x10^{-4}$- $8.8x10^{-3}$ mg arasında saptanmıştır. Avrupa İlaç Ajansı ve Gıda ve İlaç İdaresi tarafından belirlenen kabul edilebilir. Günlük alım limitleri NDMA için 96 ng/gün ve NDEA için 26.5 ng/gündür. Elde edilen değerlerin günde bir tablet alınsa bile kabul edilebilir alım limitlerinin üzerinde olduğu görülmüştür.*

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Anahtar Kelimeler: *Headspace GC-MS, ilaç, N-nitrosodietil amin (NDEA), N-nitrosodimetil amin (NDMA), sartan*

INTRODUCTION

Nitrosamines are chemically highly active amine derivatives with the R_1R_2N-N=O functional group. R_1 and R_2 denote alkyl or aryl groups. The vast majority of nitrosamines are classified as carcinogens by the International Agency for Research on Cancer (IARC). *N*-nitrosodiethylamine (NDEA) and *N*-nitrosodimethylamine (NDMA) are included in group 2A (probably carcinogenic to humans) [1].

N-nitrosamines are formed as a result of the reaction of an amine with a nitrosating agent. Nitrosing agents can be nitrous acid, nitrogen oxides, nitrosyl species and nitrite salts. When a nitrosating agent reacts with primary amines, the primary amine is rapidly converted to alcohol and nitrogen. When secondary amines react with the nitrosating agent, they form nitrosamines with the functional group R_1R_2N-N=O. When tertiary amines react with the nitrosating agent, nitrosamine formation does not occur [2].

Nitrosamines formed in drugs are caused by contaminated starting materials and intermediates, reagents, solvents, catalysts, errors made in the production process, recovered and recycled materials. For example, when azide is used as a reagent during tetrazole synthesis, hydrazoic acid is formed due to acidic conditions. The released hydrazoic acid can also lead to amine formation. In addition, the remaining azide can form gaseous by-products such as nitrogen and nitrogen oxides when sodium nitrite is added. Failure to maintain the proper pH or temperature and not adding the reagents in the proper order are examples of errors in the production process. The water used in production may also contain nitrosamines due to environmental pollution. If necessary precautions are not taken or equipment is not cleaned between customer orders, nitrosamine formation is inevitable.

In addition, nitrosamines can be formed after the drugs are produced, depending on the storage conditions, packaging materials and decomposition processes of the active substances [3].

In June 2018, the Food and Drug Administration (FDA) announced that *N*-nitrosodimethylamine impurity, which may have genotoxic potential, has been found in some drugs with the active ingredient valsartan in China. Then, drugs with valsartan active substance began to be studied not only in China but also in all European Union countries [4]. Studies have been extended for all sartans with tetrazole group such as losartan, irbesartan, candesartan, olmesartan. As a result of these studies, the presence of nitrosamines has been detected in many drugs. In 2019, the detection of *N*-nitrosodimethylamine impurity in ranitidine-containing drugs that do not contain sartan increased the concerns [5]. Studies have shown that nitrosamines can be formed both during and after the manufacture of drugs, depending on storage conditions. In November 2019, the Singapore government announced that N-nitrosodimethylamine impurity was found in drugs containing the active ingredient metformin [6]. In August 2022, the Food and Drug Administration reported that nitrosamines have been detected in drugs containing sitagliptin, which are commonly used in type 2 diabetes patients [7]. After all these explanations, studies have been started to determine whether drugs contain nitrosamines all over the world [6, 8-19]. However, there is no study done on this subject in our country. It is extremely important to know that how much nitrosamine, which is threaten human health, presence in which drugs.

The European Medicines Agency and the Food and Drug Administration have established acceptable daily intake limits for nitrosamines. These values are 96 ng/day for NDMA and 26.5 ng/day for NDEA [4].

Within the scope of this study, the NDMA and NDEA amounts of drugs containing sartan and its derivatives as active ingredient (valsartan, losartan, irbesartan, telmisartan, olmesartan and candesartan) sold in Turkey were determined.

MATERIAL AND METHOD

Materials

Certified standards of *N*-Nitrosodimethylamine and *N*-Nitrosodiethylamine were purchased from

Sigma Aldrich (Gillingham, UK). All chemicals used were of analytical reagent grade and were at least 99.5% pure. All drug samples were obtained from pharmacies in Turkey.

Preparation of Drug Samples for Analysis

0.1 g of the drug samples, which were crushed into powder, were weighed and placed in glass centrifuge tubes. 2 ml of dimethylsulfoxide was added to them and mixed using a vortex mixer until dissolved at room temperature. Then, the solutions were transferred to the headspace vial [20].

Headspace GC-MS Analysis

Headspace GC-MS analysis was performed using an Agilent 7890 A GC System with an Agilent 5975 C MS and an Agilent 7697A Headspace Auto-sampler. Headspace GC-MS operating conditions are shown in Table 1 [20].

Table 1. Headspace GC-MS operating conditions

Headspace Parameters			
Instrument Used	Agilent 7697 A		
Oven Temperature	120°C		
Sample Line Temperature	125°C		
Transfer Line Temperature	130°C		
Gas Pressure	103 kPa		
Equalization Time	15 min		
GC Parameters			
Instrument Used	Agilent 7890 A		
Column	DB WAX (50 m, 0.20 mm, 0.20 µm)		
Carrier Gas	Helium		
Flow Rate	2 ml/min		
Injector Temperature	240°C		
Detector Temperature	240°C		
Temperature Program	Ramp rate (°C/min)	Temperature (°C)	Hold time (min)
	-	40	2
	10	120	2
	25	230	5
MS Parameters			
Instrument Used	Agilent 5975 C		
Ionization Mode	EI (70 eV)		
Mode	SIM		
m/z values	NDMA	NDEA	
	74, 42, 43	102, 57, 56, 44, 42	

Quality Control and Quality Assurance

All analyses were repeated three times for each sample. Under the applied headspace GC-MS conditions, the retention times of NDMA and NDEA were 10.1 and 11.3 min, respectively. The peaks of nitrosamines are shown in Figure 1. For NDMA m/z 74, 42, and 43 were monitored (SIM), with m/z 74 used for quantitation; and for NDEA m/z 102, 57, 56, 44, and 42 were monitored, with m/z 102 used for quantitation (Figure 2a and 2b). Calibration standards were prepared in the range of 0.05 – 200 mg l^{-1} for NDMA and 0.05 – 20 mg l^{-1} for NDEA. In all cases, the correlation coefficients were found to be greater than 0.9995. The calibration curves were created from seven calibration standards and are shown in Figures 3a and 3b. The limit of detection (LOD) was determined to be three times the standard deviation of the blank test values. The limit of quantification (LOQ) was taken as three times the LOD. The obtained values are given in Table 2.

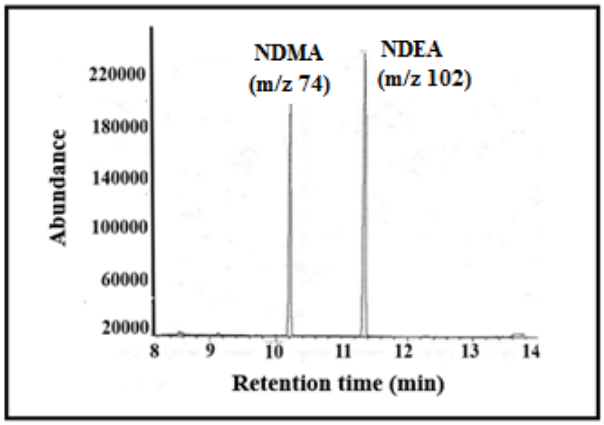

Figure 1. Under the applied headspace GC-MS conditions, peaks belonging to NDMA and NDEA standards

Table 2. The values of retention time, correlation coefficient, LOD and LOQ of NDMA and NDEA

Nitrosamines	Retention Time (min)	Correlation Coefficient (R^2)	LOD (mg / l)	LOQ (mg / l)
NDMA	10.1	0.9999	0.004	0.013
NDEA	11.3	0.9998	0.001	0.003

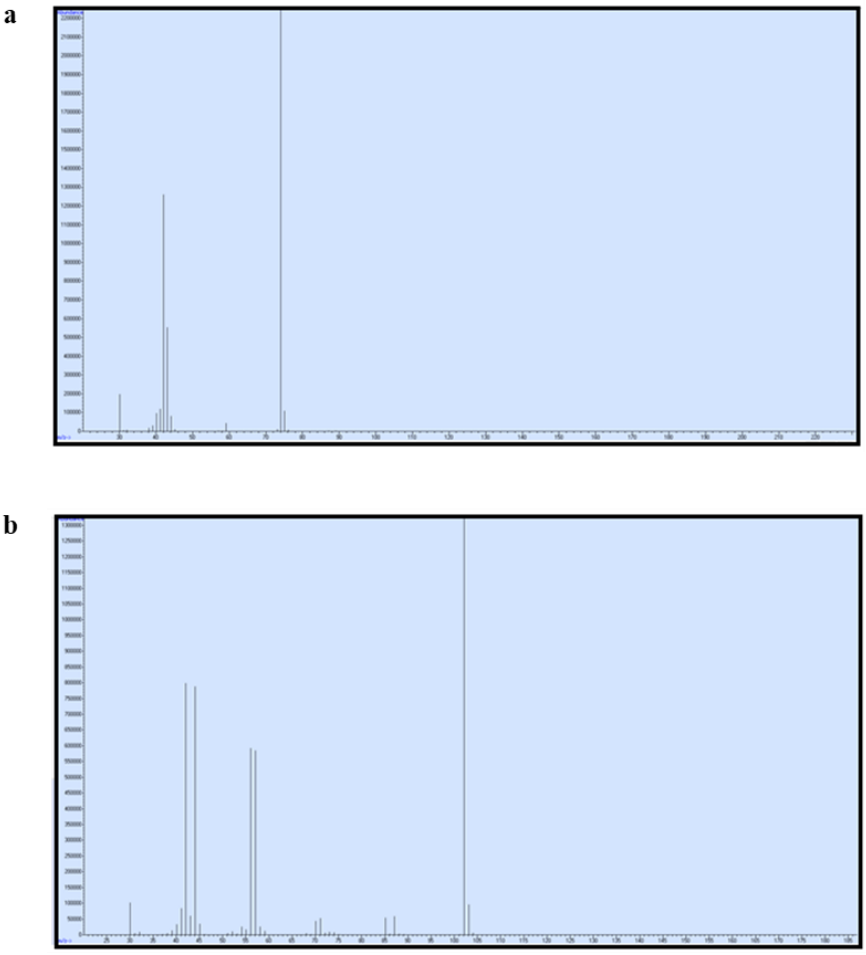

Figure 2. Mass spectrums of **(a)** NDMA and **(b)** NDEA

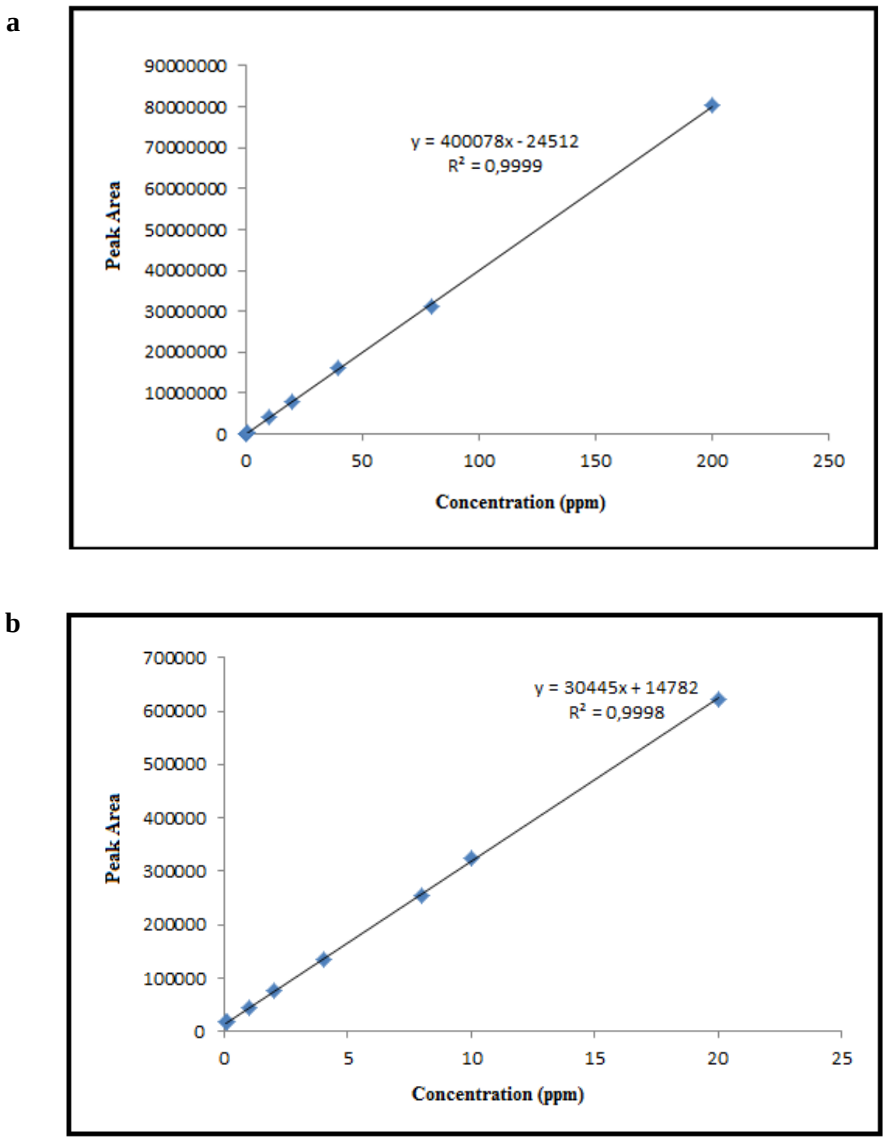

Figure 3. Calibration curves of **(a)** NDMA and **(b)** NDEA

RESULT AND DISCUSSION

The amounts of *N*-nitrosodimethylamine and N-nitrosodiethylamine detected in drug samples are shown in Table 3. Both NDMA and NDEA were detected in all of the drugs examined. The nitrosamine chromatograms of some drug samples were given in Figure 4a and 4b. The average NDMA concentrations were found ranging from 3.43 to 34.14 mg kg^{-1}, while NDEA levels were in the range of 1.09 to 6.78 mg kg^{-1} in drugs containing valsartan. The average NDMA concentrations determined in drugs containing losartan were between 18.41 and 67.05 mg kg^{-1}, and NDEA concentrations are between 2.96 and 16.05 mg kg^{-1}. The average concentrations of NDMA and NDEA in drugs containing irbesartan were in the range of 4.73 - 27.40 mg kg^{-1} and 1.94 - 5.88 mg kg^{-1}, respectively. A single drug with telmisartan active substance was examined, and the mean NDMA concentration was 1.71 mg kg^{-1} and the mean NDEA concentration was 0.62 mg kg^{-1}. It was observed that the mean NDMA concentrations ranged between 1.80 and 7.47 mg kg^{-1}, and the mean NDEA concentrations ranged between 1.53 and 20.13 mg kg^{-1} in drugs with olmesartan active ingredient. In drugs with candesartan active substance, mean NDMA contents were found between 11.10 and 31.73 mg kg^{-1}, and mean NDEA contents were between 10.46 and 22.48 mg kg^{-1}. While the highest NDMA concentrations were found in drugs with

losartan active ingredient, the highest NDEA concentrations were found in drugs with candesartan and olmesartan active ingredient.

Table 3. Amounts of NDMA and NDEA detected in drug samples (N=3)

Active Ingredient of the Drug	NDMA (mg kg^{-1})	NDEA (mg kg^{-1})
Valsartan	18.28 ± 0.06	6.27 ± 0.02
Valsartan	3.43 ± 0.01	6.78 ± 0.02
Valsartan	27.83 ± 0.09	1.09 ± 0.01
Valsartan	34.14 ± 0.11	1.39 ± 0.01
Valsartan	8.00 ± 0.02	5.61 ± 0.02
Valsartan	6.40 ± 0.02	1.18 ± 0.01
Losartan	18.41 ± 0.06	11.13 ± 0.03
Losartan	53.49 ± 0.13	13.06 ± 0.03
Losartan	29.56 ± 0.10	2.96 ± 0.01
Losartan	67.05 ± 0.15	16.05 ± 0.05
Irbesartan	4.73 ± 0.01	1.94 ± 0.01
Irbesartan	24.25 ± 0.08	3.62 ± 0.01
Irbesartan	27.40 ± 0.09	5.88 ± 0.02
Telmisartan	1.71 ± 0.01	0.62 ± 0.01
Olmesartan	6.64 ± 0.02	20.13 ± 0.06
Olmesartan	1.80 ± 0.01	4.20 ± 0.01
Olmesartan	7.47 ± 0.02	1.53 ± 0.01
Kandesartan	16.14 ± 0.05	22.48 ± 0.06
Kandesartan	11.10 ± 0.03	13.21 ± 0.03
Kandesartan	31.73 ± 0.10	10.46 ± 0.03

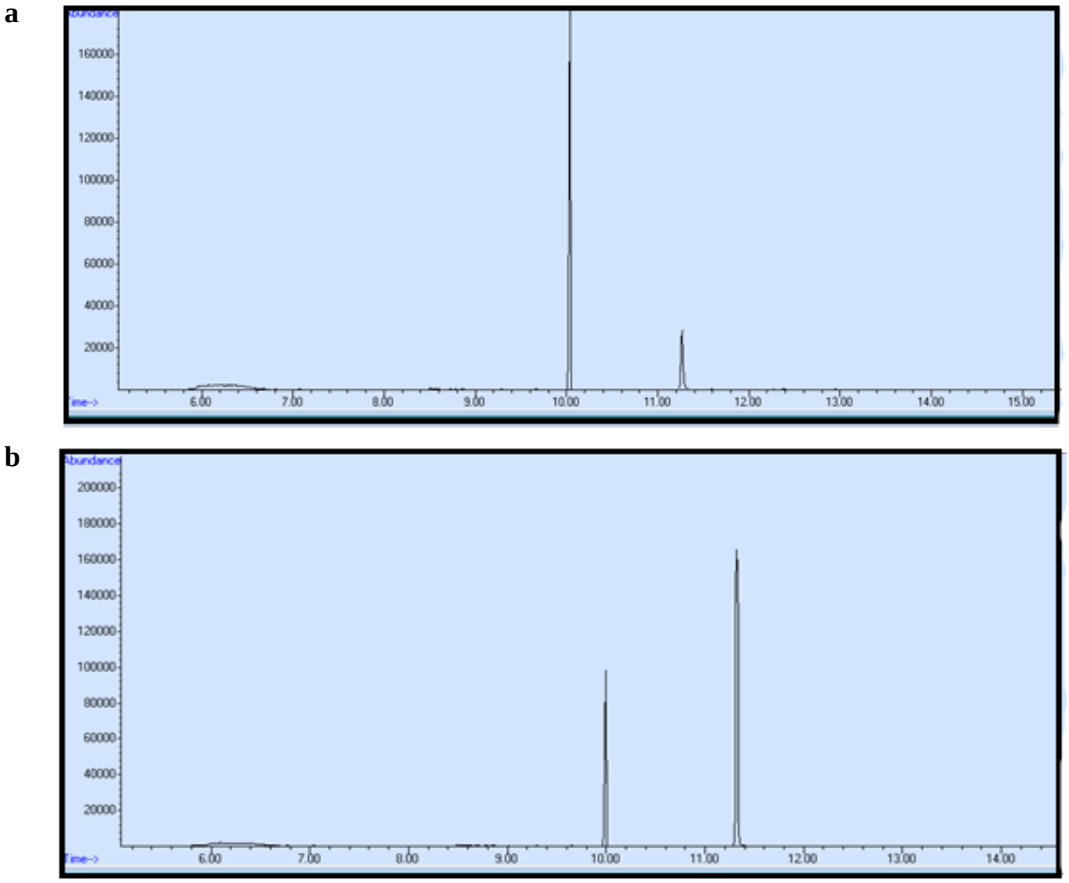

Figure 4. The nitrosamine chromatograms of drugs containing **(a)** valsartan and **(b)** olmesartan

The NDMA and NDEA amounts in each tablet of the examined drug samples are given in Table 4. The amounts of NDMA in each tablet of drugs with valsartan active ingredient were between $1.1x10^{-3}$ and $1.4x10^{-2}$ mg, the amounts of NDEA were between $4.4x10^{-4}$ and $2.9x10^{-3}$ mg, the amounts of NDMA in each tablet of drugs with losartan active ingredient were between $6.9x10^{-3}$ and $1.7x10^{-2}$ mg, NDEA amounts were between $6.9x10^{-4}$ and $5.1x10^{-3}$ mg, the amounts of NDMA in each tablet of drugs with irbesartan active ingredient were between $2.5x10^{-3}$ and $8.5x10^{-3}$ mg, NDEA amounts were between $9.6x10^{-4}$ and $1.8x10^{-3}$ mg, the amounts of NDMA in each tablet of drugs with olmesartan active ingredient were between $3.6x10^{-4}$ and $2.9x10^{-3}$ mg, NDEA amounts were between $3.3x10^{-4}$ and $8.8x10^{-3}$ mg, the amounts of NDMA in each tablet of drugs with candesartan active ingredient were between $1.4x10^{-3}$ and $4.2x10^{-3}$ mg, NDEA amounts were between $1.4x10^{-3}$ and $2.9x10^{-3}$ mg. The amount of NDMA in each tablet of the drug with the active ingredient of telmisartan was determined as $1.2x10^{-3}$ and the amount of NDEA was determined as $4.3x10^{-4}$. The acceptable daily intake limits specified by the European Medicines Agency and the Food and Drug Administration are 96 ng/day for NDMA and 26.5 ng/day for NDEA. When these values are expressed in milligrams, they will be $9.6x10^{-5}$ mg for NDMA and $2.65x10^{-5}$ mg for NDEA. When Table 4 is examined, it is seen that the values obtained are above the acceptable intake limits even if one tablet was taken per day.

Table 4. Amounts of *N*-nitrosodimethylamine and *N*-nitrosodiethylamine in each tablet of the drug samples examined

Active Ingredient of the Tablet	Amount of Active Ingredient in the Tablet (mg)	NDMA (mg/tablet)	NDEA (mg/tablet)
Valsartan	160	$6.5x10^{-3}$	$2.2x10^{-3}$
Valsartan	160	$1.1x10^{-3}$	$2.2x10^{-3}$
Valsartan	160	$1.4x10^{-2}$	$5.3x10^{-4}$
Valsartan	160	$1.1x10^{-2}$	$4.4x10^{-4}$
Valsartan	160	$4.2x10^{-3}$	$2.9x10^{-3}$
Valsartan	160	$3.2x10^{-3}$	$5.8x10^{-4}$
Losartan	100	$8.5x10^{-3}$	$5.1x10^{-3}$
Losartan	100	$1.7x10^{-2}$	$4.1x10^{-3}$
Losartan	50	$6.9x10^{-3}$	$6.9x10^{-4}$
Losartan	50	$1.2x10^{-2}$	$2.9x10^{-3}$
Irbesartan	300	$2.5x10^{-3}$	$1.0x10^{-3}$
Irbesartan	150	$6.4x10^{-3}$	$9.6x10^{-4}$
Irbesartan	150	$8.5x10^{-3}$	$1.8x10^{-3}$
Telmisartan	80	$1.2x10^{-3}$	$4.3x10^{-4}$
Olmesartan	40	$2.9x10^{-3}$	$8.8x10^{-3}$
Olmesartan	40	$3.6x10^{-4}$	$8.5x10^{-4}$
Olmesartan	20	$1.6x10^{-3}$	$3.3x10^{-4}$
Kandesartan	16	$2.1x10^{-3}$	$2.9x10^{-3}$
Kandesartan	8	$1.4x10^{-3}$	$1.7x10^{-3}$
Kandesartan	8	$4.2x10^{-3}$	$1.4x10^{-3}$

Table 5 was created in order to compare the amounts of nitrosamines detected in the examined samples with the values in the literature. When Table 5 is examined, it can be seen that the values we obtained for drugs containing the active ingredient valsartan are close to the values in the literature. However, it seems that the values we obtained for drugs containing the active ingredients losartan and irbesartan are higher than the studies in the literature. Since there is no information in the literature about the NDMA and NDEA contents of drugs containing the active ingredients telmisartan, olmesartan and candesartan, no comparison could be made. As mentioned above, there are many factors that contribute to the formation of nitrosamines in drugs. Contaminated starting materials and intermediates, reagents, solvents, catalysts, errors made in the production process, recovered and recycled materials, and manufacturers without sufficient process knowledge are among these. In addition, nitrosamines may

form after the drugs are produced, depending on storage conditions, packaging materials and degradation processes of active substances. Taking all these factors into consideration, in many countries, necessary precautions have begun to be taken and strict controls have begun to be carried out during and after the production stages. It is thought that the lower amounts of nitrosamines detected in studies in the literature compared to our study are due to the reasons mentioned above.

Table 5. Comparison of the amounts of nitrosamines detected in the analyzed samples with the values in the literature

Active Ingredient of the Drug	NDMA (mg kg^{-1})	NDEA (mg kg^{-1})	Reference
Valsartan	3.43 – 34.14	1.09 – 6.78	This study
Valsartan	0.004	----	[11]
Valsartan	0.10 – 137.60	0.07 – 6.90	[12]
Valsartan	0.06 – 99.79	0.11 – 8.84	[22]
Valsartan	17.57	----	[16]
Valsartan	0.01518 – 59.3	----	[18]
Losartan	18.41 – 67.05	2.96 – 16.05	This study
Losartan	----	0.08 – 0.23	[12]
Losartan	----	0.07 – 0.20	[22]
Irbesartan	4.73 – 27.40	1.94 – 5.88	This study
Irbesartan	----	0.11 – 0.12	[12]
Irbesartan	----	0.10 – 0.14	[22]

Today, it is known that nitrosamines are mutagenic, carcinogenic and teratogenic. While nitrosamines, which are extremely harmful to human health, were previously found in water, processed foods and cosmetic products, they began to be found in medicines after 2018 [21]. Since these drugs are used in the treatment of high blood pressure and type 2 diabetes, they are used by many people over a certain age. Therefore, it is of great importance to take the necessary precautions to prevent the formation of nitrosamine impurities.

Within the scope of this study, 20 different drugs containing sartan and its derivatives were examined, and both NDMA and NDEA were detected in all of the tablets examined. The FDA's recommended method was used to determine NDMA and NDEA levels, and as a result, it was seen that the amounts of both impurities determined were above acceptable limit values. Thus, the nitrosamine contents of some drugs containing sartan and its derivatives used in Turkey have been revealed. It is of great importance as it is the first study conducted on this subject in our country. Considering that the presence of nitrosamines has been found not only in sartan group drugs but also in many drugs with different active ingredients in various countries, it is obvious that similar studies should be carried out. In this context, it is thought that the study carried out will shed light on the conduct of similar studies and set an example.

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AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

ETHICS COMMITTEE APPROVAL

The authors declare that the ethics committee approval is not required for this study.

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