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Evaluation of Nicotine Transdermal Patches Available on the Domestic Market

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Abstract: The use of transdermal patches with nicotine is a better way to quit smoking because it ensures a similar concentration of nicotine in the blood as when smoking and reduces the morning desire for a cigarette. The aim of this work was to analyze the behavior of the matrix with the active substance under conditions that are close to skin conditions. A total of 3 samples were collected from local market. The analysis was performed after 0.5, 1, 4, 10, 16 and 24 hours for each sample. The concentration of released nicotine for samples at 50 RPM ranged in the following range: sample 1 43.87 %-115.23 %; sample 2 40.56 %-114.70 %; sample 3 43.53 %-117.13 %. The concentration of released nicotine for the samples at 100 RPM ranged in the following range: sample 1 45.14 %-120.82 %; sample 2 49.05 %-120.79 %; sample 3 44.73 %-118.51 %. It was determined that most of the nicotine is released already after 4 hours. The samples also show very similar concentration results after 10 hours, and for all three samples the result was 0.096 mg/ml.

INTRODUCTION

Nicotine is the main psychoactive compound in tobacco and has driven its widespread use since ancient times. It is a tertiary amine composed of pyridine and pyrrolidine rings (Figure 1). Predominantly found in its (S)-nicotine form, it can constitute up to 3% of dried Nicotiana tabacum leaves.In some tobacco species, such as Nicotiana rustica, it can be present in much higher concentrations, around 14% (Sansone et al., 2023; Benowitz et al., 2009).

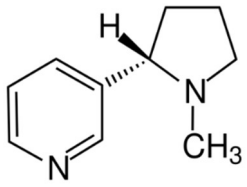

Figure 1: Chemical structure of nicotine

Nicotinic acetylcholine receptors are members of a superfamily of ligand-gated pentameric ion channels, and are widely distributed in the living world, from plants to mammals. These receptors can have different roles that depend on their localization in the tissue. In neural tissues, they are involved in cognition, addiction and cell growth, while present in other tissues, they contribute to various functions, such as inflammation and immunity (Garduño-Sánchez et al., 2023). The biological effects of nicotine are diverse and include negative effects on the cardiovascular system and addiction, as well as positive effects, such as improving cognitive functions in some conditions (Hall et al., 2014; Wang et al., 2023).

Once tobacco smoke reaches the alveoli, nicotine is rapidly absorbed, and blood concentrations rise rapidly during smoking. After inhalation, large amounts reach the brain within about 10 to 20 seconds, crossing the blood-brain barrier.Nicotine is also well absorbed through the skin. It is extensively metabolized in the liver, and six primary metabolites have been identified. It is excreted by glomerular filtration and tubular secretion, thus largely via the kidneys (Benowitz et al., 2009).

Nicotine can be used in experimental pharmacology, as a pesticide, and to alleviate withdrawal symptoms, or as an aid to smoking cessation. Various formulations of nicotine replacement therapy, such as nicotine gum, transdermal patch, nasal spray, inhaler, sublingual tablets, and lozenges, are commercially available and are intended for the indication of smoking cessation (Choi et al., 2003).

Transdermal patches represent a special pharmaceutical form of a drug and can be used in various indications. By using this form, it is possible to avoid numerous problems associated with, for example, oral administration of an active principle, such as: first-pass metabolism, degradation by digestive enzymes, degradation of the drug in the acidic gastric medium, irritation of the gastrointestinal mucosa, etc. It also enables use in patients who cannot receive the drug in another way or when a specific condition requires gradual release of the drug over a longer period of time. Currently, different transdermal patches are available on the market for use in the treatment of smoking cessation, pain relief, osteoporosis, contraceptive patches, angina pectoris and cardiac disorders. However, formulations that would be more suitable for the delivery of some more challenging drugs are in various stages of development. When formulating transdermal patches, special attention should be paid to the physicochemical properties of the active and inactive components, as well as the possibility of application over a longer period of time (Al Hanibali et al., 2019).

The use of nicotine patches compared to chewing gum has certain advantages, as it primarily provides therapeutic levels of nicotine from the first day of treatment with minimal effort. Patches are commercially available in three doses (sizes) and most smokers start with the highest dose for the first 4 to 8 weeks, followed by a systemic withdrawal period of 2 to 8 weeks. During this period, progressively smaller doses are used. Two types of nicotine patches are available, reservoir and matrix passive diffusion, where one type is worn only when awake, during the day, with the highest dose of 15 mg of nicotine during 16 hours, and the other can be worn both during the day and overnight, and delivers 21 mg of nicotine during 24 hours (Jarvis and Sutherland, 1998).

The aim of this work was to study the scientific literature and provide the latest information in the field transdermal applications of nicotine. The main aims included the following: determining the release of contents from the patch sample using the HPLC method, measure the percentage and concentration of released nicotine by sampling points, and compare and discuss the obtained results.

EXPERIMENTAL

Chemicals

The following chemicals and reagents were used for purposes of analysis: ammonium acetate (Carlo Erba), ammonium hydroxide (Sigma Aldrich), potassium hydroxide (Merck), acetonitrile, HPLC purity (Fischer chemical).

Apparatus and methods

For the dissolution of transdermal patches in the European Pharmacopoeia (Ph. Eur. XI), three devices are listed: apparatus with a blade above the disc, apparatus with a spatula above the cell and rotating cylinder apparatus. Which apparatus will be used depends on the composition, type and dimensions of the patch (Council of Europe, 2023). In this work, an apparatus with a spatula above the disk was used (Figure 2.).

The principle of the disk is to hold the patch at the bottom of the glass of the dissolution apparatus, whereby the space between the bottom of the glass and the disk is minimal. The disk keeps the patch flat and facing the scapula. The distance between the blade and the disk is 25±2 mm. The medium temperature is 32±0.5 °C (skin temperature). The glasses are covered to reduce evaporation of the medium.

The analysis was performed on an Erweka DT 826 dissolution apparatus. As a dissolving medium potassium dihydrogen phosphate buffer, pH = 5.0 was used. The phosphate buffer is made by dissolving 2.72 g of KH_2PO_4 in 1000 ml of water, and adjusting the pH with a 1 M solution of potassium hydroxide (KOH). Blade rotation speed was 50 and 100 revolutions per minute. The total duration of the dissolution was 24 hours, with sampling at several points starting from the 30th minute and after 1, 4, 10, 16 and 24 hours. Medium volume was 500 ml and sampling volume was 10 ml with medium change.

Six glasses of the dissolution apparatus were filled with a specified volume of medium. The apparatus parameters were then set, and the system was allowed to stabilize at the designated values. Once stabilized, six discs containing properly placed samples were immersed in the glasses, initiating the analysis.

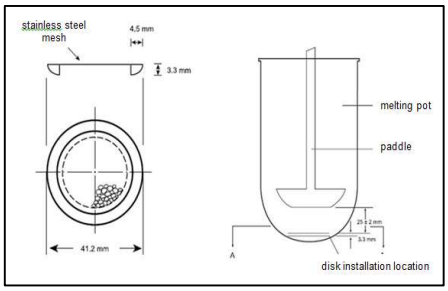

Figure 2: Apparatus with a spatula above the disk

To set the chromatographic parameters, a modified HPLC method was used for rapid and simultaneous determination of nicotine (Jablonski et al., 2006; Vlasceanu et al., 2016).

Table 1: HPLC analysis parameters

MP A	Acetate buffer (pH = 10)	Oven temperature	40 °C
MP B	Acetonitrile	Autosampler temperature	20-25 °C
Flow rate of MP	1.8 ml/min	Sample injection volume	25µl
Detection (UV)	260 nm	Analysis time	40 min

Gradient program of the mobile phase for HPLC separation

Time (min)	MP A (vol %)	MP B (vol%)
0	100	0
30	65	35
32	100	0
40	100	0

Samples

The Patches containing nicotine as an active substance were used for the analysis and were randomly marked as Sample 1-3. The following commercially available preparations were tested: Nicorette 15 mg/16 h, Nicorette 25 mg/16 h and NicoretteSkin 25 mg/16h (Figure 3.).

Figure 3: Test samples (Nicorette 15mg/16h, Nicorette 25mg/16h and NicoretteSkin 25mg/16h)

RESULTS AND DISSCUSION

Release profiles of samples at 50 RPM

For the first sample analysis, a medium volume of 500 ml was selected, and the speed of rotation of the paddle per minute was set to 50 RPM. After the medium was prepared and the apparatus reached the set parameters, the analysis of six samples was started. The autosampler is set to sample after 30 minutes, then after 1, 4, 10, 16 and after 24 hours. After dissolution, the analysis was continued on the HPLC apparatus. The chromatograms of all samples are shown in Figure 4. Results are shown in Table 2.

Table 2: Released nicotine (%) in different time intervals at 50 RPM

#	Time (h)	Sample 1 (% of nicotine)	Sample 2 (% of nicotine)	Sample 3 (% of nicotine)
1	0.5	43.86	40.56	43.53
2	1	61.06	60.89	60.72
3	4	99.43	97.74	100.06
4	10	111.20	109.69	111.76
5	16	113.26	112.14	114.75
6	24	115.23	114.70	117.13

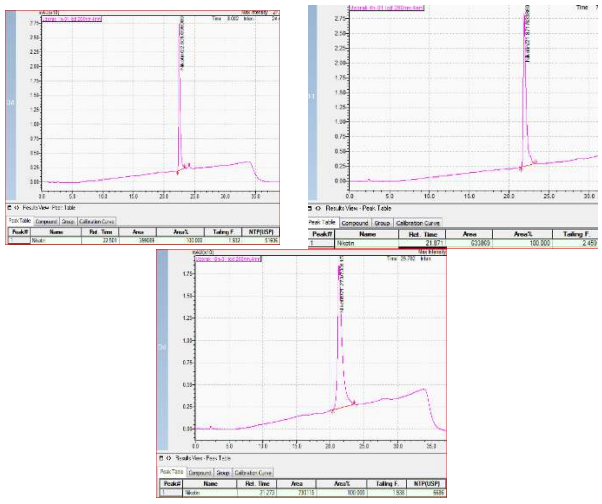

Figure 4: Chromatograms of samples

Release profiles of samples at 100 RPM

For the second sample analysis, a medium volume of 500 ml was selected, and the speed of rotation of the paddle per minute was set to 100 RPM. After the medium was prepared and the apparatus reached the set parameters, the analysis of six samples was started. The autosampler is set to sample after 30 minutes, then after 1, 4, 10, 16 and after 24 hours. After dissolution, the analysis was continued on the HPLC apparatus.
Results are shown in Table 3.

Table 3: Released nicotine (%) in different time intervals at 100 RPM

#	Time (h)	Sample 1 (% of nicotine)	Sample 2 (% of nicotine)	Sample 3 (% of nicotine)
1	0.5	45.15	46.05	44.73
2	1	62.95	65.92	62.27
3	4	103.85	104.35	102.50
4	10	116.33	116.05	113.16
5	16	118.70	118.08	115.91
6	24	120.82	120.79	118.31

Comparison of results at 50 RPM and 100 RPM

Table 4. and Table 5. show RSD values for all samples at 50 RPM and 100 RPM.

Table 4: RSD (%) values in different time intervals at 50 RPM

#	Time (h)	Sample 1 (% RSD)	Sample 2 (% RSD)	Sample 3 (% RSD)
1	0.5	0.98	3.95	1.68
2	1	1.07	1.48	1.64
3	4	1.14	1.36	1.29
4	10	1.19	1.52	0.84
5	16	1.18	1.64	1.35
1	0.5	0.98	3.95	1.68

Table 5: RSD (%) values in different time intervals at 100 RPM

#	Time (h)	Sample 1 (% RSD)	Sample 2 (% RSD)	Sample 3 (% RSD)
1	0.5	2.16	2.45	3.62
2	1	1.37	2.21	3.64
3	4	1.48	2.12	2.84
4	10	1.46	2.15	2.42
5	16	1.61	234	2.70
6	0.5	2.16	2.45	3.62

The RSD values of the samples show a rather uneven release of nicotine. If we follow the % RSD values, we can see that Sample 2 at RMP 50 has a large deviation, which is not the case for the other two Samples. High RSD values are not related to a specific sample, but are randomly scattered, which indicates possible differences in the patch formulations.
In Table 6. is shown average concentration (mg/ml) of released nicotine for all samples and time intervals at 50 RPM and 100 RPM. Figure 5. and Figure 6. show graphically the nicotine release profiles of all samples in the given time intervals.

Table 6: Average concentration (mg/ml) of released nicotine for all samples and time intervals at 50 RPM and 100 RPM

50 RPM				
#	Time (h)	Sample 1 (mg/ml)	Sample 2 (mg/ml)	Sample 3 (mg/ml)
1	0.5	0.038	0.035	0.038
2	1	0.052	0.052	0.052
3	4	0.083	0.082	0.084
4	10	0.092	0.091	0.092
5	16	0.092	0.091	0.093
1	0.5	0.092	0.091	0.093
100 RPM				
#	Time (h)	Sample 1 (mg/ml)	Sample 2 (mg/ml)	Sample 3 (mg/ml)
1	0.5	0.039	0.042	0.039
2	1	0.054	0.056	0.053
3	4	0.087	0.088	0.086
4	10	0.096	0.096	0.094
5	16	0.096	0.096	0.094
1	0.5	0.096	0.096	0.094

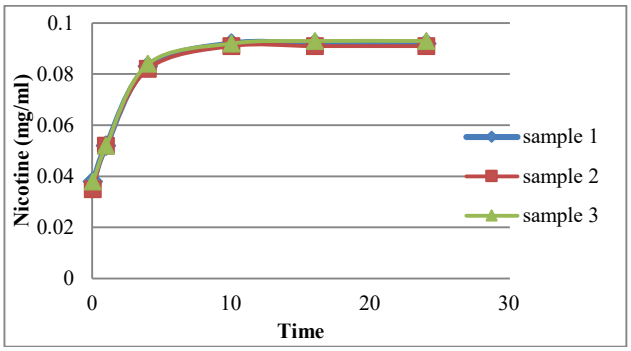

Figure 5: Graphical representation of released nicotine (mg/ml) in different time intervals at 50 RPM

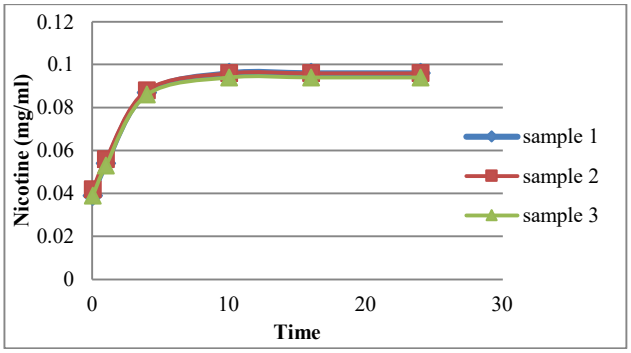

Figure 6: Graphical representation of released nicotine (mg/ml) in different time intervals at 50 RPM

CONCLUSION

Transdermal administration offers precise control over drug levels in the blood, allows for less frequent dosing, bypasses first-pass metabolism in the liver and gastrointestinal inactivation, enables easy treatment discontinuation, and provides a non-invasive method of drug delivery. Because of the advantages that transdermal application offers more than other methods of drug administration, intensive work is being done on its development. Disadvantages of transdermal patches are high production costs, which ultimately lead to a higher product price and aesthetic acceptability.

The aim of this work was to analyze the behavior of the matrix with the active substance under conditions that are close to skin conditions, and then to find a suitable method for HPLC determination of the content of the active substance in the samples. A total of 3 samples were collected from local market. The analysis was performed after 0.5, 1, 4, 10, 16 and 24 hours for each sample, and at revolutions of 50 RPM and 100 RPM. The concentration of released nicotine for samples at 50 RPM ranged in the following range (for the indicated time intervals): sample 1 43.87%-115.23%; sample 2 40.56%-114.70%; sample 3 43.53 %-117.13 %. The concentration of released nicotine for the samples at 100 RPM ranged in the following range (for the indicated time intervals): sample 1 45.14%-120.82%; sample 2 49.05%-120.79%; sample 3 44.73 %-118.51 %. It was determined that most of the nicotine is released already after 4 hours. The samples also show very similar concentration results after 10 hours, and for all three samples the result was 0.096 mg/ml.

A slightly different HPLC method was adopted and used in this study for a fast and simple screening of nicotine from transdermal patches. These tests have shown that on the basis of the used pharmacopoeia test „Paddle over Disc“ it is possible to successfully compare different formulations from the market and evaluate their quality.

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Summary/Sažetak

Upotreba transdermalnih flastera s nikotinom je bolji način za prestanak pušenja, jer osigurava sličnu koncentraciju nikotina u krvi kao kod pušenja i smanjuje jutarnju želju za cigaretom. Cilj ovog rada bio je da se ispita ponašanje matriksa s aktivnom supstancom u uslovima koji su bliski uslovima kože. Ukupno su prikupljena 3 uzorka s lokalnog tržišta. Analiza je obavljena nakon 0,5, 1, 4, 10, 16 i 24 sata za svaki uzorak. Koncentracija oslobođenog nikotina za uzorke na 50 obrtaja/min kretala se u sljedećem rasponu: uzorak 1 43,87 %-115,23 %; uzorak 2 40,56 %-114,70 %; uzorak 3 43,53 %-117,13 %. Koncentracija oslobođenog nikotina za uzorke pri 100 obrtaja/min kretala se u sljedećem rasponu: uzorak 1 45,14 %-120,82 %; uzorak 2 49,05 %-120,79 %; uzorak 3 44,73 %-118,51 %. Utvrđeno je da se većina nikotina oslobađa već nakon 4 sata. Uzorci također pokazuju vrlo slične rezultate po pitanju koncentracije nikotina nakon 10 sati, a za sva tri uzorka rezultat je bio 0,096 mg/ml.