Comparison of Nitrazepam Tablets Release Profiles

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The amount of bioavailable active substance is essential in demonstrating therapeutic drug efficacy. *In vitro* technique regarding the comparison of released quantity of active substance from drug can be a relevant anticipation test for *in vivo* drug characteristics. Comparison is usually conducted between test generic drug and a referent, innovative product (1). This comparative study shows the release of nitrazepam content from preparations Trazem® tablets 5 mg (Bosnalijek - test product) and Mogadon® tablets 5 mg (ICN Iberica S.A., Barcelona, Spain - referent product).
Based on the results obtained from the analysis, similarity factor f_2 may be calculated. It is a parameter that, according to FDA guidelines (US Food and Drug Administration), measures similarity of dissolution profiles between two preparations. When two dissolution profiles are identical, $f_2 = 100$. In case when f_2 value ranges between 50 and 100, FDA defines that such two dissolution profiles may be considered similar (2).

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Introduction

Nitrazepam is a psychotropic drug, benzodiazepine derivative. Its basic effect is hypnotic, and it also has anxiolytic, anticonvulsive and myorelaxant properties. All the effects of this drug are a result of potentiating of the gamma-aminobutyric acid (GABA) activity in the central nervous system. Following oral application, nitrazepam is well and rapidly absorbed from the gastrointestinal system. Peak plasma concentration is achieved in approximately 90 minutes. By most of its part, the drug binds to plasma proteins. Nitrazepam is characterized by a long elimination half-life that ranges between 24 and 29 hours.

Experimental part

In vitro dissolution (content release) of nitrazepam was performed according to general procedure USP<711> apparatus 2, Method of rotating paddle. Use 0.1 mol/l of hydrochlo-

ric acid, 900 ml as a medium, at temperature of 37 °C ± 0.5 °C, with mixing speed 50 rpm. Sample medium was taken every 5 minutes during 30 minutes, and nitrazepam assay was determined by spectrophotometric method.

Principle:
Spectrophotometric method

Reagents:
Standard solution

Weigh 12.5 mg of Nitrazepam standard into 50 ml volumetric flask, dissolve in 0.5% v/v solution of hydrochloric acid in methanol and dilute with the same to volume.

Pipette 1 ml of this solution into 50 ml volumetric flask, dilute with 0.1 mol/l hydrochloric acid to volume.

Test solution

Test is to be performed on 12 tablets. The solution from each vessel is to be taken every 5 minutes.

Procedure:

Measure the absorbance of the test solution in 1 centimeter flow cell and the absorbance of the standard solution at 280 nm in a 1 centimeter cell, using 0.1 mol/l hydrochloric acid as blank (Table 1, 2).

Table 1. Test parameters

Apparatus 2	Method of rotating paddle
Medium	Hydrochloric acid 0.1 mol/l, 900 ml
Temperature	37 °C ± 0.5 °C
Mixing Speed	50 rpm
Number of Tested Tablets	12
Testing Cycle	5 min
Total Time	30 min

Table 2. Reagents and Standards

Reagents	All the reagents have analytical purity
Standard Substance	Nitrazepam working standard Assay of Nitrazepam 100.3 %

The following systems for dissolution were used: Erweka DT 80 and peristaltic pump IPC 80. The spectrophotometric analysis was performed using UV-VIS spectrophotometer Shimadzu UV-1601.

Table 3. Review of comparison of dissolution profile of TRAZEM® tablets 5 mg with reference to MOGADON® tablets 5 mg

		MOGADON® tablets 5 mg						TRAZEM® tablets 5 mg					
Time (min)	Tab	5	10	15	20	25	30	5	10	15	20	25	30
Amount of nitrazepam Dissolved (%)	1	70.97	78.35	79.11	79.11	7853	78.54	78.92	82.89	82.33	81.76	81.00	80.05
	2	78.54	82.70	82.51	82.14	81.57	81.00	77.22	82.14	82.14	81.38	80.62	79.87
	3	65.29	72.48	74.00	74.94	75.13	75.32	78.73	81.76	81.38	80.62	80.05	79.11
	4	69.08	76.46	78.16	78.92	79.11	78.92	70.02	83.46	83.65	83.08	82.33	81.38
	5	71.16	79.30	79.68	79.68	79.30	78.92	64.54	77.97	78.92	78.54	77.78	77.22
	6	72.48	78.73	80.43	81.00	81.00	81.19	67.56	83.65	85.16	84.79	84.03	83.46
	7	78.92	82.14	82.14	81.57	80.81	80.24	88.19	94.16	93.49	92.73	91.79	91.03
	8	75.89	80.62	80.62	80.05	79.49	78.92	81.76	88.19	88.38	87.62	86.87	85.92
	9	65.48	77.03	78.92	79.11	78.73	78.35	81.57	90.27	89.52	88.57	87.81	86.87
	10	59.99	75.89	77.59	77.40	76.84	76.27	78.92	88.19	88.19	87.25	86.49	85.73
	11	77.40	79.11	78.54	78.92	77.97	76.84	81.38	87.25	86.68	86.11	85.16	84.60
	12	66.81	78.73	81.19	81.57	81.38	81.00	81.38	92.55	91.79	91.03	90.27	89.52
Mean		71.00	78.46	79.41	79.53	79.17	**78.79**	77.52	86.03	85.97	85.29	84.52	**83.73**
SD		5.97	2.79	2.30	2.01	1.92	1.91	6.79	4.83	4.46	4.36	4.31	4.31
RSD		8.41	3.56	2.89	2.52	2.42	2.42	8.76	5.61	5.19	5.11	5.10	5.14
f_2							**67.4**						

SD - Standard deviation, RSD - Relative standard deviation, f_2 - Factor of similarity

Results

The results of examination are given in tables and graphs (Table 3; Figure 1, 2, 3).

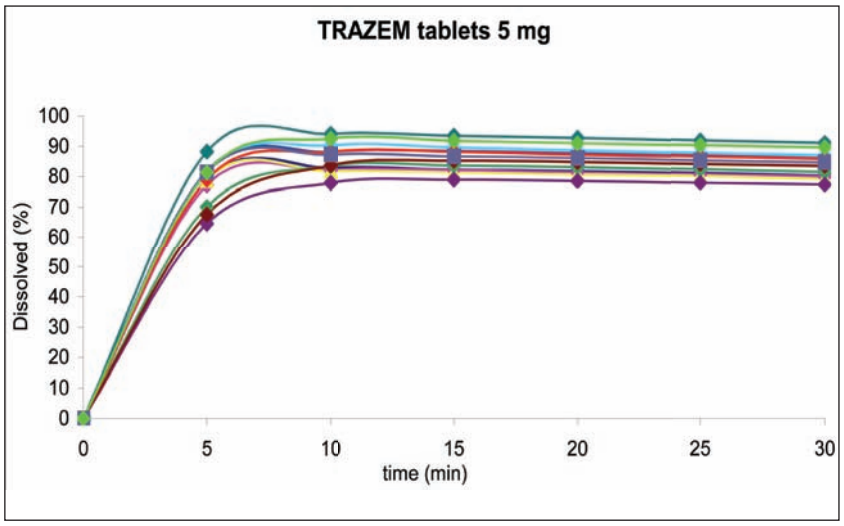

Figure 1. Graph review of dissolution profile of nitrazepam for TRAZEM® tablets 5 mg

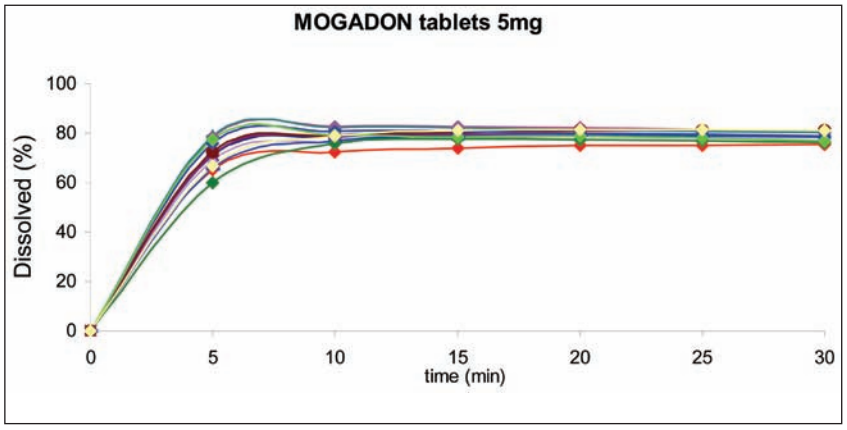

Figure 2. Graph review of dissolution profile of nitrazepam for MOGADON® tablets 5 mg

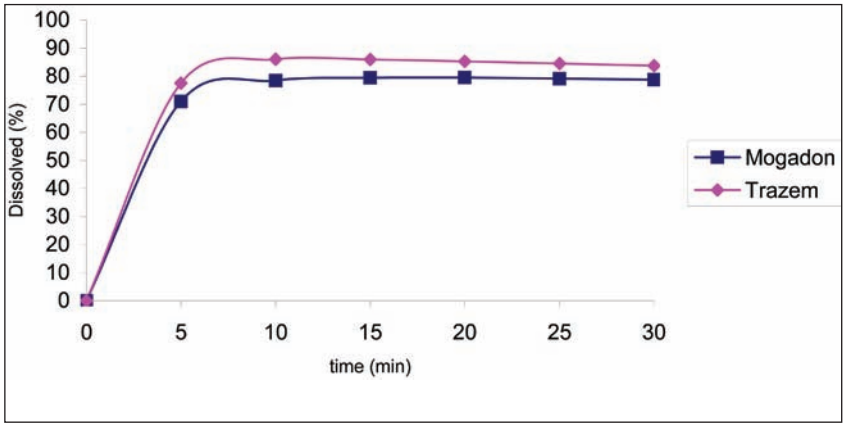

Figure 3. Graph review of average value of dissolution profile of nitrazepam for TRAZEM® tablets 5 mg (◆) and MOGADON® tablets 5 mg (■)

Figure 1 represents graphical display of nitrazepam release from Trazem® tablets (12 samples of tablets) in the sampling cycle of every five minutes for the period of 30 minutes.

Figure 2 represents graphical display of nitrazepam release from Mogadon® tablets (12 samples of tablets) in the sampling cycle of every five minutes for the period of 30 minutes.

Figure 3 represents graphical display of mean values of nitrazepam release profile for Trazem® tablets 5 mg (◆) and Mogadon® tablets 5 mg (■).

In view of the results, factor of similarity f_2, which is a measure of similarity of dissolution profile for two preparations, can be calculated.

For calculating f_2 the following formula is used:

$$f_2 = 50 \cdot \log_{10}\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \cdot 100\right\}$$

If f_2 value is between 50 and 100, the two dissolution profiles are to be considered similar (3).

The results showed the factor of similarity between TRAZEM® tablets 5 mg/ and MOGADON® tablets 5 mg to be 67.4.

Conclusion

Based on the conducted comparative analysis regarding the release of nitrazepam content from said preparations, the following has been established:

1. After 30 minutes of testing, 78.79% of nitrazepam from Mogadon® tablets and 83.73% of nitrazepam from Trazem® tablets were released (Table 3).

2. Similarity factor of release profiles was 67.4, which points that those two products have similar dissolution profiles.

Based on the presented obtained results, it can be concluded that the tested preparations are similar.

References

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