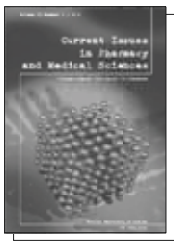

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Dissolution testing of tablets within and beyond expiration date with olanzapine as pharmaceutical ingredient

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ABSTRACT

The expiration date is a guarantee from the manufacturer that a drug product will remain chemically stable - and thus maintain its full potency and safety - prior to that date. Authors of this study have checked whether tested drug product has a similar dissolution profile beyond and within expiration date. In this paper, dissolution study of Zyprexa (Olanzapine as an Active Pharmaceutical Ingredient) 10 mg tablets was conducted in three different mediums, in the same way as comparison in-vitro and in-vivo tests during investigation of bioavailability and bioequivalence at clinical trials phase. Obtained results demonstrated that dissolution profiles of tested and reference product are essentially similar, which was statistically confirmed by means of similarity factor.

Keywords: olanzapine, dissolution test, HPLC, expiration date of drug product

INTRODUCTION

A study relevant to drug products beyond the expiration date conducted by Anna Serafin (Medical University of Łódź, Department of Hospital Pharmacy, Faculty of Pharmacy) was base to write this paper. Doctoral thesis successfully demonstrated, that it is possible for many outdated drug products to achieve appropriate content of active pharmaceutical ingredient, thus it is interested to investigate others physicochemical parameters such as dissolution.

A subject of this study 2-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine hereinafter called olanzapine, belongs to class of second generation derivative antipsychotic agents, the so-called atypical antipsychotics. As atypical antipsychotics are generally classified those drugs, which in contrast to classical antipsychotics (e.g. haloperidol), have greater affinity for serotonin 5-HT2 receptors than for dopamine D2 receptors and cause fewer extrapyramidal symptoms (EPS) and improve negative symptoms[2]. Olanzapine is well absorbed following oral administration in both the fed and fasted states, and is extensively metabolized with higher clearance in male than in female [12].

Dissolution testing has become an essential tool in the pharmaceutical industry at various stages of development, manufacturing and marketing [4]. Such tests are a suitable method for quality control and in-vivo versus in-vitro correlation of release active substance from drug product. Dissolution profile tests were performed in order to assess the possibility of use tablets with Olanzapine as an active pharmaceutical ingredient which are beyond expiration date. Different dissolution media were used: 0.1 M hydrochloric acid, phosphate buffer solution pH 4.5 and phosphate buffer solution pH 6.8. The concentrations of Olanzapine were measured by validated HPLC method for the oral tablets. Full description of validation of Olanzapine dissolution method will be thoroughly presented in doctoral thesis *Dissolution testing of tablets within and beyond expiration date – selected finished medicinal products from drugs acting on the central nervous system.*

MATERIALS AND METHODS

Chemicals and standard

Hydrochloric acid 35–38 % was obtained from Chempur, sodium hydroxide, potassium dihydrogen phosphate, ortho-phosphoric acid 85%, trifluoroacetic acid and acetonitrile (HPLC grade) were used from J.T. Baker. Olanzapine – batch number 150404 (in-house reference standard) has been used as a working standard for in vitro dissolution tests. Identification of this substance has been confirmed by IR and HPLC method. The potency of working standard (99.57%) has been taken into consideration in all calculations.

Instruments

HPLC system equipped Waters Alliance 2695 Separation Module (autosampler with cooler, gradient pump), Waters 2487 Dual Absorbance Detector, column oven. The data was recorded using Empower2 software. As dissolution system Pharma Test PTWS 3E (paddle) was equipped.

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Chromatographic conditions

The analysis was carried out on Zorbax SB-C18 column, 1.8 µm, 4.6 mm x 50 mm using a mobile phase acetonitrile: 0.1% trifluoroacetic acid (in ratio 17:83 v/v) with UV detection at 259 nm. Flow rate of 1 ml/min was applied, the column was maintained at 25°C throughout the analysis. A 10 µl of tested sample was injected and the chromatogram was recorded for 3 min. Retention time of Olanzapine was 2.0 min. ± 0.3 min. Mobile phase was prepared by mixing 10 ml of trifluoroacetic acid with 1000 ml of water and 170 ml of acetonitrile was added to obtain final solution.

Dissolution conditions

Following parameters of the dissolution method were applied as below:

- Apparatus: type paddle,
- Dissolution media:
  a) 0.1 M hydrochloric acid water solution,
  b) Phosphate buffer solution pH 4.5,
  c) Phosphate buffer solution pH 6.8,
- Volume: 1000 ml,
- Agitation: 100 rpm,
- Sampling time points: 10, 15, 20 and 30 minutes.

Dissolution medium preparation:

- *Preparation of 0.1 M hydrochloric acid water solution*
  800 ml of water was transferred to 1000 ml volumetric flask. 8.9 ml of HCl was added and it was diluted to 1000 ml with water.
- *Preparation of phosphate buffer solution pH 4.5*
  6.80 g of KH_2PO_4 was dissolved in 1000 ml of water. Obtained pH value was 4.5 ± 0.05.
- *Preparation of phosphate buffer solution pH 6.8*
  Solution A: 13.6 g of KH_2PO_4 was weighed and transferred into a 500 ml volumetric flask, next it was diluted to 500 ml with water.
  Solution B: 4.0 g of NaOH was weighed and transferred into a 500 ml volumetric flask, next it was diluted to 500 ml with water. The solutions were stirred until complete dissolution.
  Dissolution medium: 250 ml of solution A and 118 ml of solution B were transferred to 1000 ml volumetric flask and diluted to 1000 ml with water. To obtain the pH value 6.8 ± 0.05, 10 % solution of H_3PO_4 was added.

Drug products

General information:

- Appearance of tablets: white, biconvex, film-coated tablets; 10 mm in diameter, with blue inscription "LILLY 4117" printed on one side of the tablet.
- Quality composition of the product:
  Active substance – Olanzapine,
  Excipients – lactose monohydrate, hydroxypropylcellulose, crospovidone, microcrystalline cellulose, magnesium stearate, hypromellose, titanium dioxide, carnauba wax, shellac, macrogol, polysorbate 80, indigo carmine (E132).

Detailed information:

- Product name: Zyprexa 10 mg oral tablets
- Origin of the product: Spanish market
- Manufacturer: Eli Lilly Nederland BV, the Netherlands
- Batch number: A088877 (beyond expiration date – 05.2007), A651000 (within expiration date – 02.2012)

Zyprexa tablets were stored throughout whole period in the following conditions: temperature 25 ± 2°C and relative humidity 60 ± 5% which is in line with manufacturer recommendations. In this study the effect of time was only taken into account. No other factors such increased temperature and relative humidity were examined in the context of dissolution profiles.

The method for dissolution of olanzapine from uncoated oral tablets has been validated in order to demonstrate that the developed technique is suitable for its intended purpose. The validation includes study of the selectivity, the linearity, the accuracy and the precision of the method. Moreover the additional method for control of degradation products was developed and it has been fully validated on the basis of Q2(R1) 'Validation of Analytical Procedures: Text and Methodology'. Selectivity of the method was proven for placebo and degradation products. Prior to dissolution testing of Zyprexa, imputity test of batch beyond expiration date and within expiration date were conducted. Each single unknown impurity was below 0.1% and total impurities were 0.39% and 0.23% (for A088877 and A651000 batch respectively). Obtained results are much lower than bias of dissolution method and therefore will be disregarded in the calculation.

RESULTS AND DISCUSSION

Dissolution tests have been conducted on 12 dosage units of the tested product: Zyprexa 10 mg tablets (batch no.: A088877) versus 12 dosage units of the reference product: Zyprexa 10 mg tablets (batch no.: A651000).

For the comparison of dissolution profiles, similarity factor f_2 was applied. This statistical method is gaining popularity due to its recommendation by various regulatory committees [5–7]. Dissolution profiles are considered similar if the calculated f_2 value is between 50 and 100.

The similarity factor f_2 as defined by FDA and European Medicines Agency is a logarithmic reciprocal square root transformation of one plus the mean squared (the average sum of squares) differences of drug percent dissolved between the test and reference products:

$$f_2 = 50 \cdot \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}\left|R_t - T_t\right|^2\right]^{-0,5} \cdot 100\right\}$$

where:

- f_2 – similarity factor
- n – number of time points
- R_t – is the mean percent reference drug dissolved at time t after initiation of the study
- T_t – is the mean percent test drug dissolved at time t after initiation of the study

An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar [3, 10].

For batch-to-batch quality testing, selection of the dissolution medium is based, in part, on the solubility data and the dose range of the drug product in order to ensure that sink conditions are met. The term sink conditions is defined as the volume of medium at least greater than three times that required to form a saturated solution of a drug substance[1]. Each mediums chosen to determined the similarity of products within expiration date and beyond expiration date fulfill the requirements of sink conditions.

The media properties such as pH, solubility of active drug product, ionic strength, wetting ability, buffer capacity were taken under consideration during the optimising of dissolution methods[11].

Raw data have been collected and shown in table form (tables 1–3).

Table 1. Dissolution profiles of Zyprexa 10 mg tablets within expiration date (batch no.: A651000) and beyond expiration date (batch no.: A088877) in 0.1 M hydrochloric acid water solution

Zyprexa batch no.: A651000				Zyprexa batch no.: A088877			
Time [min.]	Dissolution [%]	Average	RSD	Time [min.]	Dissolution [%]	Average	RSD
10	61.9	**62.4**	4.8	**10**	74.6	**63.0**	11.6
	60.7				60.9		
	59.1				69.6		
	65.9				56.2		
	61.6				61.6		
	67.4				70.7		
	61.8				52.7		
	59.4				69.3		
	59.4				57.7		
	64.9				63.1		
	59.9				52.5		
	66.5				66.8		
15	89.1	**87.2**	3.3	**15**	97.3	**90.3**	4.3
	86.2				86.8		
	84.6				94.2		
	85.8				87.0		
	92.9				87.1		
	85.2				90.5		
	88.0				88.4		
	84.1				93.4		
	85.0				86.5		
	85.2				93.6		
	91.6				85.6		
	88.1				92.7		
20	99.6	**97.8**	1.4	**20**	99.0	**99.0**	3.3
	96.5				94.6		
	96.3				97.4		
	99.0				95.6		
	99.4				94.4		
	98.9				97.2		
	98.7				100.8		
	96.5				103.6		
	95.3				100.5		
	98.0				103.4		
	97.7				99.0		
	98.2				102.7		
30	103.6	**100.9**	1.6	**30**	100.1	**101.7**	3.7
	100.3				96.5		
	98.3				97.8		
	101.8				97.5		
	101.3				97.5		
	102.1				100.2		
	102.6				104.3		
	99.1				105.9		
	99.0				105.4		
	101.0				105.6		
	100.1				103.8		
	101.6				105.5		

Table 2. Dissolution profiles of Zyprexa 10 mg tablets within expiration date (batch no.: A651000) and beyond expiration date (batch no.: A088877) in phosphate buffer solution pH 4.5

Zyprexa batch no.: A651000				Zyprexa batch no.: A088877			
Time [min.]	Dissolution [%]	Average	RSD	Time [min.]	Dissolution [%]	Average	RSD
10	49.6	**66.2**	13.5	**10**	68.2	**60.5**	14.2
	62.0				63.0		
	71.7				65.5		
	75.0				51.2		
	63.4				46.5		
	72.6				65.7		
	50.8				47.8		
	62.9				52.2		
	72.8				67.0		
	76.1				62.0		
	65.0				70.5		
	72.8				66.2		
15	78.4	**84.7**	4.4	**15**	77.0	**82.5**	6.8
	88.5				84.4		
	85.5				85.7		
	85.7				84.1		
	85.7				74.4		
	85.9				92.8		
	75.8				74.8		
	87.6				85.0		
	85.8				86.6		
	86.3				84.3		
	86.3				76.6		
	85.3				84.5		
20	90.6	**91.5**	2.1	**20**	88.8	**88.6**	3.2
	94.1				86.5		
	91.2				88.4		
	89.7				88.8		
	91.6				81.4		
	88.6				89.4		
	91.5				89.3		
	94.8				86.7		
	92.0				89.9		
	93.0				91.9		
	91.6				90.3		
	88.9				92.0		
30	95.9	**94.7**	1.7	**30**	91.6	**92.1**	3.1
	95.6				93.1		
	94.5				93.1		
	92.8				92.0		
	94.6				93.2		
	91.8				92.9		
	97.1				92.5		
	96.3				83.4		
	95.7				93.1		
	93.4				93.5		
	95.6				92.6		
	92.7				94.7		

Table 3. Dissolution profiles of Zyprexa 10 mg tablets within expiration date (batch no.: A651000) and beyond expiration date (batch no.: A088877) in phosphate buffer solution pH 6.8

Zyprexa batch no.: A651000				Zyprexa batch no.: A088877			
Time [min.]	Dissolution [%]	Average	RSD	Time [min.]	Dissolution [%]	Average	RSD
10	36.5	**46.4**	15.1	**10**	57.6	**49.7**	14.8
	39.7				37.7		
	47.9				47.6		
	59.2				55.4		
	48.1				45.0		
	58.9				55.3		
	48.3				57.5		
	42.2				37.6		
	43.0				47.3		
	47.9				55.4		
	41.9				44.9		
	42.8				54.8		
15	54.1	**68.8**	9.7	**15**	78.9	**69.4**	9.5
	66.4				60.5		
	66.7				74.1		
	78.3				70.6		
	60.7				61.5		
	77.7				73.6		
	70.1				74.4		
	70.9				60.5		

	67.9				73.8		
	72.6				70.4		
	71.1				61.3		
	68.7				73.0		
	67.0				78.9		
	83.0				74.6		
	77.2				81.7		
	84.7				81.9		
	68.0				76.6		
20	85.3	**78.6**	7.3	**20**	82.2	**80.0**	3.6
	80.3				78.7		
	79.8				84.0		
	78.0				81.3		
	81.5				81.7		
	80.2				76.4		
	78.1				82.2		

In order to comparison similarity of dissolution profiles, mathematical evaluations were performed. According to *Appendix I - Dissolution testing and Similarity of Dissolution Profiles of the GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr.*) published by The European Agency for the Evaluation of Medicinal Products states "Where more than 85% of the drug is dissolved within 15 minutes, dissolution profiles may be accepted as similar without further mathematical evaluation".

In accordance with aforementioned guideline *"The relative standard deviation or coefficient of variation of any product should be less than 20% for the first point and less than 10% from second to last time point"*. Therefore obtained variations (RSD) of each time point in three dissolution media are comparable and not statistically significant.

Table 4. Mathematical evaluations – similarity factor assessment

Similarity factor f_2 value			
Medium	0.1 M HCl	Phosphate buffer pH 4.5	Phosphate buffer pH 6.8
f_2 value	Not concerned mathematical evaluations are not necessary	69.7	82.1

As shown above, dissolution profiles of the Olanzapine tablets demonstrated release of the drug substance greater than 85% within 15 minutes (for 0.1M HCl), therefore it was accepted that dissolution profiles were similar. Similarity factor f_2 has been applied for statistical assessment of dissolution profiles similarity (table 4 – for phosphate buffer pH 6.8 and phosphate buffer pH 4.5). Obtained values are over 50, thus it has been proven that profiles are similar.

CONCLUSIONS

In this study it was concluded that Zyprexa 10 mg tablets with beyond expiration date have essentially similar dissolution profiles to Zyprexa 10 mg tablets within expiration date. In this connection tablets should be distributed in comparable way in human body and be expected as bioequivalence. Theoretically, in relation to dissolution profiles, Zyprexa 10 mg tablets could be use even 3 years after expiration date. Obviously it is prohibited to release such drug product to the market. Apart of the law regulations, there are many scientific aspects need to be explained, e.g. in-vivo clinical studies, physico-chemical tests of tablets, toxicology, etc. Thus the conclusions reported here for Olanzapine as active ingredient, must be interpreted with caution and just only in the light of in-vitro study.

Currently there are not many publications in which dissolution study of expired drugs were described. Referring to the existing scientific research, authors of this study have obtained similar conclusions [8, 9]. Moreover the Shelf Life Extension Program (SLEP) has been established as a joint program of *the United States Department of Defense and the Food and Drug Administration* where medications are tested for safety and stability for extended periods of time in controlled storage conditions. They concluded that in many cases, medications remain effective for years past their printed expiry dates.

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