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Comparison of the pharmaceutical properties of paracetamol tablets belonging to different companies in the Northern Cyprus pharmaceutical market

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Abstract

Paracetamol (PAR) tablets are commonly used over the counter formulations among the patients as analgesic and antipyretic. Therefore, the determination of the quality of these widely used tablets is important. On Northern Cyprus drug market, paracetamol formulations are provided various by pharmaceutical companies from different countries like Turkey, UK and local companies. In this study, three different brands (A, B, C) of traditional PAR (500 mg) tablets, selected for the evaluation of the pharmaceutical properties, were tested according to United States Pharmacopeia (USP) 32. Similarities and differences between conventional PAR tablets that are available in Northern Cyprus drug market were evaluated.

Keywords

Dissolution profiles, Northern Cyprus pharmaceutical market, paracetamol tablet, quality control.

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INTRODUCTION

World Health Organization (WHO) describes *'quality control in pharmaceutics'* as "the all necessary procedures to provide the purity of a specific drug formulation". The quality control studies include the controls of all pharmaceutical properties of starting materials and finished product during and after the production to ensure quality (Bhowmik *et al.,* 2014).

According to pharmacopoeias; quality control tests on tablets can be listed as weight variation, hardness, diameter and thickness, friability, dissolution and content uniformity. It is necessary to carry out all these tests on the tablets during production and before blistering (Mathur *et al.,* 2015).

Paracetamol (PAR) is widely used as an antipyretic and analgesic drug in patients of all age groups. It doesn`t show any serious adverse effect but dose is limited for both children and adults; the dose should be arranged as 150 mg and 4 g respectively (Oscier and Milner, 2009). PAR is mostly metabolized by liver and eliminated via the urine. Side effects such as maculopapular rashes on the skin, urticaria, met- hemoglobinemia and some gastrointestinal symptoms can be seen when used at high doses and for a long-term (Yoon *et al.,* 2016).

On the Northern Cyprus drug market, there are conventional paracetamol formulations in the forms of tablet, coated tablet, suspension and suppository manufactures by different companies from different countries.

In this study, the quality control studies have been performed on conventional PAR tablets which are frequently used in the Northern Cyprus pharmaceutical market. Furthermore, difference (f1) and similarity (f2) factors have been calculated for PAR tablets in order to evaluate their dissolution data.

MATERIALS AND METHODS

Materials

PAR was purchased from Rochem, Turkey. Three different brands of PAR tablets (500 mg) were chosen and entitled as PAR A (Batch: 010), PAR B (Batch: 05), PAR C (Batch: 004).

Methods

Stock standard solution of paracetamol

A solution of PAR in 0.1 N HCL at the concentration of 100 µg / mL was prepared as a stock solution. Seven different concentrations of PAR solutions were prepared using the stock solution. The wavelength at which paracetamol showed

maximum absorbance was determined using UV spectroscopy at 243 nm and a calibration line was drawn. (Mathur *et al.*, 2015; TF 2017). Necessary analytical parameters for the assay of PAR were determined by ANOVA test.

LOD and LOQ determination

The limit of detection (LOD) and the limit of quantitation (LOQ) values were calculated using the following equations.

Limit of detection = 3 SD / m

Limit of quantitation = 10 SD / m

Where;

SD: Standard deviation of absorbance

m: Slope of the calibration curve (Nagashree, 2015).

In vitro quality control characteristics of paracetamol tablets

Determination of thickness and diameter: The thickness and the diameter of paracetamol tablets from each brand were measured using Erweka tester.

Hardness test: The test was performed by a hardness tester (Erweka) on 10 PAR tablets for each brand (Gundogan *et al.*, 2008).

Friability Test: 10 PAR tablets were weighed precisely on an analytical balance (initial weight) and placed into the friabilator (Erweka) for 4 minutes at 25 rpm. Then, the tablets were weighed again to calculate the weight difference. Then, the tablets were weighed again to calculate the weight difference and percentage friability was calculated (Comoglu and Gonul 2005). (2005).

Weight variation: Deviation values in the weight of PAR tablets were determined according to United States Pharmacopeia (USP) 32, using the Shimadzu analytical balance (Mathur *et al.*, 2015).

Disintegration test: Disintegration that is the preliminary stage of drug dissolution is a process of breaking the tablet into granules and is defined as the part of in vitro and in vivo correlation. Disintegration time of PAR tablets was determined in distilled water at 37 °C by USP disintegration apparatus (Erweka) (Gundogan *et al.*, 2008).

Content uniformity test: The amount of PAR in each tablet from different brands was detected by using UV spectrophotometry. A standard solution was prepared by using pure PAR and 0.1 N HCl. Sample solutions were prepared using 20 tablets from each brand in 0.1 N HCl. The absorbance values of the prepared solutions were detected spectrophotometrically at 243 nm (Shimadzu 1202 UV-VIS spectrophotometer). The PAR amount in each tablet was calculated using the calibration equation previously determined by Sahle *et al.* (2012). The experiment was conducted as triplicated.

Dissolution tests: Dissolution tests on PAR tablets were performed using USP paddle

method at 50 rpm. 900 ml of 0.1 N HCl solution (at 37 ± 0.5°C) was used as dissolution medium. The samples were withdrawn at specific time intervals and assayed using Shimadzu 1202 UV-VIS spectrophotometer at 243 nm. The percentage of cumulative PAR amounts released from the tablets were calculated. The experiment was conducted as triplicated and cumulative PAR release graph was plotted versus time for each brand of PAR tablet.

Comparison of the dissolution profiles

In this study, difference (*f1*) and similarity (*f2*) factors that compare the dissolution profiles of a pair of drug products were applied to the dissolution data. These factors are useful to calculate the difference between percent drug dissolved per unit time for a test and a reference product. The difference ($f1$) and similarity ($f2$) factors are defined by the following equations (Comoglu and Gonul, 2015).

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} X100$$

$$f_2 = 50 \log \left\{ \left(1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right)^{-0.5} X100 \right\}$$

RESULTS AND DISCUSSION

Results of assay of paracetamol

The calibration line of paracetamol is shown in Figure 1. Analytical method validation parameters for the determination of paracetamol by UV spectrophotometric method are given in Table 1.

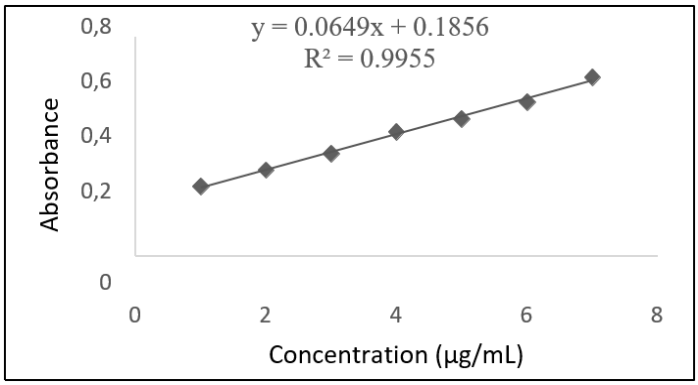

Figure 1: Calibration line of paracetamol.

Table 1: Analytical method validation parameters for the assay of PAR.

Parameters	Results
Linearity range (µg/mL)	1-7
Slope (m)	0.0649
% RSD* of m	0.46
SE* of m	0.03
Intercept (n)	0.1856
RSD* of n (%)	6.5
SE* of n	0.006
Determination coefficient (r^2)	0.995
LOD (µg/mL)	0.0198
LOQ (µg/mL)	0.06
% RSD* for precision	1.81
RSD* for accuracy	0.27

*RSD: Relative Standard Deviation
*SE: Standard Error

Quality control test results

The results obtained from the quality control tests are as shown in Table 2.

Table 2: Quality control test parameters.

PAR tablets	Weight (g) (Mean±SD)	Diameter (cm)	Thickness (cm)	Hardness (kg/cm^2) (Mean±SD)	Friability (%) (Mean±SD)	Disintegration time (min.sec) (Mean±SD)	Content uniformity (%) (Mean±SD)
PAR A	0.563 ± 0.010	1.270	0.397	12.85 ± 1.90	0.366 ± 0.02	1.10 ± 0.0001	99.35 ± 0.52
PAR B	0.452 ± 0.078	1.290	0.523	21.5 ± 3.54	0.316 ± 0.04	2.45 ± 0.0001	98.43 ± 0.43
PAR C	0.664 ± 0.023	0.741	0.520	34.37 ± 2.09	0.222 ± 0.001	1.40 ± 0.0003	95.65 ± 0.48

*SD: Standard Deviation

The results of content uniformity of three different brands of PAR tablets show that amount of PAR drug available in all formulations are between in the range of 90-110%. According to USP 32 PAR tablet criteria, content uniformity of all of the PAR tablets were determined to be optimum.

Tablets require a certain amount of hardness to withstand mechanical strength of handling during manufacturing and packaging. On the other hand, the dissolution time and disintegration of the tablets are two parameters related to their hardness. According to pharmacopoeias, the suggested minimum value for tablet hardness is 4 kg. All PAR tablets included in the study fulfilled the hardness criteria. The percentage friability value that is directly affected by the hardness in tablets should be less than 1. Accordingly, the percentage friability of all tested PAR tablets were found to be less than 1. The difference factor ($f1$) is comparative to the average difference among the three profiles, whereas similarity factor ($f2$) is inversely proportional to the average squared difference among the three profiles with emphasis on the larger difference among the time points. The evaluation of these factors are suggested for the comparison of dissolution profile by FDA

guideline. According to guideline, $f1$ values should be between 0-15, and $f2$ should be vary between 50 -100. The calculated are shown in Table 3.

Table 3: Difference ($f1$) and similarity ($f2$) factors for reference (PAR A) versus test products (PAR B and C).

	PAR B	PAR C
***f*1 values**	6.50	5.93
***f*2 values**	77.63	79.41

For tests (PAR B and PAR C) versus reference (PAR A), $f1$ values revealed that the dissolution profiles of tests were similar to the profile of the reference. Releasing the active material in an expected time explain the basic therapeutic effect of the dosage form. According to USP 32, conventional PAR tablets have to release at least 80% of the labelled amount in 30 minutes. As can be seen in dissolution profiles (Figure 2), all PAR tablets release the active drug as suggested by USP 32.

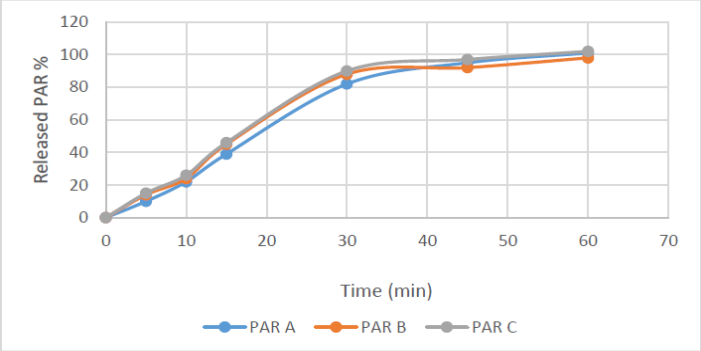

Figure 2: Dissolution profiles of conventional paracetamol tablets.

Zero order, first order and Hixson-Crowell kinetics were applied to the dissolution data of conventional PAR tablets and the results are shown in Table 4. As seen from the table, first order kinetic gives the highest determination constant (R^2).

Table 4: Kinetic parameter results of dissolution data for conventional PAR tablets.

		PAR A	PAR B	PAR C
Zero Order Kinetic	RMS	173.767	423.543	244.229
	k0	0.088	0.283	0.177
	R^2	0.821	0.711	0.638
First Order Kinetic	RMS	1.305	0.915	0.525
	k1	0.066	0.169	0.131
	R^2	0.992	0.997	0.994
Hixson-Crowell	RMS	3.692	4.688	4.527
	k4	0.095	0.099	0.070
	R^2	0.908	0.734	0.806

RMS: Residual Mean Square
k_0: Rate constant of the investigated kinetic
R^2: Determination coefficient

CONCLUSION

As a conclusion, three conventional PAR tablets that were bought from North Cyprus drug market, fulfill all the USP 32 pharmacopeia standards. When the release kinetics of the PAR tablets (PAR A, B and C) were examined, it was detected that the most appropriate kinetics is the first-degree release. This release kinetics is an expected kinetic model for immediate release tablet formulations. According to the results of the study, it can be concluded that all examined PAR tablets display immediate release and are compatible with the data provided by their manufacturers.

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