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Short Communication

EVALUATION OF USP BASKET AND PADDLE DISSOLUTION METHODS USING DIFFERENT GENERIC ATENOLOL TABLETS

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Abstract

Atenolol is a widely used drug for treating heart conditions available worldwide under various trade names by several generic pharmaceutical manufacturers. The purpose of this study was to evaluate and compare the dissolution performance of several commercially available generic atenolol tablets using both basket and paddle methods described in the United States Pharmacopeia-National Formulary (USP-NF), USP 33-NF 28. The substantial differences in dissolution performance observed among the atenolol oral dosage forms tested have implications concerning the equivalency and standards of multisource products available on the international market. The paddle method was found to be simple and produced more reliable and reproducible release profile of all generic brands compare to basket method.

Key words: *Atenolol tablets, Basket method, Paddle method, United States Pharmacopeia.*

Farklı Jenerik Atenolol Tabletlerde USP Sepet ve Palet Çözünme Yöntemlerinin Değerlendirilmesi

Atenolol dünya çapında çeşitli jenerik farmasötik üreticileri tarafından farklı ticari isimlerle piyasaya sunulan, kalp hastalıkları tedavisinde yaygın olarak kullanılan bir ilaçtır. Bu çalışmanın amacı, piyasada bulunan çeşitli jenerik atenolol tabletlerde, USP33-NF28 de tanımlanan sepet ve palet yöntemlerinin her ikisi de kullanılarak çözünme özelliklerinin değerlendirilmesi ve karşılaştırılmasıdır. İncelenen atenolol oral formlarının çözünme özellikleri arasında önemli farklılıklar gözlenmiş olup, bu durumun uluslararası pazarda yer alan çok kaynaklı ürünlerin eşdeğerlik ve standartlarına ilişkin etkileri bulunmaktadır. Palet yönteminin sepet yöntemine göre tüm jenerik ürünlerin salım profillerinin elde edilmesinde daha güvenilir, tekrarlanabilir ve kolay bir yöntem olduğu sonucuna varılmıştır.

Anahtar kelimeler: *Atenolol tablet, Basket yöntemi, Palet yöntemi, Amerikan Farmakopesi.*

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INTRODUCTION

Atenolol (ICI 66,082, Tenormin®, (*RS*)-2-{4-[2-hydroxy-3-(propan-2-ylamino) propoxy] phenyl) acetamide is an example of the p-substituted phenoxy propanolamine series of β-adrenoceptor blocking agents (Figure1). It is prepared by chemical synthesis. It was first synthesised in 1968 and since then it has been widely used for the treatment of hypertension, cardiac arrhythmias, myocardial infarction: early intervention in the acute phase (1). The selectivity of tenormin® decreases with the increasing dosage. It is without intrinsic sympathomimetic and membrane stabilising activities, and, as with other beta-adrenoceptor blocking drugs, has negative ionotropic effects (and is therefore contra-indicated in uncontrolled heart failure). As with other β-adrenoceptor blocking drugs, its mode of action in the treatment of hypertension is unclear. It is probably the action of Tenormin® in reducing cardiac rate and contractility which makes it effective in eliminating or reducing the symptoms of patients with angina. Adsorption of atenolol following oral dosage is consistent but incomplete (approximately 40-50 %) with peak plasma concentrations occurring 2-4 h after dosing. Atenolol blood levels are consistent and subject to little variability. After oral administration atenolol is excreted in the urine to the extent of about 40 % (2-5), after intravenous administration the total unirary excretion encompasses 75-100 % of the dose, about 10-14 % appeared in the form of metabolite (2,5,6). The increase in blood pressure due to smoking and drinking coffee is significantly less with atenolol than with the non-selective agents (7). Dissolution testing is a good method for controlling quality of drug products although it cannot completely replace either *in vivo* bioavailability or bioequivalency testing (8). As early as 1948 it was recognised that while the efficiency of a compressed tablets is to some degree related to the speed of disintegration, the dissolution of the drug particles is of prime importance (9). The purpose of this study was to evaluate the comparative performance of a number of oral atenolol dosage forms available on the international market by applying the official USP dissolution basket and paddle methods, and to consider the degree of compliance to the USP dissolution requirements and the possible implications for pharmacists, physicians and patients, who use atenolol products in different countries throughout the world.

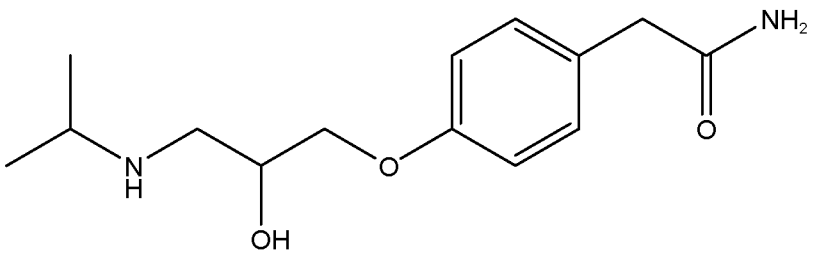

Figure 1. Chemical structure of atenolol

EXPERIMENTAL

Materials

Hydrochloric acid was obtained from BDH Chemicals (Lutterworth, UK). Atenolol tablets (15 different brands) were supplied by Greater Glasgow Health Board Quality Control Department (Glasgow, UK).

In Vitro Drug Release Studies

The in vitro generic drug release profile of various atenolol brands were evaluated employing United States Pharmacopeia (USP) paddle and basket method (10) (Pharma Test Model PIWS-11, Hainburg, Germany). Dissolution test of each brand was conducted in 900 ml of 0.1 M hydrochloric acid (HCl) solution (pH 1.2) as the dissolution medium maintained at 37°C ± 0.5°C and stirred at 50 ± 2.0 rpm. A 5-mL aliquot of the sample was withdrawn periodically at suitable time intervals and the volume replaced with an equivalent amount of the plain dissolution medium. Samples were filtered through 0.6μm filter (Millipore, Watford, UK) and analysed using UV spectrophotometer (Perkin Elmer, Beaconsfield, UK) at 275 nm. In the data analysis of each brand product, cumulative percentage of drug release was calculated using a mean of six sample measurements. Also the absorbance of samples was computed by comparing of basket and paddle methods.

Statistical Analysis

The results were analysed for variance using an ANOVA and *t-test* computer program on (DEC PC LPχ^{+} 450d2 and Tulip Vision Line^{R} dt$^{486dx/33i}$ running windows). The statistical program used were Minitab for Windows version 9.21 (1994) and Microsoft Excel version 5.0 (1984 - 1993). The output gave the variance ratios, whenever F values indicated the existence of significant variation among the basket and paddle methods, significant differences were identified by comparison of the least significant differences at the $p = 0.05$ level with the difference between the means of the atenolol preparations. The standard deviation (SD) and the coefficient of variation percent (%CV) also were determined.

RESULTS AND DISCUSSION

Atenolol is a cardioselective β-blocking drug is one of the most widely used for treating heart conditions in the world, and it is available world-wide under various trade names by several generic pharmaceutical manufacturers. Dissolution can be described as a tool that can provide valuable information about the bioavailability of a drug product. It has been well documented that the rate of which a drug dissolve from its intact of fragmented dosage forms in the gastrointestinal tract often partially or completely controls the rate of drug absorption, and in some cases, in vitro dissolution test results have been related to bioavailability.

Dissolution testing has become widely accepted as a method of controlling of drug products, there are now dissolution test requirements in the USP. However, although there are many examples of good correlation between dissolution studies and bioavailability (11-13), it is widely held that dissolution testing cannot completely replace either *in vivo* bioavailability or bioequivalency testing (14). The purpose of this study was to evaluate the comparative performance of a number of oral atenolol dosage forms available on the international market by applying the official USP dissolution basket and paddle methods, and to consider the degree of compliance to the USP dissolution requirements and the possible implications for pharmacists, physicians and patients, who use atenolol products in different countries throughout the world.

The results of dissolution profiles for atenolol tablets tested are presented in Table 1. Atenolol content in tablets was in all cases within the limits of variation recommended by the USP.

Table 1. Average cumulative percent of atenolol tablets dissolved at various sampling times for the basket and paddle apparatus.

Product and (Trade Mark)	Strength (mg)	Manufacturer	Batch #	Dissolution time (min)	Average percent dissolved	
					Basket	Paddle
Atenolol (Tenormin®)	25	Zeneca Pharmaceuticals	DH953A	6	98 ± 0.01* (6.27)**	95 ± 0.01 (4.56)
Atenolol (Tenormin)	100	Zeneca Pharmaceuticals	A17	27	98 ± 0.26 (0.63)	98 ± 0.01 (1.59)
Atenolol	25	Cox Pharmaceutical	A17	6	96 ± 0.01 (3.90)	94 ± 0.00 (1.51)
Atenolol (Totamol®)	25	CP Pharmaceuticals	10103	12	97 ± 0.00 (1.30)	93 ± 0.00 (0.98)
Atenolol (Totamol)	50	CP Pharmaceuticals	10734	20	96 ± 0.01 (2.06)	99 ± 0.00 (0.88)
Atenolol (Totamol)	100	Cp Pharmaceuticals	7891	21	97 ± 0.01 (0.64)	98 ± 0.00 (0.32)
Atenolol (Antipressan®)	25	Berk Pharmaceuticals	6022 LB	25	92 ± 0.00 (0.94)	93 ± 0.01 (0.52)
Atenolol (Antipressan)	100	Berk Pharmaceuticals	5T67 LD	27	95 ± 0.02 (2.85)	94 ± 0.01 (0.92)
Atenolol	25	Hillcross Pharmaceuticals	2434R1/1	20	97 ± 0.00 (1.40)	91 ± 0.01 (1.03)
Atenolol	50	Hillcross Pharmaceuticals	2474R1/1	25	92 ± 0.00 (1.16)	95 ± 0.01 (1.12)
Atenolol	100	Hillcross Pharmaceuticals	2466R2/1	18	96 ± 0.01 (1.22)	98 ± 0.02 (1.10)

*Coefficient of variations (% CV), $n = 6$

**Values are means ±SD of six determinations

The *in vitro* dissolution rates of different atenolol preparations (Table 1) were compared in a cross over study using USP basket and paddle methods. All preparations dissolved completely (more than 90 %) in less than 25 minutes and showed similar profiles. The absorbances of samples and the means of both methods were plotted against time. For the tablets, in all cases the Higuchi statistical model (15,16) gave a good fit. As can be seen from Figure 2-4 (25, 50 and 100 mg) for comparison of basket and paddle method it is clear the paddle method gave somewhat better dissolution than the basket method. With the 100 mg tablets it appears that there is no difference at the $p = 0.05$ level of variability between the CP, Berk, Hillcross and the Zeneca reference product.

Interestingly these are all different even through the basket method showed no differences for 100 mg tablets. Statistical comparisons of the amount of atenolol dissolved from different preparations to Zeneca (reference) by the independent *t-test* up to 4 min dissolution for basket and paddle methods shows; there is a noticeable difference between the results for the 100 mg tablets for Zeneca, Berk, CP and Hillcross (Table 2). The Zeneca tablets show a much more rapid dissolution with the paddle method than the basket method. It was noted that the Zeneca tablets dissolved very quickly once the film coat had become detached. This may be the reason for the differences between the results in Table 2, because the basket method might be expected to remove the film coating more slowly than the paddle method.

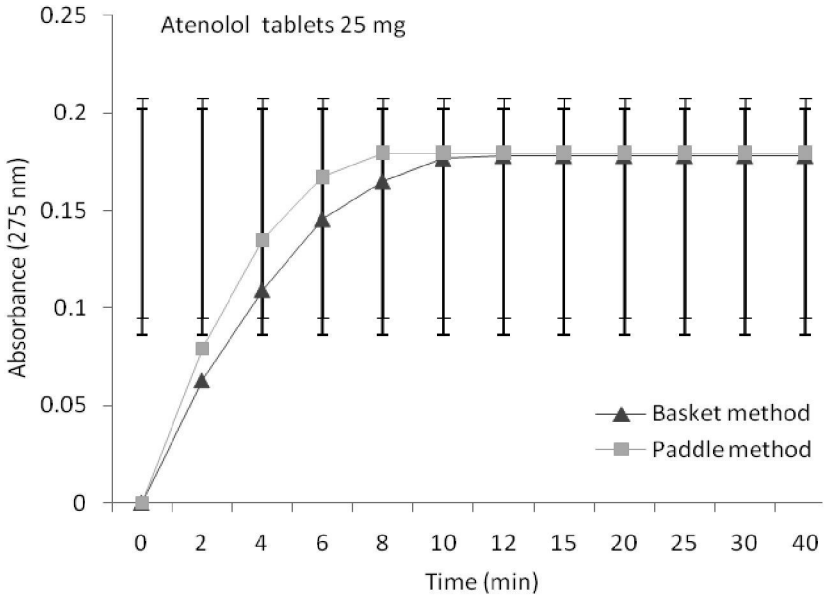

Figure 2. Comparison of the curves (means of six) of basket and paddle methods for atenolol 25 mg tablets. Error bars represent ±1 SD.

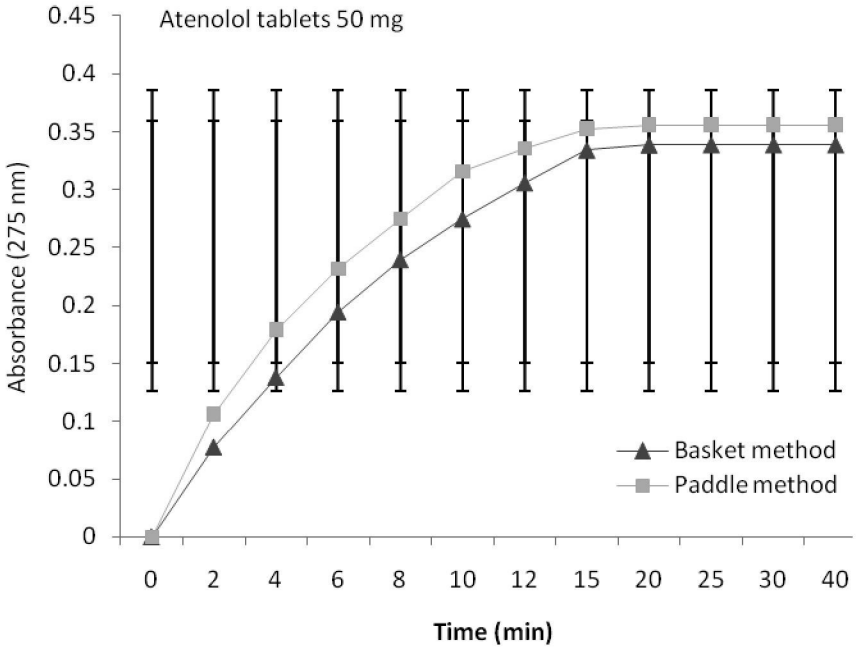

Figure 3. Comparison of the curves (means of six) of basket and paddle methods for atenolol 50 mg tablets. Error bars represent ±1 SD.

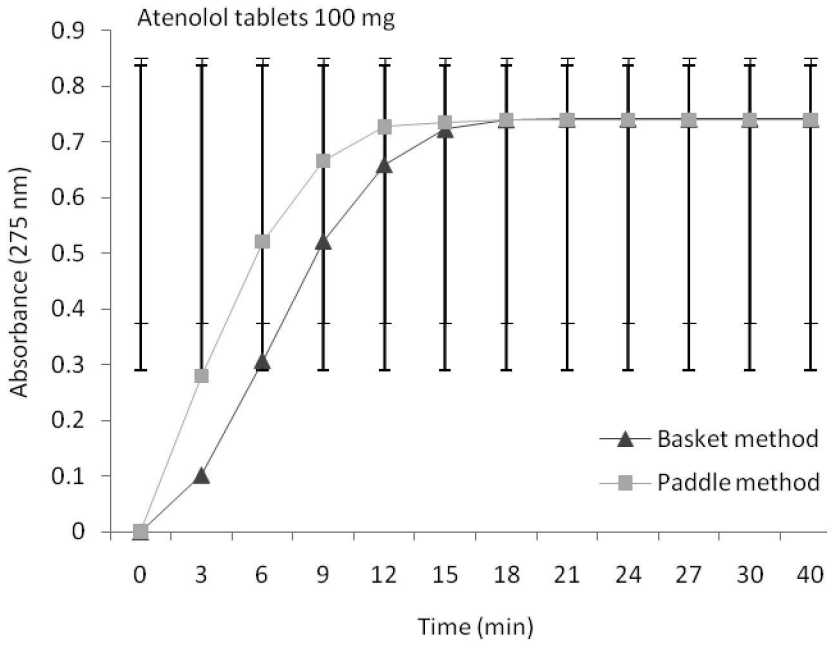

Figure 4. Comparison of the curves (means of six) of basket and paddle methods for atenolol 100 mg tablets. Error bars represent ±1 SD.

Table 2. Statistical comparisons summary for basket and paddle method.

Product (Mfg)	Strength (mg)	Mean (n = 6)		Significance level		Variation (%CV)*	
		Basket	Paddle	Basket	Paddle	Basket	Paddle
Atenolol (Zeneca)	25	0.218	0.225	$p < 0.0001$	$p < 0.0003$	20.64	18.66
Atenolol (Cox)	25	0.173	0.183				
Atenolol (Zeneca)	25	0.218	0.225	$p < 0.0001$	$p < 0.0001$	50.00	40.0
Atenolol (Cp)	25	0.110	0.135				
Atenolol (Zeneca)	25	0.218	0.225	$p < 0.0001$	$p < 0.0001$	77.06	72.0
Atenolol (Berk)	25	0.050	0.063				
Atenolol (Zeneca)	25	0.218	0.225	$p < 0.0001$	$p < 0.0001$	65.60	59.55
Atenolol (Hillcross)	25	0.077	0.092				
Atenolol (Zeneca)	100	0.720	0.762	$p < 0.1300$	$p < 0.0070$	2.77	2.88
Atenolol (Cp)	100	0.740	0.740				
Atenolol (Zeneca)	100	0.720	0.762	$p < 0.4100$	$p < 0.0002$	1.52	4.37
Atenolol (Berk)	100	0.709	0.724				
Atenolol (Zeneca)	100	0.720	0.762	$p < 0.8100$	$p < 0.0003$	0.14	5.11
Atenolol (Hillcross)	100	0.718	0.723				

*Variation (% CV) of mean from Zeneca reference standard

There were little differences in dissolution rate between same dosage preparations supplied by different generic manufacturers. Differences in dissolution may influence bioavailability of atenolol product between different manufacturers. Fraser F.J. et al. (1973) has suggested that differences in bioavailability in digoxin tablets are probably the result of difference in dissolution rate (17). These differences in dissolution rate may be largely due to variation in particle size and also it is apparent that standards of processing vary from manufacturer to manufacturer. Statistical summary following ANOVA on dissolution profiles of various atenolol preparations between basket and paddle methods at significance level $p = 0.05$ comparing F values for intra-group variations are given in Table 3.

Table 3. Statistical summary using ANOVA on dissolution profiles of various atenolol preparations between basket and paddle methods.

Product (Mfg)	Dosage (mg)	F values		Average comparison $p = 0.05$ (F)
		Basket method	Paddle method	
Atenolol (Zeneca)	25	15.68	9.88	Significantly different
Atenolol (Zeneca)	100	10.38	9.37	Significantly different
Atenolol (Cox)	25	23.91	16.11	Significantly different
Atenolol (CP)	25	56.11	27.88	Significantly different
Atenolol (CP)	50	373.23	43.30	Significantly different
Atenolol (CP)	100	185.25	29.29	Significantly different
Atenolol (Berk)	25	367.83	143.83	Significantly different
Atenolol (Berk)	100	259.11	194.07	Significantly different
Atenolol (Hillcross)	25	139.76	67.36	Significantly different
Atenolol (Hillcross)	50	125.31	59.34	Significantly different
Atenolol (Hillcross)	100	184.30	213.63	Significantly different

As can be seen from (Figures 2-4) it is obvious that the paddle method gave significantly better dissolution than the basket method at each formulation studied. The differences in the drug release in the basket apparatus and the paddle apparatus were probably due to the differences in the basic design of these two apparatus. The paddle apparatus makes it a better stirring device which leads to faster dissolution rates when compared to the basket apparatus. However, the basket used in the rotating basket apparatus act as a sample holder confining the dosage form in a relatively smooth flow of dissolution medium with minimal mechanical abrasion. This leads to slower dissolution rates when compared to the rotating paddle apparatus. In order to evaluate the reproducibility of the different dissolution testing methods, six runs of each method from each lot were performed. From each series of six runs the coefficient of variation of the average percent dissolved was calculated at each of the sampling times. It is apparent from the coefficient of variations listed in Table 1 that the dissolution profiles obtained with rotating paddle apparatus are generally more reproducible than the rotating basket apparatus.

CONCLUSION

The rotating paddle method that was used during this investigation allows evaluation of dissolution from all atenolol solid dosage form preparations with reproducible results. The method is simple to use and inexpensive to construct. The results indicate that the rate of

release, *in vitro*, of a hydrosoluble drug such as atenolol can be accurately controlled through choice of the USP apparatus used.

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