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Research Article

COMPARISON OF THE DISSOLUTION OF REFERENCE DISPERSIBLE TABLETS OF AMOXICILLIN VERSUS TWO GENERICS MANUFACTURED IN MOROCCO

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ABSTRACT

The price of drugs is an essential factor in any pharmaceutical policy. In this context, generic drugs play a predominant role. In Morocco, the market of the generic drugs is in net progression since it represents nowadays 30 % of the national market. But this development should not be at an expense of quality. Thus, trials of dissolution in vitro have been imposed using European Pharmacopeia (EP). The aim of our study is to establish a comparison between the profiles of dissolution of reference and two generic amoxicillin products (Tablet 1 g). The percent release of reference and two generics at 45 minutes were less than accept criteria of EP (75 %). While at 90 minutes the reference and generic II released more than 75 % namely 88.89% and 81.87% respectively. Results illustrate the importance of the trial of dissolution in the monitoring of manufacturing quality of solid oral forms.

Keywords: Amoxicillin, Reference, Generic, Dispersible tablets, Dissolution.

INTRODUCTION

The generic drug has emerged in Morocco since the 60s before experiencing great strides in the last two decades. The project of bioequivalence of generic drugs is one of the priorities of the health sector in Morocco. Bioequivalence testing is required to ensure the quality of generic drugs, raising any suspicion on the part of health professionals and patients about their effectiveness. Similarly, this approach is ensuring a level of awareness and competitiveness of Moroccan pharmaceutical industry in the international market. Indeed, Morocco has long applied the same procedures adopted in Europe, namely the in vitro dissolution test form of the bioavailability of a drug [1,2].

In Morocco, antibiotics are one of the most prescribed therapeutic classes. Among these antibiotics, amoxicillin is the antibiotic most used. In 2009, there were more than 23 specialty generics. In general practice, the tablets are the most widely used dosage forms, mainly the dispersible form.

Jinginger et al showed that both formulations of the same active ingredient (generic example), can lead to different therapeutic effects in terms of their dissolution profile [3,4]. In effect, poor dissolution of active ingredient can cause a low bioavailability which may lead to therapeutic ineffectiveness firstly and secondly a spread of resistance [5-7]. Defects in the formulation or manufacturing process may be responsible for the development of generic drugs of poor quality [8].

The aim of this work is to compare the dissolution profiles of two generics amoxicillin (Tablet 1 g), manufactured by national laboratories versus reference.

MATERIALS AND METHODS

Samples collection

The reference (Tablet 1 g) and two specialty generics (**I-II**) (Tablet 1 g) were obtained from three different laboratories (Casablanca, Morocco).

Uniformity of mass

The Three specialties were checked for uniformity of mass using a balance previously verified and calibrate.

Disintegration test

The apparatus used comprises: the baskets animated with movements up and down, the assembly composed of six tubes with a perforated base. The number of movements per minute is 29 to 32, the temperature at 37 ± 0.5 ° C, the medium was water and the maximum time of disintegration is 15 minutes.

Dissolution test

The apparatus used is type dissolution test six positions (Hewlett). This device can work with both methods paddle and basket. For each test, six tablets are tested simultaneously for 120 minutes. The dissolution medium was 900 ml of 0.1 M HCl, the stirring speed was 50 rpm and the temperature is 37 °C [9-11].

Samples analysis

A sample of 10 ml was made in the dissolution medium, filtered and then diluted 1/10. Subsequently, the determination of the content of active ingredient was made by spectrophotometry at 272 nm (Perkin Elmer, USA). The witness was prepared in parallel weighing between 47 and 53 mg of Amoxicillin, was diluted in 50 ml of 0.1 M HCl, then performed a dilution of 1/10 and determining the optical density (OD) at 272 nm as for the test sample. The percentage dissolved was calculated using the formula:

Dissolves % = OD_T x P / OD_W x 50

OD = Optical density of test

P = Mass of Witness

DO_W = Optical density of the witness

50 = Dilution factor

RESULTS AND DISCUSSION

The results of the test for uniformity of mass are presented in table 1. It has low coefficients of variation (CV < 2%), reflecting good homogeneity of the mass of tablets from the three specialties.

Table 1: Uniformity of mass of reference and two generic (I – II)

Specialties	Reference	Generic I	Generic II
Mean (g)	1,245	1,24	1,242
Coefficient of variance (CV %)	0,4	0,7	0,5

The disintegration test was consistent for all three specialties tested, because we found that after thirty seconds no residue remains. After the disintegration of tablets, the step limits the absorption is the dissolution. The in vitro dissolution test was performed by assaying the samples from the dissolution medium. The test was considered satisfactory when there is transition from a defined quantity of active ingredient.

There are devices that are equipped either by paddles or baskets. However, studies comparing these two methods are sometimes paradoxical about their results. We performed a comparative study in our case to compare the dissolution per pallet versus basket. Table 2 express the average percentage of amoxicillin dissolved versus time, these averages are calculated on six samples for each test of reference. After 120 minutes of testing, near 98% of the active ingredient was dissolved in the paddle (apparatus 2), about 95% against the basket (apparatus 1). These results confirm that the paddle ensures good reproducibility [12], while for the basket; there was a risk of poor homogeneity of the medium with the addition the possibility of occlusion of the mesh basket. Thus the dissolution range was chosen to study the generic (**I-II**).

Table 2: Dissolution of reference amoxicillin tablet by using paddle and basket apparatus

		Time (min)						
		15	**30**	**45**	**60**	**75**	**90**	**120**
% of Active ingredient dissolved	**Paddle**	33,27	41,8	53,39	66,16	74,61	88,89	97,54
	Basket	30	40,1	50	68	72	85	95

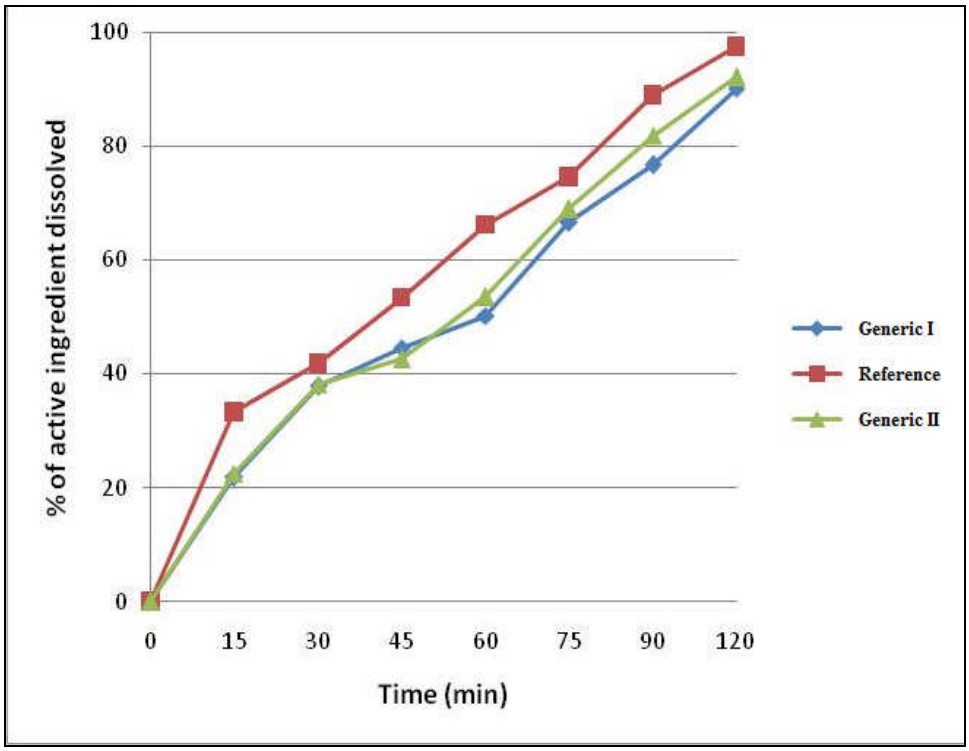

Fig. 1: Dissolution profiles of reference and two generic amoxicillin products (Tablet 1 g)

Table 3: Comparative study between dissolution of reference and generics (I – II) based on student's test.

Time (min)	**15**	**30**	**45**	**60**	**75**	**90**	**120**
Princeps/ I	11,49	4	8,75	15,98	7,98	12,22	7,33
	SD	NS	SD	SD	SD	SD	SD
Princeps / II	10,74	3,56	10,85	12,64	5,66	7	5,39
	NS	NS	SD	SD	SD	SD	NS

SD = different significant; NS = Not significant

Six kinetic are made simultaneously on paddle to determine the average curve of dissolution of each of the three specialties, thus the figure 1 represent the results obtained.

In addition a comparison test of means (Student's test) was performed between the rate of active ingredient dissolved for couples reference versus **I** and **II**, this at each sampling time in order to verify the existence or not a significant difference between the different results. The comparison of means test showed a significant difference in dissolution of tablets reference versus **I** and **II** (Table 3).

The linearization of the mean curves of dissolution by the method of Wagner, which expresses the logarithm of the percentage of active ingredient undissolved versus time, is reported in Figure 2.

The profiles of the three specialties do not have the same exponential rate, even if at the end of the trial, almost 90% of the active ingredient is passed into solution. The dispersible tablets of generic I-II dissolve more slowly than of reference. The percent release of reference and two generics at 45 minutes were less than accept criteria of EP (75 %). While at 90 minutes the reference and generic II released more than 75 % namely 88.89% and 81.87% respectively, these results due to difference in manufacturing processes. This difference in dissolution behavior can significantly affect the bioavailability of generic tablets from **I** and **II**.

In Morocco, the generic regulation is recent. It dates from 2006, after promulgation of the law 17/04 concerning the code of the drug and pharmacy. This law defines the generic drug and insists that it must have the same qualitative and quantitative composition in active substance and pharmaceutical form as the reference and whose bioequivalence with the latter must be demonstrated by appropriate bioavailability studies. The results of this work show the interest of application of the law 17/04.

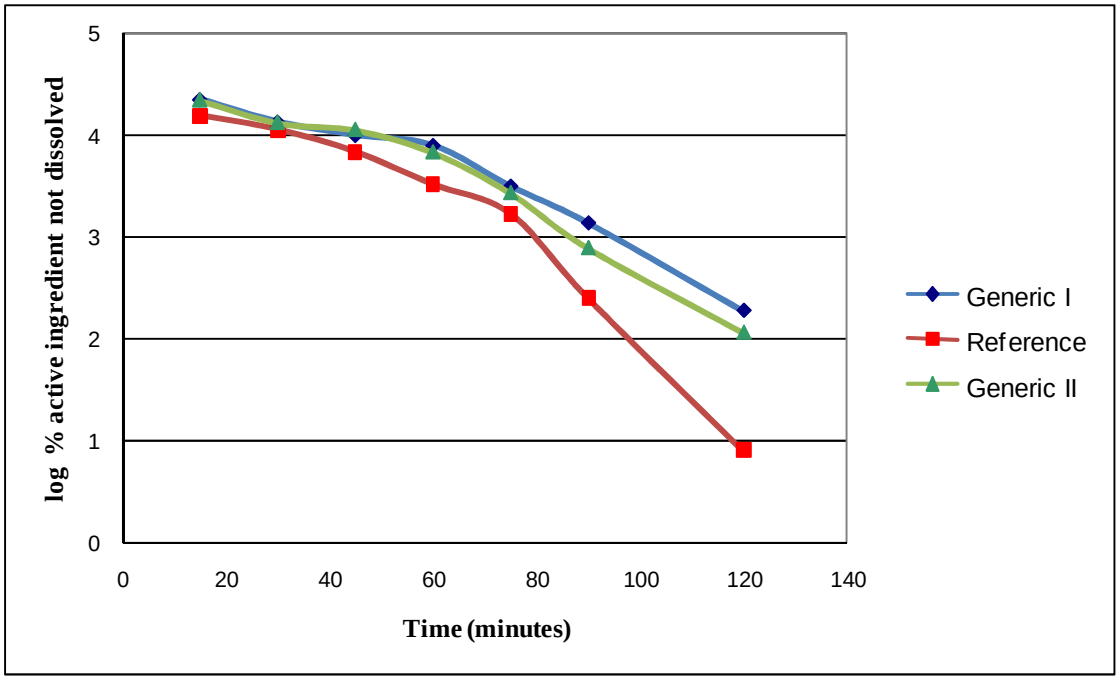

Fig. 2: Linearization of dissolution curves using the Wagner model of the three specialties

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