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EVALUATION OF SOME PHARMACEUTICAL FORMULATIONS OF LISINOPRIL THROUGH DISSOLUTION TESTING

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EVALUATION OF SOME PHARMACEUTICAL FORMULATIONS OF LISINOPRIL THROUGH DISSOLUTION TESTING (Abstract): **Aim**: Lisinopril is a drug of the angiotensin converting enzyme (ACE) inhibitor class that is primarily used in treatment of hypertension, congestive heart failure, heart attacks and also in preventing renal and retinal complications of diabetes. We compared the dissolution profiles of Lisinopril 20 mg tablets (Antibiotice S.A. Iaşi) and Zestril 20 mg tablets (Astra Zeneca). **Material and method**: Because lisinopril is a third class active substance, we performed dissolution tests in standard media at three pH values: 1.2, 4.5 and 6.8 using the paddle apparatus at 75 rpm. **Results**: Both pharmaceutical formulations present a dissolution percentage more than 85% (Q) of the labeled amount. **Conclusion**: Both pharmaceutical formulations present similar dissolution profile. **Key words**: LISINOPRIL, TABLETS, DISSOLUTION TEST

Lisinopril, a lysine analogue of enalaprilat, is a long-acting angiotensin converting enzyme inhibitor witch differs from captopril by lacking the sulhydril group. Lisinopril, discovered and developed by the Merck Sharp & Dohme Research Laboratories, is indicated for the treatment of hypertension, congestive heart failure heart attacks and also in preventing renal and retinal complications of diabetes (1,2).

According to World Health Organization lisinopril is (s)-1-[1–carboxy-3 phenylpropyl) -L-lysyl]–L-proline dyhydrate (fig. 1) (2).

Lisinopril is a white to off–white crystalline powder. It is soluble in water (1 to 10) and methyl alcohol (1 to 70), but it is practically insoluble in ethyl alcohol, acetone, chloroform and ether. Log P (octanol/water) was reported to be $=1.22$; log P (phosphate buffer 0.1 M, pH 7/octanol) $=10.2\pm0.5$ (25^0C), pKa values 2.5, 4.0, 6.7, 10.1 (25^0C) (2, 3).

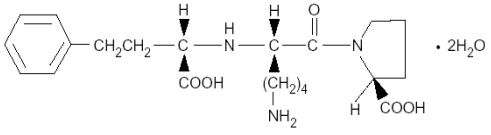

Fig. 1. Lisinopril – chemical structure

Lisinopril can be expected to be "highly soluble" at 37^0C over the entire pH-range 1-7.4. The low bioavailability of lisinopril is in line with its low permeability (2,3,4, 5,6,7,8,9).

Nowadays, the study of dissolution *in vitro* is considered a fundamental requirement in the pharmaceutical industry in order to assure the quality of solid pharmaceutical forms for oral use, guarantee the quality from lot to lot, orientate the development of new formulations and secure the uniformity, quality and performance of the drug even after modifications. On a parallel basis, this allows formulation, optimization in the development phase and, in the same

way, it allows stability studies, manufacturing process monitoring, and the establishment of *in vivo/in vitro* correlations.

The USP 29 dissolution specification for lisinopril tablets is not less than 80% (Q) dissolved in 30 minutes in 900 mL HCl 0.1M (2).

MATERIAL AND METHOD

Dissolution tests were performed according to USP 29 using :

- dissolution tester Erweka DT 808 LH - Apparatus no. 2 (paddle) ;
- medium : - HCl 0.1N, pH 1.2 buffer, pH 4.5 buffer and pH 6.8 buffer ;
- HPLC 1100 Agilent, detector DAD/ MWD and fluorescence.

The dissolution profile of the pharmaceutical formulations was studied using various dissolution medias. First, the comparative dissolution profiles of the drugs were performed using USP dissolution media (HCl 0.1N) at stirring speed of 50 rpm, then the dissolution profiles were obtained using three different dissolution media : pH 1.2 buffer, pH 4.5 buffer and then pH 6.8 buffer at a stirring speed of 75 rpm. The dissolution media volume was maintained at 900 mL in all the cases (3).

Determination of dissolved active substances was performed using a HPLC method. Lisinopril was separated on a C18 column using a mobile phase consisting of a mixture of phosphate buffer pH 2 containing 0.125% sodium hexanesulphonate and acetonitrile (72 : 28, v/v), at a flow rate of 1 mL/ min. Detection was performed at 215 nm on an Agilent 1200 HPLC system. The injection volume was 20 μL. In these chromatographic conditions, the retention time of lisinopril was 1.9 min.

RESULTS AND DISCUSIONS

Comparative dissolution profile of Lisinopril 20 mg tablets produced by Antibiotice S.A. Iaşi (A) and Zestril 20 mg tablets produced by Astra Zeneca (B) gave the results shown in tab. I when performed accordingly to USP 29. The results show that both products have similar dissolution profile as it can also be seen from the graphical representation in fig. 2.

While comparing dissolution profile of the pharmaceutical formulations with lisinopril using 900 mL pH 1.2 buffer as disso-

TABLE I
Dissolution Test in USP dissolution media

	% released lisinopril			
Time (min.)	10	15	20	30
A	89.1054	96.7536	95.7468	97.1445
B	80.5794	93.8223	94.0334	97.5769

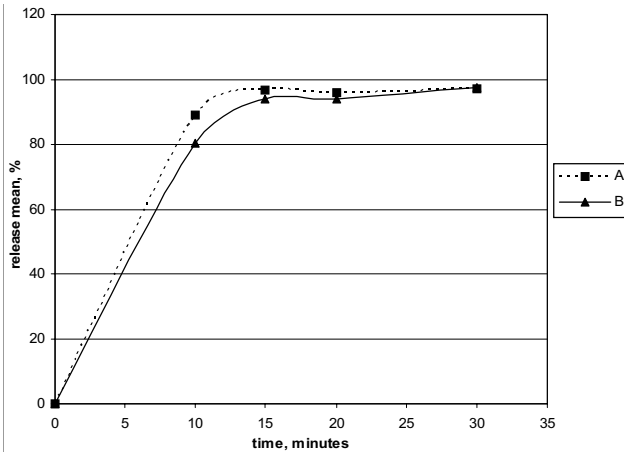

Fig. 2. Comparative dissolution profiles in USP dissolution media

lution media and stirring speed of 75 rpm, the results shown in tab. II prove that both products released more than 85 % within 15 min. of testing and that they have similar dissolution profiles. This can also be observed from fig. 3.

Each lisinopril product released a percent greater than 90% when tested in a pH 4.5 buffer as dissolution media and at stirring speed of 75 rpm. The percent increases when the released lisinopril is quantified after 30 min. – over 98%. The results are shown in tab. III and they are graphically represented in fig. 4.

The last dissolution test was performed at an almost neutral pH value (pH 6.8 buffer

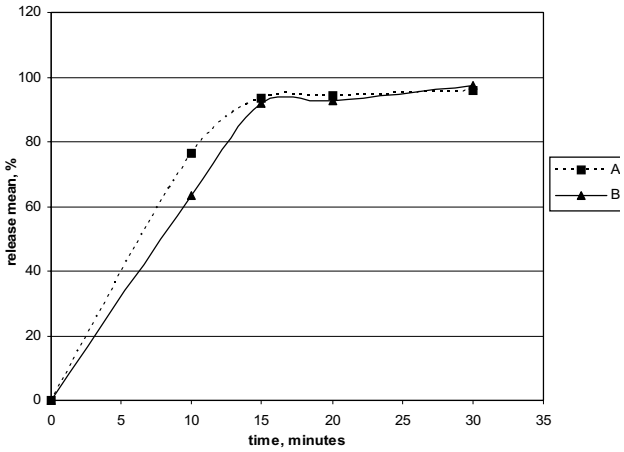

Fig. 3. Comparative dissolution profiles in pH 1.2 dissolution media

TABLE II

Dissolution Test in pH 1.2 dissolution media

% released lisinopril				
Time (min.)	10	15	20	30
A	76.5515	93.5989	94.0958	95.8547
B	63.3411	91.8680	92.7665	97.3693

TABLE III

Dissolution Test in pH 4.5 dissolution media

% released lisinopril				
Time (min)	10	15	20	30
A	51.1896	96.7726	97.7318	98.5634
B	75.5164	93.0365	95.4984	98.3925

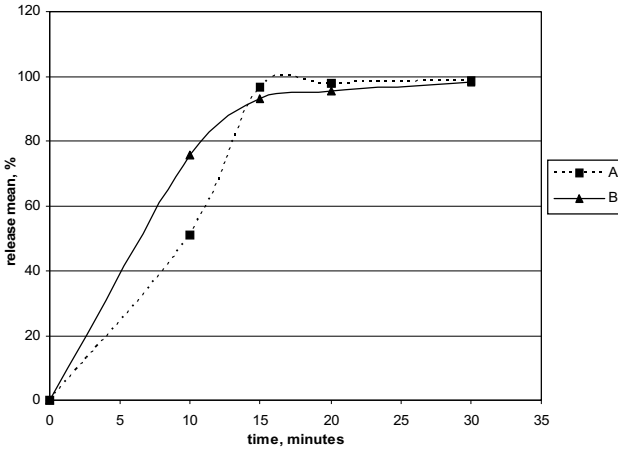

Fig. 4. Comparative dissolution profiles in pH 4.5 dissolution media

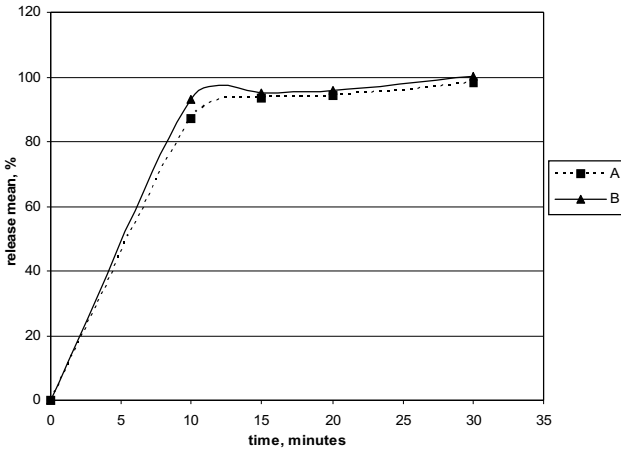

Fig. 5. Comparative dissolution profiles in pH 6.8 dissolution media

TABLE IV

Dissolution Test in pH 6.8 dissolution media

% released lisinopril				
Time (min)	10	15	20	30
A	87.1772	93.5230	94.1995	98.3643
B	93.1250	95.2389	95.9041	100.1474

was used as dissolution media). Both products released more than 85% lisinopril in the first 15 min. as it can be seen from tab. IV and fig. 5.

The dissolution rate for both products was over 85 % in 15 min. when testing their dissolution profiles at different pH values, thus it was not necessary to calculate the similarity factors.

CONCLUSIONS

Our studies led to the following results : both products present a dissolution percentage more than 85% (Q) of the labeled amount after 30 min. for lisinopril. The dissolution profiles of the studied products are almost identical.

The products develop similar dissolution profiles, thus the bioequivalence of Lisinopril 20 mg tablets (Antibiotice S.A. Iaşi) and Zestril 20 mg tablets (Astra Zeneca) was demonstrate *in vitro*.

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