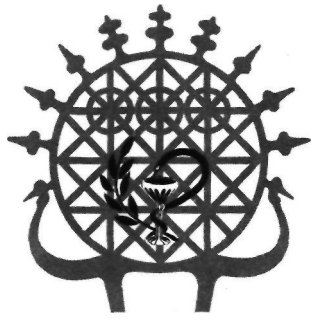
ISSN 1015 - 3918

ANKARA ÜNİVERSİTESİ
ECZACILIK FAKÜLTESİ DERGİSİ

JOURNAL OF FACULTY OF PHARMACY
OF
ANKARA UNIVERSITY

Cilt / Vol: 30
Sayı/No: 1
Yıl/Year : 2001



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Ankara-2001

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Sahibi : Prof. Dr. Seçkin ÖZDEN

Editör : Prof. Dr. Feyyaz ONUR

Ankara Üniversitesi Eczacılık Fakültesi Dergisi yılda 4 sayı yayınlanır. Yayımlanan yazıların sorumluluğu yazarlarına aittir. Dergiye gönderilen makalelerin daha önce tamamen veya kısmen başka bir yerde yayınlanmamış veya yayını için başka bir yere başvuruda bulunulmamış olması gereklidir. Makaleler, derginin arka sayfalarında yer alan yazım kurallarına uymalıdır. Dergi yalnızca üyelerine gönderilmektedir.

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Ankara Üniversitesi Basımevi,

2001

JOURNAL OF FACULTY OF PHARMACY OF
ANKARA UNIVERSITY

Published by : Prof. Dr. Seçkin ÖZDEN

Editor : Prof. Dr. Feyyaz ONUR

Journal of Faculty of Pharmacy of Ankara University is published quarterly. All the articles appeared in this journal are published on the responsibility of the author. The manuscript submitted to the journal should not be published previously as a whole or in part and not be submitted elsewhere. Manuscripts should be prepared in accordance with the requirements specified at the end of the issue. The journal is distributed to the members only.

This journal is indexed in Chemical Abstracts (CA), Excerpta Medica Database (EMBASE), Medicinal Aromatic Plants Abstracts (MAPA) and Turkish Medical Index.

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Ankara Üniversitesi Basımevi,
2001

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Ankara Üniversitesi Eczacılık Fakültesi Dergisi 2001 yılından itibaren ***YILDA 4 SAYI*** *Olarak yayınlanacaktır.*

Önemle duyurulur.

To the attention of all readers,

Journal of Faculty of Pharmacy of Ankara University will be published ***QUARTERLY*** *starting from the year 2001.*

Ankara Ecz. Fak. Derg.
30(1)1-16,2001

J. Fac. Pharm., Ankara
30(1)1-16,2001

QUALITY CONTROL STUDIES ON ENALAPRIL MALEATE TABLETS AVAILABLE ON THE TURKISH DRUG MARKET

TÜRKİYE İLAÇ PİYASASINDA BULUNAN ENALAPRİL MALEAT TABLETLERİ ÜZERİNDEKİ KALİTE KONTROL ÇALIŞMALARI

Esra **BALOĞLU** **S. Yaprak HIZARCIOĞLU**

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ABSTRACT

Enalapril maleate represents a new class of antihypertensive agents. It's an angiotensin converting enzyme inhibitor. Enalapril maleate is a pro-drug of enalaprilat. It is hydrolized to enalaprilat after oral absorption. It's widely used informs of tablet containing 5, 10 and 20 mg of enalapril maleate. Many enalapril maleate tablets have been introduced to Turkish Drug Market.

Some pharmaceutical properties, namely hardness, thickness, diameter, weight variation, friability, disintegration time, content uniformity and dissolution rates of enalapril maleate tablets produced by four different pharmaceutical companies on the Turkish Drug Market were evaluated in this study. Most of the tablets complied with the pharmacopoeia standards except hardness and friability properties.

In order to evaluate the dissolution rates; zero, first order, Hixson Crowell, Modified Hixson Crowell, RRSBW, $Q\sqrt{t}$, Higuchi, Hopfenberg equations have been studied and the best fitting equations were found to be Modified Hixson - Crowell and RRSBW kinetics.

Key words: *Enalapril maleate, Quality control, Physical controls, In-vitro availability, Turkish Drug Market*

ÖZET

Enalapril maleat antihipertansif ajanların yeni sınıfını temsil etmektedir. Anjiyotensin dönüştürücü enzim inhibitörü bir ilaç olarak bilinmektedir. Enalapril maleat, enalaprilatın ön ilacıdır. Oral absorbsiyondan sonra enalaprilata hidrolize olur. Yaygın olarak 5, 10 ve 20 mg enalapril maleat içeren tabletler halinde kullanılmaktadır. Türk İlaç Piyasasında birçok enalapril maleat tableti bulunmaktadır.

Bu çalışmada Türk İlaç Piyasasında bulunan dört farklı firma tarafından üretilen enalapril maleat tabletleri farmasötik özellikleri, çap-kalınlık, sertlik, ağırlık sapması, ufalanma-aşınma, dağılma zamanı, içerik homojenliği ve çözünme hızı açısından değerlendirilmiştir.

İncelenen tüm tabletlerin sertlik ve ufalanma-aşınma özellikleri hariç farmakope standartlarına uyduğu saptanmıştır. Dissolüsyon çalışması sonuçlarının kinetik açıdan değerlendirilmesi için 0. derece, 1. derece, Hixson Crowell, Modifiye Hixson Crowell, RRSBW, «√t, Higuchi, Hopfenberg eşitlikleri kullanılmış ve en iyi uyumu gösteren eşitliklerin RRSBW ve Modifiye Hixson Crowell olduğu saptanmıştır.

Anahtar kelimeler *: Enalapril maleat, Kalite kontrol, Fiziksel kontrol, ln-vitro uygunluk, Türk İlaç Piyasası*

INTRODUCTION

The quality assurance of the drugs marketed have gained great importance in the field of industrial and clinical presentation. Some of these studies carried out previously showed quality differences between chemically equivalent formulations (3,9, 26).

Enalapril maleate, or (S)-l-[N-[l-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline maleate, a synthetic peptidic derivate, is a long acting oral inhibitor of angiotensin converting enzyme (ACE), which reduces the plasmatic concentrations of angiotensin II and aldosterone and increases the plasmatic activity of renin (7). The orally absorbed pro-drug enalapril maleate is hydrolzed in-vivo to enalaprilat, an extremely potent inhibitor of converting enzyme. Enalapril maleate is an effective antihypertensive and can be useful in the treatment of congestive heart failure (5,19).

Various in vitro and in vivo methods have been reported for the assay of enalapril maleate. Among them are spectrophotometric (6, 7, 9, 10, 30), HPLC (6, 8, 10, 12, 21, 25, 29), radio-immunoassay (34), colorimetric, chromatographic and potentiometric titration (21) methods.

Stability studies were also carried out in several preparations. After preparing oral liquids of enalapril maleate, the formulations were kept at two different temperatures and it was stable for only 56 days at 25°C (20). Shiromani et. al. studied the effect of moisture on the physical and chemical stability of granulations and tablets of enalapril maleate. It was concluded that the bulk granulation and the tablets should be stored at room temperature or below their relative humidities and the presence of desiccant in the market package was essential (28).

Enalapril maleate tablets are among the preparations presented by numerous manufacturers. Quality control studies must be carried out after the production to the administration. Diameter-thickness, weight variation, hardness, friability, disintegration time and dissolution rate studies are necessary for the quality control experiments (11, 33).

The aim of this study was to investigate the possible quality and quantity differences between the commercially available enalapril maleate tablets.

MATERIALS AND METHOD

MATERIALS:

Enalapril maleate was supplied from Saba Pharmaceutical Company. Disintegration apparatus (D 69 Z Aymes), dissolution apparatus (PTW 2 Pharma test), spectrophotometer (Shimadzu UV-1208) were used. All materials were of analytical grade. 10 and 20 mg of enalapril maleate tablets were purchased from different pharmacies.

METHODS:

Standard curve of enalapril maleate:

Accurate volumes of 20, 40, 60 ,80, 100, 120 and 140 µL of the stock solution (1 mg/mL) of enalapril maleate were transferred into 10 mL calibrated flasks and diluted to volume with distilled water. Spectrophotometric assays were made at 209 nm (7, 21). The values were the means of five experiments.

Table 1 presented the information about the commercially available enalapril maleate tablets. The market tablets were coded as E_{1-8}

Table 1: Information about marketed enalapril maleate tablets

Sample	Label Dose (mg/tablet)	Serial number	Production Date
E_1	10	806036	6/98
E_2	10	8A 001	1/98
E_3	10	8091813	9/98
E_4	10	8061649	6/98
E_5	20	802002	2/98
E_6	20	8I005	9/98
E_7	20	8091817	9/98
E_8	20	8064662	6/98

The controls applied on all of the tablets were the following:

Weight Variation:

Weight variation studies of twenty tablets for each batch were carried out according to the T.F. 1974 (35).

Hardness:

Five tablets from each batch were examined using Monsanto hardness tester.

Disintegration time:

The tablets were examined using the USP XXII disintegration apparatus (33). Six tablets were tested for each batch. The disintegration time of tablets was compared to 15 minutes which is accepted as the general tablet disintegration time by T.F. 1974 (35).

Diameter- Thickness Ratio:

This test was applied on ten tablets from each batch using calipers. The ratio between the thickness and diameter of the tablets was controlled.

Friability:

Friability test was carried out using Roche friabiliator for ten tablets from each batch for 4 minutes.

Content Uniformity:

In order to check the content uniformity of the tablets spectrophotometric method was used. For this purpose; after the crushing of the tablet, distilled water was added and the volume was adjusted to 10 mL. The mixture was shaken for _ hour by automatic shaker. 100 µL of samples

were withdrawn and adjusted to 10 mL with distilled water and assayed by spectrophotometrically. Content uniformity studies were examined triplicate for ten tablets of each batch (33).

Dissolution Rate:

The dissolution rate studies were carried on using the USP XXII paddle method with stirring rate of 50 rpm. The dissolution medium was 900 mL distilled water at a temperature of 37 ± 0,5° C. Samples were withdrawn at the 1^{th} to15^{th} and then 20^{th}, 25^{th}, 30^{th} minutes, respectively and replaced by equal volume of distilled water. One mL of distilled water was added to 1 mL of sample and they were assayed spectrophotometrically at 209 nm (33).

Kinetic Studies:

The kinetic analysis of the dissolution data was evaluated by a computer programme (Çözüm 96) for zero, first order, Hixson Crowell, Modified Hixson Crowell, RRSBW, $Q\sqrt{t}$, Higuchi, Hopfenberg kinetics (1).

RESULTS and DISCUSSION

Figure 1 presents standard curve of calibration.

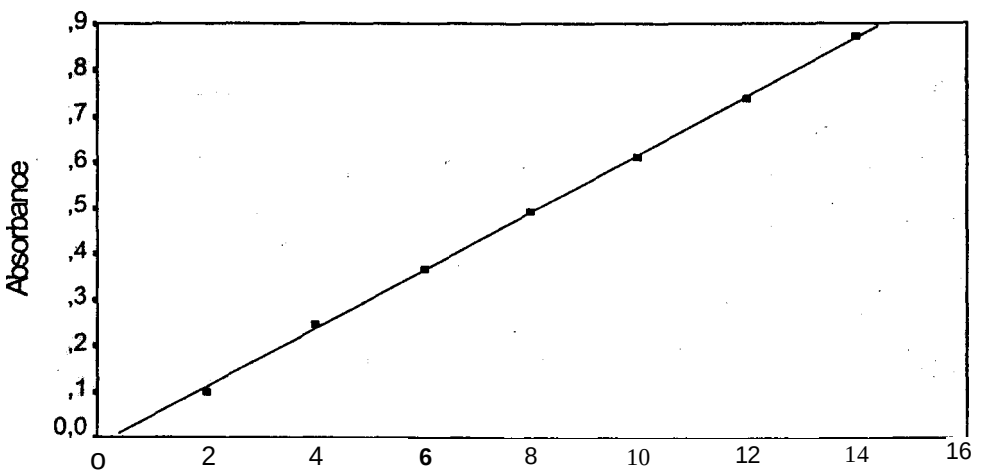

Figure 1: Standard curve of calibration

The equation of the standard curve:

$y = 0.0559x + 0.0970$

Correlation coefficient	0.96011
P Value	0.0000
Residual sum of square	0.04365
F Value	457.32487

Table 2 presents the weight variation, hardness and disintegration time data and its statistical evaluation.

Table 2: The results of controls on weight variation, hardness, disintegration time

Sample	Average Weight (g)	S (±)	CV	Average Hardness (kg)	S (±)	CV	Average Disintegration Time (min)	S (±)	CV
E_1	0,198	0,004	2,020	2,1	C,2	10,7	6,6	0,5	7,7
E_2	0,248	0,005	2,016	1,9	0,2	11,8	1	0	0
E_3	0,199	0,002	1,005	1,3	0,3	21,1	2,3	0,5	22,1
E_4	0,182	0,002	1,099	1,8	0,3	15,2	2,2	0,4	18,8
E_5	0,198	0,008	4,040	2,2	0/4	20,3	8,2	0,8	9,2
E_6	0,248	0,004	1,613	1	0	0,0	1	0	0
E_7	0,203	0,002	0,985	1,4	0,2	16,0	3,7	0,8	22,2
E_8	0,254	0,003	1,181	1,5	0	0,0	1,3	0,5	38,7

S: Standard deviation

CV: Coefficient of variation

CV= (Standard deviation / avarege) x 100

Preparation methods can cause variations on the tablets. Pharmacopoeias have limitations for weight variations of the tablets. In this study it was found out that tablets weights were changing between 0.182-0.254 g and weight variations were not over the pharmacopoeia limits (35).

There is no certain records about hardness in pharmacopoeias. But King (17), mentioned that classical tablet hardness should be 4 kg as minimum and 7 kg as maximum. Since there is no specification for enalapril maleate tablets, an average value of hardness of 4-7 kg for normal

tablets was used as a criteria. In our experiments the average hardness of the tablets was found in values between 1.0-2.2 kg. It was seen that all the tablets in our study have not enough hardness. It was seen in the quality control studies as well which were done before (2,16).

Disintegration test provides a means of control in assuring that a given tablet formula is the same from one production batch to another. There is no significant variation from batch to batch but tablets of different manufacturers can show disintegration time of variable values. According to the disintegration time, the order was $E_5 > E_1 > E_2 > E_4 > E_8 > E_7 > E3 > E_6$.

These differences between the orders were due to the preparation methods, granulation methods, particle sizes, excipients etc. Similar results were reported in previous studies (2, 31). E_2 and E_6 tablets disintegrated in the shortest time. E_6 tablets disintegrated in a short time due to their low hardness. The presence of corn starch in the tablet formulation of E_2 could be reduced the disintegration time of the tablets. Since corn starch increases the liquid penetration into the tablets (24, 28). However, in-vivo and in-vitro tablet disintegration are not accepted the same, disintegration time control is critical when physical properties of the tablets are compared. However, the disintegration times of all tablets were less than 15 minutes as given in T.F. 1974 (35). The disintegration times changed between 1 minute to 8 minutes in all tablets. According to the pharmacopoeia the disintegration values were quite suitable for enalapril maleate tablets.

In our study, the diameter / thickness ratios of the tablets determined are shown in Table 3. In pharmacopoeias there is no records about the diameter / thickness ratio of the tablets. But King (17), mentioned that a ± 5 % difference in thickness could be accepted. However, there were no differences in all the tablets. Diameter / thickness ratio must be four according to Güven (13). This ratio in enalapril maleate tablets was changing between 2.3-4.6. In the literature, it was seen that there were tablets which did not have diameter / thickness ratio as four but nothing clear about what could be the harmful (23).

The results of the friability studies are shown in Table 3. Shafer et. al. (27), mentioned that a loss was not more than 1 % was normal but especially less than 0.8 % of loss was also considered as normal.

It was found that the friability of the all tablets except E_6 was less than 1 %. It was expected that E_6 had high friability because of its low hardness. Preparing method or the ingredients can be the reason of the high friability (18).

Table 3: The results of controls on diameter - thickness ratio and friability

Sample	Diameter (cm)	Thickness (cm)	Ratio*	Loss %
E_1	0,91	0,20	4,55	0,35
E_2	0,92	0,21	4,38	0,05
E_3	0,83	0,30	2,77	0,03
E_4	0,82	0,36	2,28	0,32
E_5	0,91	0,21	433	0,46
E_6	0,94	0,34	2,76	1,18
E_7	0,82	0,30	2,73	0,18
E_8	0,95	0,40	2,38	0,07

*Diameter / Thickness

According to the USP XXII the amount of enalapril maleate in the tablets has to be between 90-110 %. It seems that the amount of drug substance in the all tablets was in the required limits. Table 4 presents the amount of enalapril maleate in the tablets.

Table 4 : Amount of enalapril maleate labelled and determined in the tablets

Sample	Labelled amount (mg)	Found amount (mg)	S (±)	CV	Found amount %
E_1	10	9,05	0,04	0,41	9035
E_2	10	9,83	0,04	0,4	98,35
E_3	10	9,74	0,04	0,4	97,47
E_4	10	9,84	0,04	0,41	98,41
E_5	20	19,28	0,08	0,42	96,45
E_6	20	18,97	0,07	039	93,37
E_7	20	18,44	0,09	0,48	92,23
E_8	20	19,47	0,07	0,34	97,36

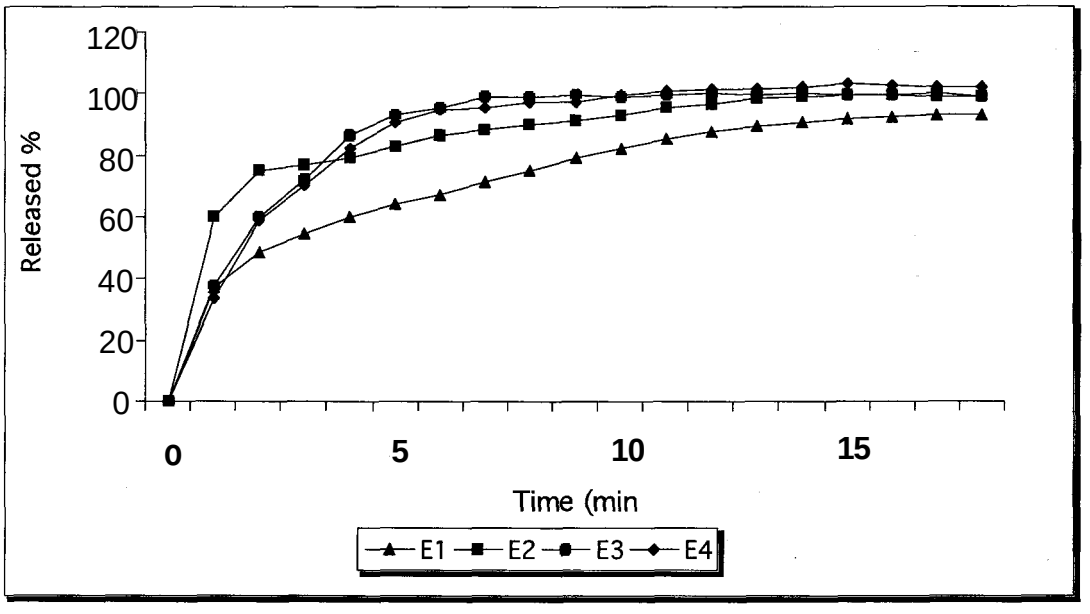

Figure 2: The dissolution profiles of the tablets containing 10 mg enalapril maleate

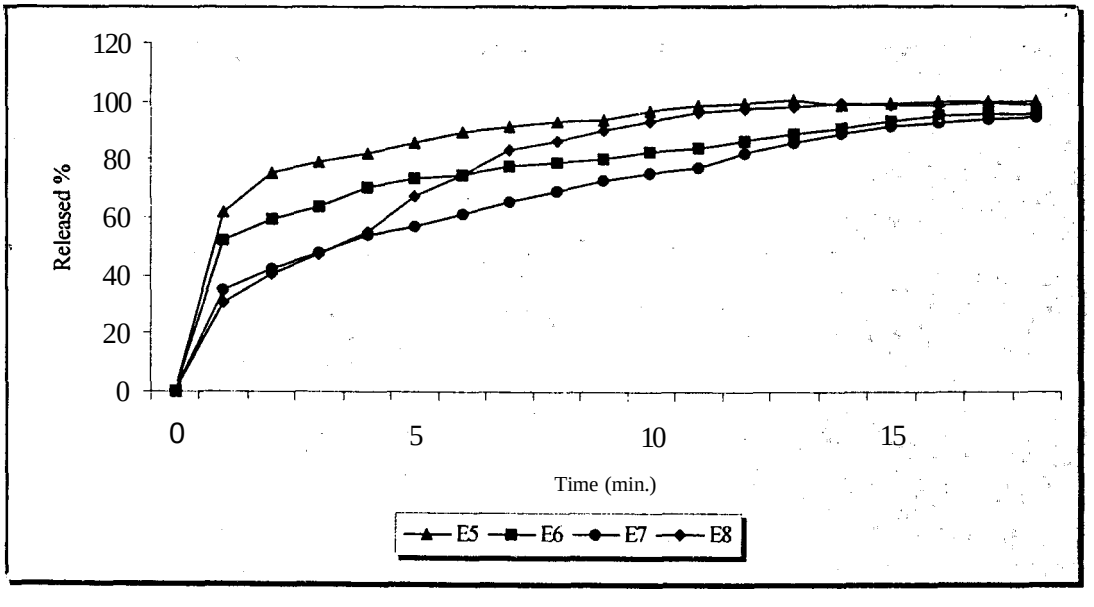

Figure 3: The dissolution profiles of the tablets containing 20 mg enalapril maleate

There are some important factors such as dissolution rate controls to constitute good formulations (14, 22). USP XXII requires that 80 % of the drug amount should dissolve in 30 minutes. The dissolution results complied with the pharmacopoeia requirement (33). All the tablets gave 80 % of enalapril maleate in the shorter time periods than 30 minutes. When dissolution studies on market tablets containing 10 mg enalapril maleate were examined at the end of 5 minutes E_1, E_2, E_3 and E_4coded tablets gave 64.08 %, 82.75 %, 92.73 % and 90.80 % of enalapril maleate, respectively. According to the results of marketed tablets containing 20 mg enalapril maleate at the end of 5 minutes E_5, E_6, E_7 and E_8 coded tablets gave 85.65 %, 73.41 %, 56.67 % and 67.62 % of enalapril maleate, respectively.

In figures 2 and 3 are shown the dissolution profiles of the tablets containing 10 mg and 20 mg enalapril maleate respectively.

The release rates of the all tablets containing 20 mg enalapril maleate except E_5 were slower than the tablets containing 10 mg enalapril maleate.

When the dissolution results were examined kinetically, it was found that the release of enalapril maleate from the all marketed tablets fitted Modified Hixson-Crowell and RRSBW kinetics. In various researches the similar results were observed for plain tablets (23, 32).

Figures 4, 5 showed the" result of RRSBW and Figures 6, 7 showed the result of Modified-Hixson Crowell kinetics, respectively.

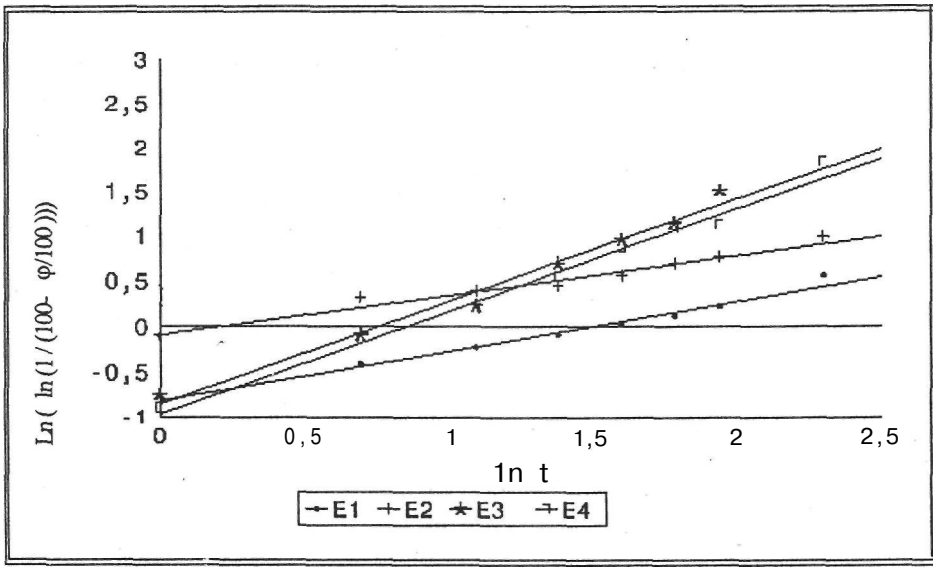

Figure 4: The RRSBW kinetics of all the tablets containing 10 mg enalapril maleate

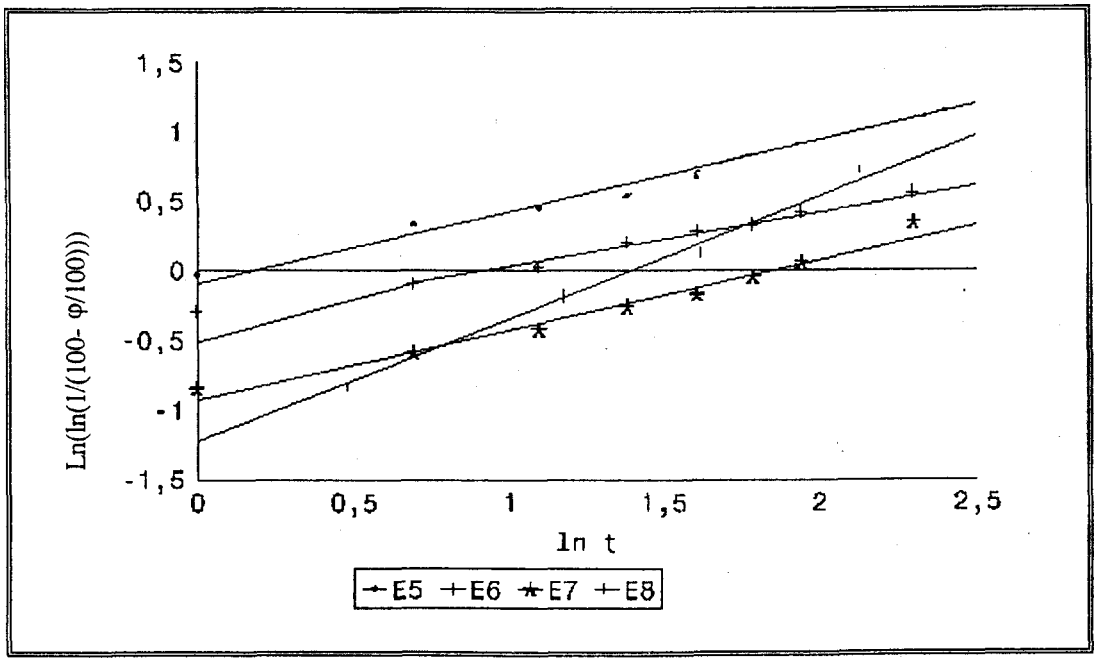

Figure 5: The RRSBW kinetics of all the tablets containing 20 mg enalapril maleate

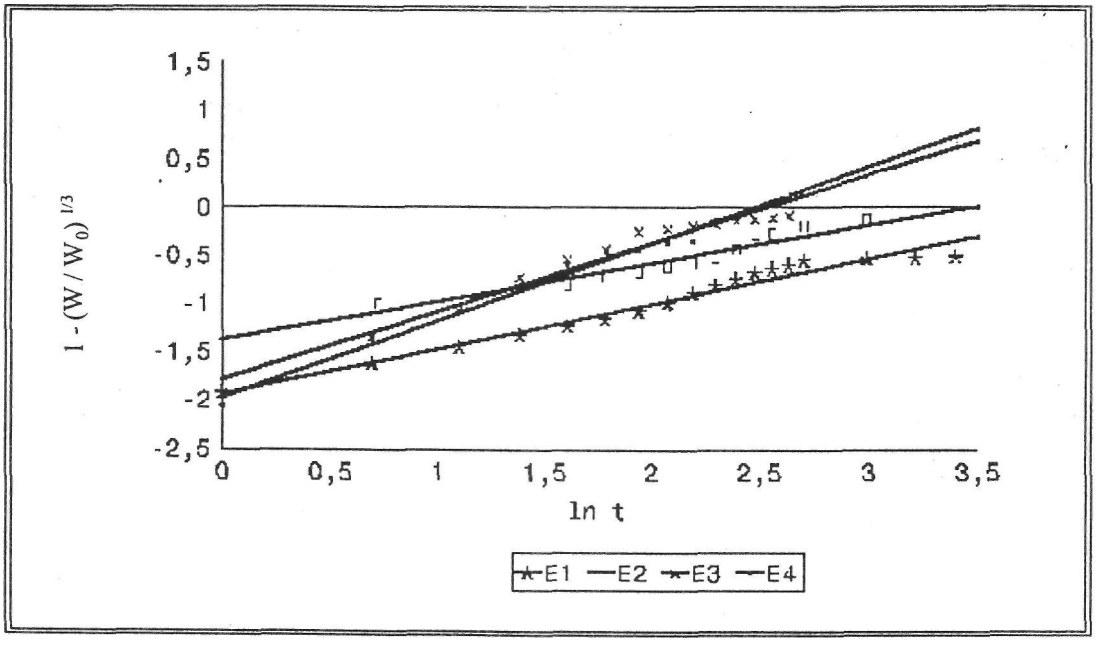

Figure 6: The Modified Hixson - Crowell kinetics of all the tablets containing 10 mg enalapril maleate

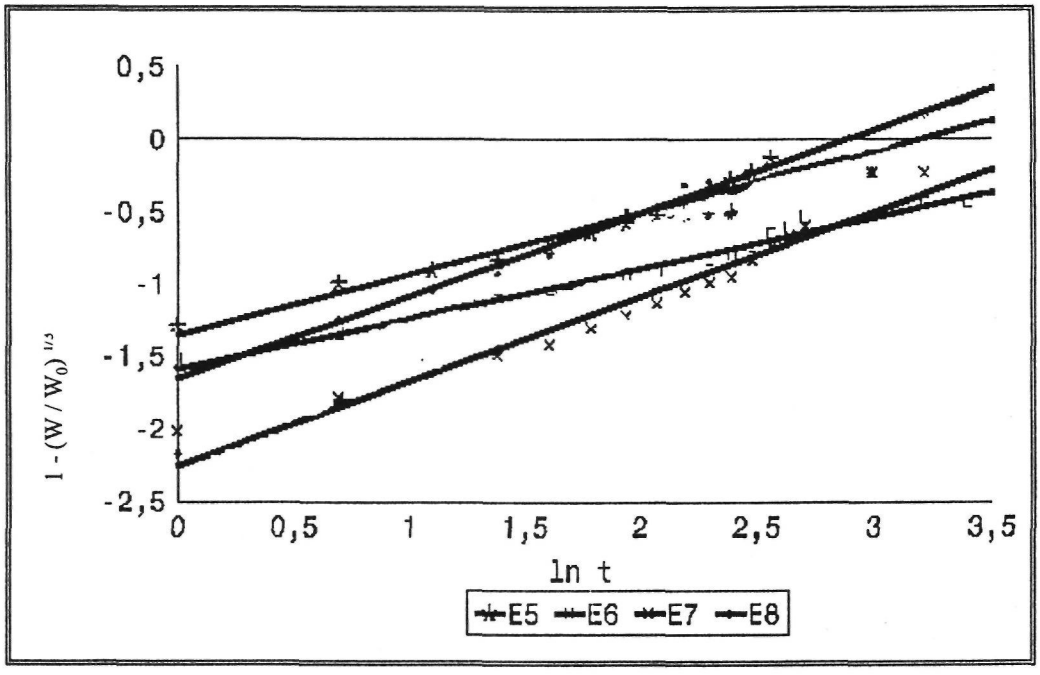

Figure 7: The Modified Hixson - Crowell kinetics of all the tablets containing 20 mg enalapril maleate

As a result, it was observed that the results of quality control studies of the enalapril maleate tablets which were produced in 1998 by different manufacturers fitted pharmacopoeias. However, the hardness of all the tablets were not enough and E_8 coded tablets friability was found 1.18%.

It is not possible to decide on the best preparation using the results obtained since there are no official comparison parameters for enalapril maleate tablets. Evaluated results show that there are differences between the dissolution rates of the tablets.

Determination of the official norm is needed to eliminate the dissolution rate differences which may produce bioavailability problems.

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Başvuru Tarihi : 2.6.2000

Kabul Tarihi : 13.12.2000