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# EFFECT OF STORAGE ON THE IN-VITRO AND IN-VIVO CHARACTERISTICS OF SOME MARKETED SUSTAINED-RELEASE CARDIOVASCULAR TABLETS

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تم فى هذا البحث دراسة بعض الخواص الفيزيوكيميائية والحيوية لأقراص عقارى النفيدبين والبروكيناميد والمتوفرة فى السوق فى صورة ممتدة المفعول هى أدلات ريتارد وبروكيناميد ديريلز.

وقد تم تقييم هذه الأقراص قبل وبعد تخزينها لمدة عام تحت الظروف العادية وعند درجات حرارة ورطوبة عالية.

وقد أظهرت النتائج عدم وجود تغيرات كبيرة فى الخواص الطبيعية والكيميائية وكذلك فى المحتوى الدوائى لهذه الأقراص بسبب التخزين. وبالرغم من وجود اختلاف إحصائى فى معدل أنطلاق الدواء قبل وبعد التخزين إلا أن هذا الاختلاف لم يعتبر اختلافا مؤثرا بالنسبة للأدوية ممتدة المفعول.

وقد أظهرت نتائج دراسة الإتاحة الحيوية اختلافا احصائيا مؤثرا فى المساحة تحت المنحنى ومتوسط تركيز الدواء فى الدم عند القمة بسبب التخزين لأقراص البروكيناميد وبإستخدام كلاب البيجال. وقد يؤثر هذا فى الإتاحة الحيوية لهذه الأقراص.

***The in-vitro and the in-vivo characteristics of the sustained-release cardiovascular drugs : nifedipine (N) and procainamide (PA), commercially available as Adalat-Retard and Procainamide durules tablets were evaluated both before and after their storage at ambient condition and under different accelerated conditions of temperature and relative humidity (RH) for twelve months. The effect of storage on the physical properties, the release rate profiles, the chemical stability and the bioavailability of these tablets in beagle dogs was studied. The results showed no or small change in the physical properties or in the drug contents of both drugs under the storage conditions of the study, indicating good physical and chemical stability of these products. In spite of statistically significant difference found in the dissolution results between the prestorage and stored tablets, this difference was not considered to be of practical significance in case of these sustained release products. The in-vivo studies indicated a statistically significant difference in the area under the curve and in the average peak concentration between the prestored tablets and the tablets stored for twelve months under ambient and at 40°C/80 % RH in case of PA durules. This is a sign for a possible change in the bioavialbility of this product with storage regardless the conditions under which the product is stored.***

## INTRODUCTION

Nifedipine (N) and procainamide (PA) are used in cardiovascular disorders. Nifedipine is a calcium channel blocking agent used as an antihypertensive drug,[1] while PA is a group 1A antidysrhythmic drug used for the suppression of arrhythmias of ventricular origin.[2] Both drugs have short half-lives ($t_{1/2}$ for N ≈ 2.5 h and that for PA ≈ 3.5 h) and are extensively used in chronic cases. Sustained-release formulations of these drugs were developed in order to decrease fluctuations of the drug concentration throughout the dosing intervals and to improve patient

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compliance.[3,4] Pharmaceutical products can be subjected to different adverse climatic conditions during their transportation and storage. Storage conditions can adversely affect the stability of these products. The stability parameters of a solid dosage form that can be influenced by environmental conditions of storage (heat, light, humidity) include not only the specific compendial requirements such as drug content and dissolution rate but also the organoleptic as well as the physical characteristics of this dosage form.[5-9] A change in these parameters can alter the bioavailability and hence, the therapeutic efficency of a given drug.

The purpose of this research was to study the effect of the recently recommended accelerated storage conditions[10] on the in-vitro and in-vivo characteristics of some commercially available, sustained-release cardiovascular drugs.

## EXPERIMENTAL

### MATERIALS

Adalat-Retard, film-coated tablets, containing 20 mg nifedipine, batch # HS 111 (Bayer, Germany) and Procainamide Durules, containing 500 mg procainamide hydrochloride (PA), lot # RB 72 (Astra Pharmaceuticals Ltd., King Langley, England) were commercially available. Nifedipine and PA hydrochloride authentic powders were supplied by Bayer (Wuppertal, Germany) and purchased from Sigma Chem. Co. (St. Louis, MO, USA), respectively. All other chemicals and reagents were of analytical grades and were used without further purification.

### METHODS

**Determination of physical characteristics**

- **Weight, thickness and diameter variation**

Twenty tablets were weighed individually and their thickness and the diameter of ten of them were measured using micrometer (Model Mitutoyo, Japan). The mean, standard deviation and coefficients of variation were calculated.

- **Hardness**

An Erweka hardness tester (Type TBH 28, Germany) was used to measure the hardness of six tablets. The hardness was expressed in terms of kilopond (Kp).

- **Disintegration time**

An Erweka disintegration apparatus (Type ZT4, Germany) was used to determine the disintegration time of six individual tablets in distilled water at 37°C.

**Determination of drug content**

The average drug content was determined by powdering ten tablets of either Adalat-Retard or PA durules in a mortar. An amount equivalent to 20 mg nifedipine and 500 mg of PA was extracted using ethanol. The filtrate was diluted with 0.1 N HCl in case of nifedipine and with 0.1 N NaOH for PA and the absorbance was measured at 238 and 275 nm, respectively.

**In-vitro dissolution study**

The release rate studies were performed using an automated tablet dissolution testing system (Caliva, Philips, England) at 37°C following the USP XXIII method 2 (Paddle) at 100 rpm for 2 hours in 750 ml 0.1 N HCl (pH = 1.2). The test was continued for at least another 6 hours in pH 7.2 dissolution media. The change in pH was achieved by adding 250 ml of 0.2 M tribasic sodium phosphate. Nifedipine concentration was continuously monitored spectrophotometrically at 238 nm, while in case of PA, samples of 5.0 ml were taken from the dissolution media at predetermined time intervals, properly diluted with 0.1 N NaOH and the absorbance was read at 275 nm. These samples were substituted with fresh dissolution media equilibrated at 37°C. The concentration was determined in each sample taking into consideration the dilution factor. The average reading of six individual tablets was recorded in both cases.

**Storage conditions**

Both Adalat-Retard and PA tablets were stored in their original containers (amber colored glass containers with plastic cap) under two different conditions: 40°C/30% relative humidity

(RH) and 40°C/80% RH. These conditions were achieved by using appropriate saturated salt solutions with excess solid in a closed desiccator kept in incubators (Heraus, B 6060) maintained at 40°C. The two products were also stored under ambient conditions (22°C/30±RH) for twelve months. Samples were tested periodically at different time intervals for their physical characteristics, drug content and their dissolution rate profiles.

**In-vivo absorption characteristics**

- **Animal study**

Five to six healthy male beagle dogs weighing between 10-14 kg were used to study the pharmacokinetic parameters of the two products (N and PA) before storage and twelve months after storage under ambient and high relative humidity conditions (40°C/80% RH). The same group of animals was used with each drug at all treatments with at least 3 weeks washout period allowed between treatments. The dogs were fasted for 24 hours prior drug administration and continued fasting until 4 hours post dosing, but allowed free access to water. Nifedipine 20 mg tablets (Adalat-Retard) or procainamide durules 500 mg tablets were administered by gastric intubation technique. Venous blood samples (5 ml) were taken from the femoral vein into heparinized tubes before drug administration and at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0 and 10.0 hr post dosing for N and at 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0 and 12.0 hr post dosing for PA. The plasma was then separated after centrifugation and transferred into polypropylene tubes and stored at -20°C pending analysis.

- **Analysis of plasma samples**

Nifedipine plasma concentrations were measured using a specific, sensitive and validated high-performance liquid chromatographic (HPLC) assay,[11] while PA samples were measured using an HPLC method developed in our laboratory.[12]

It is worth mentioning that because of N light sensitivity, all previously stated in-vitro and in-vivo experiments concerning Adalat-Retard tablets were strictly carried out under subdued light with all flasks and tubes wrapped in aluminum foil to avoid the effect of UV and daylight.

**Treatment of data**

- **In-vitro dissolution data**

A paired t-test for means of two samples was performed on samples stored for different periods of time under the two different conditions and on tablets stored for twelve months under ambient conditions in order to see whether the statistical differences (if existed) in the in-vitro dissolution data could be reflected on the in-vivo absorption characteristics.

- **Pharmacokinetic analysis**

Pharmacokinetic parameters for N and PA following oral administration were determined from the concentration-time data. The maximum plasma concentration ($C_{max}$) and the corresponding time ($T_{max}$) were obtained directly from the plasma concentration-time profiles. The area under the plasma concentration-time curve (AUC) and the area under the first moment curve (AUMC) were estimated by linear trapezoidal rule and extrapolated to infinity using the following equation:

$$AUC_{0\to\infty} = AUC_{0\to t} + C_p/K_{el} \quad \ldots\ldots\ldots \quad (1)$$

$$AUMC_{0\to\infty} = AUMC_{0\to t} + t.C_p/K_{el} + C_p/K_{el}^2 \quad \ldots\ldots\ldots \quad (2)$$

where:

$C_p$ is the last measurable concentration at time t and $K_{el}$ is the elimination rate constant determined as the slope of the terminal monoexponential decline in plasma concentration-time curve using the least square method. The elimination half-life ($t_{1/2}$) was calculated from the formula:

$$t_{1/2} = 0.693/K_{el} \quad \ldots\ldots\ldots \quad (3)$$

The mean residence time of the drugs in the body (MRT) was calculated using the following equation :

$$MRT = AUMC/AUC \quad \ldots\ldots\ldots \quad (4)$$

The percentages of the concentration at the sixth hr sampling time estimated as percentage of the maximum concentration were also calculated.

The influence of storage on these

pharmacokinetic parameters was evaluated using one-way analysis of variance (ANOVA) for repeated measurements. Duncan's multiple range test was applied to find the source of possible differences between various treatment phases of the study. Differences between two related parameters were considered statistically significant for p-value equal to or less than 0.05. All analysis were performed with a statistical software package (Statistical Analysis System, SAS Institute, Inc., Cary, N.C., USA).

## RESULTS AND DISCUSSION

### Effect of storage on Adalat-Retard tablets

#### Physical characteristcs

The effect of storage conditions on the physical properties of Adalat-Retard tablets after twelve months is shown in Table I. The results showed a slight increase in the weight and the size of tablets stored at 40°C/80% R.H., which can be attributed to an increase in moisture content.[13,14] A gradual increase in the weight and in moisture content of acetaminophen tablets prepared using either povidone or pregelatinized starch as a binder was reported when these tablets were stored at 40°C/94% R.H., while the dry atmosphere had slight effect on these parameters.[15] On the contrary, an initial decrease in the weight of tablets made of dibasic calcium phosphate dihydrate as the matrix was observed when these tablets were stored at 45°C/75% R.H.[16] The authors found that the loss in weight is equivalant to the water of hydration in the matrix indicating water release during storage. Because of the unknown exact Adalat-Retard tablet formulation, it is not possible to know which of the tablet components is responsible for water absorption leading to the increase in tablet weight.

On the other hand, storage of Adalat-Retard tablets under low relative humidity (40°C/30% R.H.) and ambient conditions resulted in no change in the tablet weight or size, Table I.

The change in hardness of Adalat-Retard tablets upon storage followed the same pattern as in case of tablet size. In other words, storage at low relative humidity resulted in no significant change in tablet hardness, while storage at 80% R.H. resulted in a slight increase in the hardness (Table I). Different effects of moisture on tablet hardness was found in the literatures. While Amidon and Middleton,[5] noted a decrease in tablet hardness stored at 25°C/93% R.H., Molokhia *et al.*,[17] observed an increase in the hardness of tablets made of different bases with different initial moisture content after storage at 40°C/90% R.H. These descrepancies can be attributed to different drugs used and/or tablet excipients employed in each case.

With regard to the disintegration time, almost no change was observed for tablets stored at 80% R.H. for up to one year, while a continuous gradual decrease was seen at 30% R.H. and under ambient conditions. This decrease may be attributed to moisture loss at the relatively high temperature (40°C).[13] The above findings suggest that changes in hardness and disintegration time are not necessary related.

#### Drug content

The average nifedipine content was determined periodically for up to twelve months of storage under different storage conditions. The results are shown in Table II. No changes in nifedipine content were observed under all conditions. These results indicated the good chemical stability of N under the conditions of this study when atmost care was taken to protect the drug from light. Similar findings were observed.[18,19] Although these results were obtained using direct UV measurement, random samples of Adalat-Retard tablets stored for various periods of time were also analyzed using an HPLC method developed in our laboratory.[11] No significant differences in the results obtained by the direct method routinely used and the HPLC assay were found. In the mean time, the HPLC chromatograms of the samples did not show any decomposition product during storage.

#### Release studies

The release rate profile of a sustained-release dosage form is far more important than its physical properties in determining the dosage form effictiveness. That

**Table I**: Physical properties of nifedipine (Adalat-Retard) tablets before and after storage for twelve months under different conditions.

| Paramenter | Storage Condition | | | |
|---|---|---|---|---|
| | Prestorage | 40°C/30 %RH | 40°C/80 %RH | Ambient condition* |
| Wight (mg) mean± (SD) | 84.21 (1.20) | 83.79 (0.79) | 87.03 (1.01) | 84.23 (1.47) |
| Thickness (mm) mean± (SD) | 2.64 (0.02) | 2.63 (0.02) | 2.66 (0.03) | 2.64 (0.03) |
| Diameter (mm) mean ± (SD) | 6.10 (0.01) | 6.11 (0.01) | 6.14 (0.01) | 6.12 (0.01) |
| Hardness (Kp) mean ± (SD) | 8.63 (0.74) | 9.19 (0.56) | 10.46 (0.62) | 8.96 (0.90) |
| Disntegration time (min) mean ± (SD) | 15.00 (0.82) | 7.50 (0.71) | 16.50 (0.58) | 6.38 (0.48) |

* Ambient condition = 22°C/30 ± 5% RH.

**Table II**: Average nifedipine content of Adalat-Retard tablets upon storage under different conditions.

| Storage condition | Average nifedipine content (%) after storage time (months) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0 | 0.5 | 1 | 2 | 4 | 6 | 9 | 12 | 12 A.C.* |
| 40°C/ 80% RH | 97.0 | 97.6 | 101.0 | 101.3 | 101.0 | 100.0 | 98.4 | 100.0 | |
| 40°C/ 30% RH | 97.0 | 98.6 | 101.3 | 99.3 | 100.3 | 101.0 | 99.0 | 98.0 | 99.6 |

* A.C. = ambient condition

is because the in-vitro release parameters may be used to predict the in-vivo behavior of the product.

The effect of storage time under different accelerated conditions on the release rate of nifedipine retard tablets is shown in Figures 1 and 2. A slight increase in the dissolution rate after two weeks followed by a gradual decrease in the extent of dissolution with time was observed, specially at 40°C/80% R.H. The initial increase was attributed to the water uptake in case of high humidity condition[9,17] and to the decreased disintegration time in case of the dry conditions. The gradual decrease in the release rate continued in case of high relative humidity, while it remained almost constant in case of the other condition after one month. This was in agreement with the results of Gordon *et al.*,[20] who reported a major decrease in dissolution of wet granulated tablets after storage at 37°C/80% R.H., while storage at room temperature had affected dissolution in only a minor fashion.

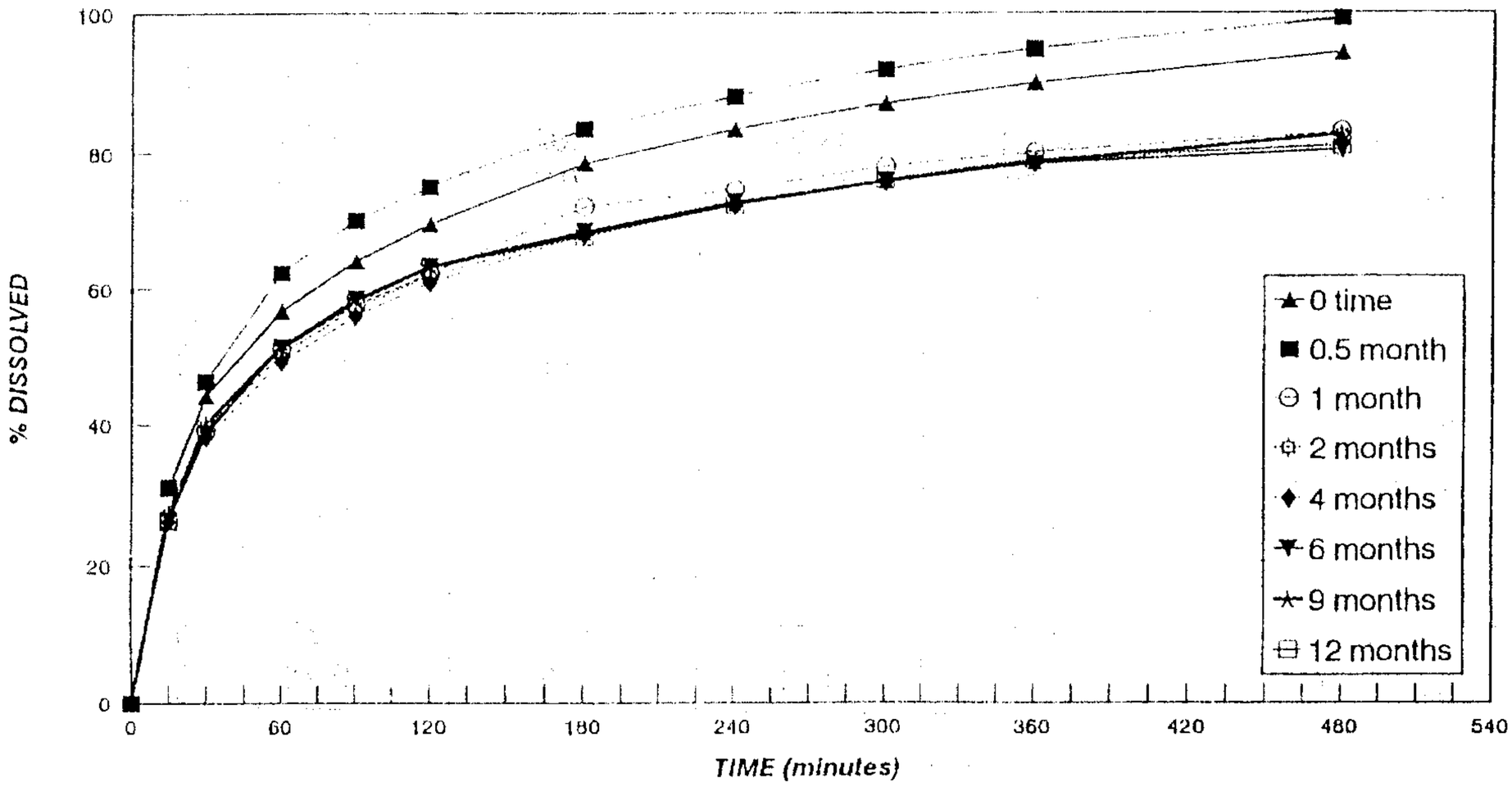


**Fig. 1:** Dissolution rate of Adalat-Retard (nifedipine) tablets stored at 40°C/30% R.H. for up to twelve momths.

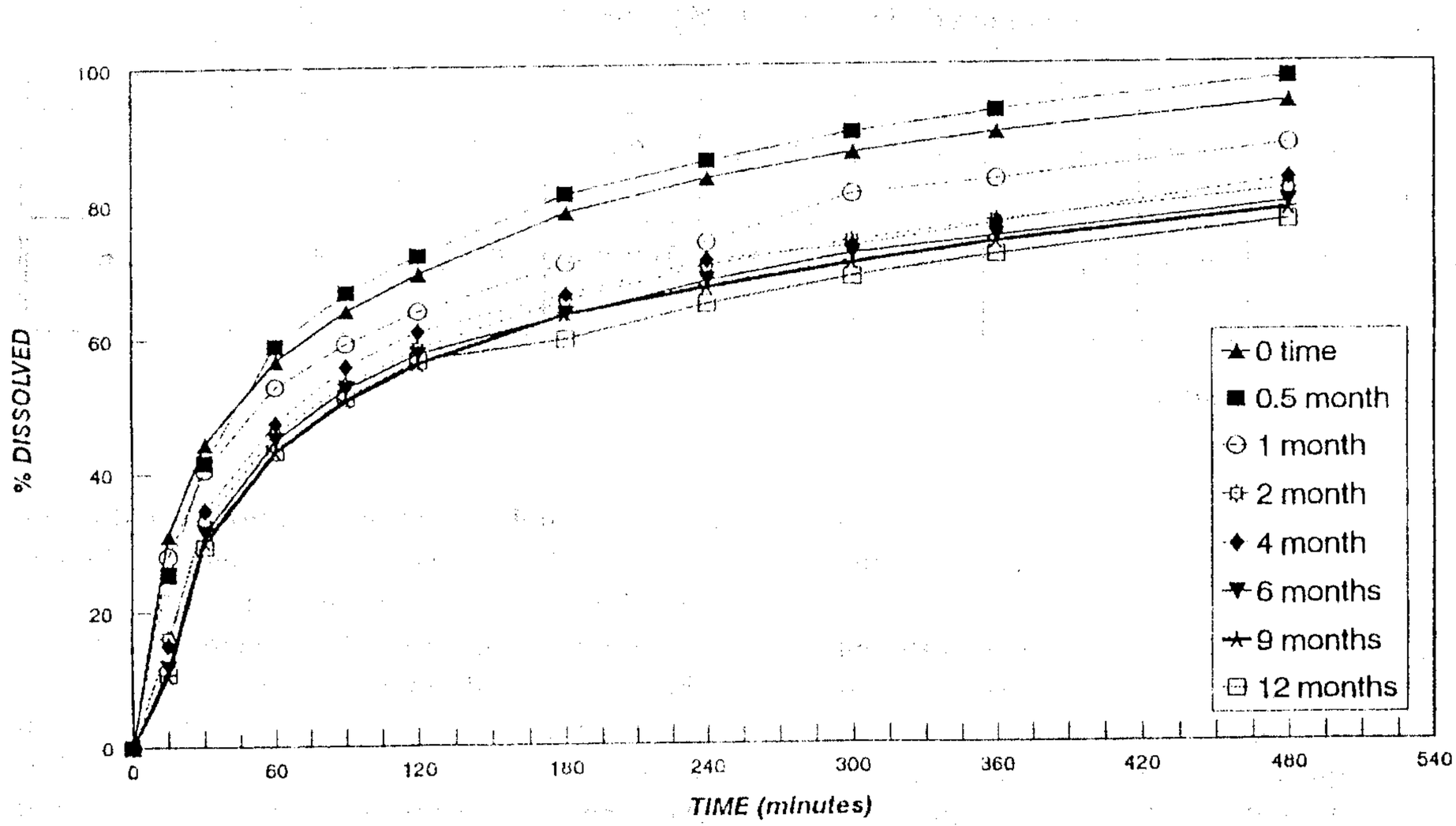


**Fig. 2:** Dissolution rate of Adalat-Retard (nifedipine) tablets stored at 40°C/80% R.H. for up to twelve momths.

A paired t-test on the dissolution data for means of two samples was performed on samples stored for different periods of time under the two storage conditions at the two and six hour points. The test was also performed on tablets stored for twelve months under ambient conditions. The results are shown in Table III. Although statistically significant differences were found between the control (prestorage) and the stored tablets, this was not seen as a practically effective difference in dissolution because it is a common practice to report the dissolution results of sustained-release products in terms of a range rather than in a single Figure.[21]

**Effect of storage on procainamide durules tablets**

**Physical characteristics**

The effect of storage conditions on the physical properties of PA tablets for up to twelve months is shown in Table IV. No significant changes were found in these properties after storing the tablets under both storage as well as ambient conditons, except for the slight increase in hardness at 40°C/80% R.H. which can be attributed to hardenning of the tablet coat.[22]

**Drug content**

The average PA content was detrmined for tablets stored for up to one year by a direct UV and a selective HPLC assay[12] and was found to be not affected. This indicates that the stability of PA tablets is not affected by these accelerated conditions used in this study (Table V).

**Release studies**

The results of the dissolution studies are shown in Figures 3 and 4. These results indicated no change in the dissolution rate of the stored PA tablets for up to twelve months under any of the storage conditions. The same statistical test used in case of N was performed on PA. The results are shown in Table VI. A similar conclusion to that mentioned in case of Adalat-Retard tablets can also be drawn in this case.

**In-vivo studies**

Beagle dogs were used to investigate the effect of storage on the pharmacokinetics of N and PA durules tablets. A good correlation between the bioavailability results obtained from dogs and humans on capsule formulations exposed to accelerated conditions was found.[23]

**Nifedipine**

The mean plasma concentration-time curves of nifedipine after the oral administration of Adalat-Retard tablets (20 mg) to beagle dogs at zero time (prestorage) and after storage for 12 months at 40°C/80% R.H. and at ambient conditions are shown in Figure 5. Table VII summarizes the mean pharmacokinetic parameters studied. Also, in this table shown is the percentage concentration at 6 hour sampling time estimated as percentage of the maximum concentration. Results from the one-way analysis of variance indicated no statistically significant differences between the three treatment periods on any of the pharmacokinetic parameters at a p value= 0.05. These results were further confirmed using Duncan's multiple test. Minimal variations in these parameters observed following storage of Adalat-Retard tablets at 40°C/80% R.H. and at ambient conditions clearely indicated a comparable rate and extent of absorption.

**Procainamide**

The results of PA in-vivo data were similarly presented in Figure 6 and in Table VIII. From these data, the mean area under the plasma concentration-time curves from zero to infinty was found to decreased by 29.97% and 17.21% following storage for 12 months at ambient conditions and at 40°C/80% R.H., respectively compared to that obtained from the prestorage treatment. The average peak concentrations ($C_{max}$) were also declined by 26.72% and 17.86% following the previous storage conditions. The differences were statistically significant in both these parameters. On the other hand, Duncan's multiple range test showed no statistically significant differences in $AUC_{0\to\infty}$ and $C_{max}$ between the two storage conditions (12 months at ambient conditions and at 40°C/80% R.H.). In the mean time, no significant differences were found between the three treatment periods with regard to the time

**Table III:** Mean percent dissolved ± SD of nifedipine from Adalat-Retard tablets at two and six hours after storage at different conditions and the results of the statistical analysis.

| Time of storage (months) | Mean % dissolved ± SD after time (hours) | | | |
|---|---|---|---|---|
| | 40°C/30% RH | | 40°C/80 %RH | |
| | 2.0 | 6.0 | 2.0 | 6.0 |
| 0.0 | 69.59±1.05 | 89.99±2.22 | 69.59±1.05 | 89.99±2.22 |
| 0.5 | 75.20±0.79 S* | 94.91±0.87 | 72.28±0.66 S | 93.20±0.96 S |
| 1.0 | 62.31±0.66 S | 80.14±0.57 S | 63.59±1.97 S | 82.00±0.82 S |
| 2.0 | 61.99±0.63 S | 78.46±0.78 S | 58.46±0.49 S | 76.94±0.66 S |
| 4.0 | 60.96±0.80 S | 78.40±1.30 S | 60.99±1.08 S | 76.50±1.02 S |
| 6.0 | 63.45±0.85 S | 78.29±1.42 S | 57.57±0.47 S | 74.58±1.21 S |
| 9.0 | 63.26±0.75 S | 78.50±1.13 S | 56.05±0.93 S | 73.70±1.30 S |
| 12.0 | 63.12±1.09 S | 79.00±1.91 S | 56.57±0.79 S | 71.86±1.00 S |
| 12.0 A.C.** | 61.95±0.56 S | 77.68±0.89 S | | |

* S : Statistically significant difference from prestored tablets; significance level = 0.05
** A.C.: Ambient condition

**Table IV:** Physical properties of Procainamide durules tablets before and after storage for twelve months under different conditions.

| Paramenter | Storage Condition | | | |
|---|---|---|---|---|
| | Prestorage | 40°C/30 %RH | 40°C/80 %RH | Ambient condition* |
| Wight (mg) mean± (SD) | 677.8 (4.38) | 675.3 (4.06) | 685.1 (3.39) | 680.8 (1.81) |
| Thickness (mm) mean± (SD) | 6.89 (0.03) | 6.80 (0.05) | 6.90 (0.02) | 6.88 (0.05) |
| Diameter (mm) mean ± (SD) | 12.08 (0.01) | 12.08 (0.01) | 12.09 (0.01) | 12.10 (0.07) |
| Hardness (Kp) mean ± (SD) | 26.78 (1.47) | 27.63 (0.93) | 30.01 (0.81) | 26.22 (0.42) |

* Ambient condition = 22°C/30 ± 5% RH

**Table V:** Average drug content of procainamide durules tablets upon storage under different conditions.

| Storage condition | Average procainamide HCl content (%) after storage time (months) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0 | 0.5 | 1 | 2 | 4 | 6 | 9 | 12 | 12 A.C.* |
| 40°C/ 80% RH | 101.5 | 101.3 | 101.3 | 101.4 | 99.0 | 100.8 | 101.0 | 101.0 | |
| 40°C/ 30% RH | 101.5 | 101.3 | 101.2 | 100.8 | 102.3 | 98.4 | 100.8 | 101.2 | 100.7 |

*A.C. = ambient condition

**Table VI:** Mean percent dissolved ± SD of procainamide HCl from procainamide durules tablets at two and six hours after storage at different conditions and the results of the statistical analysis.

| Time of storage (months) | Mean % dissolved ± SD after time (hours) | | | |
|---|---|---|---|---|
| | 40°C/30% RH | | 40°C/80 %RH | |
| | 2.0 | 6.0 | 2.0 | 6.0 |
| 0.0 | 73.85±2.63 | 96.90±1.65 | 73.85±2.63 | 96.90±1.65 |
| 0.5 | 68.64±3.86 S* | 96.34±2.26 | 74.34±2.89 | 98.07±2.22 |
| 1.0 | 69.73±3.86 | 97.77±2.80 | 70.11±2.60 S | 96.59±1.88 |
| 2.0 | 68.67±2.40 S | 97.59±3.12 | 73.88±4.06 | 99.52±1.81 S |
| 4.0 | 71.27±3.00 | 99.50±3.25 | 71.83±4.96 | 96.33±3.00 |
| 6.0 | 79.90±4.47 S | 101.7±2.04 S | 72.81±4.38 | 98.44±2.22 S |
| 9.0 | 69.13±4.77 S | 97.47±2.72 | 66.80±5.46 S | 96.10±2.34 |
| 12.0 | 70.55±5.10 | 94.35±2.09 | 80.05±4.63 S | 99.08±2.03 S |
| 12.0 A.C.** | 69.25±4.60 S | 97.57±1.29 | | |

* S : Statistically significant difference from prestored tablets; significance level = 0.05
** A.C.: Ambient condition

**Table VII:** Mean pharmacokinetic parameters of nifedipine after oral admininsstration of Adalat-Retard (20 mg) to beagle doge at zero time and after storage for 12 months at 40°C/80%RH and ambient conditions.

| Parameter* | Zero time** | Ambient conditions | 40°C/80% RH |
|---|---|---|---|
| $AUC_{0\to\infty}$ (ng.hr/ml) | 299.70±47.49 | 211.00±9.95 | 224.60±17.93 |
| $C_{max}$ (ng/ml) | 73.92±5.44 | 68.85±1.69 | 68.97±4.03 |
| $T_{max}$ (hr) | 2.40±0.40 | 1.83±0.28 | 2.17±0.38 |
| $K_{el}$ (l/hr) | 0.391±0.06 | 0.41±0.02 | 0.39±0.02 |
| t½(hr) | 1.90±0.22 | 1.70±0.08 | 1.82±0.10 |
| MRT (hr) | 3.79±0.38 | 3.29±0.17 | 3.57±0.24 |
| % conc.*** at 6 hr | 24.65±3.65 | 15.58±2.12 | 19.23±3.43 |

* Values presented as means ± S.E. of 6 dogs
** Mean ± S.E. of 5 dogs
*** Percentage of the concentration at the 6 hours sampling time estimated as % of the maximum concentration

**Table VIII:** Mean pharmacokinetic parameters of procainamide after oral admininsstration of Procainamide durules (500 mg) to beagle dogs at zero time and after storage for 12 months at 40°C/80%RH and ambient conditions.

| Parameter* | Zero time | Ambient conditions | 40°C/80% RH |
|---|---|---|---|
| $AUC_{0\to\infty}$ (ng.hr/ml) | 61.19 ± 2.39 | 42.85 ± 2.64 | 50.66 ± 2.50 |
| $C_{max}$ (μg/ml) | 7.56 ± 0.45 | 5.54 ± 0.22 | 6.21 ± 0.49 |
| $T_{max}$ (hr) | 3.20 ± 0.20 | 3.40 ± 0.24 | 3.60 ± 0.24 |
| $K_{el}$ (l/hr) | 0.228 ± 0.08 | 0.231 ± 0.03 | 0.235 ± 0.03 |
| t½(hr) | 40.08 ± 0.78 | 3.25 ± 0.45 | 3.21 ± 0.50 |
| MRT (hr) | 7.49 ± 0.59 | 6.71 ± 0.36 | 6.92 ± 0.51 |
| % conc.** at 6 hr | 75.38 ± 5.35 | 73.78 ± 2.67 | 76.22 ± 1.70 |

* Values presented as means ± S.E. of 5 dogs
** Percentage of the concentration at the 6 hours sampling time estimated as % of the maximum concentration

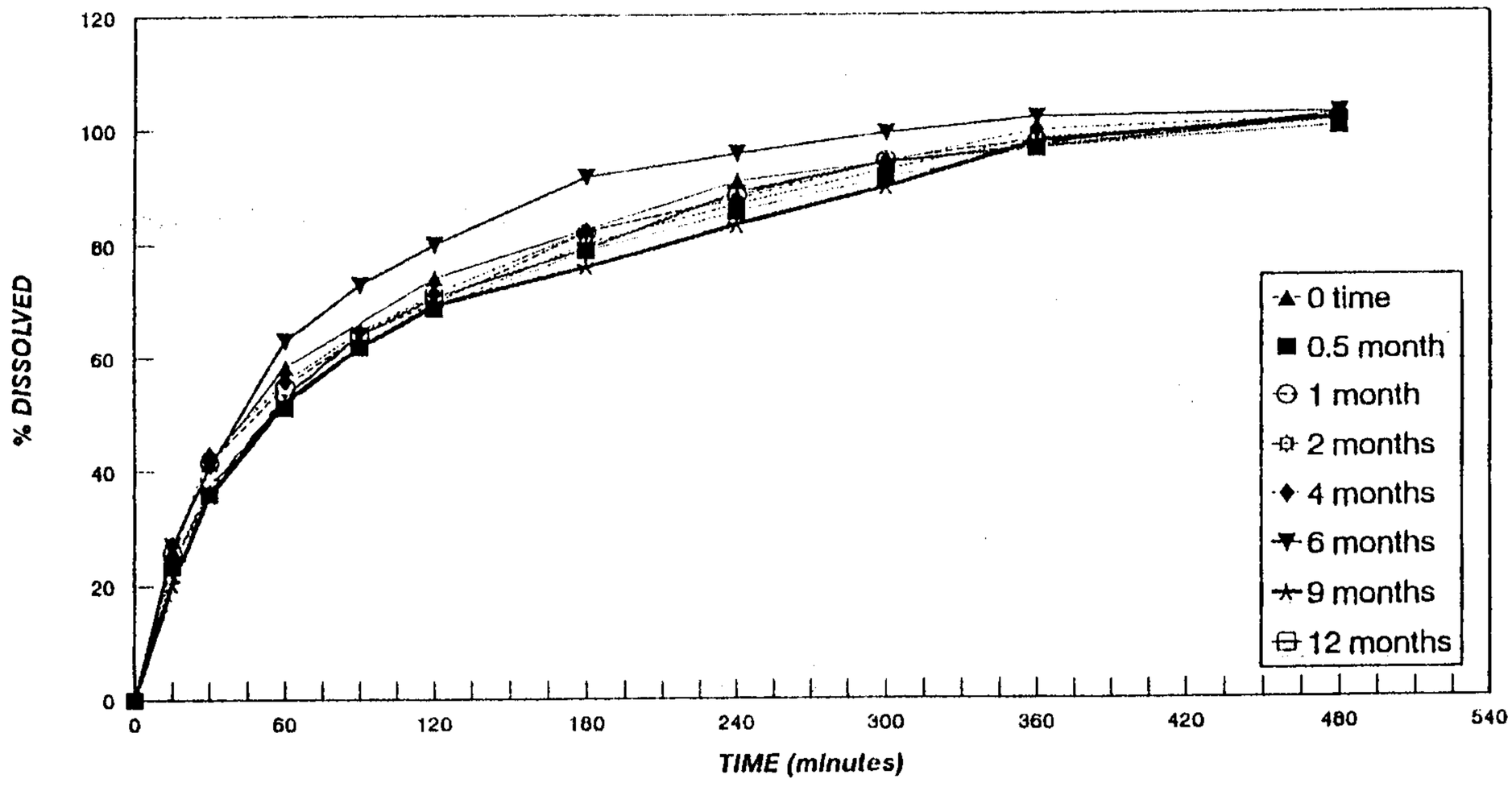


**Fig. 3:** Dissolution rate of Procainamide Durules tablets stored at 40°C/30% R.H. for up to twelve momths.

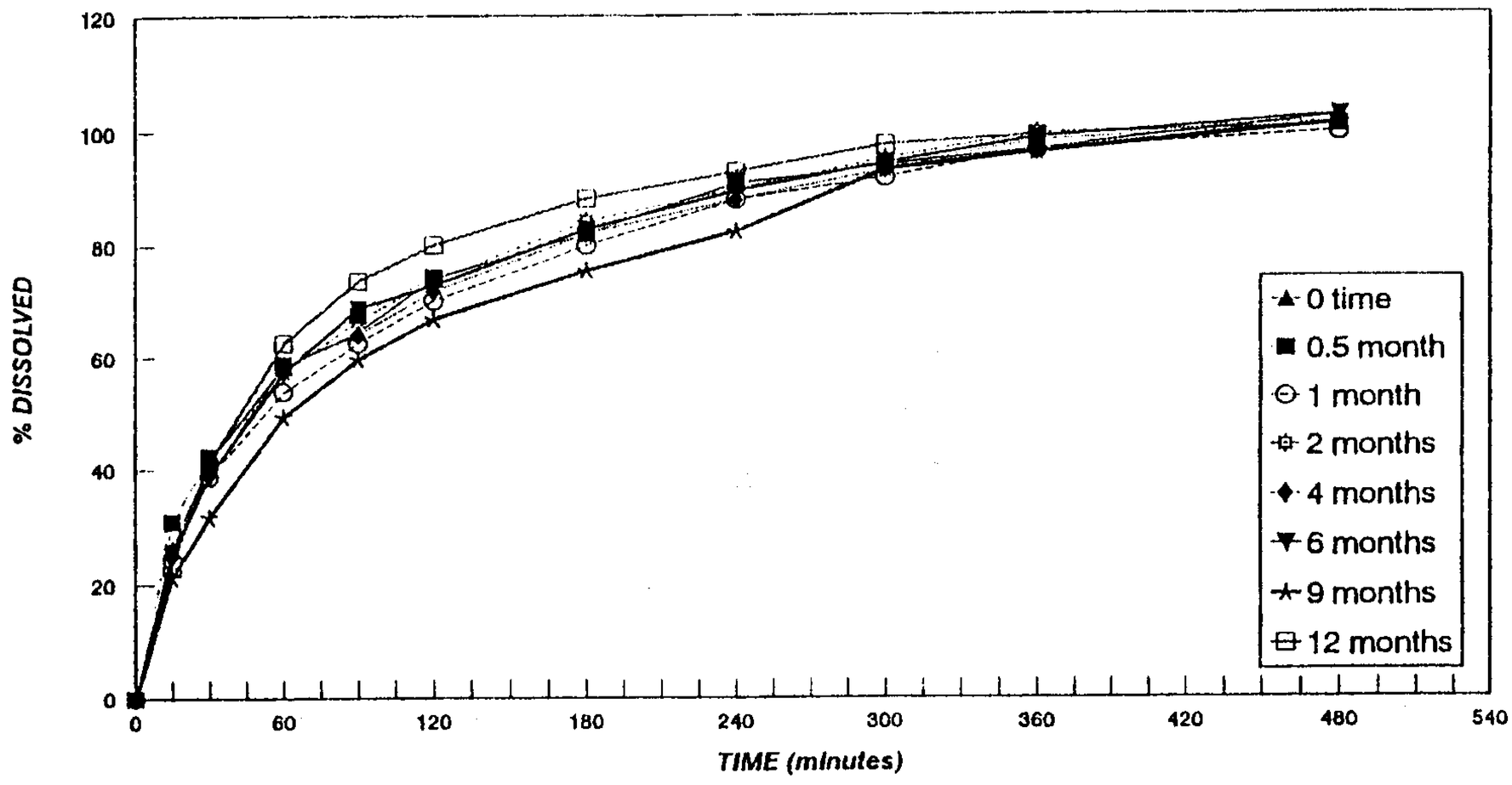


**Fig. 4:** Dissolution rate of Procainamide Durules tablets stored at 40°C/80% R.H. for up to twelve momths.

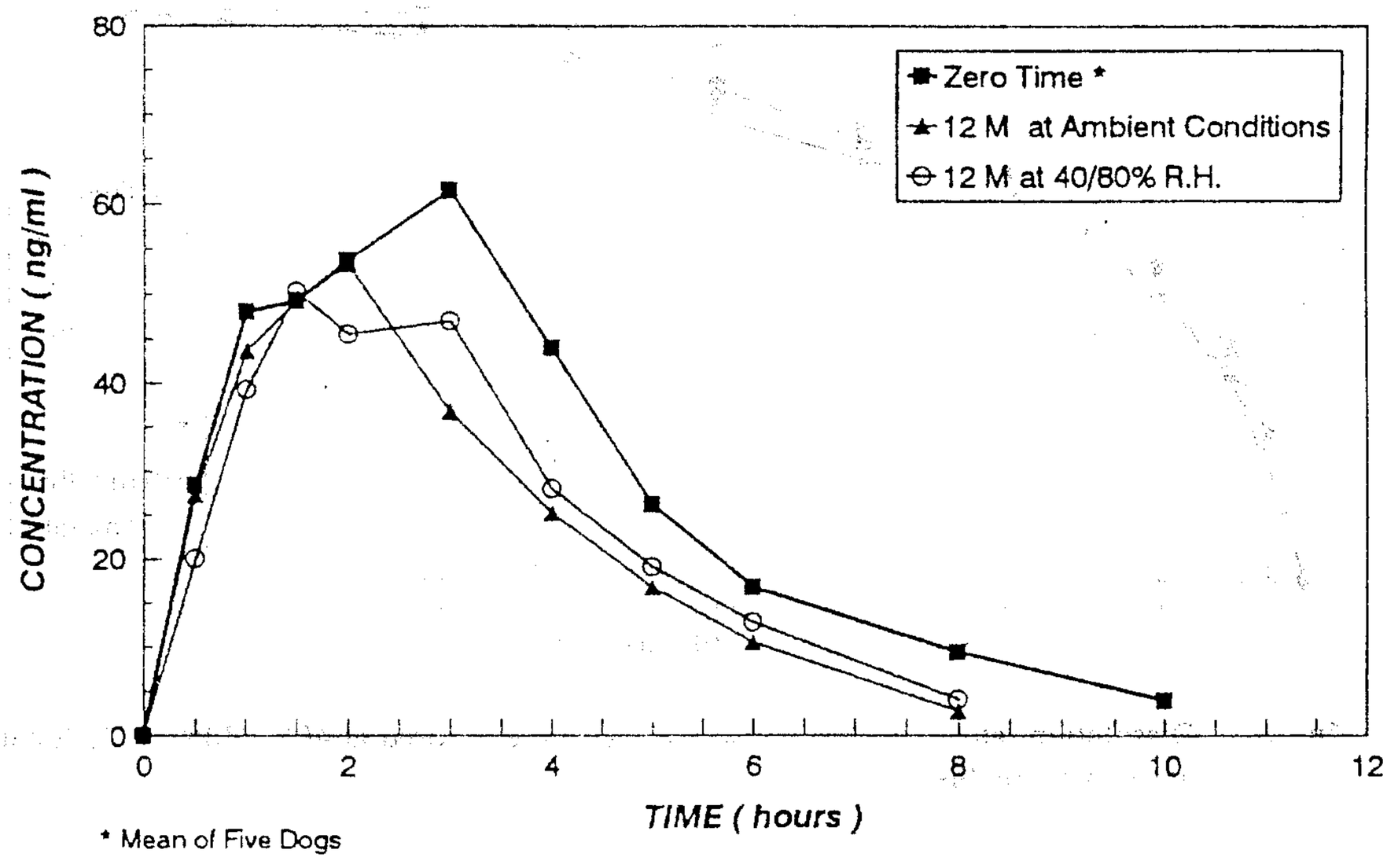


**Fig. 5:** Mean plasma concentrations of nifedipine (ng/ml) after oral administration of Adalat-Retard (20 mg) tablets to six beagle dogs at zero time and after storage at different conditions.

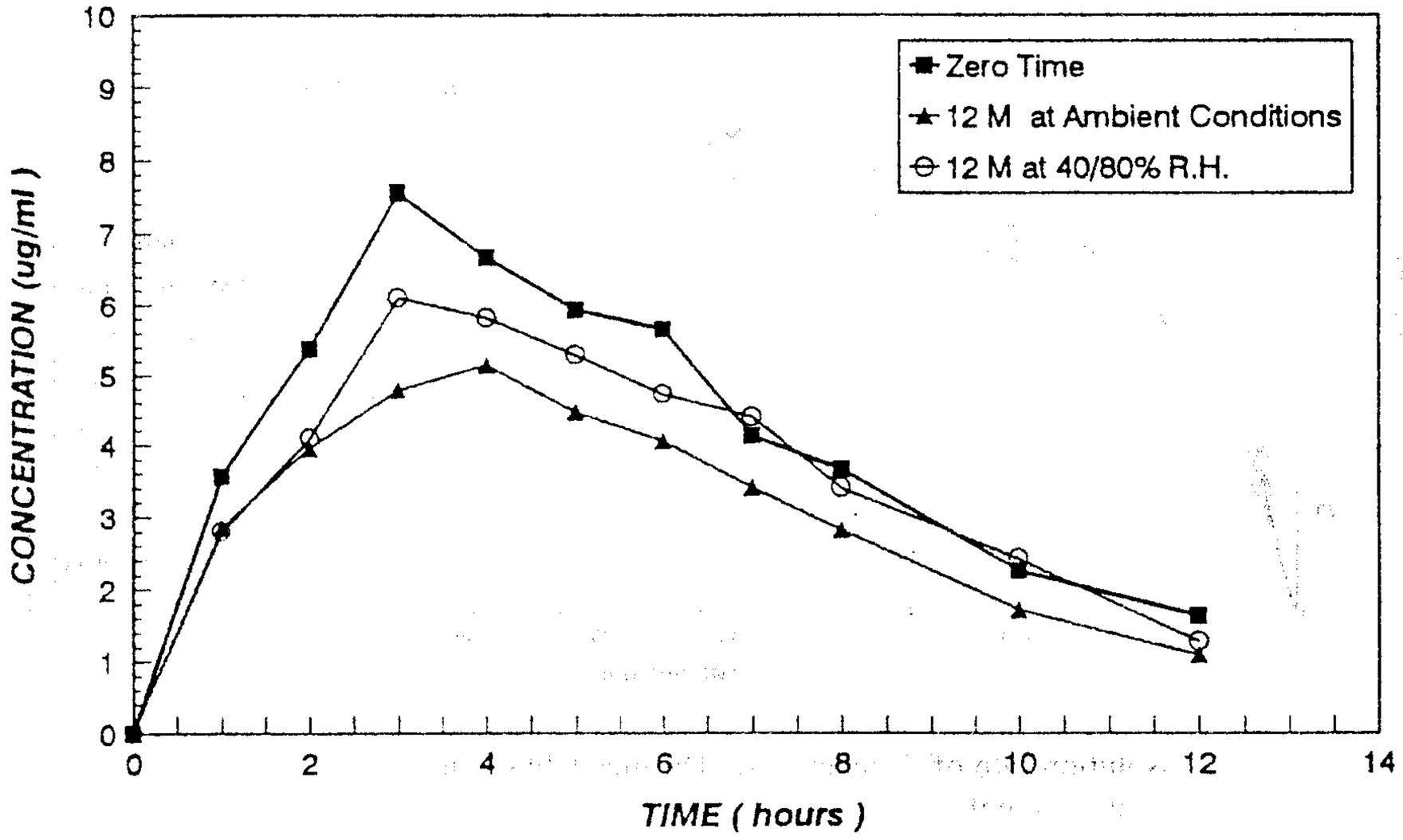


**Fig. 6:** Mean plasma concentrations of procainamide (μg/ml) after oral administration of Procainamide durules (500 mg) tablets to five beagle dogs at zero time and after storage at different conditions.

to peak plasma drug concentration ($T_{max}$), elimination rate constant ($K_{el}$), and mean residence time (MRT).

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