The Effect of some Variables on the Formulation of Captopril as Tablets

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ABSTRACT:

Captopril is an angiotensin converting enzyme inhibitor (ACEI) used to treat hypertension, congestive heart failure, and myocardial infraction.

The only dosage form available for captopril is the plain tablet in strength of 12.5,25,50 and 100mg tablet.

This investigation is concerned with factors affecting the formulation of captopril as a plain tablet dosage form of 50mg. Many trials were made to prepare satisfactory tablets for the drug by using wet – granulation methods with various additives. It was found that poly vinyl pyrrolidone (P.V.P.) as binder gave the most satisfactory tablets. At the same time a shorter disintegrantion time and slower dissolution rate were obtained with the addition of starch intragranular.

While the distintegration time and dissolution rate were faster for explotab when it was used intragranular in comparison with starch.

A comparative study on the physical properties of the prepared tablets with Capoten® (Squibb), Miniten® (APM), and Capocard® (DAD) tablets, showed that the release of drug from the selected formula was similar to that obtained from Miniten® at 0.1N HCl and 37°C.

The stability of the prepared tablet was also studied at 50°C, 60°C, and 70°C for 4 months and the calculated shelf – life was about 3.5years at 25°C.

الخلاصة:

الكابتوبريل هو مادة مانعة للانزيم المحول للانجيوتينسن (الموترات الوعائية). يستعمل في علاج ضغط الدم المرتفع ، وعجز القلب المحتقن وإحتشاء العضلة القلبية.

هذه الدراسة إهتمت بالعوامل المؤثرة على تصنيع الكابتوبريل بشكل اقراص سريعة التحرر. تم اجراء العديد من التجارب للحصول على صيغة مقبولة لهذا العقار بشكل اقراص بأستعمال طريقة الحبيبات الرطبة بأستخدام مواد مختلفة من السوَّاغ. وقد وُجِدَ ان مادة البولي فاينيل بايروليدون (P.V.P.) كمادة رابطة تعطي الصيغة التركيبية الاكثر مقبولة من الاقراص.

وفي نفس الوقت وجد انه في حالة استعمال نشاء الذرة ضمن الحبيبات فأن زمن التحطم (التفتت) كان اسرع من استعمالها خارج الحبيبات ولكن زمن الذوبان كان أبطأ من خارج الحبيبات. في الحالة الاخرى جلايكوليت الصوديوم النشوي (Explotab) عند استعماله ضمن الحبيبات فإن كل من زمن التحطم وزمن الذوبان يكونان اسرع من استعمالها خارج الحبيبات.

كذلك تم اجراء دراسة مقارنة لدراسة الخواص الفيزيائية بين الحبوب المحضّرة وحبوب الكابوتين لشركة سكويب وحبوب المنيتين للشركة المتحدة وحبوب الكابوكارد لشركة دار الدواء الاردنية ووجد بأن سرعة تحرر الدواء من الصيغة المختارة قريبة نوعاً ما من سرعة تحرره من حبوب المنيتين في ٠.١ عياري من حامض الهايدروكلوريك ودرجة حرارة ٣٧°م. تمت دراسة استقرارية الدواء في درجات حرارية مختلفة ٥٠°م ، ٦٠°م ، ٧٠°م لمدة ٤ اشهر ووُجد ان تاريخ انتهاء مفعول الدواء الحالي ٣.٥ سنة.

Introduction:

Hypertension means abnormally elevated blood pressure. Different drugs for treatment of hypertension can be used, among these are Angiotensin converting enzyme inhibitors (ACEI) such as; captopril.

Captopril is D-3-mercapto-2-methyl (propanoyl – L – praline) a potent and selective (ACEI) (Kininaze II) [1]. It was synthesized in 1976 by Ondetti and his colleagues at E.R. Squibb and Sons. It was known under the generic name of SQ14,255 then the name was changed to captopril. Captopril is a novel drug, that specifically designed to compete for the active binding site of (ACE), as such captopril inhibits the conversion of Angiotensin I to Angiotensin II [2].

It is used for treatment of mild to moderate hypertension, and in hypertensive crisis . It is the only (ACEI) that can be used for hypertension of neonate and infant [2].

In addition, captopril can be used in treatment of congestive heart failure, MI and in diabetic nephropathy[3].

The only dosage form available for captopril is the plain tablet in the strength of 12.5, 25, 50 and 100mg tablet.

It was felt of interest to study the factors that affect the formulation of captopril as a plain tablet and compare it with the standards.

Experimental Section:

Materials:

Captopril powder (Shilton Chemicals, England), Lactose, Acacia (Riedel – De – Hean A.G. Hannover, Germany), Starch (Merck, Germany), Microcrystalline cellulose (Avicel pH101, FMC corporation, Pennsylvania, USA), Poly vinyl pyrrolidone (P.V.P. K30), Carboxy methylcellulose sodium salt (C.M.C.), Hydrochloric acid, (BDH Chemicals Ltd., Pool, England), Explotab (AVEBA, Veendam, Netherlands), Magnesium stearate (Barlocher, GMBH, Germany), Capoten® (Squibb, USA), Miniten® (APM, Jordan), Capocard® (DAD, Jordan).

Instruments:

Thomas Hoover electrical melting point apparatus (England), Sartorious balance (4 digits), type A120S, GMBH, Germany, Sartorious balance type 126S MP – Germany, Tablet machine, type F3, Manesty machine Ltd., Liverpool, England, Tablet hardness tester Stokes – Monsanto (Monsanto Chemical Co., USA), Tablet disintegration apparatus, Manesty Ltd., Liverpool, England, Erweka friabilator, Germany, Nalgene syringe filter 0.2µm, 25µm surfactant free cellulose acetate membrane (Modified acrylic housing), Dissolution apparatus USP, Erweka, DT6, Germany, Swininx – 13 microfilter, Millipore Corporation, Bedford, Mass, USA.; U.V. spectrophotometer, SP8 – 100, Pyeunicam, England., Microfilter paper (Microfilter, England), Tray oven, Apex, England, Oven, 854 schwabach, memmert, Germany., Oven, (Astell hearson), Oven Gallen Kamp, B5 OV – 210, England.

Methods:

Different formulas were prepared to find the most satisfactory one using wet granulation technique.

Wet Granulation:

After 5 minutes of dry blending of drug and excipients, the binder solution was added to formulas (1 – 7, 9, 14) and (15) gradually in the mixing mortar until a satisfactory wetting was achieved (ball test). The wet mass was then granulated through a sieve no.10 and dried in tray oven

at 45°C for 30 minutes. The granules were homogenized and mixed with the disintegrant extragranularly for 10 minutes, then mixed with Mg – stearate (200mesh in size) for 2 minutes.

The final mixture was compressed using F3 tablet machine with a single punch using 7mm normal concave punches.

The same procedure was followed for the remaining formulas except that formulas (8) and (10) the disintegrant was added intra while in case of formulas (11, 12) and (13) no disintegrant was used.

Assay for Total Captopril Present in the Tablet:

Preparation of standard:

50mg pure captopril was added to 50ml of 0.1N NaOH, shaked for 5 minutes, then 1ml of it was transferred to 100ml volumetric flask. The volume was completed with 0.1N NaOH and shaken for 5 minutes. Then analyzed spectrophotometrically at 238nm[4].

10 tablets are weighed and triturated together and an amount equivalent to 50mg captopril was added to 50ml of 0.1N NaOH, shaked for 5 minutes and filtered. 1ml of the filtrate transferred to 100ml volumetric flask and completed with 0.1N NaOH and shaken for 5 minutes.

The captopril content was analyzed spectrophotometrically at 238nm[4] and determined according to the following equation:

$$\frac{Test}{STd} \times 100 = \%$$ **captopril present in tablet.**

Physical Parameter Measurement of the Tablets:

Hardness: measured using Monsanto hardness tester.

Weight variation: determined by taking 20 tablets for each formula.

Friability test: using Rock friability tester for 4minutes at 25r.p.m. by taking 10 tablets together.

Disintegration time: The disintegration of tablets was performed according to B.P. method[5] at 37°C in 0.1N HCl.

Dissolution test: The U.S.P. (basket method)[6] was used to study the release of the drug for the prepared tablets Miniten®, Capocard® (DAD), and Capoten® (Squibb) at 37°C using 900ml of 0.1N HCl solution as the dissolution medium with a constant stirring speed of 50r.p.m.[6,2]. Samples were withdrawn at 5 minutes time intervals for the next 30min.

The sample volume was replaced immediately by fresh 0.1N HCl. Samples were filtered by microfilter, diluted 5 times and analyzed spectrophotometrically at 212nm for drug content.

Effect of Binder Type:

Starch paste, acacia mucilage, carboxy methylcellulose, and poly vinyl pyrrolidone (P.V.P.) were used as binders in formulas (1,2,3) and (4) respectively. Then corn starch was removed from formula (2) and (4) to get formulas (12) and (13) respectively, to study the effect of binder on physical properties of captopril tablet in the absence of disintegrant.

Effect of Binder Concentration:

Different concentrations of P.V.P. in ethanol were used in formulas (6,4) and (5) which compared with formula (11) of the same P.V.P. concentration but without disintegrant.

Effect of Diluent Type:

Lactose, and Starch were used as diluents in formulas (4) and (7) respectively.

Effect of Disintegrant Type:

Corn starch, explotab and (avicel and corn starch) were used using formulas (4, 9,14) respectively compared to formula (13) without disintegrant

Effect of Method of Incorporation of Disintegrant:

Corn starch and explotab were used extra and intragranular in formulas (4,8,9) and (10) respectively.

Stability Study:

The effect of temperature on the degradation of captopril tablet was studied by storing some tablets of the selected formula in ambered color glass containers at different temperatures (50°C, 60°C and 70°C) for 4 months. Samples were withdrawn at desired time intervals and assayed for captopril content.

Results and Discussion:

Effect of Binder Type:

The results indicated that the use of different types of binders had an influence on physical properties of tablets and drug release as shown in Table (2).

The use of starch as a binder showed friable tablets with long disintegration time and this may be due to the property of starch paste to form tablets which are generally soft and brittle[7].

While formula 3 in which C.M.C. was used as a binder, showed low hardness, friable, capped tablets with further decrease in hardness and increase in friability after a few days of manufacture as well as they had long disintegration time. This may be related to the hygroscopicity of C.M.C. sodium.

In addition, since C.M.C. is a viscosity controller, it is conceivable that it forms highly viscid systems that resist dilution by dissolution fluids which might impede drug release [8]. The dissolution time is 40min for 100% release of drug in comparison with starch (30min).

On the other hand, formulas (2) and (4) were good acacia is a natural product so this makes it objectionable to be used as a binder due to the possibility of microbial growth, so formula (4), in which P.V.P in alcohol was used as a binder showed acceptable tablets compared with the references. In addition, P.V.P. has a tendency to be slightly hygroscopic, that the resulted tablets will not expected to be harder with age. At the same time alcohol was used with P.V.P. instead of water because it is better in case of soluble powder granulations [7].

Effect of Binder Concentration:

The results showed that using a low concentration of binder in formula (6) resulted in low hardness and high friable tablets while increase binder concentration lead to prolong disintegration and dissolution times, due to increase cohesiveness or attraction forces between particles[9].

On the other hand, when the concentration increased three times, the hardness was less and the friability was higher. This may be due to the high hygroscopicity of the concentrated P.V.P. solution [7].

Effect of Diluent Type:

The results indicate that when starch incorporated as a diluent, the organoleptic properties of tablets were unacceptable. For example; cracking occurred after a few days of compression and tend to expand after compression which may be due to its poor compressibility[7], while in case of lactose acceptable properties were obtained as shown in table (4).

Effect of Disintegrant Type:

The results showed that the use of explotab formula (9) led to a well compressed tablet with a high hardness compared with the starch formula (4) using the same compression force as illustrated in table (5), but both of them (starch and explotab) had no effect on the disintegrant time.

However, concerning the results obtained, both materials starch and explotab showed good hardness and friability with acceptable disintegration – dissolution phenomena. This may be due to that fact the captopril is a highly water soluble drug.

On the other hand, using a combination of avicel and starch formula (14) or avicel alone formula (15) as a disintegrant resulted in a harder and less friable tablet. This may be due to the good compressibility of avicel. But it is not preferred to use avicel as a disintegrant since a high compression force might destroy the capillaries within avicel structure and diminish its property as disintegrant[7].

Effect of Method of Incorporation of Disintegrant:

Table (6) shows the effect of method of incorporation of disintegrant on the physical properties of the prepared captopril tablets.

The results indicated that the hardness and friability of the prepared tablet using formula (4,8) and (9), were acceptable except for formula (10) in which the explotab was incorporated intragranularally (friability 1.4%).

The results also indicated that a longer disintegration time was obtained with both types starch and explotab when incorporated them extra. This is may be due to the high water solubility of the captopril itself.

Gorden et- al[10] stated that incorporating super disintegrant in the intragranular phase resulted in faster tablet dissolution than incorporating it in the extragranular phase or in both phases, and this is similar to our results as shown in figure (2).

While in case of corn starch, the incorporation of a disintegrant intragranular resulted in a faster disintegration but slower tablet dissolution and this is because starch is an ordinary disintegrating so when used intragranular it loses some of its disruptive force due to its encasement by the binder[7].

Kinetic Study:

Effect of Temperature:

Figure (3) shows the degradation of captopril. It appears that the degradation of drug follows first – order reaction, since straight lines were obtained when the log% remaining of captopril is plotted versus time. The rate constants were determined from the slopes of the lines and tabulated in table (7). To determine the expiration date ($t_{10\%}$), Arrhenius plot was made to predict the degradation rate constant at 25°C (K_{25}), and it is equal to 2.47×10^{-3} $week^{-1}$ as Shown in figure (4).

Since the degradation of drug follows first-order reaction, therefore, the expiration date can be calculated using the following equation[11]:

$$t_{10\%} = \frac{0.104}{K_{25}}$$

and it is equal to about 42 months (3.5 years).

No change in the hardness, friability and disintegration time were observed at the end of the 4 months. The organoleptic properties did not change at 50°C, and 60°C with a little darkness in color at 70°C which may be due to the lactose which is affected by such high temperature.

Conclusion:

The over all results of this study indicated that one could prepare satisfactory captopril plane tablets based on the followings:

1- The best binder and diluent that can be used are the P.V.P. in alcohol and lactose since they are available, cheep, compressible and compatible with captopril.

2- Formula 4 was chosen as the best satisfactory formula in comparison with the reference formulas Miniten®, and Capoten®.

3- Starch was chosen as a disintegrant since it is available, low cost and stable while avicel was excluded since it is of high cost.

4- The shelf life for the selected formula was 3.5 years.

Formula	*Captopril (mg)*	*Lactose (mg)*	*Starch (mg)*	*Acacia Mucilage (mg)*	*Starch paste (mg)*	*PVP (mg)*	*C.M.C. (mg)*	*Corn Starch (mg)*	*Explotab (mg)*	*Avicel (mg)*	*Mg-Stearate (mg)*	*Total Wt. (mg)*
1	**50**	**X**	**-**	**–**	**X**	**-**	**-**	X	-	**-**	**2**	**201.500**
2	**50**	**X**	**-**	**X**	**–**	**-**	**-**	X	-	**-**	**2**	**200.000**
3	**50**	**X**	**–**	**-**	**-**	**–**	**X**	X	-	**-**	**2**	**200.000**
4	**50**	**X**	**–**	**-**	**-**	**2X**	**-**	**X** extra	-	**-**	**2**	**201.000**
5	**50**	**X**	**–**	**-**	**–**	**3X**	**-**	X	-	**-**	**2**	**201.625**
6	**50**	**X**	**–**	**–**	**-**	**X**	**-**	X	-	**-**	**2**	**200.000**
7	**50**	-	**X**	**-**	**-**	**2X**	**-**	X	-	**-**	**2**	**201.000**
8	**50**	**X**	**-**	**-**	**–**	**2X**	**-**	**X** intra	-	**-**	**2**	**201.000**
9	**50**	**X**	**-**	**–**	**-**	**2X**	**-**	**-**	**X** extra	**-**	**2**	**201.000**
10	**50**	**X**	**–**	**-**	**-**	**2X**	**-**	**-**	**X** intra	**-**	**2**	**201.000**
11	**50**	**X**	**–**	**-**	**–**	**3X**	**-**	**-**	**-**	**-**	**2**	**201.625**
12	**50**	**X**	**-**	**2.5**	**-**	-	**-**	**-**	**-**	**-**	**2**	**201.500**
13	**50**	**X**	**–**	**–**	**-**	**2**	**-**	**-**	**-**	**-**	**2**	**201.000**
14	**50**	**X**	**-**	**-**	**–**	**2**	**-**	**X**	**-**	**X**	**2**	**201.000**
15	**50**	**X**	**-**	**-**	**-**	**2**	**-**	-	**-**	**2X**	**2**	**200.000**

Table (1): Schedule of different formulation for captopril as a plain tablet dosage form

Suggested Formula	*Type of binder*	*Hardness* ***(kg)***	*Friability (%)*	*Disintegration time (min)*	*Dissolution time for 100% release (min)*
1	starch paste	4.0	2.8	6.5	30
2	Acacia mucilage	4.0	0.9	4.0	22 – 25
3	C.M.C	3.0	6.0	8.0	40
4	10% PVP	4.0	0.7	1.3	25
Miniten®		4.5	0.5	1.0	25 – 30
Capocard®		4.0	0.8	2.0	30
Capoten®		5.0	0.5	1.0	15 – 20

Table (2): Effect of binder type on the hardness, friability, disintegration time and dissolution time of the prepared captopril tablets (formulas 1,2,3 and 4) in comparison with reference tablets.

Formula No.	***PVP binder (%)***	***Hardness (kg)***	***Friability (%)***	***Disintegration time (min)***	***Dissolution time for 100% release (min)***
4	2X	4	0.7	1.3	25
5	3X	1	7	2	25 – 30
6	X	2.5	5	1	20

Table (3): Effect of binder concentration on the physical properties of captopril tablets of suggested formulas 4,5, and 6.

Formula No.	***Diluent type***	***Hardness (kg)***	***Friability (%)***	***Disintegration time (min)***	***Dissolution time for 100% release (min)***
4	Lactose	4	0.7	1.3	25
7	Starch	1.25	5.8	1.5	40

Table (4): The effect of diluent on the physical properties of captopril tablet and the release of captopril from suggested formulas 4 and 7.

Formula No.	*Disintegrant type*	*Hardness (kg)*	*Friability (%)*	*Disintegration time (min)*	*Dissolution time for 100% release (min)*
4	Starch	4	0.7	1.3	25
9	Explotab	10	0.9	1.3	30
13	-	4	0.5	3	30
14	Starch & Avicel	5	0.6	0.66	20
15	Avicel	5	0.53	0.5	15

Table (5): Effect of disintegrant type on the physical properties of tablets in formulas 4, 9, 14, and 15

Formula No.	*Disintegrant Location*	*Hardness (kg)*	*Friability (%)*	*Disintegration time (min)*	*Dissolution time for 100% release (min)*
4	Extra (starch)	4	0.7	1.3	25
8	Intra (starch)	4	0.5	1	30
9	Extra (explotab)	10	0.9	1.3	30
10	Intra (explotab)	7.5	1.4	1	25

Table (6): A comparison between the effect of method of incorporation of disintegrant extra and intra.

Temperature (°C)	*K(months)$^{-1}$*
50°C	7×10^{-3}
60°C	10.2×10^{-3}
70°C	15×10^{-3}

Table (7): Rate constants of degradation of captopril using the selected formula at different temperatures.

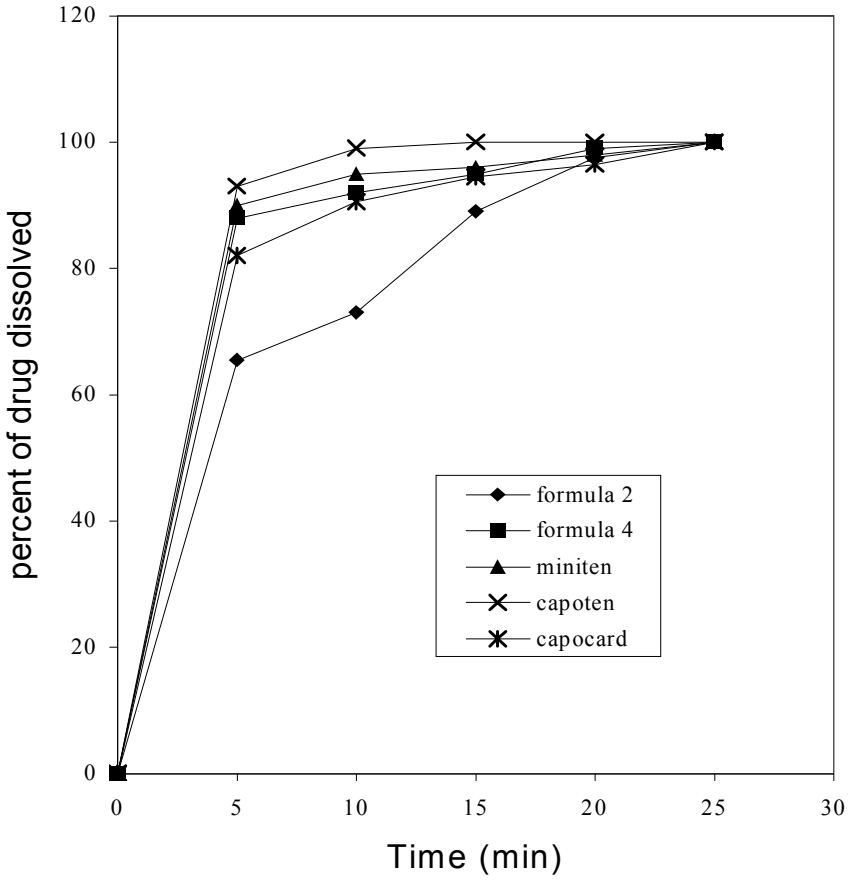

Figure (1):
Release study for formula (2) and (4) in comparison with reference formulas in 0.1N HCl and 37°C.

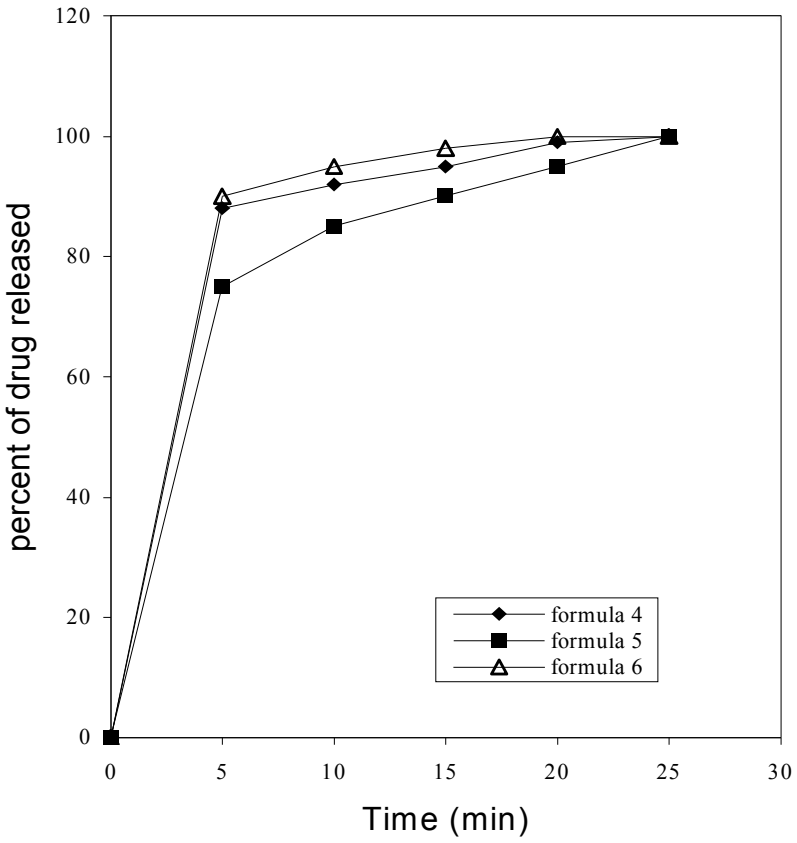

Figure (2):
Effect of binder concentration on the release of captopril from suggested formulas 4,5 and 6 in 0.1N HCl and 37°C.

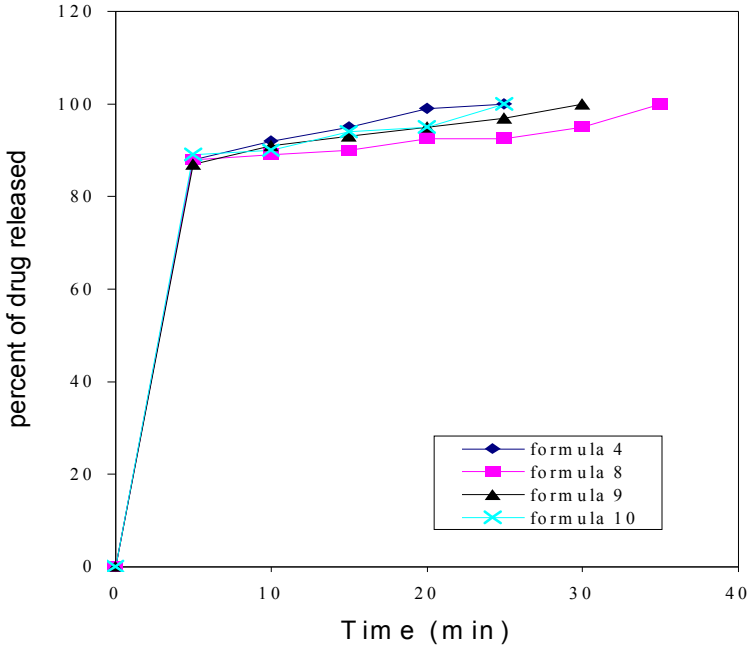

Figure (3):
Comparison between the release of captopril from formulas containing starch intra, extra (4,8) and explotab intra, extra (9,10).

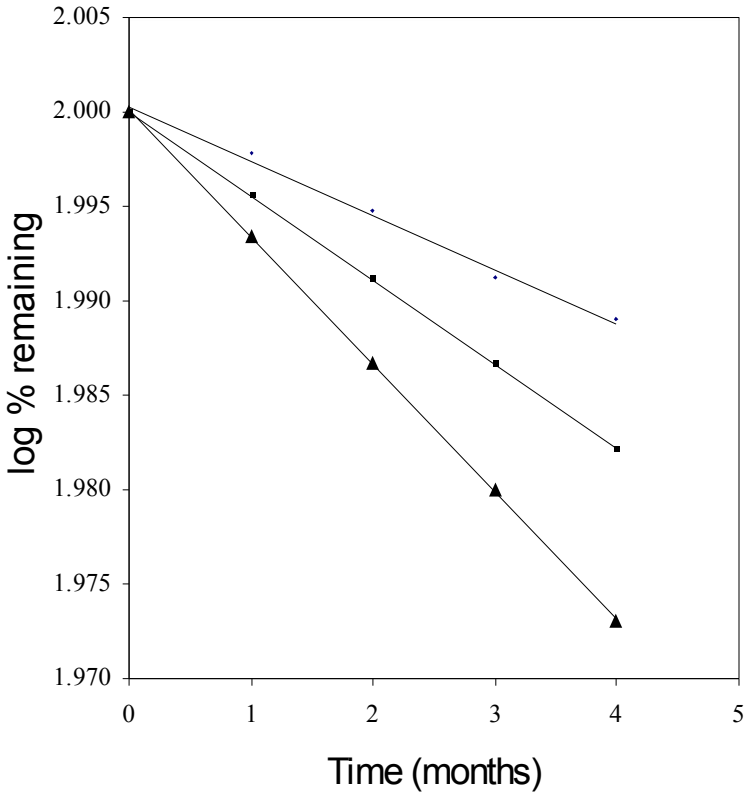

Figure (4):
Degradation curves of captopril at different temperatures (50°C, 60°C, and 70°C) using the selected formula (formula 4).

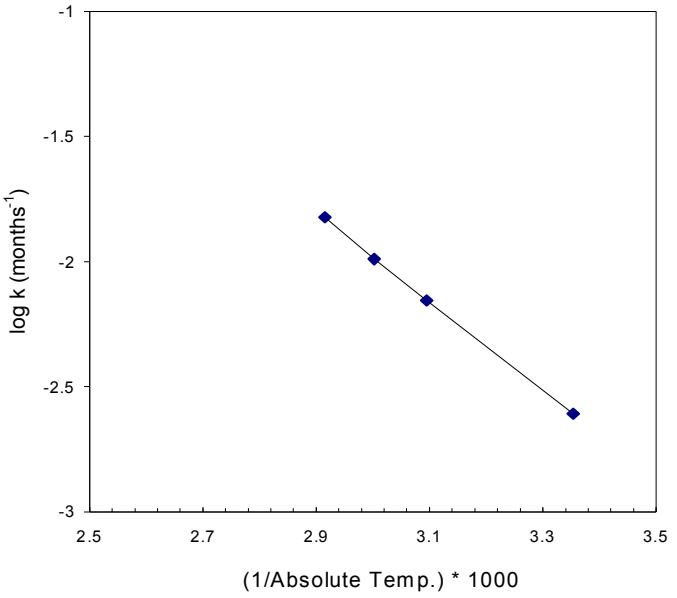

Figure (5):
Arrhenius plot for a shelf – life estimation of captopril using (formula 4).

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