Factors Affecting the Formulation of Carbamazepine Extended Release Tablet

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Abstract

Carbamazepine is an anticonvulsant agent which acts on the central nervous system and used for the treatment of epilepsy. Carbamazepine was formulated as an oral extended release tablets using ethyl cellulose as retardant substance. Different types of tablets additives such as cellulose materials (sodium carboxymethyl cellulose and microcrystalline cellulose), lactose, calcium phosphate and solubilizing agents (sodium lauryl sulphate and polyethylene glycol 6000) were utilized to study their effect on the release profile of drug from ethyl cellulose matrices. It was found that sodium carboxymethyl cellulose increased the carbamazepine release and the same effect was obtained when the same amount of microcrystalline cellulose used. The result also showed that sodium lauryl sulphate greatly enhanced the release of the drug compared to polyethylene glycol 6000. Also incorporating lactose led to an increase in the release of the drug while utilization of calcium phosphate slowed down the release of the drug. The results of this study revealed that formula which composed of 4% ethyl cellulose, 5% sodium carboxymethyl cellulose, as well as 25.6% of lactose and 1% magnesium stearate is comply with United State Pharmacopea XXVIII and showed best release profile comparable to that of the brand product Tegretol CR®. The shelf life was 3.6 years for the selected formula.

Key word: Carbamazepine, Ethyl cellulose, Extended release.

الخلاصة

كاربامازبين هو عامل مضاد للاختلاج يعمل على الجهاز العصبي المركزي ويستعمل لمعالجة الصرع .لقد تم تصييغ كاربامازبيين كحبوب فموية ممتدة التحرر باستخدام اثل سليلوز كمادة مثبطة للتحرر .تم استخدام انواع مختلفة من المواد المضافة للحبوب مثل المواد السليلوزية) كاربوكسي مثل سيليلوز الصوديوم والسليلوز مجهري التبلور (، لاكتوز ، فوسفات الكالسيوم ، والمواد المحفزة للذوبان) لوريل سلفات الصوديوم وبولي اثيلين كلايكول 6000) لتقييم تأثير هذه المواد على شكل تحرر الدواء من قوالب اثل سليلوز .لقد وجد ان الصوديوم كاربوكسي مثل سليلوز يزيد من تحرر الكاربامازبيين ونفس التأثير على التحرر قد وجد عند استخدام نفس الكمية من السليلوز مجهري التبلور .اضهرت النتائج ايضا ان اللوريل سلفات الصوديوم حفز بشكل كبير تحرر الدواء مقارنة مع بولي اثلين كلايكول 6000 . لقد وجد ان اضافة اللاكتوز يؤدي الى زيادة اكبر من تحرر الدواء بينما استخدام فوسفات الكالسيوم قلل من تحرر الدواء .كشفت نتائج هذه الدراسة ان الصيغة المكونة من 4% اثل سليلوز و 5% كاربوكسي مثل سليلوز الصوديوم، بالاضافة الى 2.5% لاكتوز و 1% ستيارات الصوديوم تتطابق مع دستور الأدوية الامريكي واعطت افضل شكل تحرر يمكن مقارنته مع المنتج القياسي تكريتول .ثابت التحلل للصيغة المنتجة هو 4.95×10^{-4} اسبوع$^{-1}$ وعمر الرف 3.6 سنة .

Introduction

Extended release tablets are those which formulated in such a manner to make the contained medicament available over an extended period of time after ingestion. Expressions as ″prolonged-action″, ″repeated-action″, and ″sustained release″ have also been used to describe such dosage forms. Extended release delivery systems mostly allow at least a twofold reduction in the dosing frequency compared to the conventional immediate release formulations and increase patient compliance as well as therapeutic performance[(1)]. Matrix systems appear to be very attractive approach from economic as well as process development and scale up points in the controlled release systems[(2)]. Matrix tablets are classified according to the type of materials used for retarding the release of drugs [(3)]. In case of fat **lipophilic** matrices, the drug which is incorporated into a melt of fat and waxes will be released by leaching out and/or dissolution of the carrier during passage throughout GIT. Among these lipophilic materials are carnauba wax, cetyl alcohol, hydrogenated vegetable oils, triglycerides, stearic acid, and polyethylene glycols[(4)]. Meanwhile **hydrophilic** matrices, a dispersed drug is released as the retarding polymer swell in the gastric fluid, forming a gel barrier through which drug will be released by diffusion or dissolution of the matrix. These hydrophilic materials include cellulose Derivatives as hydroxypropyl cellulose,sodium carboxymethyl cellulose,

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hydroxylpropylmethyl cellulose, methyl cellulose as well as carbopols, sodium alginate, xanthan and guar gums[5]. In case of **plastic** matrices which they are composed of materials characterized by their capability to form insoluble, sponge-like skeletons from which the drug is released by diffusion. Examples of such materials are the acrylic/methacrylic coplymers, ethyl cellulose, polyvinyl acetate, and polyvinyl alcohol [6]. Ethylcellulose is usually combined with water-soluble additives to impart some hydrophilic nature for films or matrices, altering its structure by virtue of pores and channels through which drug can diffuse more easily[7]. In the present study, ethyl cellulose was used as retardant substance to formulate carbamazepine matrix tablet dosage form. Extended release formulation of CBZ should be considered in patients receiving high doses of CBZ and who are suffer from intermittent adverse effects such as diplopia, nausea, dizziness, and drowsiness, offering the opportunity for converting the three or four times daily regimen to twice, or even once daily administration[8].

Materials and Methods

Materials:

Carbamazepine and microcrystalline cellulose (Avicel PH 101) kindly supplied by Samara Dug Industry (SDI). Ethylcellulose, magnesium stearate, , sodium carboxymethylcellulose and sodium lauryl sulphate from(BDH, England). Lactose from (Riedel-DeHaen, Germany). All other chemicals and solvents were of analytical grade.

Methods:

Formulation of Carbamazepine as Extended Release Tablet:

Formulas 1-9 shown in table (1) were prepared by mixing CBZ with lactose for 10 minutes, then the granulating solution (5% ethyl cellulose in absolute ethanol) was added gradually until a wet ball mass was obtained. The resultant mass was screened through 12-mesh sieve and the resultant granules were dried at 50°C for 2 hours. A second screening through 18-mesh sieve was done, followed by mixing the granules with magnesium stearate as lubricant for 2 minutes, then the resultant granules were compressed into tablets using double punch tablet machine (Korsch EKO, Germany).

Table 1: Formulation of CBZ tablet using ethyl cellulose with different additives.

Substance (mg)	Formula No								
	F1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
Carbamazepine	200	200	200	200	200	200	200	200	200
Ethyl cellulose	8.61	11.6	14.7	12.08	12.08	12.08	12.08	12.08	12.08
Sodium carboxyme-thyl cellulose				15.25				15.25	15.25
Microcrystalline cellulose					15.25				
Sodium lauryl sulphate						4.43			
PEG6000							4.43		
Calcium phosphate									75
Lactose	75	75	75	75	75	75	75	95	
Magnesium stearate	3	3	3	3	3	3	3	3	3
Total Weight of Tablet	286.6	289.6	292.7	286.6	289.6	292.7	286.6	289.6	292.7

Evaluation of Carbamazepine Extended Release Tablet :-

Hardness Test

The hardness of 3 tablets from each of the prepared formulas was measured individually by using Pharma Test equipment. An anvil driven by electric motor presses the tablet at a horizontal position and constant load until the tablet breaks [9].

Friability Test

This test was done for 20 tablets, starting by weighing them and then operating the friabilator at 25 r.p.m for 4 minutes, re-weighing the tablets to determine the loss in their weight[9].

Uniformity of Dosage Units

Five tablets were individually subjected to the following procedure. One tablet was finely powdered and quantitatively transfered, with the aid of methanol, to 100-ml volumetric flask. About 70 ml of methanol was added, shaked by mechanical means for 60 minutes. The mixture was sonicated for 15 minutes, diluted with methanol to volume, allowed to stand for 10-15 minutes, and then the clear supernatant was analyzed spectrophotometry to determine the amount of CBZ , using methanol as a blank[1].

Drug Release

This test was done for all formulas according to the USP XXVIII specifications stated in the monograph "Carbamazepine Extended-Release Tablets". The test carried out as triplicate for each formula using apparatus I (basket) at 100 r.p.m and 900 ml water as dissolution medium at 37±0.5ºC under sink conditions. At each time interval 5 ml sample was withdrawn, filtered and suitably diluted to be the absorbance within the calibration curve level. The amount of CBZ dissolved at one hour intervals was measured spectrophotometrically at maximum absorbance wavelength, 285 nm (Cecil, England). The withdrawn samples were replaced with water. The percentages of CBZ released at the specified times must conform to the following:

Time (hr.)	Amount released (%)
3	10-35
6	35-65
12	65-90
24	Not less than 75

Determination of the Release Kinetics

To study the mechanism of drug release from the matrix tablets, the release data were fitted to zero-order, first order, and Higuchi equations. Furthermore, to characterize the release behavior, i.e. to understand the mechanism, Korsmeyer-Peppas model (equation 7) was applied:

$$Q_t / Q_\infty = kt^n$$

Where, Qt is the amount of drug release at time t ; Q∞ is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the tablet; and n is the diffusional exponent indicative of the mechanism of drug release [10].

Effect of Temperature:

The effect of temperature on the degradation of CBZ in the selected formula was studied according to accelerated stability study. The study was done by storing the tablets in ovens at different temperatures of 40, 50, and 60ºC for four months. Samples were withdrawn at weekly intervals to determine the total content of CBZ by measuring UV absorbance at λ max at 285nm.

Statistical Analysis

The results of the experiments are given as a mean of triplicate samples ± standard deviation and were analyzed according to the one way analysis of variance (ANOVA) at the level of ($P < 0.05$).

Results and Discussion

Evaluation of Carbamazepine Extended Release Tablet :-

Hardness of Tablets

The hardness of prepared tablets which is shown in table (2) revealed variation which may be attributed to the differences in amount of retarding polymer, in addition to the other exciepient added. For formulas 1-3, the hardness increased as the amount of retarding polymer increased, this result may be attributed to the increase in the compressibility of the matrix resulting from the higher polymer proportion [11]. Formula 6 and 7 showed lower hardness values in comparison with other formulas and this is originated from the extremely poor compatibility of the surfactant or PEG containing granules, which may assume a wax-like physical property [12]. For other formulas in which several types of additives were included, they have higher hardness values depending on the nature of these additives. The inclusion of sodium carboxymethyl cellulose and microcrystalline cellulose may result in the consolidation of granules due to the plasticity of these materials and increase intraparticulate bonding during

compaction in addition to the homogenous distribution of bonds in the compact [13].

Table 2: Hardness of Tablets (expressed as mean ± SD).

Formula No.	Hardness (Kp)
F 1	11.2±0.65
F 2	12.3±0.36
F 3	12.8±0.14
F 4	13.0±0.24
F 5	11.9±0.07
F 6	11.5±0.20
F 7	11.4±0.33
F 8	12.2±0.12
F 9	13.5±0.06

Friability of Tablets

All formulas have lost not more than 1% of their weights. The incorporation of sodium carboxy methylcellulose and microcrystalline cellulose to the formulations resulted in improved skeleton integrity and acceptable friability as seen in table(3)[13].

Table 3: Friability of Tablets.

Formula No.	Friability (%)
F 1	1.215
F 2	0.856
F 3	0.835
F 4	1.334
F 5	0.848
F 6	0.822
F 7	0.779
F 8	0.521
F 9	0469

Uniformity of Dosage Units

Table (4) shows that all the prepared formulas which were subjected to this test complied with USP specification which is 85-115% of CBZ content in each individual tablet[1].

Table 4: Uniformity of dosage units for CBZ tablet (expressed as mean± standard) deviation.

Formula No.	Content of CBZ (%)
F 1	94.2±2.5
F 2	98.5±3.6
F 3	98.1±3.3
F 4	96.3±2.3
F 5	95.7±3.1
F 6	96.2±4.0
F 7	93.7±2.5
F 8	94.1±3.4
F 9	95.0±4.7

Variables Affecting CBZ Release From Extended Release Tablets :-

The Effect of Retarding Polymer Concentration

The release of CBZ from formulas 1-3 which they are formulated using concentrations 3%, 4% and 5% of ethyl cellulose is shown in figures (1). It appears that there is a significant difference ($P < 0.05$) in the release of CBZ from matrices of ethyl cellulose (F 1-3) when the polymer concentration was changed. These results indicated that increasing the concentration of polymer tends to decrease the drug release since the amount of CBZ released was decreased from 79% to 13% for when the concentration of polymer was increased from

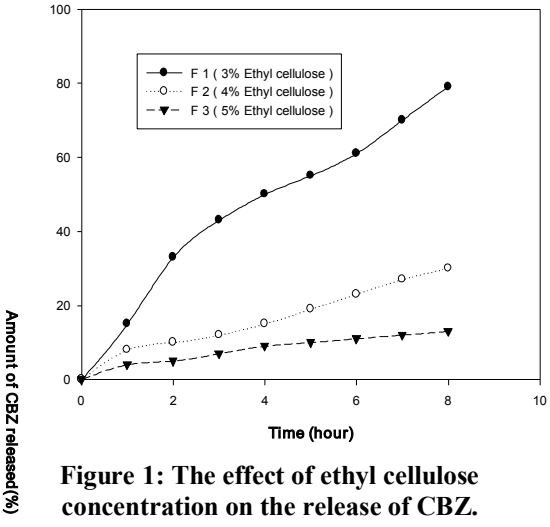

Figure 1: The effect of ethyl cellulose concentration on the release of CBZ.

This difference can be attributed to the decrease in the porosity with a concomitant increase in the tortuosity of matrix [14]. At the concentration of 4% and 5%, ethyl cellulose exhibits an extremely prolonged release as only 30% and 13% of CBZ was released after 8 hours from these matrices respectively. These findings may be due to the limited

solubility of CBZ and ethyl cellulose in water, therefore it is difficult for dissolution medium to penetrate the matrix [15]. The same effect was produced by ethyl cellulose matrices on the release of caffeine and pseudoephedrine hydrochloride [16].

The Effect of Cellulose Polymers Addition

Since ethyl cellulose is a hydrophobic insoluble polymer, two different hydrophilic, cellulose materials [the water-soluble sodium carboxy methyl cellulose and the water-insoluble microcrystalline cellulose (Avicel PH 101)] were incorporated (F 4 and F 5). Figure (2) shows that the time courses of release from formulas 4 and 5 which contain these additives are not significantly different ($P < 0.05$) although both materials enhance the release of CBZ. At first, CBZ release from formula 4 was enhanced due to the high solubility of sodium carboxymethyl cellulose; however, a relative slower release is followed when the glassy nature of this swellable polymer was changed to the rubbery state upon the contact of matrix tablet with water [17]. Recent developments in the analytical techniques as Raman/IR spectroscopy and scanning electron microscopy had revealed that such hydrophilic polymers are adsorbed on CBZ compacts through hydrogen bonding [18]. Such results are consistent with those obtained for the release of propranolol hydrochloride from matrix tablets [19]. Avicel PH 101 increased the release of CBZ from formula 5 which has a MDT comparable to that of formula 4 as shown in figure (2). Although it is water insoluble, Avicel PH 101 can absorb water to some extent; thus it acts as a pore-forming agent, enhancing the permeation of dissolution medium through the

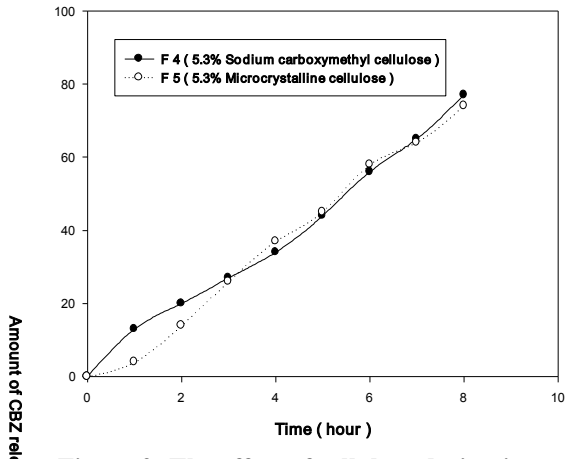

Figure 2: The effect of cellulose derivatives addition on the release of CBZ from ethyl cellulose matrix

The Effect of Adding Solublizing Agents

Since the absorption of insoluble drugs from the GIT is controlled via their dissolution, then utilization of solublizing agents in their formulation could improve the oral bioavailability of such drugs [21]. The release of CBZ from formulas 6 and 7 in which sodium lauryl sulphate and polyethylene glycol 6000 were included respectively as solublizing agents is shown in figure (3). Both agents increase the release rate of CBZ, however; a significant difference ($P < 0.05$) in the release rate between the two surfactants was observed due to the higher solublizing activity of sodium lauryl sulphate. This is may be attributed to the higher hydrophilic-lipophilic balance (HLB) value for sodium lauryl sulphate compared with polyethylene glycol 6000[22]. Moreover, cationic drugs dissolve better in anionic surfactants depending on the degree of dissociation, due to

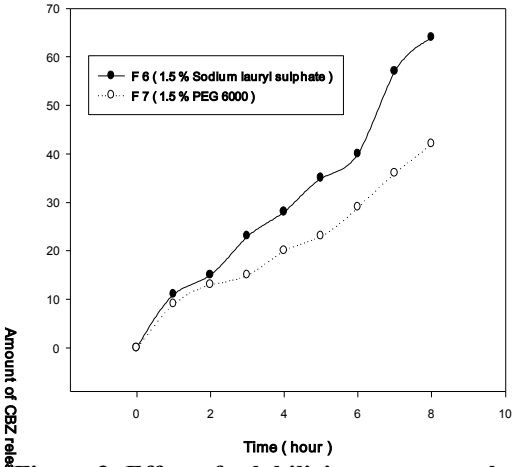

Figure 3: Effect of solubilizing agents on the release of CBZ from ethyl cellulose matrix.

The Effect of Diluent Quantity and its Type

Diluents or bulking agents are frequently added to the formulations in order to give the tablets their appropriate size. Although diluents are usually thought to be inert ingredients, they can significantly change the physical or biopharmaceutical properties of dosage forms [24]. Increasing the quantity of lactose (which is one of the mostly used diluents in tablets formulation) to 95 mg in formula 20 compared to 75 mg in formula 4 resulted in a significant increase ($P < 0.05$) in the release of CBZ as shown in figure (4) and this may be due to the high solubility of lactose so that it will act as channeling agent, permitting a rapid ingress of dissolution medium into the matrix tablets, thus facilitating drug release [25]. On the other hand,

when calcium phosphate was incorporated in formula 9, a significant reduction ($P < 0.05$) in the release rate of CBZ was observed compared to the release rate from formula 4 in which lactose was included. The slower release rate of CBZ which is the direct result for the presence of an insoluble additive in the matrix, therefore slowing down the drug diffusion and/or the medium infiltration[26]. Sodium sulphadiazine, Ketoprofen, and theophylline showed the same observations when formulated as matrix tablets with HPMC [25].

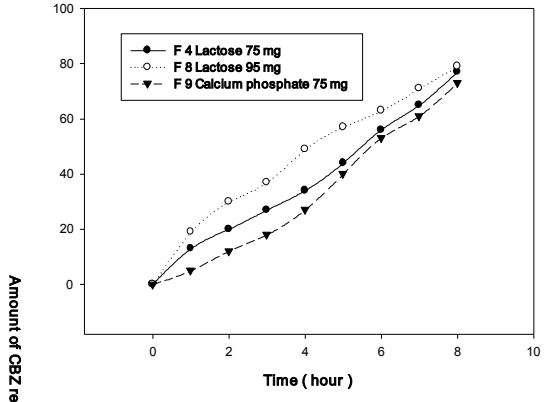

Figure 4: The effect of diluents addition on the release of CBZ from ethyl cellulose.

Determination of the Release Kinetics

Table (5) shows that n values of formulas 1-3, equals to 0.725-0.931, pointing to an anomalous (non-Fickian) diffusion mechanism with a trend toward higher values as the polymer content increased. On the other hand, higher values of kkp was determined for formula 1 with the least content of retarding polymers, suggesting the possibility of occurrence of burst effect. Formula 2 and 3 show a better fitness to zero-order and first-order respectively. It can be considered that decrease of CBZ release through increased polymer content produces a change in the release mechanism moving away from diffusion as n values becomes closer to 1.0, which also confirms that the kinetics go in the direction of zero-order release[27]. Incorporation of sodium carboxymethyl cellulose into ethyl cellulose matrices (formula 4) produced n value of 0.656 with a remarkable fitness to first-order kinetics. Meanwhile, microcrystalline cellulose in formula 5 gave an approximately unity value for n, indicating zero-order release. This variation may reflect the different behavior of each polymer since the sodium carboxymethyl cellulose will form a viscous gel through which diffusion occurs [28], and the microcrystalline cellulose has a disintegrating properties so that resulting matrix erosion [29]. Although n values for formulas 6 and 7 had revealed an anomalous diffusion, sodium laurylsulphate gave a higher kkp value indicating fast initial release with first-order kinetics due to its powerful solubilizing effect compared to polyethylene glycol 6000 which have low solubilizing ability and moderate release restriction properties [30]. In addition, increasing the quantity of lactose in formula 8 produced a lower n value with an elevated kkp value due to the high solubility of this material, thus stimulating water penetration into the matrix [24]. In contrast, calcium phosphate in formula 9 gave matrices in which CBZ release is controlled by erosion because this diluent is insoluble in water [26].

Table 5: Fitting results of formulas 1-9 for CBZ release data to different kinetic model.

Formula No.	Model								
	Zero-order		First-order		Higuchi		Korsmeyer-Peppas		
	K_0 (%h^{-1})	R^2	K_1 (h^{-1})	R^2	K_H (h$^{-1/2}$)	R^2	K_{KP} (h^{-n})	n	R^2
F1	9.229	0.9557	0.2575	0.8348	32.638	0.9869	16.748	0.788	0.9677
F2	3.646	0.9893	0.1792	0.9865	14.734	0.9378	6.437	0.725	0.9467
F3	3	0.9707	0.2303	0.9889	12.368	0.9034	2.989	0.931	0.9463
F4	9.25	0.9773	0.273	0.9902	33.247	0.9247	4.109	0.656	0.981
F5	9.21	0.9764	0.319	0.9793	33.505	0.9239	8.167	1.008	0.982
F6	11.6	0.9885	0.281	0.9931	37.04	0.9584	20.811	0.693	0.9755
F7	6.055	0.9915	0.212	0.9691	25.293	0.9474	7.466	0.876	0.9711
F8	8.943	0.9915	0.234	0.9468	31.096	0.9897	18.703	0.678	0.9948
F9	8.988	0.9804	0.346	0.9429	41.84	0.9278	4.855	1.238	0.996

Selection of the Best Formula

Although several prepared formulas met the release specifications of USP, formula 4 showed a release profile comparable to that of the brand product Tegretol CR® . The similarity factor (f 2) introduced by Moore and Flanner is used as criterion for assessment of the similarity between two dissolution profiles [31]:

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}\left|R_t - T_t\right|^2\right]^{-0.5} \times 100\right\} \text{.....(1)}$$

Where n is the number of dissolution time points, Rt and Tt are the reference and test dissolution values at time t. For the conventional tablets, a difference not exceeding 10% at any sampling time point between reference and test products may be acceptable and f 2 value of 50-100 indicates similarity in the dissolution profiles, while for sustained release tablets, the lower limit of 50 is very liberal especially for drugs with narrow therapeutic index. Therefore, the generalized equation to estimate the lower acceptable value of f 2 (f 2LX) is:

$$f_{2LX} = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}\left|R_t - \left(R_t \pm \frac{X}{100}R_t\right)\right|^2\right]^{-0.5} \times 100\right\} \text{.....(2)}$$

Where X is the percent deviation for the reference product [32]. If 10% deviation is allowed for the dissolution profiles to be similar, then the calculated f 2LX value using equation (2) will be 61.18 for Tegretol CR®. For the prepared formulas, the highest calculated f 2 value according to equation (1) is 85.22 for formula 4. Figure (5) shows the non significant difference ($P < 0.05$) in the dissolution profiles of CBZ from Tegretol CR-® and formula 4.

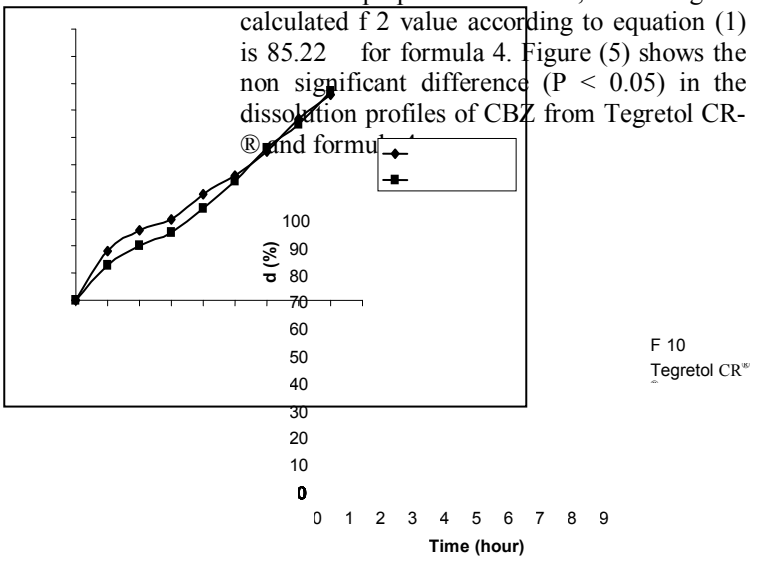

Figure 5: The release of CBZ from formula 10 compared to Tegretol CR® in water.

Stability Study: Accelerated Temperature Effect

The stability of the selected formula 4 was studied at three different temperatures ; 40ºC , 50ºC , and 60ºC for 16 weeks.The degradation of CBZ followed first-order kinetics because straight lines were obtained when logarithm of percent remaining of the drug was plotted versus time[33]. Figure (6) shows the degradation curves of CBZ at 40ºC, 50ºC and 60ºC, from which the degradation rate constant (K) at each temperature was determined from the slope of each line. The values of rate constants are summarized in table (6). The date of expiration for CBZ was determined through constructing Arrhenius plot as shown in figure (7) in order to estimate the degradation rate constant (K25) at 25ºC which was equal to 5.623 × 10-4 week-1 The following equation is used for calculating the expiration date [34] :

$$t_{10\%} = \frac{0.105}{K_{25}}$$

where t10% is the time required for a drug to lose 10% of its potency and it was found to be 185 weeks (about 3.6 years for CBZ).

Table 6: Degradation Rate Constants for CBZ in Formula 10 at 40ºC, 50ºC and 60ºC.

Temperature (ºC)	K (week^{-1})
40	1.8×10^{-3}
50	3.7×10^{-3}
60	5.9×10^{-3}

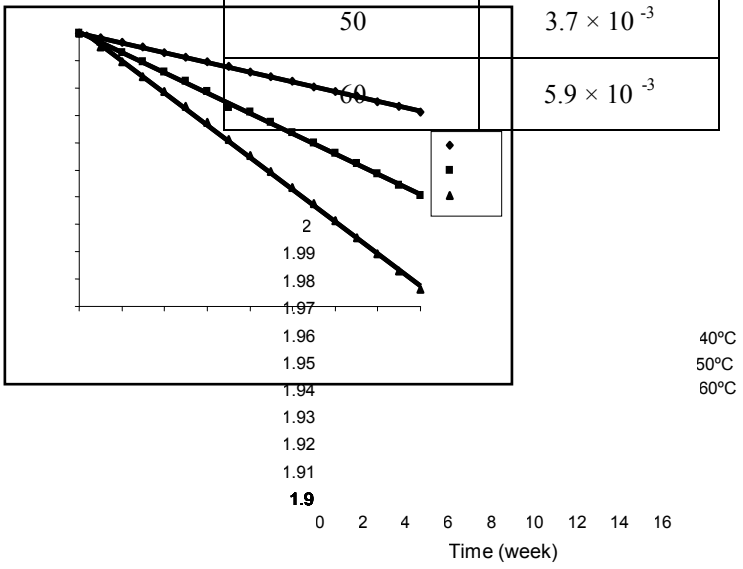

Figure 6: Accelerated degradation of CBZ in formula 10 at 40ºC, 50ºC and 60ºC.

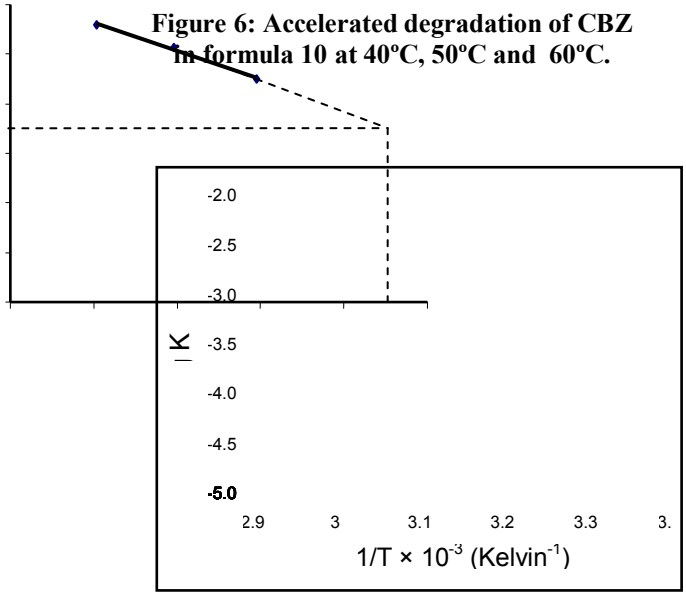

Figure 7: Arrhenius plot of CBZ in formula 10 for the estimation of the expiration date.

Conclusion

Carbamazepine extended release tablet has been successfully fabricated by using ethyl cellulose as retardant substance. In vitro release of carbamazepine was correlated with types and concentrations of the additives used in the formulation.

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