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Effect of Temperature, pH, and Sweetening Agents on Stability of Trimethobenzamide Hydrochloride Syrups: Evaluation by Factorial Design

Trimetobenzamid Hidroklorür Şuruplarının Stabiliteleri Üzerine Sıcaklık, pH ve Tatlandırıcı Ajanların Etkisi: Faktöriyel Tasarım ile Değerlendirme

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Abstract

In this study, the stability of trimethobenzamide hydrochloride (THCl) syrups was improved by using sweetening agents as sorbitol (polyhydric alcohol) and aspartame (dipeptide derivative). For this reason, accelerated stability tests at different temperatures (40±0.5°C, 60±0.5°C and 80±0.5°C) and pH (4.0 and 7.0) were carried out on THCl syrups. The ionic strength of the buffers was adjusted to 0.423 value by adding potassium chloride. The degradation rate constants (k), activation energy value (E_a), chemical half-life ($t_{1/2}$) and shelf-life (t_{90}) were calculated and evaluated.

The preparation and stability studies on THCl syrups was conducted according to the 2×2×3 factorial design as two different pH, two different sweetening agents and three different temperature. The influence of these factors on the degradation rate constant (k) was examined by using statistical analysis.

According to our accelerated stability tests findings and the results of the statistical analysis, sorbitol can be used in THCl syrups as sweetening agent and proved to be better than aspartame with respect to stability in formulations.

Keywords: Trimethobenzamide hydrochloride, pH, Temperature, Sweetening agents, Stability, Factorial design.

Introduction

Trimethobenzamide hydrochloride (THCl), is widely used as an antiemetic agent in oral, rectal and parenteral preparations and is a white crystalline powder with a slight phenolic odor. Its melting point is between 186 and 190°C and it is soluble in water, alcohol, chloroform and ether (The Merck Index, 1986; USP, 2000).

Pharmaceutical scientists routinely conduct "accelerated testing" or "stress testing" for a candidate formulation under exaggerated storage conditions to predict the stability of the

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formulation. This testing is designed to increase the degradation rate of the drug product to obtain information more quickly, allowing for rapid screening of stable, safe formulations (Nakamura et al., 2002; Guaratini et al., 2006). In view of the stability test, drug stability parameters as the degradation rate constants, k; activation energy value, E_a; chemical half-life, $t_{1/2}$ and shelf-life, t_{90} are very important (Magari et al., 2004).

From the pharmaceutical viewpoint, temperature is the most important factor in degradation for the stability of sweettening agents during storage. A number of reports in the literature have discussed the effect of temperature on the stability of liquid pharmaceutical formulations (Sevgi, 1993; Pesek and Matyska, 1997). In addition, the pH of the system greatly affects the stability of syrup and aqueous solutions (Gupta Das et al., 1986; Zajac et al., 2007).

According to our knowledge, in literature no study has been carried out to formulate syrup preparation to demonstrate the influence of formulation variables on the stability of THCI with sweetening agents in syrup formulations using a factorial approach. Thus the aim of the present investigation was to carry out a statistical study on preparation of syrup formulation using factorial design approach and to explore its application.

In our study the preparation and stability studies on THCI syrups were performed and the influence of these factors on the degradation rate constant (k) was examined by using statistical analysis. Factorial design is the design of choice for simultaneous determination of the effects of several factors and their interactions (Bolton, 1990). It may be useful for screening purpose or as an aid in identifying individual effects in complex systems and offers a good degree of accuracy. Factor effectiveness can be expressed with a mathematical model which explains the influence numerically (Scheffler, 1974; Öner and Alpar, 1991).

The objective in this work is to outline 2×2×3 factorial design and to study the effect of three factors; sweetening agent, temperature and pH on the degradation rate constant (k) of THCI from syrup formulations. The ideal syrup formulation was found by evaluation of these findings.

Experimental

Materials

THCl and Aspartame were supplied from Deva İlaç Sanayi Tic. A.Ş. and Bilim İlaç Sanayi Tic. A.Ş. Turkey, respectively. Other chemicals were of reagent grade and were purchased from E. Merck (Germany).

Blood agar, eosin metilen blue (EMB) agar and sabouraud dextrose agar (SDA) were purchased from Oxoid (England), E. Merck (Germany) and Difco (USA), respectively.

Thin layer chromatography (TLC) solvent system was designed as; Chloroform : Methanol : Ammonia 25% (30:10:0.1).

Buffer solutions: Mc Ilvain citric acid/phosphate buffer and Sorensen phosphate buffer systems were used for pH 4.0 and pH 7.0, respectively.

Methods

Preparation of THCI syrup formulations

Aspartame and sorbitol were used as sweetening agents at a concentration of 2% in THCI syrups. Aspartame (N-L-α-aspartyl-L-phenylalanine methyl ester) is a synthetic sweetener, has a taste like sucrose and is free of a metallic aftertaste. It has been used in diet products, beverages and also in pharmaceutical industry (Tunçel and Araman, 1989). Formulations were prepared in Mc Ilvain citric acid/phosphate buffer systems at pH 4.0 and Sorensen phosphate buffer system at pH 7.0. The ionic

strength of the buffers that should be of the same value to eliminate the ionic effect on the decomposition of the active ingredient, was adjusted to 0.423 by adding potassium chloride based on the pH of the buffer solution.

Before conducting any stability tests, all the obtained formulations were filtered through a 45 μm pore sized membrane. The list of syrup formulations prepared is presented in Table 1.

Table 1. List of syrup formulations prepared.

Code of formulations		F1	F2	F3	F4
Trimethobenzamide hydrochloride		1 g	1 g	1 g	1 g
Aspartame		5 g	5 g	-	-
Sorbitol		-	-	5 g	5 g
Buffer solutions	Mc Ilvain citric acid / phosphate buffer systems (pH 4)	25 mL	-	25 mL	-
	Sorensen phosphate buffer system (pH 7)	-	25 mL	-	25 mL
*Liquid formulations q.s.p.		50 mL	50 mL	50 mL	50 mL

*Formulations consist of 20% propylene glycol, 11% ethanol, %5 glycerin and distilled water.

Viscosity of syrups

The viscosity of the samples was measured at 25°C, using a BROOKFIELD DVII viscometer with a rotor No. RV 1, at 100 rpm.

Microbiological tests

The prepared four THCI syrup formulations were investigated microbiologically. 100 μL sample of each formulation were taken and incubated in blood agar, EMB agar and SDA at 37±0.5°C for 48 hours. SDA was also used as another process in which the incubation conditions were changed into 6 days, at 25±0.5°C. At the end of the incubation period, the number of colonies was counted.

Blood agar was used for determination of all kinds of bacterial growth, EMB agar for gram (-) bacterial growth, and SDA for fungal growth (Denyer et al., 2004).

Factorial Design Experiments

THCI syrups formulations were evaluated by 2×2×3 factorial design. The independent variables were two sweetening agents, two different pH, and three temperatures. The independent variables and their codes and levels were shown in Table 2.

In this study, the results of degradation rate constants (k; at 40±0.5°C, 60±0.5°C and 80±0.5°C) found from syrup formulations which were exposed to stability tests were taken as the dependent variable. The statistical evaluation of the results was carried out by analysis of variance (ANOVA) using a commercially available statistical program (SPSS 15.0).

Table 2. Levels of the independent variables investigated.

Variables	Level		
	(0)	(1)	(2)
sweetening agent	Aspartame	Sorbitol	-
pH	4	7	-
temperature (°C)	40	60	80

The accelerated stability test of THCI in syrup

The syrup formulations given in Table 1 were kept at 40±0.5°C, 60±0.5°C and 80±0.5°C in stability test cabins and the amount of THCI was determined with thin layer chromatography (TLC) method every day.

Thin layer chromatography (TLC)

TLC was used for quantitative determination of THCl. Silica gel 60 F_{254} pre-coated (Art.5715 Merck) plates were used. The plates were developed in a solvent system composed of chloroform: methanol: ammonia %25 (30:10:0.1) (Clarke, 1986). The spots were visualised by fluoresence quenching under UV light (254 nm). The area of spots were measured by external standard one-point method at 259 nm on a TLC-Scanner (Schimadzu-CS-920; D_2-lamp, λ=259 nm, Mode=ABS, AZS=on, Linearizer=0).

Kinetic calculations

The degradation rate kinetics was determined by plotting logarithm (log) of the concentration of drug remaining versus time (first-order process). The kinetic parameters as degradation rate constant (k), activation energy value (E_a), half-life ($t_{1/2}$) and shelf-life (t_{90}) were obtained from the slopes (m) of the straight lines at each temperature. Each experiment was done in four times (analysed with TLC-scanner) and average values were taken for the evaluations (Mendez et al., 2006).

The degradation rate constants (k) were calculated with Arrhenius equation (Eq. 1); $t_{1/2}$ and t_{90} values of formulations were determined at 40±0.5°C, 60±0.5°C and 80±0.5°C according to Eq. 2 and 3.

$$\log \frac{k_2}{k_1} = \frac{E_a(T_2 - T_1)}{2.303\ RT_2T_1} \qquad \text{Eq. 1}$$

$$t_{1/2} = \frac{\ln 0.5}{k} = \frac{0.693}{k} \qquad \text{Eq. 2}$$

$$t_{90} = \frac{\ln 0.9}{k} = \frac{0.105}{k} \qquad \text{Eq. 3}$$

$$m = -\frac{k}{2.303} \qquad \text{Eq. 4}$$

where; T is Temperature (Kelvin); R is gas constant.

Results and Discussion

Viscosity of syrups

The viscosity results of prepared syrup formulations were given in Table 3. The syrups prepared with aspartame and sorbitol, were significantly different at the same pH when evaluated statistically.

When the dosage forms show unequal biological activities, from the pharmaceutical viewpoint, it is important to know the factors that will be effective for stability. One of these factors is the pH of the medium (Pramer and Gupta, 1991). The variations of the pH also showed a significant effect on the viscosity of the formulations. The viscosity characters of syrups depend upon the temperature and the concentration and, are effective on the stability. The application of viscosity in pharmaceutics includes mixing, fluid flow, passage through an orifice, release of drug etc (Lewis, 1990).

Table 3. Viscosity results of THCI syrup formulations (n=3).

Viscosity of Syrups (cP ± SD)			
F1	F2	F3	F4
13.3 ± 0.1	12.8 ± 0.1	15.6 ± 0.2	15.0 ± 0.2

$p<0.05$,F1 vs F2; $p<0.01$,F3 vs F4;
$p<0.001$,F1 vs F3; $p<0.001$,F2 vs F4.

Microbiological tests

The results obtained in the microbiological investigation revealed that there was not any microbial growth in the syrups. The number of colonies was determined as constant at the end of the incubation time for all samples. The images obtained after incubation can be seen in Figure 1.

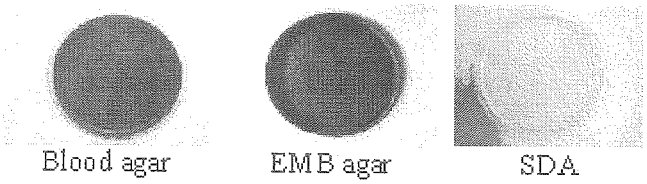

Figure 1. The images obtained after incubation.

The accelerated stability test of THCI in syrup

There is no reported study on the stability of THCI with sweetening agent in syrup formulations. But, there were many studies in which the stability of sorbitol and aspartame was investigated (Kim et al., 1997; Barry et al., 1982; Sevgi, 1993).

It was determined that aspartame was very unstable under the illuminated conditions and the degradation of aspartame was the fastest at pH 7.0 (Kim et al., 1997). In other studies it was seen that the pH of the system greatly affected the thermal stability of aspartame in aqueous solutions (Prudel and Davidkova, 1981; Kim, 1997). Temperature was shown to be an important factor for the stability of aspartame during storage. As the temperature increased, the amount of aspartame remaining unconverted decreased (Holmer, 1984; Prudel et al., 1986).

In another paper where sorbitol and phenylpropanolamine hydrochloride stability was studied, it was suggested that sorbitol at pH 6 had no significant effect (Barry et al., 1982).

In this study, the effect of sweetening agents, temperature and pH on the stability was investigated and it is the first study which investigates their interaction with THCl in a syrup formulation. The data were evaluated by calculating THCl amount remained in the syrups.

The degradation curves and Arrhenius plots are shown in Figures 2-5 and Figure 6, respectively. The results are the means of four experiments. In practice, the well-known Arrhenius theory is used to make a rapid stability prediction, to estimate a drug product shelf-life during early stages of its pharmaceutical development (Gil-Alegre et al., 2001). The data obtained from the accelerated stability test of THCI formulations are given in Table 4.

According to mathematical and kinetic analysis of the results, THCI in liquid formulations have shown degradation by mechanism of first order kinetic reaction (Tables 5 and 6, Figures 2-5). This finding is consistent with the results of previous researchers (Özol, 1986; Özsoy, 1991). The parameters of regression lines calculated with the first order treatment for time versus

remaining percent of THCI and degradation constants calculated with the Eq. 4 and slope (m) were shown in Table 6.

Table 4. The degradation rate constants (k), t_{90}, $t_{1/2}$ values of formulations at 40±0.5°C, 60±0.5°C and 80±0.5°C.

Code of formulation	Temperature (°C)	k (hour^{-1})	t_{90} (hour)	$t_{1/2}$ (hour)
F1	40	5.750×10^{-4}	182.608	1205.217
	60	3.530×10^{-3}	29.745	196.317
	80	5.392×10^{-3}	19.473	128.523
F2	40	6.445×10^{-3}	16.291	107.525
	60	15.04×10^{-3}	6.981	46.077
	80	18.39×10^{-3}	5.709	37.683
F3	40	7.676×10^{-5}	1367.899	9028.139
	60	2.207×10^{-4}	475.335	3140.009
	80	5.469×10^{-4}	191.866	1267.142
F4	40	3.198×10^{-5}	3283.302	221669.793
	60	1.151×10^{-4}	912.250	6020.851
	80	2.942×10^{-4}	356.900	2355.540

Table 5. The activation energies (E_a), the degradation rate constants (k_{25}), t_{90} and $t_{1/2}$ values at room temperature (25 °C).

Code of formulation	E_a (cal.mol^{-1})	k_{25} (hour^{-1})	t_{90} (hour)	$t_{1/2}$ (hour)
F1	12020.879	4.189×10^{-4}	250.656	1654.332
F2	5632.242	5.540×10^{-3}	18.953	125.090
F3	10782.099	3.262×10^{-5}	3218.884	21244.635
F4	12025.686	1.796×10^{-5}	5846.320	38585.740

Table 6. The parameters of regression lines calculated with the treatment of first order kinetics at 40±0.5°C, 60±0.5°C and 80±0.5°C.

Code of formulation	Temperature (°C)	m	Int.	r^2	k (hour^{-1})
F1	40	-2.50×10^{-4}	2.00	0.9849	5.750×10^{-4}
	60	-1.53×10^{-3}	2.00	0.9959	3.530×10^{-3}
	80	-2.34×10^{-3}	2.00	0.9900	5.392×10^{-3}
F2	40	-2.79×10^{-3}	2.00	0.9990	6.445×10^{-3}
	60	-6.53×10^{-3}	2.00	0.9996	15.04×10^{-3}
	80	-7.98×10^{-3}	2.00	0.9984	18.39×10^{-3}
F3	40	-3.33×10^{-5}	2.00	0.9900	7.676×10^{-5}
	60	-9.58×10^{-5}	2.00	0.9878	2.207×10^{-4}
	80	-2.37×10^{-5}	2.00	0.9958	5.469×10^{-4}
F4	40	-1.38×10^{-5}	2.00	0.9589	3.198×10^{-5}
	60	-5.00×10^{-5}	2.00	0.9817	1.151×10^{-4}
	80	-1.27×10^{-4}	2.00	0.9807	2.942×10^{-4}

m : Slope
Int.: Intercept value
r^2 : determination coefficient
k : degradation rate constant

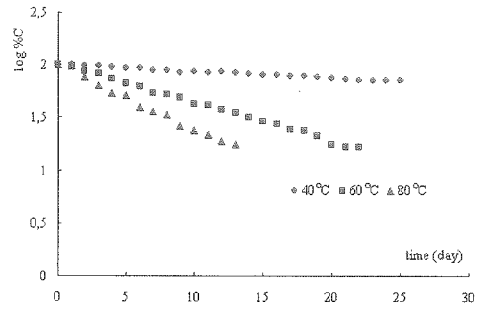

Figure 2. Degradation curves for F1 formulation at 40±0.5°C, 60±0.5°C and 80±0.5°C.

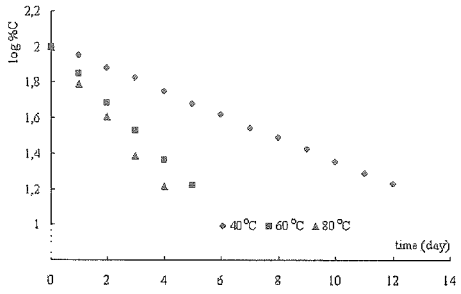

Figure 3. Degradation curves for F2 formulation at 40±0.5°C, 60±0.5°C and 80±0.5°C.

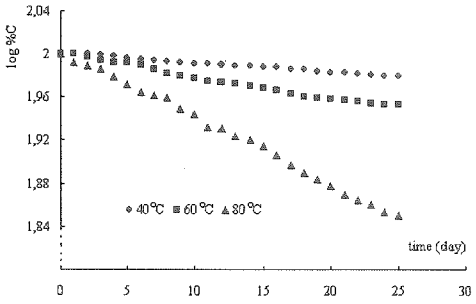

Figure 4. Degradation curves for F3 formulation at 40±0.5°C, 60±0.5°C and 80±0.5°C.

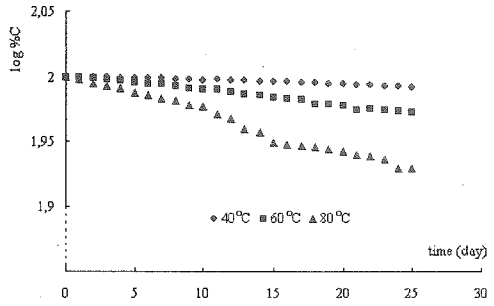

Figure 5. Degradation curves for F4 formulation at 40±0.5°C, 60±0.5°C and 80±0.5°C.

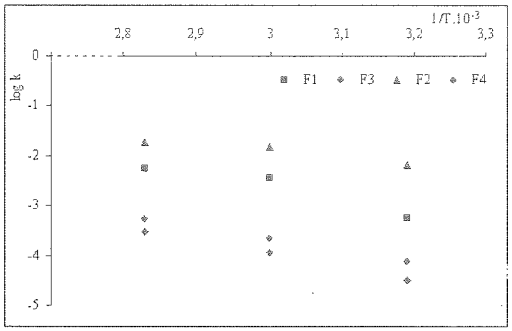

Figure 6. Arrhenius plots of THCI formulations.

The reaction rate constant (k_{25}) at room temperature was determined with aid of k_{60} (60±0.5°C) according to Eq. 1, and $t_{1/2}$, t_{90} values at room temperature were calculated by using Eq. 2-3. These results were shown in Table 5.

The shelf lives ($t_{1/2}$) were between 37.683 and 221669.793 hour (Table 4). The activation energies (E_a) of the formulations were found between 5632.242 and 12025.686 cal.mol^{-1} (Table 5). The degradation rate constants (k) of THCI were between 1.796×10^{-5} and 5.540×10^{-3} hour^{-1} respectively, at 25°C (Table 4).

As it can be seen from the Tables 4 and 5, all the formulations were affected by the change of temperature. The differences in all kinetic parameters were more dramatic between 40±0.5 °C and 60±0.5°C than the difference between 60±0.5°C and 80±0.5°C. $t_{1/2}$ and t_{90} showed a sharp decrement when the temperature increased (Table 4 and 5).

When the parameters were investigated at room temperature, it was seen that the most stable formulation was F4 with the highest $t_{1/2}$ and t_{90} values (Table 5).

Factorial design is a useful tool in order to characterize multivariable processes; and gives the possibility to separate the important factors among the others, and identifies any possible interactions between them (Paterakis et al., 2002). Application of factorial design experiments to pharmaceutical problems has appeared to be extremely useful in recent years (Özyazici et al., 1997).

The factorial design model was applied to the evaluation of our stability study. The effect was calculated from the change in the degradation rate constants (k). Figures 7-9 and Tables 7-8 show the interactions of sweetening agents, temperature and pH.

The factors; sweetening agent, temperature and pH are separately effective on the degradation rate constants (k) of THCl. The results of analysis of variance for k are listed in Table 8 ($p<0.01$). According to the results, all factors when coupled, are also significantly effective on degradation of THCl ($p<0.01$) (Figure 7-9). Furthermore as it can be seen in Table 8, the interactions between sweetening agents, temperature and pH were also statistically significant ($p<0.01$). As a summary we can state that all factors are effective on the degradation rate of THCl when they are evaluated together or separately. Moreover, there is a significant interaction between all of these factors chosen as independent variables.

Taking into consideration the average climatic conditions of hot areas in our country, it can be stated that THCI syrup formulations should be stored in a cool place, especially when prepared with aspartame. We found that syrups prepared with sorbitol were more suitable than aspartame at extreme temperature conditions (Table 4, Figures 2-5 and 9). Sorbitol had very slight effects on the stability of THCI syrup formulations. These results were in agreement with the findings of the earlier reports (Barry et al., 1982; Gupta Das et al., 1986).

Table 7. Results of descriptive statistics.

s.a.	pH	T	Mean × 10^{-3}	Std. Deviation × 10^{-3}	N
0	0	0	0.5468	0.11018	4
		1	3.4734	0.03775	4
		2	5.5740	0.21189	4
		Total	3.1981	2.15694	12
	1	0	6.3312	0.13063	4
		1	15.0975	0.29296	4
		2	18.7500	0.41569	4
		Total	13.3929	5.44988	12
	Total	0	3.4390	3.09394	8
		1	9.2854	6.21636	8
		2	12.1620	7.04949	8
		Total	8.2955	6.59875	24
1	0	0	0.0767	0.00004	4
		1	0.2254	0.00543	4
		2	0.5398	0.10867	4
		Total	0.2806	0.20947	12
	1	0	0.0275	0.00516	4
		1	0.1127	0.02804	4
		2	0.2622	0.03686	4
		Total	0.1341	0.10421	12
	Total	0	0.0521	0.02651	8
		1	0.1690	0.06305	8
		2	0.4010	0.16628	8
		Total	0.2074	0.17825	24
Total	0	0	0.3117	0.26141	8
		1	1.8494	1.73631	8
		2	3.0569	2.69543	8
		Total	1.7393	2.11339	24
	1	0	3.1794	3.37057	8
		1	7.6051	8.01202	8
		2	9.5061	9.88591	8
		Total	6.7635	7.75046	24
	Total	0	1.7455	2.74344	16
		1	4.7272	6.34016	16
		2	6.2815	7.75176	16
		Total	4.2514	6.16655	48

s.a.: sweetening agent; T: temperature

Table 8. Results of analysis of variance for 2×2×3 experiments.

Source	df	Sum of Squares	Mean Squares	F	p
s.a.	1	785.009	785.009	27056.909	0.000*
pH	1	302.911	302.911	10440.436	0.000 *
t	2	170.032	85.016	2930.245	0.000 *
s.a. ^{x} pH	1	320.828	320.828	11057.990	0.000 *
s.a. ^{x} t	2	146.596	73.298	2526.361	0.000 *
pH ^{x} t	2	28.867	14.433	497.475	0.000 *
s.a. ^{x} pH ^{x} t	2	31.952	15.976	550.648	0.000 *
Error	36	1.044	0.029		
Corrected Total	47	1787.240			

s.a.: sweetening agent; t: temperature (°C)
Symbol (*) indicates a significant difference: *p<0.01

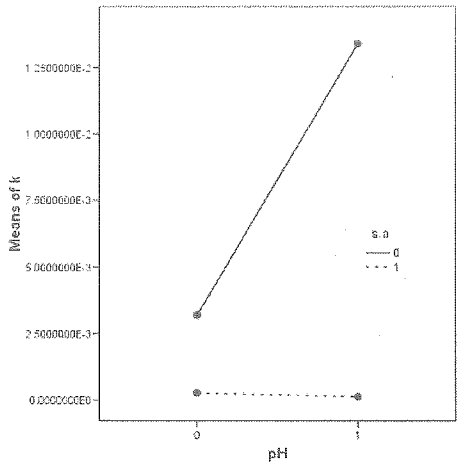

Figure 7. Interaction of between sweetening agent (s.a.) and pH on the degradation rate constant

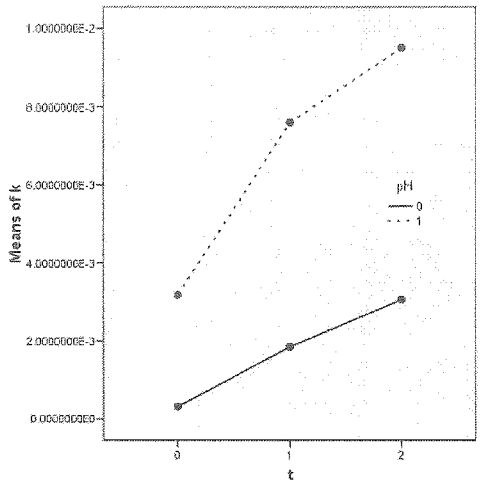

Figure 8. Interaction of between pH and temperature (t °C) on the degradation rate constant.

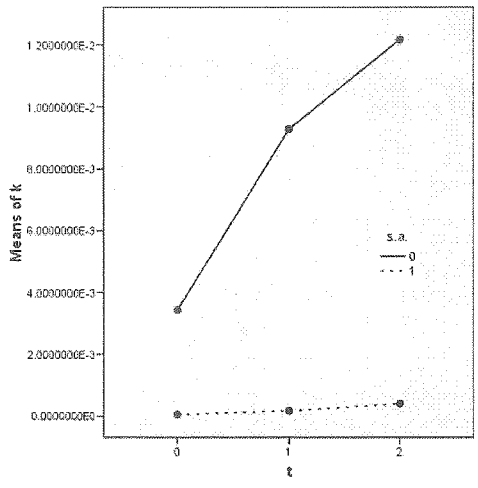

Figure 9. Interaction of between sweetening agent (s.a.) and temperature on the degradation rate constant.

According to our findings, pH was more effective on the stability of THCl in the syrup formulations which were prepared with aspartame than sorbitol (Table 5, Figure 7). At pH 7.0, the activation energy was found to be greater for sorbitol. However, at pH 4.0 the activation energy was greater for preparing aspartame than sorbitol. These findings of the present study are concordant to results of the other researchs. It was reported that aspartame was most stable between pH 4.0 and pH 5.0, decreasing in stability under more acidic and neutral conditions (Özol, 1986; Butchko, 2002). Schiffman et al. (2000) showed that aspartame in citrate-phosphate buffer solutions was most stable over the pH range 4.0-5.0, becoming less stable as the pH increased or decreased. The results of this study showed that it was impossible to use aspartame in drugs for long shelf-life, but it was suitable for extemporaneously-prepared syrups, at pH 4.0 than pH 7.0.

These findings led us to conclude that the increment in rate of THCl decomposition as a function of time could be attributed to the sweetening agent, the pH value and the temperature. In present study, sorbitol was better than aspartame as sweetening agent in syrup formulation at higher temperatures and pH 7.0.

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Özet

Bu çalışmada, Trimetobenzamid hidroklorür şuruplarının stabilitesi, tatlandırıcı ajan olarak sorbitol ve aspartam kullanılarak tayin edildi. Bu amaçla, hızlandırılmış stabilite testleri THCl şuruplarında farklı sıcaklık (40±0.5°C, 60±0.5°C ve 80±0.5°C) ve pH'larda (4.0 ve 7.0) yapıldı. Tamponların iyon şiddetleri potasyum klorür ilavesi ile 0.423'e ayarlandı. Bozunma hız değişmezi (k), Aktivasyon enerjisi (E_a), yarılanma ömrü ($t_{1/2}$) and raf ömrü (t_{90}) hesaplandı ve değerlendirildi.

THCl şuruplarının hazırlanma ve stabilite çalışmaları, 2 farklı pH, 2 farklı tatlandırıcı ajan ve 3 farklı sıcaklık, 2×2×3 faktöriyel tasarım ile düzenlendi. Bu faktörlerin etkisi, istatistik analiz kullanılarak bozunma hız değişmezi (k) üzerindeki etkisi incelendi.

Hızlandırılmış stabilite çalışmaları bulguları ve sonuclarına göre, Trimetobenzamid hidroklorür şuruplarında sorbitol tatlandırıcı ajan olarak kullanılabilir ve stabilite bakımından, formülasyonlarda aspartamdan daha iyidir.

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