

Studying the Effect of a Maltitol Solution on the Stability of Water Soluble Vitamins

Khalil Sakeer^{1✉}, Hind Al-Zein²

¹Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, The Syrian International Private University for Science and Technology, Syria.

²Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Damascus University, Syria.

ABSTRACT

The stability of vitamins in a liquid dosage form is still considered a challenge to pharmacists to obtain a stable formula. The objective of this study was to formulate multi-water soluble vitamin oral solutions, study the stability of this formulation at accelerated conditions 40 ± 2 °C / $75\% \pm 5\%$ RH for two months and investigate the effect of the pH and the percent of a maltitol solution on the stability of the vitamins. Results showed that using a 30% maltitol solution gave a pronounced improvement in the stability of vitamins compared with a sorbitol solution, and the pH had a critical role on the stability of vitamins so the vitamins had an optimum stability at pH between 3.5 – 4.

Keywords: water soluble vitamins, maltitol solution, accelerated condition, sorbitol solution.

INTRODUCTION

Maltitol (4-O- α -D-glucopyranosyl-D-glucitol) is a disaccharide consisting of a glucose unit linked to a sorbitol one via an α -1,4 bond.¹ A maltitol solution is used in oral pharmaceutical formulations as a bulk sweetening agent, either alone or in combination with other excipients, such as sorbitol. A maltitol solution is also used as a suspending agent in oral suspensions as an alternative to sucrose syrup since it is viscous, non-cariogenic, and has a low calorific value. It is also non-crystallizing and therefore prevents 'cap-locking' in syrups and elixirs.² However, maltitol has a relatively low energy value estimated at 10 kJ g^{-1} and the heat of dissolution [-66.83 J/g] is four times that of sucrose [-16.70 J/g], which prepares this polyol for specific applications like chewing gum or tablets with low calories and refreshing taste.³ Sorbitol is D-glucitol, is a hexahydric alcohol related to mannose and is isomeric

with mannitol.³ In liquid preparations,⁴ sorbitol is used as a vehicle for sugar-free formulations and as a stabilizer for drugs⁵, vitamins^{6,7}, and antacid suspensions, and in syrups, it is effective in preventing crystallization around the caps of bottles. The formulating of an aqueous multi-vitamin solution is a very complicated process because each vitamin has a stable pH value and separated preferable dissolving liquid. For example, ascorbic acid (vitamin C) is stable at a neutral pH value, but some studies^{8,9} showed the effect of pH on the aerobic degradation of ascorbic acid in an aqueous solution which was proceeded by a first-order reaction. The maximum rate of degradation occurred at pH 4 near the $\text{pK}_{\text{a}1}$ of ascorbic acid, and the minimum rate was at pH 5.6. On the other hand, thiamine (vitamin B1) is stable at lower pH values. Williams *et al*¹⁰ studied the stability of thiamine and concluded that thiamine was increasingly unstable in a solution as the pH rose. Therefore, the aim of this study was formulating a multi-water soluble vitamin oral solution (ascorbic acid, thiamine, riboflavin, pyridoxine, niacin amide) by using a maltitol solution as the main vehicle and evaluating the effect of the

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✉ E-mail: sakeer1981@hotmail.com

accelerated condition 40 ± 2 °C / $75\% \pm 5\%$ RH on the stability of vitamins.

EXPERIMENTAL SECTION

Material and Chemicals

The following materials were used: ascorbic acid (vitamin C) (Anhui Harrest.Co, China), thiamine hydrochloride (vitamin B1) (DSM, Germany), pyridoxine hydrochloride (vitamin B6), niacin amide (vitamin PP) and edetate disodium (Sinochem Jiangsu. Corp, China), riboflavin5-phosphate (vitamin B2) (DSM, France), glycerin (Mptmusim mas, Indonesia), sucrose (National Syrian Co., Syria), propylene glycol (Dangschat, Germany) , methylparaben (nipagin) and propylparaben (nipasole) (Universal Marketing Consuftancy Ez. Co., China) , Na citrate dehydrate (DSM, China), sorbitol solution (Cargill, Germany), Poly Oxyl 40 Hydrogenated Castor Oil (Cremophor RH40) (BASF, Germany), maltitol solution (BMP, Germany). All reagents and solvents used were of analytical grade (Scharlau, Spain).

Preparation of Oral Solution

The oral solution formulations were prepared in two steps: 1- Vehicle solution, and 2- Vitamin solution.

1- Vehicle solution: Four oral solution formulations were prepared as follows:

(I) 150 ml of deionized water were heated to 90 °C and 250 g of sucrose were added and mixed on a magnetic mixer at 500 rpm till a clear solution was obtained. Then the solution was cooled to 70 °C. **(II)** In another beaker, premix1 was prepared by heating 50 g of propylene glycol to 70 °C, methylparaben 1 g and

propylparaben 0.1 g were added and mixed on a magnetic mixer at 500 rpm till a clear solution was obtained, and then 15 g of polyoxyl 40 hydrogenated castor oil were added with continuous stirring till a clear solution was obtained. **(III)** The premix1 was added over the prepared solution in step **(I)**. **(IV)** After mixing for 10 min the solution was cooled to 60 °C. Glycerin 75 g (and/or a sorbitol solution and/or a maltitol solution) and edetate disodium 250 mg were added at 60 °C and mixed for 10 min. Then the solution was cooled to 25-30 °C.

2-Vitamin solutions: Vitamin solutions were prepared in two steps: **(I)** 25 ml of deionized water were kept at 25 °C. Then the following materials were added according to the following order (each material was added after the previous one to ensure that the former one was dissolved): edetate disodium 125 mg, thiamine 600 mg , pyridoxine 600 mg , and niacin amide 1.15 mg. **(II)** Another solution was prepared by dissolving 125 mg of edetate disodium in 25 ml of deionized water, then 7 g of ascorbic acid were added and the solution was mixed for 15 min. The solution which was prepared in step **(I)** was added over the solution which was prepared in step **(II)**. Finally, 0.3 g of riboflavin were added and stirred until dissolved.

The vitamin solutions were added over the vehicle solution and the final volume was adjusted at 500 ml by deionized water. The final solutions were stirred for 15 min and the beakers were covered with aluminum paper. The compositions of the prepared formulation are presented in Table 1.

Table 1: The composition of oral solution formulation, the quantities in (g) for 500 ml

Item	Ingredient	Formula 1	Formula 2	Formula 3	Formula 4
1	Ascorbic acid	7	7	7	7
2	Thiamine hydrochloride	0.6	0.6	0.6	0.6
3	Pyridoxine hydrochloride	0.6	0.6	0.6	0.6
4	Niacin amide	1.15	1.15	1.15	1.15

Item	Ingredient	Formula 1	Formula 2	Formula 3	Formula 4
5	Riboflavin 5-phosphate	0.3	0.3	0.3	0.3
6	Nipagine	1	1	1	1
7	Nibasole	0.1	0.1	0.1	0.1
8	Cremophor RH 40	15	15	15	15
9	Edta Na	0.5	0.5	0.5	0.5
10	Propylene glycol	50	50	50	25
11	Glycerin	75	100	100	100
12	Sucrose	250	-	-	-
13	Sorbitol solution 70%	-	150	150	100
14	Maltitol solution	-	75	75	150
15	Na citrate	-	-	2.5	-

The determination of the pH was carried out directly after the preparation, and it ranged between 3.5 – 4 for formula 1, 2 and 4 and it was 5.5 for formula 3. Before the solutions were kept in a controlled cabinet (Mettler, Germany) at $40 \pm 2^\circ\text{C}$ / $75\% \pm 5\%$ RH, their closures were closed under nitrogen gas in order to expel the oxygen out of the bottle.

Instrumentation: Assay of Vitamins

The HPLC system (Knauer, Germany) consists of an HPLC manager system (Smartline manager 5000, V6702), constant solvent delivery system (Smartline Pump 1000, V7603), and a spectrophotometer detector (Smartline PDA detector 2800, V7606, Knauer, Germany) equipped with an autosampler (Smartline autosampler 3950, Knauer, Germany) and fitted with a 20 μml sample loop. The analytical column employed was a Eurosphere 100 C18 (250×4.6 mm i.d., 5 μm particle size, Knauer, Germany). The data were captured using

Microsoft Windows-XP based chemistry. The dilution liquid was comprised of HPLC water 81% v/v, acetonitrile 13% v/v, methanol HPLC 5.95% v/v and triethylamine 0.05% v/v. The pH of this liquid was adjusted by phosphoric acid to 3 by using a pH meter (Wissenschaftlich-technische Werkstätten GmbH and co KG, Germany). While the mobile phase was prepared by dissolving 100 mg of n-hexane sulphonic acid sodium in 100 ml of a dilution liquid. The dilution and mobile phases were filtered through a 0.45 μm Millipore filter before being used and degassed in an ultrasonic bath (Ultrasonic Elma, Germany). All the samples were injected at a flow rate of 1 ml/min. The detector was programmed at a wavelength of 210 nm.

Preparation of Standard Solutions

Thiamin hydrochloride 50 mg, riboflavin -5- sodium phosphate anhydrous 25 mg, pyridoxine hydrochloride 50 mg, niacin amide 100 mg and ascorbic acid 600 mg

were accurately weighed (Denver instrument AA-200, USA). These were transferred to 100 ml volumetric flasks and 100 ml of dilution liquid was added into the flask and mixed on a magnetic mixer at the 600 rpm for 15 min. Then 20 ml of this solution were diluted to 50 ml by a dilution liquid and mixed for 5 min.

Statistical Analysis

All the data were statistically analyzed by T-test student two tails by SPSS statistical software (SPSS Version 13). Results were quoted as significant where $p < 0.05$.

RESULTS AND DISCUSSION

Separation and Detection

Fig.1 demonstrates the separation of water-soluble vitamins in a single run using a Eurosphere 100 C18 column. As shown in Fig.1, the vitamins were well separated, the system suitability was controlled by adjusting the RSD (relative standard deviation) for five injections to be not more than (2%), and the chromatographic system requirement was determined based on other previous studies.^{11,12}

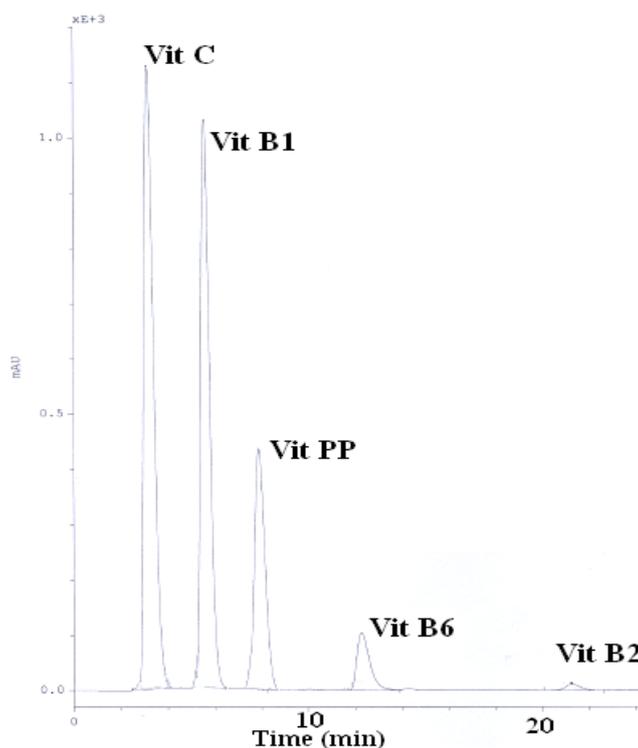


Figure 1: Chromatogram of standard solution

The Effect of an Accelerated Storage Condition on the Stability of Ascorbic Acid (Vitamin C)

Table 2 and Figure 2 show the percent of ascorbic acid stored at $25 \pm 2^\circ\text{C} / 40\% \pm 5\% \text{RH}$ for one month on the shelf and after storage for one and two months at an accelerated condition ($40 \pm 2^\circ\text{C} / 75\% \pm 5\% \text{RH}$). It is clear that ascorbic acid underwent a minimum

decomposition in formula 3 where the decomposition of ascorbic acid after two months at an accelerated condition was in the following order formula 1>formula 2> formula 4>formula 3. The pH value of formula 3 was 5.5 which might play a critical role in the increment of the stability of the ascorbic acid.

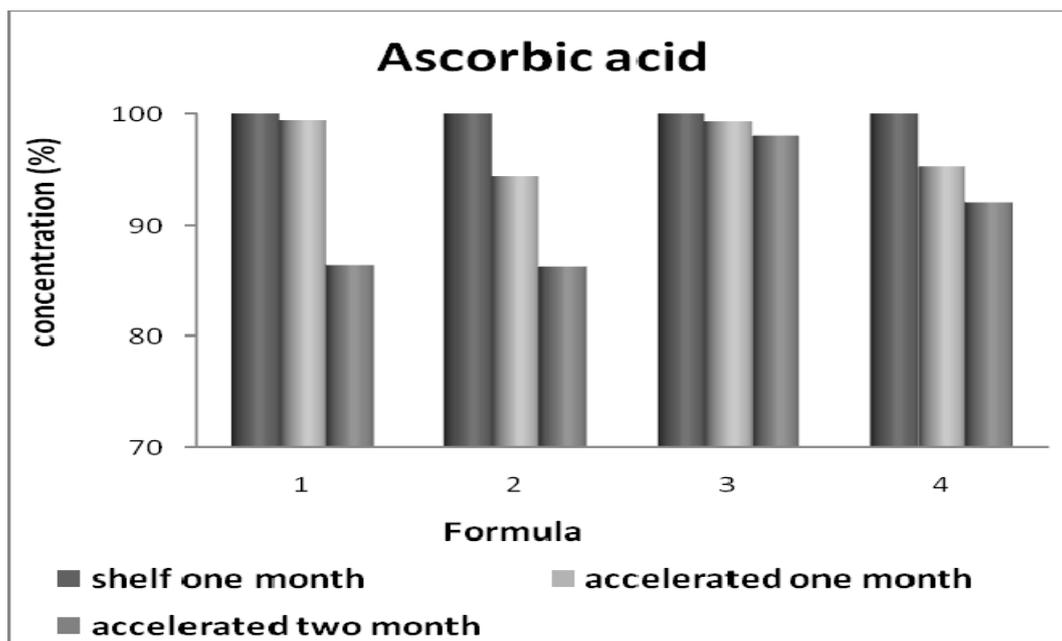


Figure 2: The percent of ascorbic acid (vit C) when stored at $25 \pm 2^\circ\text{C} / 40\% \pm 5\% \text{RH}$ for one month on the shelf and after storage for one and two an accelerated condition ($40 \pm 2^\circ\text{C} / 75\% \pm 5\% \text{RH}$).

Table 2: The results of vitamin's assay on the shelf and under accelerated conditions

		Ascorbic acid	Thiamine	Riboflavin	Niacin amide	Pyridoxine
Formula 1	Shelf one month	99.9±1.01	1.27±99.13	1.76±99.46	1.65±99.56	1.291±99.2
	Accelerated one month	99.36±1.1	90.74±1.45	92.07±1.34	97.40±1.78	95.64±1.87
	Accelerated two months	86.38±1.15	82.16±1.47	86.58±1.53	92.61±1.56	94.87±1.95
Formula 2	Shelf one month	99.74±1.29	99.23±1.28	99.94±1.87	99.45±1.61	99.1±1.87
	Accelerated one month	94.41±1.34	93.25±1.87	93.16±1.48	97.20±1.91	98.85±1.64
	Accelerated two months	86.27±1.39	81.86±1.92	88.88±1.56	92.45±1.01	92.25±1.86
Formula 3	Shelf one month	99.92±1.83	98.23±1.81	99.93±1.01	99.91±1.84	99.45±1.78
	Accelerated one month	99.27±1.32	75.93±1.87	93.86±1.75	96.40±1.86	97.46±1.97
	Accelerated two months	98.06±1.28	56.69±1.65	84.92±1.64	94.80±1.91	95.16±1.66
Formula 4	Shelf one month	98.37±1.34	99.49±1.31	99.98±1.85	99.54±1.75	99.82±1.71
	Accelerated one month	95.20±1.68	92.41±1.84	95.94±1.56	99.23±1.84	99.36±1.95
	Accelerated two months	91.97±1.35	87.16±1.76	93.21±1.67	98.72±1.47	99.69±1.97

Previous studies^{8,9} showed the effect of pH on the aerobic degradation of ascorbic acid in an aqueous solution, which was proceeded by a first-order reaction. The maximum rate of degradation occurred at pH 4 near the pKa1 of the ascorbic acid, and the minimum rate was at pH 5.6. On the other hand, the percent of a maltitol solution in formula 4 was 30% which is evidence of the

effect of a maltitol solution in decreasing the rate of degradation of ascorbic acid, where some studies¹³ demonstrated an increased stability of ascorbic acid and thiamine when glycerin or propylene glycol was substituted for part of the water in an oral multivitamin liquid. In a study of the stability of ascorbic acid per se for 3 weeks at 45 °C, DeRitter *et al*¹⁴ found increasing

stability as the moisture content decreased.

The Effect of an Accelerated Storage Condition on the Stability of Thiamine Hydrochloride (Vit B1)

Table 2 and Figure 3 show the percent of ascorbic acid stored at $25 \pm 2^\circ\text{C} / 40\% \pm 5\% \text{RH}$ for one month on the shelf and after storage for one and two months at an accelerated condition ($40 \pm 2^\circ\text{C} / 75\% \pm 5\% \text{RH}$). The decomposition of thiamine after two months was in the

following order formula 3 > formula 2 > formula 1 > formula 4. It is worthy to note that the percent of a maltitol solution in formula 4 was 30% which has a pronounced effect on increasing the stability of this formula, while the pH value of formula 3 was 5.5 which played a negative role on the stability of thiamine. Williams *et al*¹⁰ studied the stability of thiamine and concluded that thiamine was increasingly unstable in solution as the pH rises.

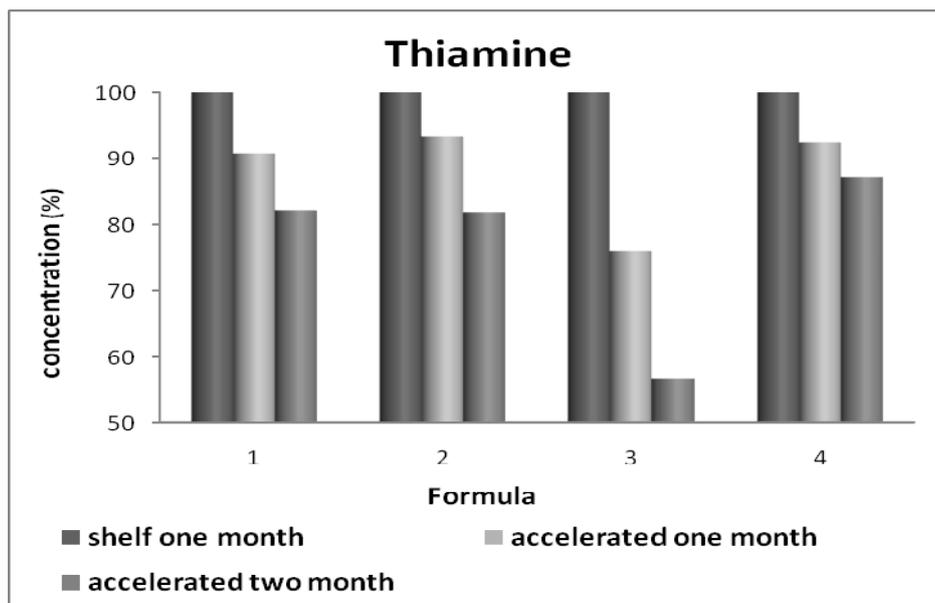


Figure 3: The percent of thiamine (Vit B1) when stored at $25 \pm 2^\circ\text{C} / 40\% \pm 5\% \text{RH}$ for one month on the shelf and after storage for one and two months at an accelerated condition ($40 \pm 2^\circ\text{C} / 75\% \pm 5\% \text{RH}$).

The kinetics of the degradation of thiamine have been studied by various researchers^{15,16,17,18} who have reported first-order reactions with a rate increasing with increasing pH. Yao and Hsu¹⁹ prepared multivitamin solutions in a syrup, glucose, sorbitol or sucrose solution at pH 3.2, 4.5 and 7.0, and stability studies showed that at 41.5°C and 60°C , thiamine was more stable at pH 3.2 while pH 7 is the best for the stability of ascorbic acid.

The Effect of an Accelerated Storage Condition on the Stability of Riboflavin 5-phosphate (Vit B2)

Table 2 and Figure 4 show the percent of ascorbic acid stored at $25 \pm 2^\circ\text{C} / 40\% \pm 5\% \text{RH}$ for one month on the shelf and after storage for one and two months at an accelerated condition ($40 \pm 2^\circ\text{C} / 75\% \pm 5\% \text{RH}$). The decomposition of riboflavin after two months was in the following order formula 3 > formula 1 > formula 2 > formula 4. The percent of a maltitol solution in formula 4 was 30%.

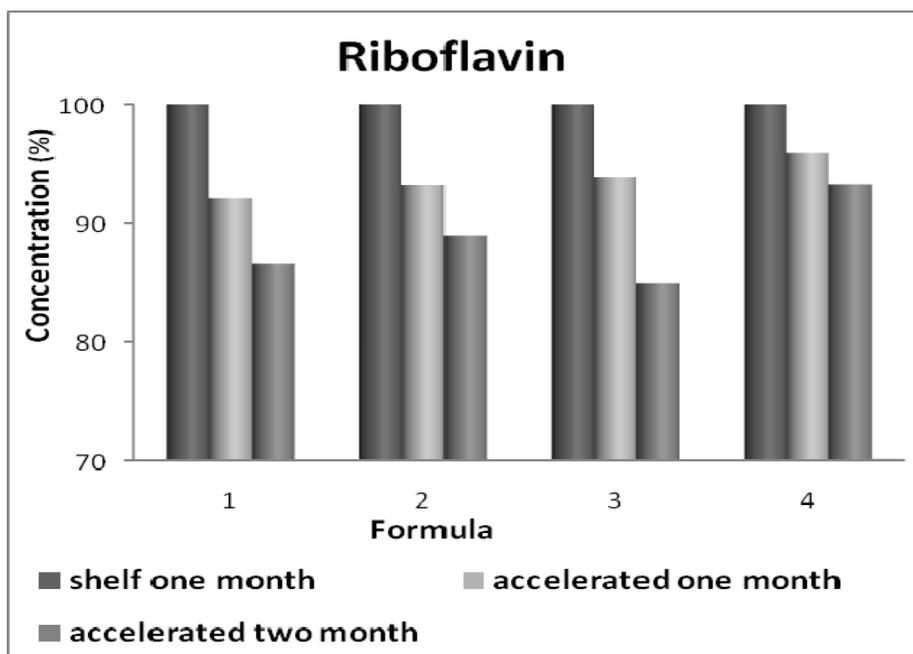


Figure 4: The percent of riboflavin (Vit B2) when stored at $25 \pm 2^\circ\text{C} / 40\% \pm 5\% \text{RH}$ for one month on the shelf and after storage for one and two months at an accelerated condition ($40 \pm 2^\circ\text{C} / 75\% \pm 5\% \text{RH}$)

Some studies^{20,21} showed that the decay of riboflavin-5-phosphate exposed to light is dependent on the temperature, pH, and light intensity and wavelength, and those studies reported that thiamine, riboflavin, and ascorbic acid in syrups could be stabilized by replacing sucrose, vanillin, and various aldehyde-rich essential oils with sorbitol, sodium saccharin, edetate disodium, and the essence of banana or apple.

The Effect of an Accelerated Storage Condition on the Stability of Pyridoxine Hydrochloride (Vit B6) and Niacinamide (Vitamin PP)

Table 2, Figure 5 and Figure 6 show the percent of pyridoxine and niacinamide, when stored at $25 \pm 2^\circ\text{C} / 40\% \pm 5\% \text{RH}$ for one month on the shelf and after storage for one and two months at an accelerated condition ($40 \pm 2^\circ\text{C} / 75\% \pm 5\% \text{RH}$).

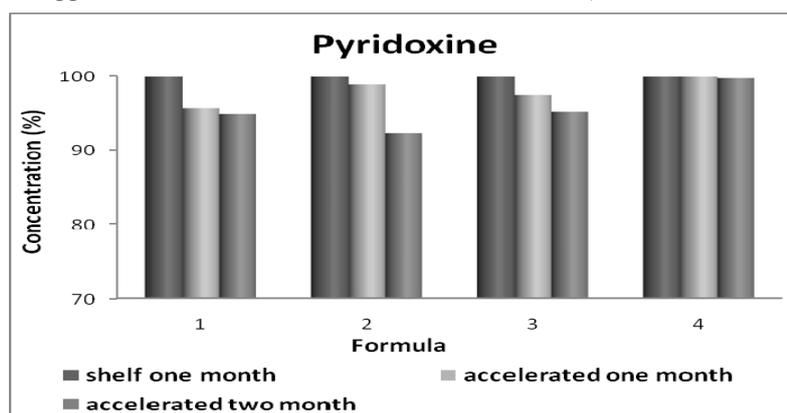


Figure 5: The percent of Pyridoxine (Vit B6) when stored at $25 \pm 2^\circ\text{C} / 40\% \pm 5\% \text{RH}$ for one month on the shelf and after storage for one and two months at an accelerated condition ($40 \pm 2^\circ\text{C} / 75\% \pm 5\% \text{RH}$).

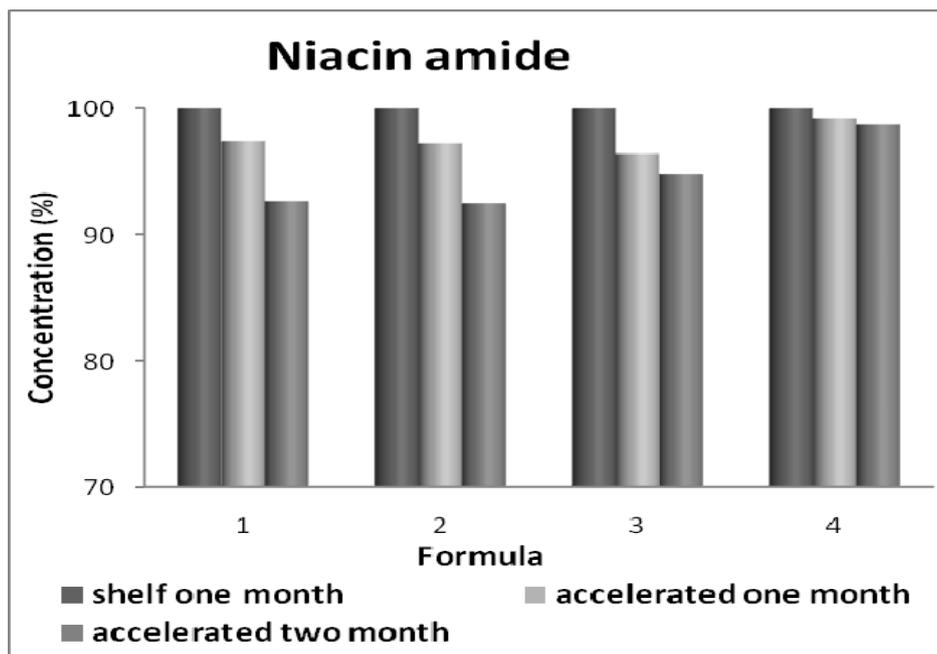


Figure 6: The percent of Niacinamide (Vit PP) when stored at 25 ± 2 oC / $40\% \pm 5\%$ RH for one month on the shelf and after storage for one and two months at an accelerated condition.

Generally pyridoxine and niacinamide are considered stable vitamins¹⁹ and their degradation rates are very small when compared to other vitamins, where the pyridoxine or niacinamide decomposition percent did not exceed 7% after storage for two months at an accelerated condition.

Conclusion

This study provides a primary estimation of a) the effect of a maltitol solution when the percent of maltitol solution increased, the stability increased, b) the effect of pH where the optimum pH values were ranged between 3.5 – 4 on the stability of some water soluble vitamins. Further study should be done at higher temperatures to

predict the shelf life and to investigate the degradation of the product. Outcomes of this work may provide a basis for a strategy to develop the formulation of a multi water and/or oil soluble vitamin aqueous solution, syrup and oral drop dosage forms.

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دراسة تأثير محلول المالتيتول maltitol solution على ثباتية بعض الفيتامينات المنحلة في الماء

خليل ساكير¹ وهند الزين²

¹ قسم الصيدلانيات والتكنولوجيا الصيدلانية، كلية الصيدلة، الجامعة السورية الدولية الخاصة للعلوم والتكنولوجيا، سوريا
² قسم الصيدلانيات والتكنولوجيا الصيدلانية، كلية الصيدلة، جامعة دمشق، سوريا

ملخص

تعد ثباتية الفيتامينات في الأشكال الصيدلانية السائلة من التحديات التي تواجه الصيادلة في الحصول على صيغة دوائية ثابتة. إن الهدف من هذه الدراسة هو صياغة محاليل فموية محتوية على فيتامينات منحلة بالماء، ودراسة ثباتية هذه الصيغ في شروط من درجة حرارة $2 \pm 40\%$ م° ورطوبة نسبية $5 \pm 75\%$ لمدة شهرين والتحري عن تأثير الباهاء ونسبة محلول المالتيتول maltitol solution على ثباتية الفيتامينات. أظهرت النتائج أن استخدام محلول المالتيتول بنسبة 30% أعطى تحسناً ملحوظاً في ثباتية الفيتامينات بالمقارنة مع استخدام محلول من السوربيتول sorbitol solution عند النسبة نفسها، كما أظهرت النتائج أن الباهاء pH أيضاً يمتلك تأثيراً ملحوظاً على ثباتية الفيتامينات؛ فقد أبدت الفيتامينات أفضل ثباتية عند قيمة باهء بين (4-3.5).
الكلمات الدالة: فيتامينات منحلة بالماء، محلول المالتيتول، شروط ثبات مسرّح، محلول السوربيتول.

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