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MARKETED VITAMIN B-COMPLEX INJECTABLES : STABILITY AND MUTUAL INTERACTION

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ABSTRACT

The Vitamin B-complex injectables in the Bangladesh drug market have been studied for the sability and mutual interactions of the active ingredients. It was found that the preparation without nicotinamide in the formulation has more stability than that of the preparation having nicotinamide.The presence of nicotinamide in a formulation containing four B-vitamins causes the degradation of thiamine to a sub-standard level within one year of the 2 year's shelf-life.

INTRODUCTION

There are several pharmaceutical industries, both national and multinational in Bangladesh who formulate and market vitamin B-complex injections. Interestingly, there are two types of formulations available in the drug market, the one containing 4 ingredients included nicotinamide, pyridoxine hydrochloride, riboflavin-5-phosphate sodium and thiamine hydrochloride. The other formilation contains 3 ingredients excluding nicotinamide only. The Drug Administration of Bangladesh, a regulatory authority has given permission to both these formulations.

In the literature[1], the most stable vitamin-B is considered to be nicotinamide and the labile B-vitamins which are likely to present problem of instability in dosage form are folic acid, pantothenic acid, cyanocobalamin and thiamine.

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Taub *et al.* reported[2] that thiamine in parenteral solution in admixture with riboflavin and nicotinamide exhibit maxium stalility with respect to potency and clarity of solution at pH 4 under a nitrogen atmosphere. In admixture with iron compounds, thiamine was more stable in the presence of ferrous gluconate than of iron peptonate or ferric ammonium citrate and again, the optimum pH was 4. In these studies it was found that thiamine mononitrate is somewhat more stable than the hydrochloride.

At the same time, in other reports[3-5], it was reported that the interaction between thiamine and riboflavin is greatly intensified by nicotinamide, however, this has little effect on the stability of nicotinamide inself. The pH can be betwen 4 and 8.

It was thus of interest to investigate the actual role of nicotinamide on the marketed B-complex injectables as well as the preparations involving the authentic model formulation of vitamins.

METERIALS AND METHODS

Materials: The samlpes of marketed vitamin injectables of different pharmaceuticals were bought from drug-shops at maximum retail price. The samples have been properly checked for their physical appearance, batch number and shelf-life. The samples were then coded for analysis. The reference standards of nicotinamide (99%), pyridoxine hydrochloride (99%) thiamine hydrochloride (95%) and riboflavin-5-phosphate sodium (71.5% as riboflavin) were obtained from Gonoshasthaya Pharmaceuticals Ltd.

Analysis of Vitamin B-complex Injectables : A high performance liquid chromatographic (HPLC) procedure for the simultaneous determination of vitamin B_1, B_2, B_6 and nicotinamide in pharmaceutical preparation was developed and evaluated[6]. This HPLC method using either a PIC reagent B-6 or a PIC reagent B-7 from Water Associates was found to be suitable for routine quality control use in few pharmaceutical firms in Bangladesh.

Shelf-life and Accelerated Study of Vitamin B-complex Injectables: To predict the stability of the vitamin B-complex injctables, both the shelf-life and accelerated testing approch are adopted. The marketed vitamin B-complex injections having manufacturing date of two different but adjacent year of the same manufacturer were purchased from the local market. The analysis of these samples were performed in the same day using HPLC.

Besides, two ampoules/vials of each category of the same batch were heated at 60^0c for 21 days and two ampoules/vials of each category of the same batch as that of accelrated one were kept at room temperature. Then every sample was analysed using HPLC and the results of analysis were tabulated. In addition to that, some physical parameters observed prior to analysis were also noted.

Studies on the Mutual Interactions Among the Ingredients of Vitamin B-complex Injection : Several proposed formulations of vitamin B-complex injections were prepared containing individual viamin at similar ratios to that claimed to be present in a marketed formulation but at different combination to investigate interaction among the ingredients used in vitamin B-complex injections. Two types of formulations were made : (i) one in simple distilled water vehicle and the (ii) other in a typical formulated vehicle that included disodium editate and benzyl alcohol. The pH of the solutions were found in the range of 2.8 to 4.These formulated samples were also kept at two different conditions as mentioned above. All these samples were then analysed for their individual content using HPLC.

RESULTS AND DISCUSSION

Shelf-life and Accelerated Stability Studies : The marketed products of vitamin B-complex injectables manufactured in two different but adjacent year of the same brand collected from the market were analysed to determine the loss of each active ingredient of the injectables formulated by the same company. The results of this comparative study are presented in Table 1.

It can be seen from Table 1 that a significant reduction of potency in one year shelf-life (in some cases, more than a year) was observed in case of thiamine where the formulation included nicotinamide. The potency of thiamine has been undergone to sub-standard level. However, there is no loss of thiamine content in the formulations (except one) that excluded nicotinamide even after the expiry date.

Marketed B-vitamin injections were then subjected to accelerated aging tests. It was suggested by Garrett[7] that it may be practical in some cases to predict stability on the basis of one elevated temperature. Accordingly, the coded injectables were kept at one elevated temperature i.e., at 60^oc for 21 days and the results thus obtained were compared with those obtained at room temperature. The analytical results obtained using HPLC in PIC-B6 medium from these experiments are tabulated in Table 2.

TABLE 1 : Results of Marketed B-vitamin Injections Based on Manufacturing Dates (Using PIC- B7)*

Company code	Manufac-turing date	Nicotina-mide mg/2 ml (claim 100 mg)	Pyridoxine mg/2 ml (claim 10 mg)	Thiamine mg/2 ml (claim 50 mg)	Riboflavin mg/2 ml (claim 4 mg)	Loss of Thiamine during shelf-life (%)
IP_1	9/1991	118.4	12.2	44.0	7.6	
	5/1990	110.4	13.2	34.0	5.6	22.7
IP_2	7/1991	110.5	11.0	48.0	5.6	
	12/1990	106.2	11.6	40.4	5.0	16.7
IP_3	8/1991	102.4	11.4	49.4	5.6	
	8/1990	103.1	11.0	44.0	4.5	10.2
IP_4	8/1991	--	131.1**a**	115.3**b**	6.6**c**	
	5/1989	--	133.1	113.2	6.6	1.8
IP_5	5/1991	--	118.7**a**	88.3**b**	11.9**d**	
	5/1990	--	113.2	71.5	11.9	19.0
IP_6	8/1991	--	10.4	52.8	3.5	
	11/1990	--	9.5	51.9	4.2	1.7

* Date of analysis : 02.07.1992 ; **a.** Each 2 ml contains 100 mg pyridoxine ; **b.** Each 2 ml contains 100 mg thiamine ; **c.** Each 2 ml contains 6.4 riboflavin ; **d.** Each 2 ml contains 10 mg riboflavin.

TABLE 2 : Results of Marketed B-vitamin injections Under Normal and Accelerated Condition (60^0C for 21 days)*

Company code	Condition	Nicotinamide mg/2 ml (clain 100 mg)	Pyridoxine mg/2 ml (claim 10 mg)	Thiamine mg/2 ml (claim 50 mg)	Riboflavin mg/2 ml (claim 4 mg)	Manufacturing date	Physical change	
							Appearance	Smell
A.	Normal Temperature	109.8	9.6	39.2	3.4	12/1990	Slightly changed	Slight bad Smell
	Accelerated	120.0	9.0	22.6	2.0		Changed	Bad smell (Obnoxious)
B.	Normal Temperature	108.5	10.1	48.5	3.8	10/1990	Changed	Slight bad Smell
	Accelerated	111.3	9.7	43.6	3.3		Changed	Bad smell (Obnoxious)
C.	Normal Temperature	103.0	7.0	48.6	4.8	11/1990	Slightly changed	Slight bad Smell
	Accelerated	120.0	9.0	22.6	2.0		Changed	Bad smell (Obnoxious)
D.	Normal Temperature	103.0	9.3	47.4	3.8	9/1990	Slightly changed	Slight bad Smell
	Accelerated	117.4	8.5	32.6	2.0		Changed	Bad smell (Obnoxious)
E.	Normal Temperature	Not given	99.0[a]	94.4[b]	6.2[c]	1/1991	As such	No bad smell
	Accelerated	;;	98.0	93.9	6.2		No change	No bad smell
F.	Normal Temperature	Not given	9.5	51.9	4.2	11/1990	Normal colour	No bad smell
	Accelerated	;;	9.0	47.0	3.9		No change	No bad smell

* Date of analysis : 26.07.1992 **a**. Each 2 ml contains 100 mg pyridoxine
b. Each 2 ml contains 100 mg thiamine **c**. Each 2 ml contains 6.4 riboflavin.

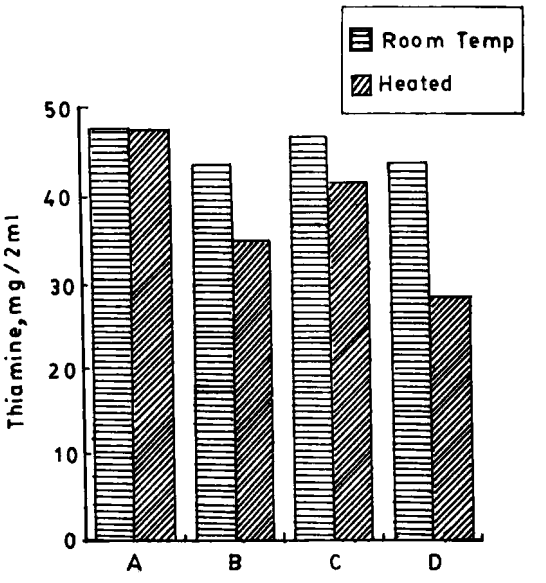

FIGURE 1

Loss of Potency of Thiamine due to Mutual Interaction in Distilled Water

Key : **A** = Thiamine, **B**= Thiamine + Nicotinamide, **C**=Thiamine+Riboflavin, **D**=Thiamine+Riboflavin + Nicotinamide

It appears from Table 2 that thiamine in the formulation having 4 ingredients undergoes drastic degradation, whereas remains almost stable in the formulation having 3 ingredients (excluding nicotinamide).

Mutual Interaction in Water : To find out the mutual interaction, several simple combinations of authentic vitamins in duplicate were made in distilled water and kept separately at room temperature and at 60^0c for 15 days. The initial concentration of the active vitamin has been kept in accordance with the marketed injectables. The samples were then analysed for the determination of the content of the active ingredients. The analytical results obtained from these experiments regarding the fate of thiamine are presented in Figure 1.

It is quite clear from Figure 1 that the stability of thiamine is very much affected when it is used in combination with only nicotinamide or in combination with nicotinamide and riboflavin. The loss of thiamine occurs in both normal temperature and heated condition. Thiamine also looses its poency when it is used with riboflavin but this loss is not so pronounced. As expected, there is more loss

of thiamine in each case when heated at 60^0c for 15 days. However, no loss of the potency of thiamine was observed in normal and heated condition in the case of single thiamine formulation.

Similar loss of potency of thiamine was also found to occur in the preparations using the typical formulated vehicles.

CONCLUSION

As because the presence of nicotinamide in B-complex injectables causes thiamine more unstable, therefore, the manufacturers should prepare vitamin B-complex injectable by omitting nicotinamide from the formulations. However, there should be alternative arrangements to accomodate nicotinamide in the formulation. In that case, the manufacturers can think of any of the two options. The first option is to formulate two formulations : one is for single nicotinamide and another can be made containing 3 other ingredients such as B_1, B_2, and B_6, then prior to inject these two formulations can be mixed. The second option is to use of the compartmentalised of the two chamber ampoules.

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