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Comparison of the stability of different tablet formulations containing folid acid, vitamin B6 and B12

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One possible consequence of moderately elevated levels of plasma homocysteine is an increased risk of premature vascular disease [1]. Several studies encourage the view that intake of folate, vitamin B6 and B12 above the current recommended dietary allowance may be important in the primary prevention of coronary heart disease [2–6]. The stability of a formulation depends, amongst other factors, on the compatibility of the active components with the excipients. The detection of solid-solid interactions in drug dosage form development programs is of great importance [7]. Previous studies were undertaken to establish the compatibility of folic acid, vitamin B6 and B12 with a number of commonly used direct tableting excipients by comparing the DSC curves of folic acid, vitamin B6 and B12 each of the investigated excipients with curves for 1 : 1 mixtures of the vitamins and excipients [8]. The main objective of the present study was to examine the stability of different vitamin B formulations containing various direct tableting excipients in physical powder mixtures. Another aim was to compare the stability of uncoated and coated vitamin B tablets containing the most compatible excipients. Table 1 summarizes the $t_{1/2}$ values of folic acid and vitamin B6 in the presence of various direct tableting excipients containing lactose in different proportion. The results are in good accordance with the results of the DSC study and demonstrate that the presence of lactose in the physical mixture significantly decreased the stability of Vitamin B6. Table 2 compares the expiration time and activation energy values of vitamins in uncoated and coated tablets. The results indicate that the coating polymer has a protective function against moisture. With increasing coating level the expiration time values increased, thus indicating the improved stability of tablets.

Table 1: Half life values of active ingredient's decomposition (days ± STD, $T_1 = 40\,^\circ C$, $T_2 = 60\,^\circ C$) in physical mixtures containing lactose excipients

	Active ingredients	
Direct tableting excipients	Folic acid	Vitamin B6
Without excipients	1630.95 ± 22.3	3046.41 ± 45.4
Cellactose	1324.05 ± 46.3	937.18 ± 31.7
Ludipress	1241.99 ± 49.6	700.92 ± 28.2
Tablettose	1010.21 ± 25.2	666.75 ± 18.7

Table 2: Expiration times and activation energy values calculated at 22 °C ($T_1 = 40\,^\circ C$, $T_2 = 60\,^\circ C$) for different tablets (RSD 5%)

	Expiration times (t_{exp}, days):			Activation energy (KJ/mol)		
	Folic acid	Vitamin B6	Vitamin B12	Folic acid	Vitamin B6	Vitamin B12
Uncoated	245.59	260.28	478.09	36.09	23.36	108.45
Coated 1	504.16	571.15	932.20	51.55	56.86	120.44
Coated 2	1351.32	861.61	1004.16	69.75	60.08	123.58

3. Experimental

3.1. Materials

Folic acid (Fluka), vitamin B6 hydrochloride (Fluka), cyanocobalamin (vitamin B12, Fluka), maltodextrin-coated vitamin B12 (vitamin B12 1% SD, BASF), Avicel PH101 (FMC Europe NV, Belgium), Cellactose (Meggle GmbH, Germany), Ludipress (BASF, Germany), magnesium stearate (Ph.Hg.VII.), Tablettose, (Meggle GmbH, Germany), Povidone (Kollidon 12, 25, 30, BASF), Pharmacoat 606 (Shin-Etsu Chemical Co Ltd, Japan).

3.2. Preparation of tablets

Wet granulation of the selected direct tableting excipients was carried out in a Stephan UMC 5 electronic apparatus (Stephan Maschinen GmbH, Wien) equipped with a chopper to obtain granules of compositions different from the direct tabletting excipients available. In the course of the granulation process, the revolution number was kept constant at 900 1/min and 40%w/w of distilled water was atomized under vacuum. The granulated mass was dried in a hot air drier (Labor-Innova, Hungary) at 40 °C for 24 h. Before tableting, granules were sieved through a sieve of 0.8 mm diameter. The obtained granules were homogenized with the active ingredients and the lubricant. The compression of tablets was carried out with Wick single punch tableting machine using biconvex punches of 8 mm diameter. The composition of the uncoated tablets was as follows: Avicel PH101: 67%w/w, Kollidon 25: 4%w/w, Kollidon CL: 4%w/w, magnesium stearate: 0.25%w/w, folic acid: 1.25%w/w, vitamin B12: 0.1%w/w, maltodextrin: 9.9%w/w, vitamin B6: 12.5%w/w.

3.3. Fluidized-bed coating of tablets

The tablets were coated in Aeromatic STREA-1 (Switzerland) fluidized bed coating equipment. The process parameters were the following:
Quantity of tablets: 200 g, coating material: 10% w/w Pharmacoat 606 dispersion, atomising method: bottom-spray coating, atomising pressure: 1.5 bar, feeding rate of the coating dispersion: 8.3 ml/min. Coating temperature: 35 °C. Drying time: 90 s each atomising periods. The polymer weight of tablets: Coated 1: 5.8 mg, Coated 2: 11.8 mg.

3.4. High performance liquid chromatography

The active ingredient content of the prepared tablets was determined using an HPLC method indicative of stability. Pump: Shimadzu LC-9 (Shimadzu Corporation, Instruments, Japan). UV Detector: Shimadzu SPD-6AV. Control and regulation unit: Shimadzu C-R4 AX.

3.5. Storage of tablets and calculation of decomposition rate constants

The uncoated and coated tablets were transferred into each of the 3 desiccators (at 22 °C, 40 °C, 60 °C and 80 °C) and stored at 75% R.H. for a 6 month storage period. Physical mixtures of drugs (folic acid, vitamin B6, vitamin B12) and excipients were kept under the same storage conditions. The logarithms of undecomposed active substance concentrations, determined by HPLC, were plotted versus time, and from these graphs the respective decomposition rate constants (k) and expiry dates (t_{exp}) were determined using following equations:

$$C_t = C_0 e^{-kt} \text{ (Eq. 1) and } t_{exp} = 1/k \ln 1.1111$$

$$\text{Arrhenius equation : } \ln(k_2/k_1) = (E/R)[(T_2 - T_1)/T_2T_1],$$

where E is the activation energy (J/mol), and k_1 and k_2 are the decomposition rate constants at different T_1 (K) and T_2 (K) temperatures.

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