Stability Studies on the Conventional and Multi-unit Dose Tablets of Theophylline: Temperature Effects

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Abstract:
The study was carried out to evaluate thermal effects on the physical and chemical stability of the conventional and multi-unit (MU) dose tablets of theophylline. The latter (MU) consists of a prompt release and sustained release components in a unit dose of the tablets. Conventional (A) and matrix (B) granules were formed by wet and melt (wax) granulation technique respectively. To form the MU dose tablets, granules of A and B were mixed together in the ratio 1:1 (A: B) and compressed to tablets of weight 308 ± 5.8mg, diameter 12.5mm and thickness 3.34 ± 0.2mm. Conventional tablets consisting of (A) only were also formed. The conventional and MU tablets were stored under different temperatures 40°C to 70°C for 10 days. At selected time intervals after the thermal exposure, the tablets were allowed to cool and evaluated for drug content, tensile strength, disintegration times and dissolution profiles. Also, the thermal degradation rates of the tablets at the various temperatures were determined. The degradation generally followed first order rate kinetics (R2=0.95). By applying the Arrhenius plot; the degradation rate constant at ambient temperature, 30°C was obtained and used to estimate the shelf life (i.e. the time taken for the drug content to decrease to 90% of the original value). It was observed that with the MU tablets only, there was a slight increase in tablet hardness and disintegration times after their exposure to high temperatures (greater than or equal to 50°C), attributable to partial melting of the wax in the MU formulation and subsequent formation of welded bonds upon cooling. The shelf life for the MU and the conventional tablets were about 5.6 years and 5.2 years respectively. Thus, the new MU formulation increased the shelf life slightly. Also the tablets becomes slightly harder upon thermal exposure but without serious effect on the dissolution profiles of the tablets.

Keywords: Theophylline, multi-unit dose tablets, thermal effects, Arrhenius plot, shelf life.

Introduction

A previous study[1] showed that the crushing strength of tablets decreased when exposed to heat for a long time. Such thermal effect on the mechanical strength of the tablets may in turn affect the disintegration and possibly the dissolution profiles of the tablets. The decrease in mechanical strength can be attributed to irreversible weakening of the interparticulate bonding due to thermal expansion of the tablets. The difference between the previous and the present study is that the tablets used in the previous study had no low melting substance (wax) in their formulation whereas in the present study the multiunit (MU) dose tablets have in their formulation a wax needed to produce the matrix granules (the sustained release fraction of the MU tablets). It is expected that during thermal exposure, the wax content may melt and upon cooling form welded bonds to increase tablet hardness similar to the phenomenon of asperity melting[2]. Hence, the first objective of the present study is to investigate the effect of thermal exposure on the mechanical strength and the implication for the disintegration and dissolution profiles of the tablets.

A second objective is to investigate the role of the more hydrophobic environment provided by the presence of wax in the MU formulation on the thermal degradation rate of the active content (theophylline) and hence, its effect on the shelf life of the new product. The role of the wax in these aspects will be determined by comparing the thermal effects in the MU tablets which has wax in their formulation with tablets made from granules of theophylline obtained by the conventional granulation with starch mucilage[3]. The latter tablets are referred to here as conventional tablets and do not contain wax in their formulation.

Materials and methods

Materials: Carnuba wax (Halewood Chemicals Ltd, England) is a fine waxy solid with melting point of 82-88°C, yellowish in colour and was used as the granulating agent and as the matrix former in preparing the matrix granules. Maize starch (BDH, Chemical, Poole, UK) was used as binder in the form of mucilage (20%w/v) to produce the conventional granules. Dried maize starch B.P (5%w/w) was also used as disintegrant, while magnesium stearate (Sakai Chem Co, Japan) was used as lubricant at a concentration of 0.5%w/w in the tablet formulations. The test drug was theophylline (Sigma Chemical Company, St Louis, MO) and was ▶

received as gift from Vitaboitics Nigeria Ltd.

Methods

Granulation and tableting

Details of these procedures have been described previously in part 1 of the study[4]. The conventional (A) and the matrix (B) granules of the drug were made by wet and melt granulation technique respectively. Conventional tablets were made by compressing A only, whereas the MU tablets were formed by mixing the granules A and B in a ratio 1:1, followed by compression. Resulting tablets were of weight 308 ± 5.8mg, diameter 12.5mm and thickness 3.34 ± 0.2mm. The tablets were stored in airtight containers in a dessicator at least 24h before their evaluation.

Thermal exposure of the tablets:

Samples of the tablets (conventional and multiunit) were stored at room temperature 28-30°C and at elevated temperatures 40, 50, 60, 70°C for a maximum of 10 days. Samples were removed at daily intervals and evaluated for drug content and hardness. Disintegration times and dissolution tests were also carried out on the fresh and stored samples. Details of these procedures have been presented in part 1 of this study.[4]

Determination of shelf life

The method of accelerated stability testing of pharmaceutical products based on the principles of chemical kinetics has been demonstrated by Jones and Grimshaw[5]. According to this technique, the degradation rate constants (k values) for the decomposition of a drug in solution at various elevated temperatures are obtained by plotting some function of concentration against time. The logarithms of the specific rates of decomposition (i.e. log-k) are then plotted against the reciprocals of the absolute temperatures and the resulting line is extrapolated to room temperature (in our situation, 30°C) to obtain the degradation rate at room temperature. Such graphs are referred to as Arrhenius plots, which are based on equation 1 below. The k_{30}°C is used to obtain a measure of the stability of the drug under ordinary shelf conditions. Thus,

$$\log k = \log A - E_a/2.303RT \quad (1)$$

where k is the specific reaction rate, A is a constant known as the Arrhenius factor or the frequency factor, E is the energy of activation, R is the gas constant, 1.987calories/deg mole and T is the absolute temperature in degree kelvin. A number of factors other than temperature may affect the reaction velocity. Among these are humidity, solvents, catalysts and light[6].

In the determination, the tablets were assayed for drug content following the method of Jones and Grimshaw[5] at daily intervals following thermal exposure. The plot of log of residual amount versus time was linear (R^2 0.95), indicating a first order rate degradation kinetic. The first order equation is thus:

$$\log m_t = \log m_o - kt/2.303 \quad (2)$$

where mo is the initial amount and mt is the residual amount in time, t. The Arrhenius plot of log k_1 versus reciprocals of the absolute temperatures (in the range 313 to 343k) was constructed to obtain linearity (correlation coefficient = 0.96) which upon extrapolation to the y - axis gave the values of k_1 at room temp (30°C) to be 5.52×10^{-5} day^{-1} (conventional tablets) and 5.15×10^{-5} day^{-1} (MU tablets).

Now, it is assumed that a product has expired when the active content falls to 90% of the initial drug content[7,8]. By substituting the values of m_t = 90%, mo =100% and the k_1 values as above in equ 2, the shelf life (t) for the two products were obtained. The test was carried out on three batches of the tablets and the mean values of k_1 were used to calculate the shelf life. An example of the calculation of shelf life is shown thus:

Making t (shelf life) in equation 2, the subject of the formula, gives:

$t = 2.303/k \log m_o/m_t$ where m_o =100% and m_t = 90%

$t = 2.303/ 5.15 \times 10^{-5}$ day^{-1} log 100/log 90

Thus the shelf life (t) for MU tablets = 2044 days (about 5.6years).

For the conventional tablets, the substitution gave

$t = 2.303/ 5.52 \times 10^{-5}$ day^{-1} log 100/log 90

where t = 1907 days (about 5.2years).

RESULTS AND DISCUSSION

Thermal effects on the physical stability of the tablets.

Tensile strength and disintegration times: The results of the effect of different temperatures on the tablet tensile strength (T) are presented in Fig 1. With the MU tablets there was a slight increase in tablet hardness after exposure of the tablet to higher temperatures (50°C) for more than 7 days. This increase in T values was associated with a corresponding increase in the disintegration time of the tablets (Fig 2). It is well known that harder tablets disintegrate less readily. The increase in hardness of the MU tablets could be as a result of melting of the wax in the MU tablets during thermal exposure, which upon cooling led to formation of welded bonds in the tablets. Compression at high temperatures has been found to lead to the formation of such welded bonds due to heat generated during compression[9,10]. With the conventional tablets there was no noticeable increase in T values, attributable to their formulation. There was however a two fold increase in their disintegration times after 5 days of thermal exposure (Fig 2), perhaps due to drying of the tablets. Drying will delay capillary sorption of water into the tablets, and hence a delay in disintegration times.

Dissolution profiles of the tablets:

The effect of thermal exposure on the dissolution profiles of the tablets is shown in Fig 3. From the result, there was a gradual reduction in dissolution rates with increase in temperature for both the conventional and the MU tablets but the effect was not severe. For instance, for the MU tablets stored at room temp, 30°C, the dissolution rate was 52.7mgh^{-1}, which fell to 47.8mgh^{-1} after thermal exposure (70°C, 10 days). This decrease in dissolution rate was also observed for the conventional tablets, which dropped from 193.3mgh^{-1} at 30°C to 148.3mgh^{-1} after thermal exposure at 70°C for 10 days. Most probably the exposure of the tablets to the high temperature may have caused further drying of the tablets; hence a delay in their wettability during the dissolution tests.

Shelf life: The importance of this aspect of the study is to enable us predict the shelf life of the formulation when stored at room temperature. It ▶

was first established that the kinetics of degradation followed a first order rate (R2=0.95). Previous workers[8] also established a similar kinetics for the thermal degradation of Rauwolfia vomitoria tablets. The first order rate plots for the MU and conventional tablets are shown in Fig 4. The values of the first order degradation rate constants (k_1) are presented in table 1. The Arrhenius plots (log k_1 versus 1/T), where T is the absolute temperature (^{0}k) are presented in Fig 5. From the y intercept, it was estimated that the values of degradation rate constants at room temperature were 5.15×10^{-5} day^{-1} (MU tablets) and 5.52×10^{-5} day^{-1} (conventional tablets). The shelf lifes were 5.2years (conventional tablet) and 5.6years (MU tablet).

The data agreed with the published shelf life of conventional theophylline tablets (Asmanol F, Vitabiotics Nigeria Limited). The results also showed that the formulation of theophylline in the MU tablets did not in any way reduce the shelf life of the product rather it increased it slightly.

Conclusion: The study has shown that high temperatures as often encountered in the tropics can alter the hardness, disintegration and dissolution profiles of the MU tablet and to a less extent in the conventional tablets. Furthermore, the new (MU) formulation of the drug did not alter the shelf life of the product significantly.

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Table 1: Estimated k_1 and log k_1 values at different absolute temperatures.

Absolute temperature (0k) x 10-3	K_1 x 10-3	Log k_1
MU tablets		
3.30	0.0515±0.0002	- 4.29
3.19	0.092±0.0004	- 4.03
3.09	2.303±0.03	- 2.64
3.00	3.455±0.02	- 2.46
2.92	4.376±0.05	- 2.36
Conventional tablets		
3.30	0.0552±0.0004	- 4.25
3.19	0.092±0.0005	- 4.03
3.09	2.53±0.02	- 2.60
3.00	3.69±0.04	- 2.43
2.92	4.15±0.03	-2.38

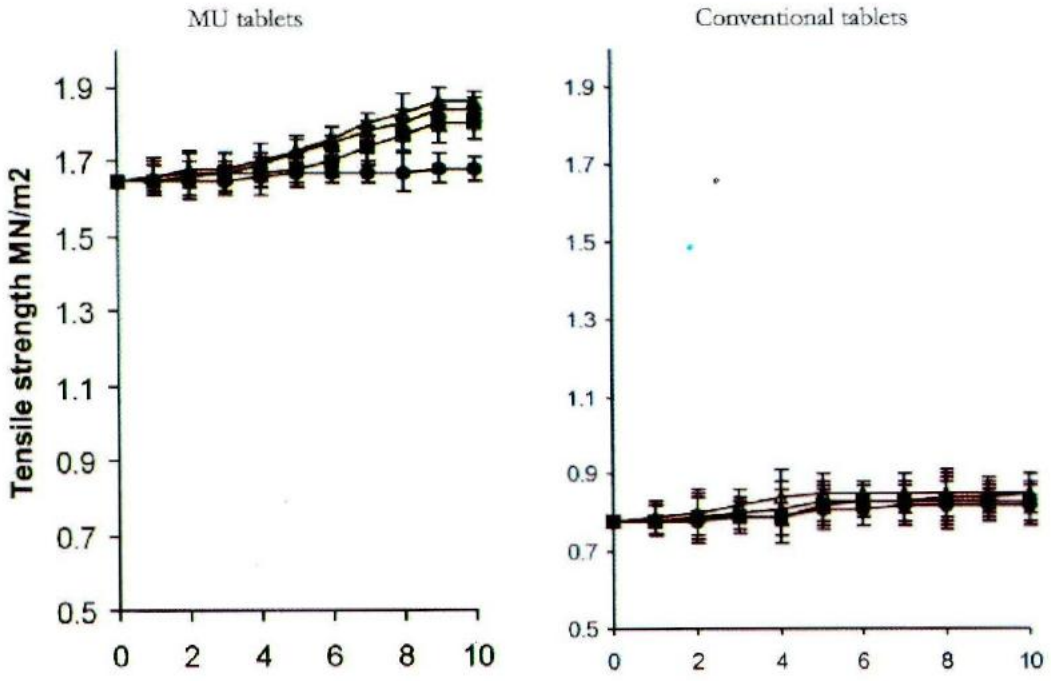

Fig 1: Effect of temperature on the tensile strength of MU and conventional tablets; storage temperature 40°C (●), 50°C (■), 60°C (▲) and 70°C (△).

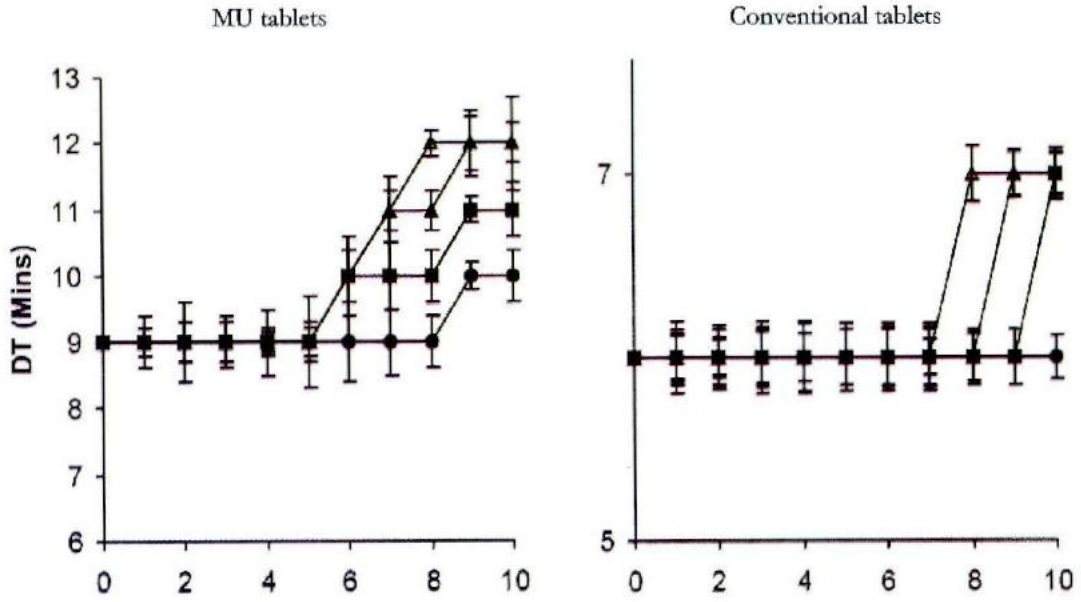

Fig 2: Effect of temperature on the disintegration times of MU and conventional tablets; storage temperatures: 40°C (●), 50°C (■), 60°C (▲) and 70°C (△).

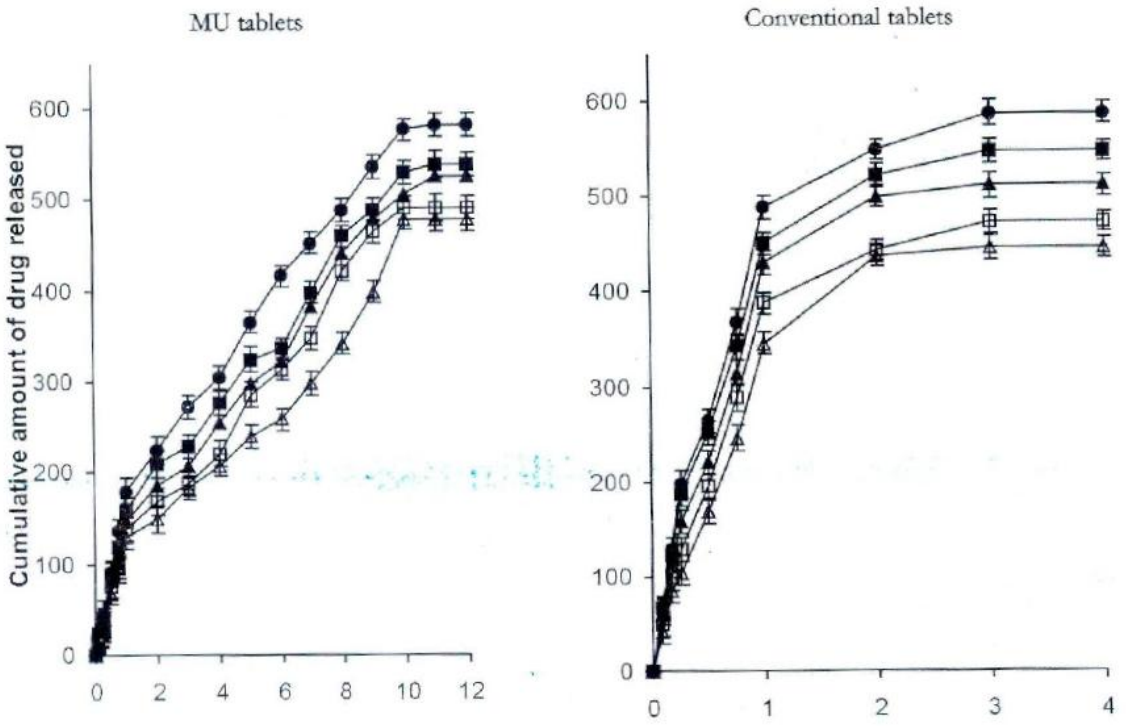

Fig 3: Effect of temperature on the drug dissolution profiles of the MU and conventional tablets; storage temperatures 30°C (●), 40°C (■), 50°C (▲) 60°C (□) and 70°C (△), duration of storage of the samples, 7days.

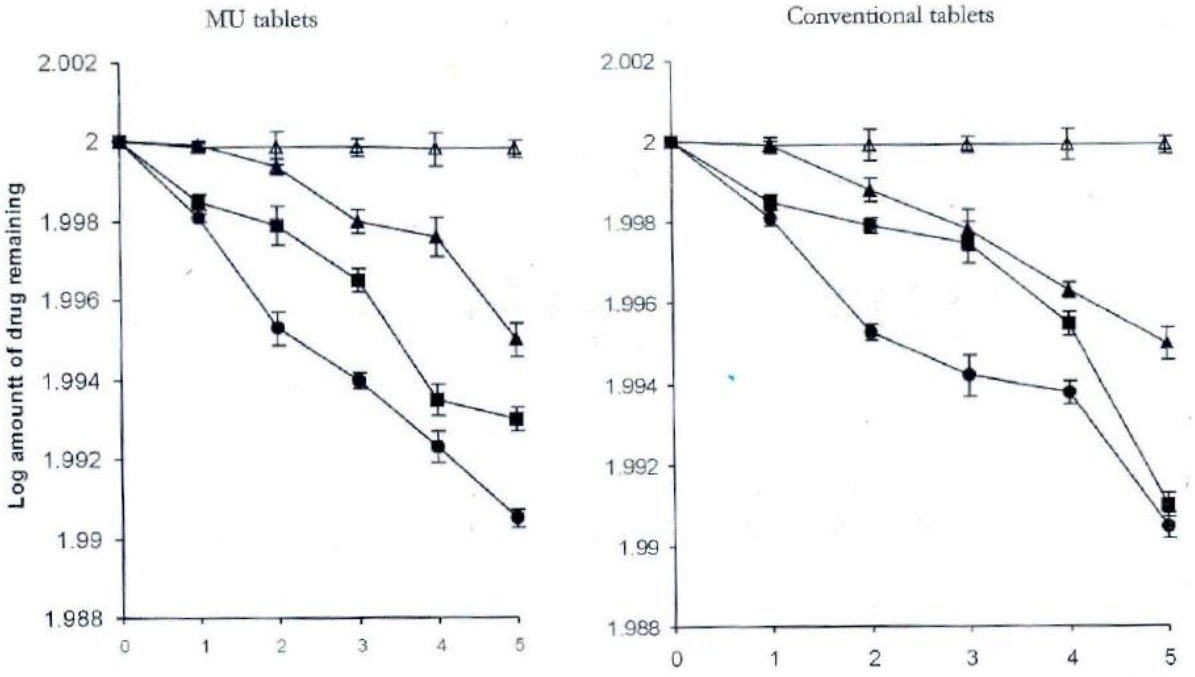

Fig 4: Plots of first order rate for the degradation of theophylline in the MU and conventional tablets; storage temperatures 40°C (△), 50°C (▲) 60°C (■) and 70°C (●).

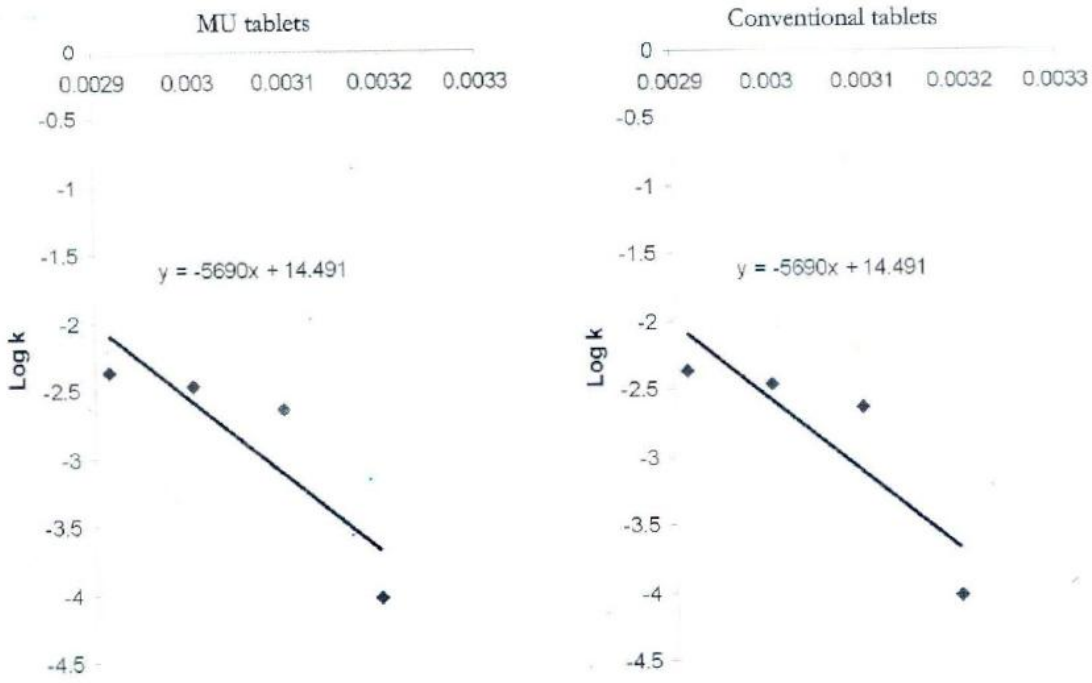

Fig 5: Arrhenius plot for predicting shelf life of the conventional and MU tablets of theophylline at room temperature