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

Uhumwangho, M.U and Okor, R.S
Department of Pharmaceutics and Pharmaceutical Technology,
University of Benin, Benin City, Nigeria

Abstract:
The study was carried out to compare the moisture effects on the drug content, mechanical strength, disintegration times and dissolution rates of conventional and multi-unit (MU) dose tablets of theophylline. Conventional (A) and matrix (B) granules of the drug were formed by wet and melt (wax) granulation techniques respectively. To form the MU 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. The tablets were stored under different relative humidities (i.e. 1%, 78% and 100%) for 7 days (time for maximal moisture sorption). At daily intervals after the exposure, the tablets were evaluated for drug content, tensile strength, disintegration times and dissolution rates. Drug content and dissolution rates were hardly affected by exposure to moisture even at the high humidity (RH 100%). However, the tablets became progressively softer (as reflected by the decrease in tensile strength values) and disintegrated more rapidly, particularly after exposure to the high humidity, (RH 100%). These effects were more marked in the conventional tablets which also showed the higher capacity for moisture uptake. The difference relates to the presence of the hydrophobic wax in the MU tablets but which was absent in the conventional tablets.

Keywords: Theophylline, multi-unit dose tablets, moisture effects, tensile strength, dissolution rates.

Introduction:

Theopylline is a methylxanthine derivative (Fig 1), which is often indicated for the treatment of asthma[1]. The term conventional tablets is used here to refer to tablets made from granules prepared by the conventional wet granulation method (i.e. wet massing the drug powder with starch mucilage)[2]. On the other hand, the term multiunit dose tablets is so called because the tablets consist of two or more components with different release profiles (e.g. an initial fast release followed by a sustained release) in a unit dose. A recent study[2] has shown that multi-unit dose tablets of theophylline can be designed to provide therapeutic blood levels for 12h after an initial prompt release. The two component formulation consisted of the conventional and matrix granules of theophylline in the ratio 1:1, which were compressed to tablets. The conventional granules were obtained by wet granulation and the matrix granules by melt (wax) granulation[3].

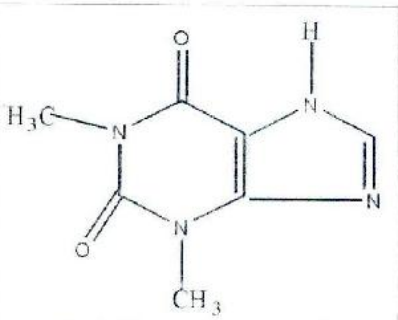


Fig 1: Chemical structure of theophylline anhydrous

Previous studies[4,5] have shown that moisture sorption can weaken the interparticulate bonding in tablets resulting in the formation of soft tablets and hence faster disintegration rates. Moisture sorption may also promote hydrolytic degradation of the active content. Hence, it was necessary to investigate the physico-chemical stability of this modified new dosage form of theophyline to the high humidity as encountered in the tropics. In the first part of the study, we compared the moisture effects on the active content, mechanical strength, disintegration times and dissolution profiles of the conventional and the MU tablets, to see whether the inclusion of the hydrophobic wax in the MU formulation would ameliorate the moisture effects without impairing the release profile designed for the MU tablets.

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

Wet granulation to form the conventional granules: A sample of the theophylline powder (100g) was wet-massed with 35ml of starch mucilage (20%w/v) to reach the granulation point. Hence, the content of starch binder in the resulting granules was 16.7%w/w. The wet mass was pressed through a sieve of aperture size 1.7mm, spread thinly on trays and then dried at 50°C for 1h in a hot air ▶

oven (Kottermann, Germany). The half dried mass was pressed through a sieve of aperture size 710µm and dried finally at 50°C for 2h to moisture content of 2.1 ± 0.3%w/w. These granules are designated here as A.

Melt granulation to form the matrix granules: The wax material (20g) was melted in a stainless steel container in a water bath at a temperature higher than the melting point of the wax (i.e. 90°C). A sample of the theophylline powder (100g) was then added to the melted wax and mixed well with a glass rod, then allowed to cool to room temperature (30°C). The mass was pressed through a sieve of mesh 10 (aperture size; 710µm) to produce matrix granules that will not disintegrate in aqueous fluids to their primary (powder) particles. These granules are designated here as B.

Preparation of the multi-unit dose tablets: The conventional (A) as well as the matrix granules (B) were mixed together in the ratio 1:1 (A: B). In the mixture, the total drug content in a tablet was 300mg; representing the contribution from A and B granules. This was the proportion of A to B, which gave the desired release profile modeled to release a prompt dose (200mg) in the first 1h followed by a sustained release at an average rate of 36mgh:[1] over the next 11h, when two tablets were used in the dissolution test.

To form the tablets, the conventional granules, (A) and its admixtures with B in the ratio 1:1 (A: B) were compressed using a single punch tableting machine (Manesty Type F3, Poole, England) at a constant load (30 arbitrary units on the load scale) to form flat faced tablets of diameter 12.5mm, thickness 3.34mm and mean weight 308±5.8mg. The drug content in each tablet was 300mg. Magnesium stearate (0.5%w/w) and dried maize starch powders (5%w/w) were added to the granules prior to compression. The tablets were allowed to equilibrate in a dessicator, 24h before their evaluation.

Preparation of storage conditions for the tablets: Glass chambers of different relative humidities (RH) 1%, 78% and 100% were made. To obtain RH 1%, a dessicator was charged with dried silica gel. To obtain RH 78%, a beaker containing a supersaturated solution of sodium chloride (500ml) was placed in a glass chamber while to obtain RH 100%, a beaker of distilled water (500ml) was placed in the glass chamber. Samples of the tablets (20 each) were placed in each of these chambers for a period of 7 days. It was considered that longer exposure times might lead to microbial degradation of the tablets. The experiment was conducted at ambient temperature (28 - 30°C). At different time intervals, the tablets were evaluated for drug content, tensile strength, disintegration times and dissolution rates. The tests were carried out in triplicate. The RH 1% served as control (moisture free-environment) while RH 78 % lies within the range of relative humidities often encountered in the tropics[6]. The RH 100% represents an exaggerated relative humidity for accelerated stability testing.

Determination of moisture uptake: The weights of ten (10) tablets were individually determined and the mean weight (Mo) obtained. The tablets (10) each was stored under different relative humidities, RH 1%, 78% and 100% at room temperature for 7 days. At selected time intervals the samples were removed from the chambers to determine their mean weight, Mt. The percentage (%) moisture uptake (degree of hydration of the tablet) was calculated from the expression:

$$\frac{Mt - Mo}{Mo} \times 100\% \qquad (1)$$

This experiment was carried out in triplicate by using different batches of the tablets.

Determination of drug content in the tablets: Twenty (20) tablets were ground to a fine powder. An aliquot of the powder equivalent to 300mg of the drug was weighed and transferred to a 100ml conical flask containing 50ml of 0.1NHCl and mixed to dissolve the drug. The mixture was filtered into a volumetric flask and the filtrate made up to 100ml with 0.1NHCl. A 5ml aliquot was withdrawn, appropriately diluted and its absorbance read at 272nm in a UV/VIS Spectrometer (Model Spectronic 21D, Bausch and Lomb, USA). The average absorbance of triplicate determinations was recorded. The theophylline content was calculated from a standard calibration curve. Tablets which had been exposed to different RH for various time intervals were used in the test.

Determination of tablet tensile strength (T) and disintegration times (DT): T, is the stress needed to fracture a tablet by diametral compression. It is given by the expression[7]:

$$T = 2P/Dt \qquad (2)$$

where P is the fracture load that causes tensile failure of a tablet of diameter, D and thickness, t. The fracture loads (Kg) of ten tablets were determined individually with the Monsanto hardness tester, following Brook and Marshal[8]. The mean values of the fracture loads were used to calculate the T values for the various tablets. To measure DT values, the method described in the British Pharmacopoeia[9] was followed using water maintained at 37±20C as the disintegration fluid. Six tablets were used in each determination, which was carried out in triplicate and the mean results reported.

Dissolution test: The method of Okor et al[10] was followed. Two tablets were placed in a cylindrical basket (aperture size 425µm, diameter 20mm; height 30mm), which was immersed in 800ml of leaching fluid (0.1N hydrochloric acid maintained at 37± 2°C). The fluid was stirred at 100rpm with a single blade GallenKamp stirrer (Model APP No 4B 5784A). Samples of the leaching fluid (5ml) were withdrawn at selected time intervals with a pipette fitted with a cotton wool plug and replaced with an equal volume of drug-free dissolution fluid. The samples were suitably diluted with blank dissolution fluid and were analysed for content of theophylline spectrophotometrically at max, 272nm (Model Spectronic 21D, Bausch and Lomb, USA). The samples were filtered before assay. The dissolution test was carried out in quadruplicate and the mean results reported. Individual results were reproducible to ± 10% of the mean. Generally, tablets that had been subjected to different storage conditions of relative humidity were used in the disintegration, dissolution and hardness tests, in order to measure the moisture effects on the physical stability of the tablets.

RESULTS AND DISCUSSION

Moisture uptake potential of the tablet: The results of moisture potential of the tablets are shown in Fig 2. It was observed that the moisture uptake of the conventional ►

tablets were generally (about 300%) higher than that of the MU tablets. This observation could be as a result of the presence of the hydrophobic carnuba wax in the formulation of the MU tablets.

Effect of relative humidity on the physical stability of the tablets.
Tensile strength (T): The MU tablets were harder than the conventional tablets even before their exposure to the various humidity conditions, attributable to the plastic nature of carnuba wax which was present in the MU but absent in the conventional tablets. As can be seen in Fig 3 the tablets generally became softer upon exposure to the high humidities (RH 78% and 100%) while there was no obvious change in the T values of tablets exposed to RH 1% (control). For instance, with the MU tablets T values dropped from 1.65MNm^{-2} (control) to 0.94 MNm^{-2} after exposure (7 days) to the high humidity, RH 100% (i.e. a 76% decrease in T value). In the case of the conventional tablets, T values decreased from 0.78 MNm^{-2} (control) to 0.32 MNm^{-2} (i.e. a 144% decrease in T). The conventional tablets were therefore more affected. The decrease in T is attributable to the tablets absorbing moisture at the high humidity, which weakened the interparticulate bonding in the tablets resulting in the formation of soft tablets as previously reported[4,5,11]. The conventional tablet which showed the higher capacity for moisture uptake (Fig 2), were consequently more affected.

Disintegration times (DT): The results of the effect of relative humidity on DT values of the tablets are presented in Fig 4. Tablets stored under RH100% for 7 days disintegrated faster compared with those stored under RH 1% or 78% for the same period. For instance, at RH 100% DT dropped from 9mins to 4mins (MU tablets) and from 6mins to 2mins (conventional tablets). The drop in DT was 67% in the conventional tablets but only 55% in the MU tablets. The decrease in DT was therefore more marked in the conventional tablets. By contrast tablets exposed to RH1% hardly displayed any change in DT which shows that the decrease in DT of the tablets after their exposure to the high humidity is again attributable to moisture sorption. The conventional tablets were again more affected because of their higher capacity for moisture uptake.

Moisture effect on drug content: As can be seen in table 1 there was no obvious change in the drug content of the tablets after their storage for 7days even at the high humidity, (RH, 100%), indicating that the drug was not susceptible to hydrolytic degradation. This is because the amide and ester linkages usually susceptible to hydrolysis are not in the chemical structure of theophylline (Fig 1).

Dissolution profiles of the tablets: The dissolution profiles of the tablets are shown in Fig 5 and the dissolution parameters obtained from these curves are presented in table 2. The only noticeable change due to moisture exposure was in the prompt release of the drug, mp (i.e. the release in the first 1h). For the MU tablets, the mp value increased from 180mg (control, samples stored under RH 1%) to 238mg (samples stored under high humidity, RH 100%). In the case of the conventional tablets, mp increased from 488mg to 516mg correspondingly. This slight increase in the prompt release can be attributed to swelling of the tablets due to moisture sorption which in turn increased tablet porosity for a more rapid aqueous leaching of the drug during the dissolution test. The rapid disintegration of the tablets following moisture sorption may have also contributed to the increase in the prompt release. Now, the measuring parameters modeled for the dissolution profile of the MU tablets were mp = 200mg m8 = 600mg, t8 = 12h, and k1= 0.24h-1 (first order dissolution rate constant)[2] where m8 is the maximum release in time t8. From the data in table 2 and Fig 5, exposure of the MU tablets to a high humidity did not appreciably alter the desired dissolution profile for the MU tablets. In fact, the slight increase in the prompt release is an advantage as it means that therapeutic levels of the drug can be achieved rapidly.

Conclusion: The study has shown that high humidity as encountered in the tropics can alter the hardness, disintegration and to a less extent the dissolution profiles of the MU and conventional tablets to different degrees. The conventional tablets were more sensitive to these moisture effects meaning that the MU formulation ameliorated the moisture effects but without serious alteration of the designed release profile. Nevertheless, both tablets should be protected from moisture as much as possible.

References

1. Ukena D, Harnest U, Sakalauskas R, Magyar P, Vetter N, Steffen H, Leichtl S, Rathgeb F, Keller A, Steinijans VW. Comparison of addition of theophylline to inhaled steroid with doubling of the dose of inhaled steroid in asthma. Eur. Respir. J. 1997;10: 2754 - 2760.
2. Uhumwangho MU, Okor RS. Modeling of drug release from multi-unit dosage tablets of theophylline. Afr J Bio Tech. 2007; 6: 2519 2525.
3. Uhumwangho MU, Okor RS. Modification of drug release from acetaminophen granules by melt granulation technique-consideration of release kinetics. Pak. J. Pharm. Sci. 2006;19 (1) 22-27.
4. Uhumwangho MU, Okor RS. Effect of humidity on the disintegrant property of á-cellulose. Acta Pol. Pharm. 2005b; 63: 39-44.
5. Uhumwangho MU, Iwuagwu MA. Effect of relative humidity on the mechanical properties of some brands of paracetamol tablets. Int. J Sci. and Techn. Res. 2006; 3: 22-29.
6. Leong GC, Adeleke BO. Certificate, Physical and Human geography. West African Edition, University Press Limited, Ibadan, 1981; 178 - 184.
7. Fell JT, Newton JM. Determination of tablet strength by diametral test. J. Pharm. Sci. 1970; 59: 688 689.
8. Brook DB, Marshall K. Crushing strength of compressed tablets 1: comparison of testers. J. Pharm. Sci. 1968; 57: 481- 484.
9. British Pharmacopoeia. Her Majesty's stationary office, London. 2002: A236.
10. Okor RS, Otimenyin S and Ijeh I. Coating of certain matrix cores with aqueous based systems of acrylate methacrylate, a water soluble copolymer and drug release profiles. J. Control. Rel. 1991;16: 344 354.
11. Uhumwangho MU, Okor RS. Humidity effect on the disintegrant property of -cellulose and the implication for dissolution rates in paracetamol tablets. Pak ..J Sci. Ind. Res. 2005a; 48: 8 -13. ▶

Table 1: Drug content of the conventional and MU tablets after their storage for 7 days at different relative humidities at room temperature 30°C.

Dosage forms	Relative humidity (%)	Drug content of: Fresh samples	Aged samples (7days)
Conventional tablets			
	1	97.3±4.1	95.2±3.9
	78	96.1±3.3	94.3±2.1
	100	98.8±3.5	96.3±4.6
MU tablets			
	1	96.2±3.1	94.3±4.3
	78	97.5±3.6	95.4±3.9
	100	95.8±2.9	94.7±3.8

Note: Drug content was expressed as %w/w of initial amount = 300mg

Table 2: Effect of relative humidity on drug release parameters (m_s, m_p, t_s and k_1) of the MU and conventional tablets, duration of exposure 7 days.

Dosage form	Dissolution parameters evaluated	Test relative humidities (%): 1	78	100
MU tablets				
	m_s (mg)	580±3.5	583±2.6	582±2.9
	m_p (mg)	180± 2.2	204±2.5	238±1.9
	t_s (h)	11±0.7	11±0.5	11±0.9
	k_1 (h^{-1})	0.27±0.03	0.32±0.05	0.37±0.04
Conventional tablets				
	m_s (mg)	586±4.2	585±3.8	586±4.1
	m_p (mg)	488±2.5	506±2.2	516±2.8
	t_s (h)	3±0.5	3±0.3	3±0.2
	k_1 (h^{-1})	1.26±0.3	1.31±0.5	1.44±0.6

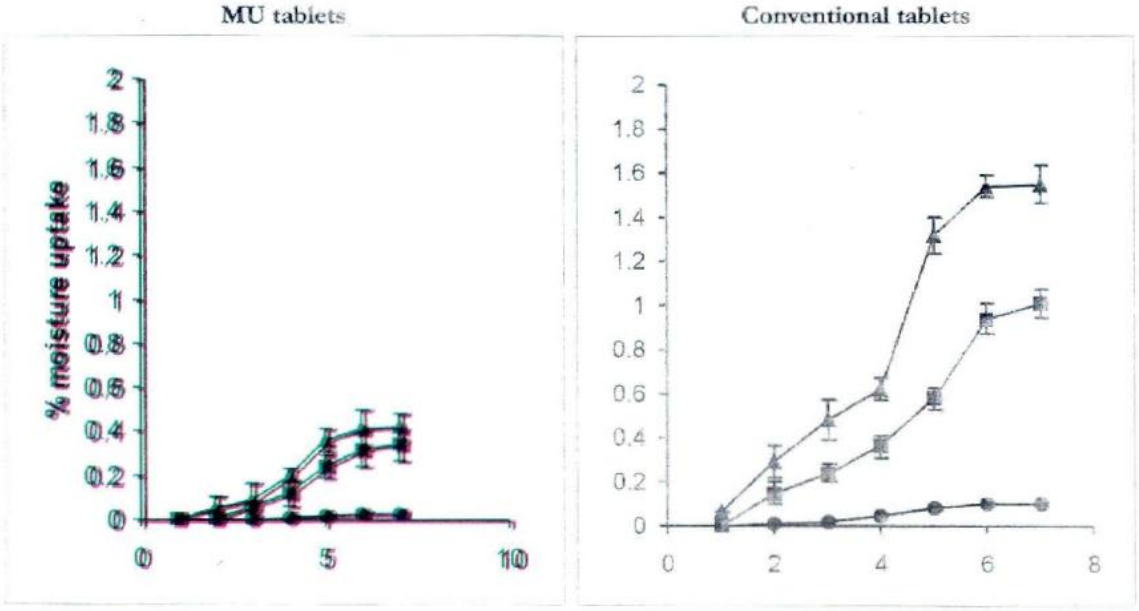
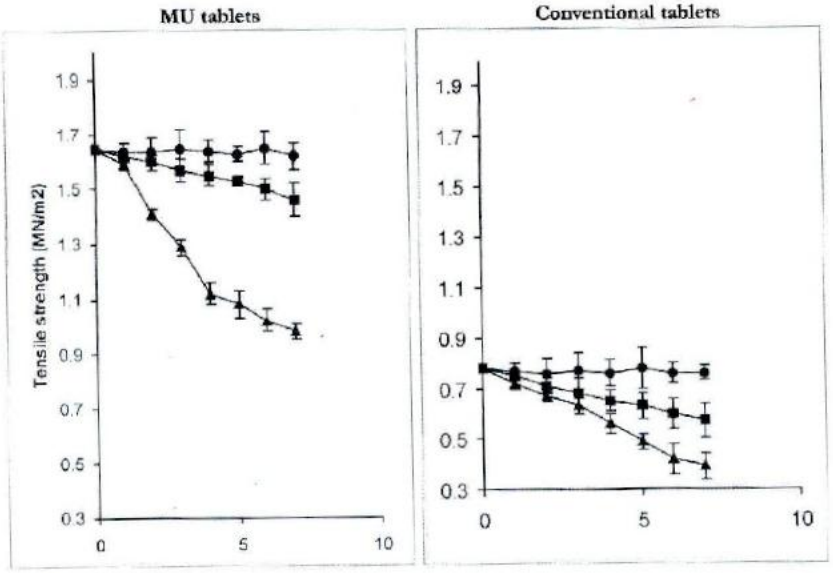
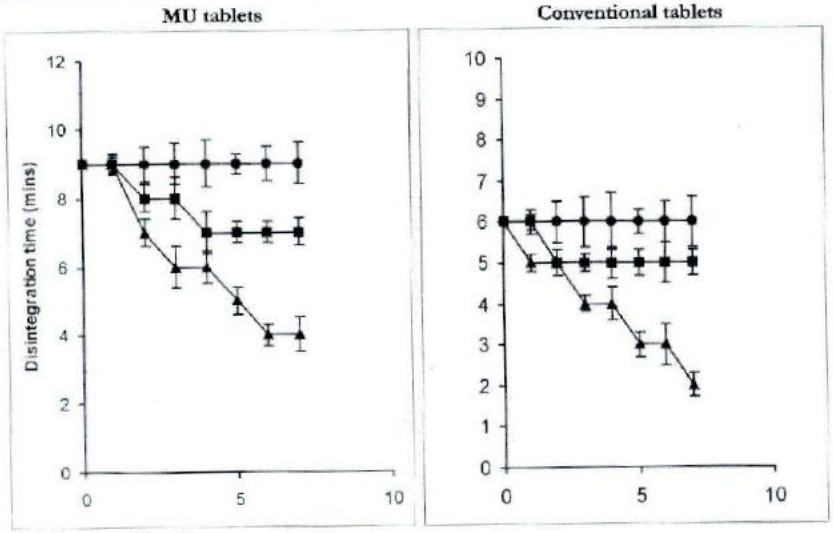


Fig 2: Effect of different relative humidities RH 1%(●), RH78% (■) and RH100% (▲) On the moisture uptake of conventional and MU tablets of ratio 1:1 (A: B).



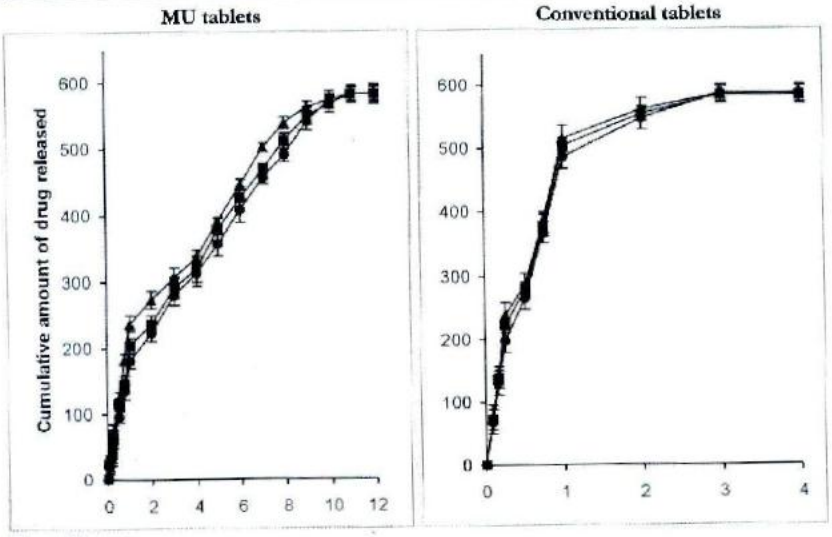
Storage time (days)

Fig 3: Effect of different relative humidities RH 1%(●), RH78% (■) and RH100% (▲) on the tensile strengths of the conventional and MU tablets of ratio 1:1 (A: B).



Storage time (days)

Fig 4: Effect of different relative humidity RH 1% (●), RH78% (■) and RH100% (▲) on the disintegration time of conventional and multiunit dose tablets



Time (h)

Fig 5: Drug release profiles of the MU and conventional tablets after their storage for 7days at different relative humidities, RH1% (●), RH 78% (■), RH100% (▲), at room temperture 300C. NIP