A model of multi-unit dose tablets of theophylline (dose, 600 mg) has been designed to give a prompt release dose (200 mg) in the first 1 h and the remaining sustained release dose (400 mg) to be released over 11 h at a first order release rate constant of 0.24 h⁻¹. The prompt release component (A) consisted of conventional granules of the drug while the sustained release component (B) was made up of matrix granules of the drug obtained by melt granulation i.e. granulating the drug powder with a melted wax (carnuba). To form the multi-unit dose tablets, granules of A and B were mixed together in various proportions in the ratios (A: B) 2:1, 1:1 and 1:2. The disintegration times of the tablets and their dissolution profiles were measured to investigate consistence with the model. The results showed that the tablets generally disintegrated readily within 10 min irrespective of the proportion of A to B. Of the various formulations tested, only the formulation consisting of A and B in the ratio 1:1 gave dissolution profile that was comparable to that of the model. The following were the dissolution parameters of this formulation: the maximum release (mₚ) = 580 mg, prompt release dose (mₚ) = 180 mg, time to attain maximum release (tₚ) = 11 h and first order release rate constant (k₁) = 0.27 h⁻¹ which is comparable with the release data for the model. The other formulations deviated by giving mₚ and tₚ that were either too high or too low compared with those of the model. The indication is that the prompt release dose was not determined only by the amount of A in the multi-unit dose formulation but also by the amount of B, attributable to the deformation of granules of A into B during tableting.

Key words: Theophylline, modeling, drug release, multi-unit dose tablets.

INTRODUCTION

Multi-unit (MU) dosage forms consist of multiparticulate systems of small discrete individual units such as pellets, granules, microcapsules or microparticles of the same drug but of different release profiles. They are normally formulated into a single unit dosage form by filling them into hard gelatin capsules or compacting them into rapidly disintegrating tablets (Follonier and Doelker, 1992; Bodmeier, 1997). They are expected to provide an initial prompt release followed by a sustained release to increase the duration of biologic activity of the drug. MU dosage forms may also consist of particles of different drugs to be released at different sites to prevent pharmacokinetic interaction. Only the former was considered in the present study.

Theophylline is a methylxanthine derivative, which is often indicated for the treatment of asthma (Ukena et al., 1997). It is rapidly and almost completely absorbed after oral administration in solution or tablet with a bioavailability of 96% (Hendeles et al., 1977). The biologic half-life of the drug is about 4.5 h and the usual oral dosage regimen is 60 to 200 mg every 3 to 4 h with a maximum dosage of 600 mg/day (BPC, 1980). Since asthma is a chronic disease requiring prolonged treatment and theophylline half-life is short, several efforts have been made to develop sustained release dosage forms of the drug. Such efforts include the formation of floating lipid pellets of the drug to increase gastric retention and prolong release (Hamdani et al., 2006). The formation of matrix tablets using hydroxypropylmethylcellulose (HPMC) as binder (Moneghini et al., 2006). Reza et al. (2002) employed polyvinyl acetate and povidone as matrix former to form sustained release tablets of the drug. The work of Ochoa et al. (2005) has shown that melt granulation of...
Figure 1. Model of dissolution profile of the multiunit dose tablets showing the prompt release dose (m_p = 200 mg) and time to attain it t_p (1 h), the maximum release (m_x = 600 mg) at t_x = 12 h.

THEORETICAL CONSIDERATIONS

Modeling of the desirable drug release profile for the multi-unit dose tablet

The model (Figure 1) was developed based on the following considerations:

(i) The conventional dose of the tablet is 200 mg 3 times daily to a maximum daily dose of 600 mg (BPC, 1980). This means that the total daily dose in the MU dosage form should be 600 mg divided into a prompt release dose (200 mg) and the sustaining dose, 400 mg.

(ii) From the drug pharmacokinetics, the t_{max} (time for peak absorption or to attain peak plasma level) is 2 h (BPC, 1980), therefore the prompt dose should be released at least 1 h giving another 1 h to attain the peak plasma concentration.

(iii) The sustained release dose (400 mg) will be released over 11 h at an average rate of 36 mg h^{-1} such that the time for maximum release will be 12 h for the dose to be taken once 12 hourly.

(iv) Drug release from the system is based on first order rate kinetics, which is the most frequently reported rate order kinetic in the literature for the dissolution of drug particles and their solid dosage forms (Richards, 1972; Eichie and Okor, 2002). Preliminary investigation in the present study also confirmed the literature report.

(v) The first order rate kinetics is given by the equation (Richards, 1972):

\[ \log m_t = \log m_0 - 0.43k_1t \]  \hspace{1cm} (1)

where \( m_0 \) is the initial amount of drug (400 mg) at the beginning of the sustained release, \( m_t \) is the residual amount (36 mg) of drug in time, \( t, 10 \text{ h} \) (i.e. 1 h before maximal release), \( k_1 \) is the first order release rate constant. Hence, substituting these values in equation 1, gives:

\[ \log 36 = \log 400 - 0.43k_110 \]

\[ 1.556 = 2.602 - 0.43k_110 \]

\[ 1.556 - 2.602 = -4.3k_1 \]

\[ -1.046 = -4.3k_1 \]

From where,

\[ k_1 = 1.046/4.3 = 0.24 \text{ h}^{-1} \] indicating that the sustained release will proceed at a first order rate, 0.24 h^{-1}.

With known values of \( m_0 \) and \( k_1 \), the amounts of drug release at predetermined time intervals were estimated from equation 1, and the data were plotted to give the theoretical release curve (Figure 1). The main features of the release profile of the model are the prompt release dose (m_p = 200 mg), maximum release (m_x = 600 mg) and the time to attain it (t_x = 12 h). Thus, the ideal MU dosage form should display this drug release profile. An example of the calculation of amount released after a given time interval is as follows:

Given that the time for prompt release \( t_p = 1 \text{ h} \) and \( m_p = 200 \text{ mg} \), at 5 h sampling time, the interval between 5 h and \( t_p \) will be \( t - t_p = 5 - 1 = 4 \text{ h} \). Hence, the value of \( m_t \) in 4 h will be given by:
Figure 2. Model of the plasma level profile of the conventional dosage form based on the drug (theophylline) pharmacokinetics. $C_{\text{max}} = 6.4 \, \text{mg/ml}$, $k_a = 0.023 \, \text{min}^{-1}$, $k_e = 0.00257 \, \text{min}^{-1}$, minimum therapeutic level = 5 mg/ml and minimum toxic level = 9 mg/ml. Note that the bioactive period is only 130 min (about 2 h).

$\log m_t = \log 400 - 0.43 \times 0.24 \times 4$

$\log m_t = 2.602 - 0.4128$

$\log m_t = 2.1892$, and $m_t = 155 \, \text{mg}$

Therefore, the residual amount is 155 mg and the amount released will be $400 - 155 = 245 \, \text{mg}$ in the 4 h interval after $t_p$. The cumulative release including the $m_p$ will be $(245 + 200) \, \text{mg} = 445 \, \text{mg}$.

The expected effect of this modified release profile (Figure 1) on the duration of bioactivity of the drug was obtained by modeling the absorption/elimination curves for the conventional as well as the MU dose tablets.

Theoretical estimation of the duration of bioactivity following a single dose (200 mg) of the conventional tablets form

This was achieved by modeling the absorption/elimination curve for the conventional tablets. The model for the absorption curve (Figure 2) was developed based on the following considerations:

(i) From the literature (Hendeles et al., 1977), the percentage bioavailability of theophylline tablets is 96%; therefore the amount that will be bioavailable at $t_{\text{max}}$ following a prompt release dose (200 mg) will be $0.96 \times 200 \, \text{mg} = 192 \, \text{mg}$.

(ii) The relationship between the peak plasma concentration ($C_{\text{p}}$), the apparent volume of distribution ($V_d$) and the bioavailable dose ($D$) is given by (Raymond and Graig, 2000):

$D = C_{\text{p}}V_d$ .................................................. (2)

For theophylline, $V_d = 30,000 \, \text{ml}$ (BPC, 1980) and $D = 192 \, \text{mg}$, which gives $C_{\text{p}} = D/V_d = 192 \, \text{mg}/30000 \, \text{ml} = 0.0064 \, \text{mg/ml}$ or 6.4 $\mu$g/ml as the peak plasma level at $t_{\text{max}}$ (2 h).

(iii) The peak plasma concentration 6.4 $\mu$g/ml will be attained in 2 h at an average rate of 0.053 $\mu$g/ml/min being the quotient of 6.4$\mu$g/ml/120 min. (iv) The absorption curve is based on the first order rate kinetics (Richards, 1972), thus:

$\log C_{\text{p}} = \log C_0 + 0.43k_at$ ......................... (3)

where $C_{\text{p}}$ is the plasma concentration in time $t$, $C_0$ is plasma concentration in the first sampling time (say at 10 min) and $k_a$ is the absorption rate constant. Thus, at $t = 10 \, \text{min}$, $C_0 = 0.53 \, \mu$g/ml being the product of 10$ \times$ 0.053 $\mu$g/ml. At peak plasma concentration, $C_{\text{p}} = C_{\text{max}} = 6.4 \, \mu$g/ml and $t = t_{\text{max}}-10$ that is $(120 - 10) = 110 \, \text{min}$.

Substituting in equation 3, the values of $C_{\text{p}}$, $C_0$ and $t$ gives

$log 6.4 = log 0.53 + 0.43k_at$ 110

$0.8062 = -0.2757 + 47.3 \, k_a$

$0.8062 + 0.2757 = 47.3 \, k_a$

From where:

$k_a = 1.085/47.3 = 0.023 \, \text{min}^{-1}$.

Substituting the $k_a$ and $C_0$ values into equation 3 gave the plasma concentrations at the various time intervals up to the $t_{\text{max}}$ (2 h) as given in Figure 2.

The elimination curve was based on the first order elimination kinetics:

$log C_{\text{p}} = log C_{\text{max}} - 0.43k_et$ ......................... (4)

where $k_e$ is elimination rate constant $= 0.693/t_{1/2}$ and $t_{1/2}$ for theophylline $= 4.5 \, \text{h}$ (BPC 1980), hence $k_e = 0.00257 \, \text{min}^{-1}$. $C_{\text{p}}$ is the plasma concentration at time $t$ and $C_{\text{max}}$ is the peak plasma concentration before elimination begins. Substituting into equation 4, the values of $C_{\text{max}} = 6.4 \, \mu$g/ml and $k_e = 0.00257 \, \text{min}^{-1}$ gave the values of $C_{\text{p}}$ at the various time intervals in the elimination phase. For instance, at 20 min into the elimination phase, $log C_{\text{p}} = log 6.4 - 0.43 \times 0.00257 \times 20 = 6.1 \, \mu$g/ml. The duration of bioactivity was estimated by considering the minimum therapeutic plasma level, which is 5 $\mu$g/ml (BPC 1980).
Estimation of the duration of bioactivity following a single dose of the multi-unit dose tablets

This was achieved by modeling the absorption/elimination curve for the MU dose tablets. The model (Figure 3) was developed based on the following considerations:

(i) The peak plasma concentration due to the prompt release fraction is 6.4 µg/ml, \( t_{\text{max}} = 2 \) h, the minimum therapeutic level is 5 µg/ml while the minimum toxic level is 9 µg/ml (BPC, 1980).

(ii) There would be a plateau between the \( t_{\text{max}} \) (2 h) to 13 h assuming that drug release and absorption are sustained for the next 11 h after attaining peak plasma concentration in 2 h. The plateau in the plasma level profile will arise if the absorption and elimination rates are equal. The absorption rate was estimated to be 1.17 µg/ml/h as follows:

As given previously (Figure 1), the sustained release dose (400 mg) should be released in 11 h (i.e. average release rate is 36 mg/h). Since the oral bioavailability is 96%, the absorption rate will be 0.96 \times 36 \text{mg/h} = 35 \text{mg/h}. The corresponding rate of increase in plasma concentration is given as 35 \text{mg/h} / V_d = 1.17 \text{µg/ml/h}, given that \( V_d = 30,000 \text{ml} \). Hence, the absorption rate in the sustained release phase is \( 1.17 \text{µg/ml/h} \). On the other hand, the average elimination rate in the sustained release phase was estimated to be 0.80 µg/ml/h on the basis that \( t_{1/2} \) is the time for peak plasma concentration (6.4 µg/ml) to fall to 50% of its original value. Given that \( t_{1/2} \) for theophylline = 4.5 h (BPC, 1988), the average rate of drug elimination will be \( (6.4/2) \text{µg/ml} / 4.5 \text{h} = 0.8 \text{µg/ml/h} \). Both average absorption and elimination rates can be approximated to unity. Hence, in the modeling the absorption and elimination rates were assumed to be equal, thus giving rise to the plateau in Figure 3. This means that the peak plasma level attained in 2 h will be sustained for 11 h before elimination commences at same rate as for the conventional tablets (Figure 2). The duration of bioactivity of the MU tablets was estimated by considering that the therapeutic plasma level of the drug is 5 µg/ml as indicated in Figure 3.

MATERIALS AND METHODS

Materials

Carnauba wax (Halewood Chemicals Limited, England) is a fine waxy solid with melting point of 82 - 88 °C, yellowish in colour and was used as the granulating agent and the matrix former. Maize starch (BDH, Chemical, Poole, UK) was used as binder in the form of mucilage (20%, w/v) to produce the conventional granules. The maize starch (5%, w/w) was also used as disintegrant, as dried powder. Magnesium stearate (Sakai Chemical Company, 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 a gift from Vitaboitics Nigeria Limited.

Wet granulation to form the conventional granules

A sample of the theophylline powder (100 g) was wet-massed with starch mucilage (20%, w/v). 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 1.7 mm, spread thinly on trays and then dried at 50 °C for 1 h in a hot air oven (Kottermann, Germany). The half dried mass was pressed through a sieve of aperture size 710 µm and dried finally at 50 °C for 2 h 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 (20 g) 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 (100 g) 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; 710 µm ) to produce matrix granules that will not disintegrate in aqueous fluid 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 different proportions in the ratios 2:1, 1:1, 1:2, (A: B). In each mixture, aliquots of the granules were selected such that the total drug content in a tablet was 300 mg; representing the contribution from A and B granules.

Tableting

The conventional, (A) and the matrix (B) granules, or their admixtures (A and B) were compressed using a single punch tableting machine (Manesty Type F5, Poole, England) at a constant load (30 arbitrary units on the load scale) to form flat faced tablets of diameter 12.5 mm. The weights of the tablets varied depending on the formulation but the drug content in each tablet remained 300 mg. Magnesium stearate (0.5%, w/w) and dried maize starch powder (5%, w/w) were added to the granules prior to compression. The tablets were allowed to equilibrate in a dessicator, 24 h before their evaluation.
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 (Fell and Newton, 1970):

\[ T = \frac{2P}{\pi} \]  

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 (1968). 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 (2002) was followed using water maintained at 37°C. The disintegration times and slightly higher tensile strengths, but the differences were not statistically significant (p > 0.05). The DT and T values of tablets of B were however significantly higher than those of A which indicated that carnuba wax (the matrix former) promoted particle deformation and bonding during tableting as previously reported (Uhumwangho and Okor, 2006).

RESULTS AND DISCUSSION

Tablet disintegration times and tensile strength

The disintegration times (DT) of the multi-unit dose tablets are 6, 8 and 9 min for multi-unit dose tablets in the ratios (A: B) 2:1, 1:1 and 1:2 respectively. This showed that all the multi-unit dose tablets disintegrated readily during disintegration test. The tablet tensile strengths (T) for the multi-unit dose tablets were (MNm²) 1.56, 1.62 and 1.67. Thus, tablets with higher proportion of granules B (i.e. the matrix granules) tended to give slightly longer disintegration times and slightly higher tensile strengths, but the differences were not statistically significant (p > 0.05). The DT and T values of tablets of B were however significantly higher than those of A which indicated that carnuba wax (the matrix former) promoted particle deformation and bonding during tableting as previously reported (Uhumwangho and Okor, 2006).

Release profiles of tablets of the components A or B

The release curves for A and B measured separately are given in Figure 4. The features of the release profile for A include a high prompt release dose (348 mg) and a slow \( t_p \) (5 h) while that of B include a low prompt release (156 mg) and a prolonged \( t_p \) (12 h). Thus A alone suffers the deficiency of a sustained release while B suffers the deficiency of inadequate prompt release needed for immediate relief of clinical symptoms. Hence, the need to include A and B in a unit dose.

Release profiles of the multi-unit (MU) dose tablets

The release profiles of the multi-unit dose tablets are presented in Figure 5. The dotted line in the graph represents the release profile for the model. The actual (empirically determined) release curves for the MU dose tablets of compositions of A and B are presented as full lines in the graph for comparison with the model. The release parameters deduced from these curves are presented in Table 1. From where it can be seen that the multi-unit tablets of composition 1:1 (A: B) gave a comparable release profile as that of the MU model (Figure 1). The values of the release parameters for the multi-unit tablets of composition 1:1 (A: B) being, \( m_0 \) (180 mg), \( t_p \) (11 h) and \( k_1 \) (0.27 h⁻¹) against the corresponding values for the model \( m_0 \) (200 mg), \( t_p \) (12 h) and \( k_1 \) (0.24 h⁻¹). By incorporating a prompt release fraction (A) up to 300 mg in the multi-unit tablets, it was possible to achieve a prompt release dose of nearly 200 mg in the first 1 h. With A alone in the tablet, virtually all the 300 mg drug content was released in the first 1 h. This means that the presence of B in the multi-unit dose for tablets lowered the extent of prompt release from A. Also, it was expected that the MU formulation of composition A (200 mg) and B (400mg) would provide the targeted prompt release dose.
of 200 mg (Figure 1), which was not the case. The actual prompt release was 128 mg; considerably less than the targeted 200 mg. This observation relates to the deformation of A and B particles into each other during tableting such that the tablets did not disintegrate to particles of A and B separately. Ideally, MU tablets should disintegrate yielding the component particles intact so as to retain the individual release characteristics of the components (Lehmann, 1968).

Consideration of the effect of the modified release profile on the duration of drug activity

It was not possible at this stage of this work to determine clinically the duration of bioactivity of the modified (MU) dosage tablets because of the need to obtain ethical approval for clinical trials on new products. However, by modeling the absorption/elimination curves of the conventional and the modified dosage forms it was estimated that the duration of bioactivity following a single dose of the conventional dosage form would be about 2 h (Figure 2) as against 12 h for the modified (MU) dosage form (Figure 3). This means that the modified dosage form can be taken once 12 hourly.

Conclusion

The study has shown that multi-unit dose tablets consisting of A and B in the ratio 1:1 will give a prompt release followed by a prolonged and sustained release as designed in the model. Since particles of A and B are deformed into each other during tableting, it would be erroneous to assume that the amount of A in the multi-unit dose tablets would automatically represent the prompt release dose.

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