

Research Article

Estimation of the release profiles of multi-unit dose tablets of theophylline from the release profiles of their components

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Abstract

Purpose: *The objective of this study is to investigate whether the drug release profile of a multi-unit dose form consisting of fast and slow release components can be predicted from the release profiles of their components by simple summation.*

Method: *The fast release component consisted of conventional granules of theophylline made by wet massing the drug powder with starch mucilage (20%w/v). The slow release component consisted of matrix granules of the drug made by triturating the drug powder with melted carnuba wax (i.e. melt granulation). Each type of granules was compressed to tablets of weight 100, 150 or 200mg. To form the multi-unit dosage tablets of drug content 300mg each, the conventional and matrix granules were mixed in the ratio 1:2, 1:1 and 2:1, and compressed. The tablets were subjected to dissolution test and from the experimental release curve the prompt release (m_p) in the first 1h, the maximum release (m_∞) and the time to attain it (t_∞) were obtained.*

Result: *For a given composition of the multi-unit dose tablets, the theoretical release curve was obtained by summation of the release from each component at the different time intervals. The m_p values of the theoretically estimated release curves were generally higher, while their t_∞ values were generally shorter than the corresponding values for the experimental curves.*

Conclusion: *The indication is that drug release from the multi-unit dose tablets was more retarded than could be theoretically estimated. Apparently, the two components interfere with each other's release.*

Keywords: *single-unit and multi-unit dose forms, release profiles, theophylline*

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INTRODUCTION

Single (unit) dosage forms usually consist of drug particles of same release profile while a multi-unit dosage system consists of particles (units) of different drug or same drug particles but of differing release profiles with respect to onset, rate and the maximum release, etc^{1, 2}.

Capsules or tablets can be used either as single unit or multi-unit dosage forms for controlled release applications by formulating them with special excipients^{3, 4}. Multiple-unit dosage forms offer advantages over the single-unit systems¹ by producing an initial prompt release followed by a sustained release to prolong the initial therapeutic effect, thus obviating the need for repeat dosage. The release rate of drug particles may be retarded by a process of melt granulation whereby the drug powder is triturated with a melted wax to form matrix granules which do not disintegrate to their primary (powder) particles upon contact with aqueous fluid⁵.

A recent study⁶ showed that tableting rather than encapsulation of the matrix particles is more effective in prolonging the release of the test drug. Hence, the present study focused on the tablet formulation only. In that study, multi-unit tablets of theophylline were formulated by mixing conventional and matrix granules of the drug in various proportions.

The objective of the present study was to investigate whether the release profile of the multi-unit dose tablets can be predicted from the known profiles of the individual components that make up the multi-unit system. Theophylline was considered a candidate for the multi-unit dose formulation because it is indicated for the treatment of chronic asthma requiring prolonged medication.

MATERIALS AND METHODS

Carnauba 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 matrix former. Maize starch (BDH, Chemical, Poole, UK) was used as binder in the form of mucilage (20%w/v) and as a disintegrant in the form of a dried powder (5

%w/w) in the tablets, 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 theophylline (Sigma Chemical Company, St Louis, MO) was a gift from Vitaboitics Nigeria Ltd.

METHODS

Melt and conventional granulation techniques:

The method earlier described⁷ was followed. In the procedure the wax material (20g) was melted in a stainless steel container in a water bath at 90°C. A sample (100g) of the theophylline powder (melting point 270-274°C) was then added to the molten wax and mixed well with a Kenwood mixer (model A901P England) for 5mins. The theophylline was therefore thermally stable at the melting point of the wax. The mixture was allowed to cool at room temperature for 1h and then pressed through a sieve of aperture size; 710µm and dried in a vacuum oven (model A2904, Gallenkamp, England) at 25°C for 1h to produce matrix granules that will not disintegrate in aqueous fluid to their primary (powder) particles⁵. Conventional granules of theophylline were produced by wet-massing a sample of the theophylline powder (100g) with 20%w/v starch mucilage (38ml). The wet-mass was screened and dried in a vacuum oven at 25°C for 1h. Moisture content was analysed with a moisture analyzer (Denward Instruments Ltd, UK) and were 2.4±1.1%w/w (conventional) and 2.2±1.1%w/w (melt granulation).

Formulation of multi-unit dosage forms

The conventional (A) and the matrix granules (B) were mixed together in different proportions in the ratios (A: B) 2:1,1:1,1:2 (Table 1). In each mixture, aliquots of the granules were selected such that the total drug content in a tablet was 300mg. The conventional and the matrix granules, or their admixtures 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. The

Table 1: Formulation of the single-unit and multi-unit dose tablets

Amount (mg) of drug per tablet:			
Single unit dose tablets	multi-unit dose tablets		Ratio
A(mg)	B (mg)	A+B (mg)	A:B
100	200	300	1:2
150	150	300	1:1
200	100	300	2:1

Note: A = Conventional granules; B = Matrix granules

Table 2: Release parameters of tablets of the single-unit tablets of the conventional (A) and the matrix granules (B)

Drug load per tablet (mg)	A		B	
	m_{∞} (mg)	t_{∞} (h)	m_{∞} (mg)	t_{∞} (h)
100	190	3	192	5
150	290	3	284	6
200	388	3	396	8

Note: Two tablets were used in each dissolution test

Table 3: A comparison of the empirical and theoretical release parameters for the multi-unit dose tablets

Evaluation parameters	Formulation of the multi-unit dose tablets, ratio A:B					
	1:2		1:1		2:1	
	E	T	E	T	E	T
m_{∞} (mg)	578	584	580	574	584	580
m_p	128	198	180	280	240	428
t_{∞} (h)	12	8	11	6	9	5

Note: E = empirical and T = theoretical

weights of the tablets varied depending on the formulation but the targeted drug content was 300mg each. In another aspect of the study, tablets of A or B only with varied drug content 100, 150 and 200mg were also formed. In each case 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 desiccator, 24h before their evaluation.

Dissolution test: The method described previously by Okor et al⁸ was followed. Two tablets were placed in a cylindrical basket

(aperture size 425 μ m: diameter 20mm; height 30mm), which was immersed in 800ml of leaching fluid (0.1N hydrochloric acid maintained at $37 \pm 2^{\circ}\text{C}$). The fluid was stirred at 100rpm with a single blade Gallenkamp stirrer (Model APP No 4B 5784A. Cat No: SS530). 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

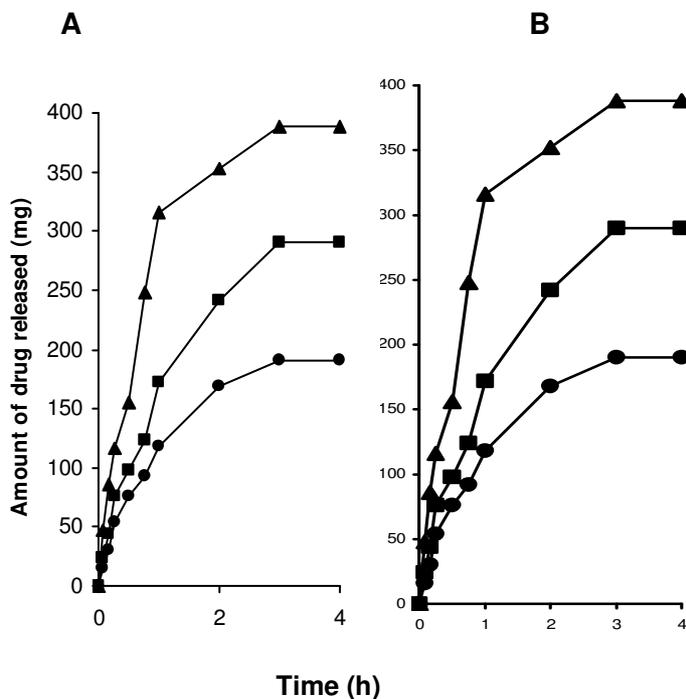


Fig 1: Release profiles of the single-unit tablets of the conventional (A) and matrix granules (B). The drug loading (mg) in each of the tablets are indicated on the curves.

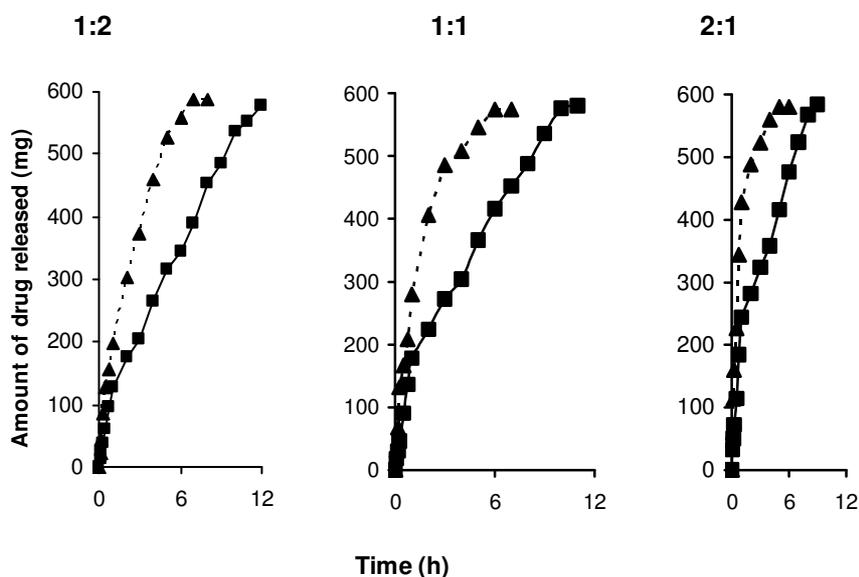


Fig 2: Release profiles of the multi-unit dose tablets showing theoretical (..▲..) and the empirical release (■) release curves of the different formulations

spectrophotometrically at λ_{max} , 272nm (Spectronic 21D, Bausch and Lomb, USA). The samples were filtered using No. 1

Whatmann filter paper before assay. The amounts released were expressed as a percentage of the initial amount of drug in the

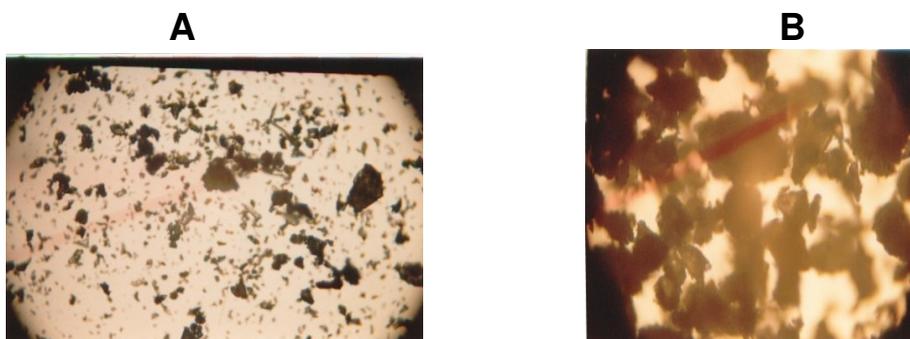


Fig 3: Photomicrograph ($\times 40$) of drug particles resulting from disintegration of the single-unit tablets of the conventional (A) or matrix granules (B)

capsule or tablet. The dissolution test was carried out in quadruplicate and the mean results reported. Individual results were reproducible to $\pm 10\%$ of the mean. The release data were subjected to student t test $p > 0.05$ to test for significance of difference between paired data.

Estimation of the theoretical release curves: The theoretical release curves for the multi-unit dose tablets comprising of two components (A and B) were obtained by summation of the individual release from A and B at a given time interval. Thus, if the release from A at 1h point was 172mg and that from B was 108mg, the estimated release for the multiunit dose tablet at 1h point will be $172\text{mg} + 108\text{mg} = 280\text{mg}$.

RESULTS

Dissolution profiles of the single unit tablets: The data are presented in Fig 1. Expectedly, the tablets of the conventional granules gave a faster release as reflected by their shorter t_{∞} values (3h) compared with those of tablets of the matrix granules (5 to 8h) (Table 2).

Dissolution profiles of the multi-unit dose tablets

The empirical and the theoretically estimated release curves are presented in Fig 2. The empirical release was more retarded than was theoretically estimated. This is reflected by the differences in the m_p and t_{∞} values (Table 3) obtained from the empirical and the theoretical

release curves. The empirical m_p values were general lower while their t_{∞} values were generally longer than the corresponding values for the theoretical release curves. The difference was up to 56% (m_p values) and 45% (t_{∞} values).

DISCUSSION

The slow release from tablets of matrix granules is attributable to the hydrophobic nature of the carnuba wax, which was used as the matrix former. Besides, the tablets of the matrix granules disintegrated to larger particles compared with the particles resulting from disintegration of the conventional tablets (Fig 3). Hence, the matrix particles exposed a lower surface area for the dissolution. This point was made earlier to the effect that the matrix granules unlike the conventional granules would not in turn disintegrate to their primary (powder) particles⁵.

The observation that the release from the multi-unit dose tablets was slower than theoretically estimated from the profiles of individual components indicates that the components in the multi-unit dose tablets affected each other's release. Presumably, the release of one component into the dissolution medium would alter the concentration gradient for mass transfer from the other component. For instance, the rapid dissolution of drug from the conventional granules into the dissolution medium would be expected to lower the concentration gradient

for mass transfer from the matrix granules, or vice versa

CONCLUSION

The indication is that the release profile of a multi-unit dosage form cannot readily be deduced from the individual profiles of its components. Hence, the optimal formulation of the multi-unit dosage form that would give the desired release profile must be experimentally determined.

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