

PHARMACEUTICAL TECHNOLOGY

MULTI-UNIT DOSAGE FORMULATIONS OF THEOPHYLLINE
FOR CONTROLLED RELEASE APPLICATIONS

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Abstract: The study was carried out to investigate the drug release profiles of multi-unit dosage formulations of theophylline consisting of both the fast and slow release components in a unit dose. The fast release component consisted of conventional granules of theophylline formed by mixing the drug powder with starch mucilage (20% w/v) while the slow release component consisted of wax granulations of theophylline formed by triturating the drug powder with a melted Carnauba wax (drug:wax ratio, 4:1). The granules were either filled into capsules or tableted. In the study design, the drug release characteristics of the individual fast or slow release particles were first determined separately and then mixed in various proportions for the purpose of optimizing the drug release profiles. The evaluating parameters were the prompt release in the first 1 h (m_p), the maximum release (m_∞) and the time to attain it (t_∞). Total drug content in each capsule or tablet was 300 mg and two of such were used in dissolution studies. The release kinetics and hence the release mechanism was confirmed by measuring the linear regression coefficient (R^2 values) of the release data. The release kinetics was generally most consistent with the Higuchi square root of time relationship ($R^2 = 0.95$), indicating a diffusion-controlled mechanism. The m_p (mg) and t_∞ (h) values for capsules and tablets of the conventional granules were (420 mg, 3 h) and (348 mg, 5 h), respectively, while for the capsules and tablets of the wax granulations m_p and t_∞ values were (228 mg, 9 h) and (156 mg, 12 h), respectively, indicating that a combination of wax granulation and tableting markedly retarded drug release. In the multi-unit dose formulations where the conventional and wax granulations were mixed in the ratios 2:1, 1:1 and 1:2 (conventional: matrix), the m_∞ and t_∞ values for the capsules were (378 mg, 6 h), (326 mg, 6 h) and (272 mg, 7 h), respectively. The corresponding values of m_∞ and t_∞ for the tablets were (240 mg, 9 h), (180 mg, 11 h) and (128 mg, 12 h) against the set target (200 mg, 12 h). The indication is that tableting rather than encapsulation can more effectively control drug release from the systems.

Keywords: Theophylline, sustained release, dissolution rate, multi-unit dosage forms

Theophylline is a methylxanthine derivative, which is often indicated for the treatment of asthma. It is rapidly and completely absorbed after oral administration in solution or tablet. The biological 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. To reduce the frequency of administration and hence improve patient compliance a sustained-release formulation of theophylline is desirable. Besides, the conventional dosage form can produce what may be considered an initially too high drug release with the attendant risk of side effects, hence the need for controlled release. This is achievable through a multi-unit dose design (1, 2). A multi-unit dosage form consists of particles (units) of differing release profiles with respect to onset, rate and the maximum release, etc. In this regard, polymer films of differing permeability have been frequently employed to modify drug release from drug particles.

A few examples mentioned in the literature include: films with the drug as a solution in a polymer matrix, e.g. monolithic devices (3-5) polymer coated reservoir devices (6), polymeric colloidal particles (microparticles or nanoparticles) either in the form of reservoir or matrix devices (4, 5) and osmotically "controlled" devices (7, 8). These methods are, however, complicated and expensive requiring the use of organic solvents as coating fluid. Besides, the organic solvents are potentially hazardous to the environment. Hence, an alternative approach, which was considered in the present study, is melt granulation whereby the drug powder is triturated with a melted wax serving as a hydrophobic retard release agent. The resulting granules consist of the drug particles dispersed in a wax continuous matrix. Hence, the release from such matrix systems has been found to follow diffusion controlled mechanism (9). Various waxes have been investigated as release retardants including Carnauba

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wax, glyceryl monooleate and its monostearate, beeswax and goatfat (10-13). Of these, Carnauba wax is considered the most suitable as it produces compressible and free flowing granules (14). It was therefore selected for the present study.

In the study design, conventional granules of the drug were used as the prompt release component while the wax (matrix) granulations constituted the slow (sustained) release component of the multi-unit dosage forms. The objective of the study was to investigate the proportions of the fast release component relative to the slow release component in the multi-unit dose system that will optimize the drug release profile. Based on the conventional dosage regimen of theophylline reported above, the prompt release dose should be 200 mg; the remaining 400 mg (out of the maximum daily dose of 600 mg) will be released steadily over the next 11 h at an average rate of about 35 mg h⁻¹. A capsule or tablet with drug content 600 mg is considered too large. Hence, in the dosage design the maximum daily dose (600 mg) is achievable by giving two capsules or tablets of 300 mg each to the patient. Therefore, two capsules or tablets each of 300 mg strength were used in the dissolution tests.

EXPERIMENTAL

Materials

Carnauba wax (Halewood Chemicals Ltd, England) is a fine waxy solid with melting point of 82-88°C, yellowish in color and was used as the matrix former. Maize starch (BDH, Chemical, Poole, UK) was used as binder in the form of mucilage (20% w/w) and as disintegrant, as 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 Vitabiotics Nigeria Ltd.

Methods

Melt granulation technique

The wax material (20 g) was melted in a stainless steel container in a water bath at 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.

Wet granulation technique

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 ± 0.5% w/w.

Mixing of the granules to form the multi-unit dosage forms

The conventional (A) as well as the matrix granules (B) were mixed together in different pro-

Table 1. Disintegration time (DT), friability and tensile strengths of tablet of the conventional (A) and the matrix granules (B).

Granulation type	Evaluation parameters		
	DT (min)	Friability (%)	T (MNm ⁻²)
A	6	0.56	1.25
B	10	0.18	1.87

Table 2. Linear regression coefficients (R² values) of capsules and tablets of the conventional (A) and matrix granules (B).

Dosage forms	R ² values based on the rate order:		
	Zero order	First order	Higuchi model
Capsules			
A	0.5069	0.9362	0.9587
B	0.4065	0.9523	0.9632
Tablets			
A	0.5273	0.9815	0.9504
B	0.6346	0.9424	0.9821

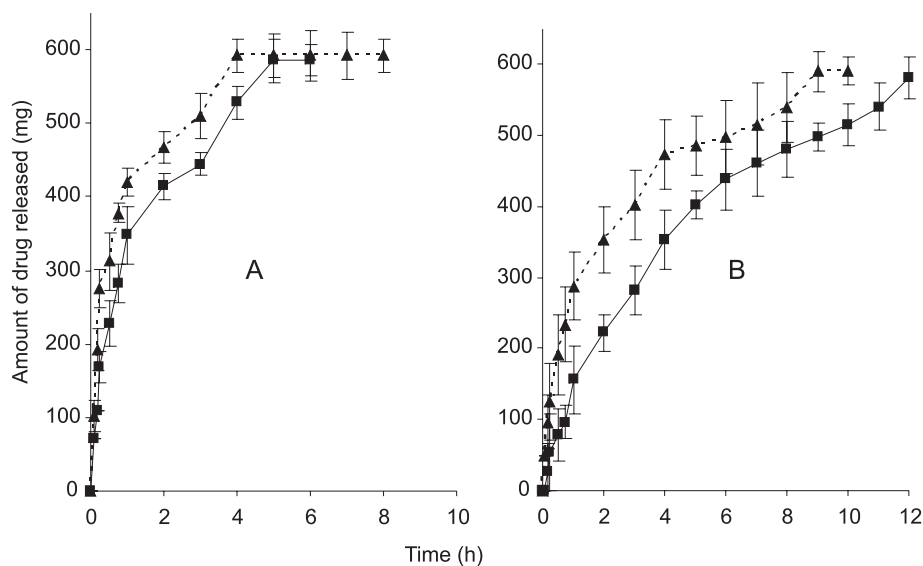


Figure 1. Dissolution profiles of capsules (▲) or tablets (■) of the conventional granules (A) or the matrix granules (B).

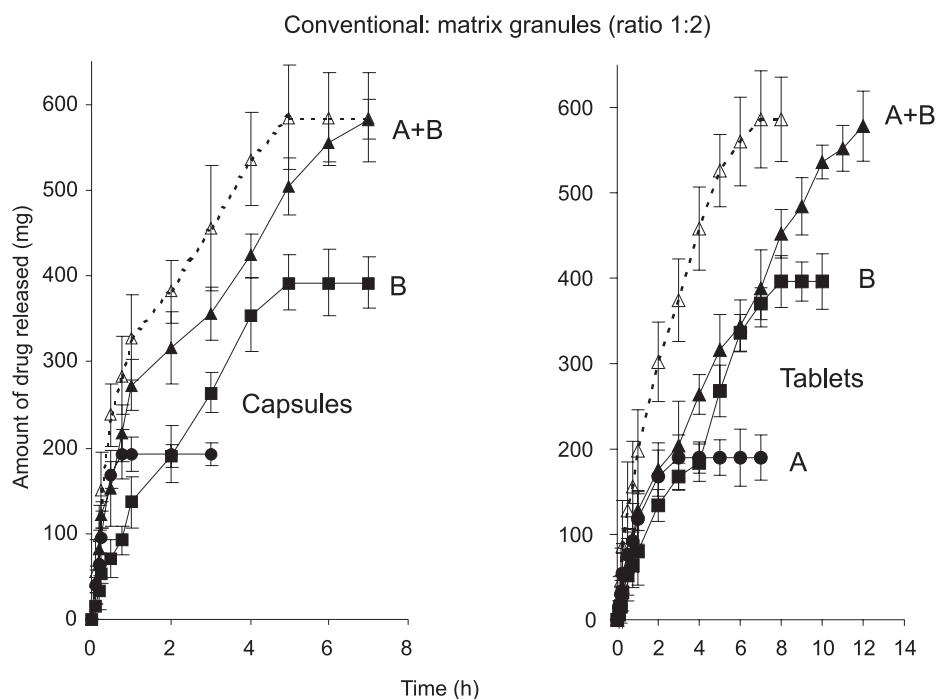


Figure 2a. Cumulative release of theophylline from capsules or tablets of the conventional granules (A) containing the drug 200 mg (●) and the release from capsules or tablets of the matrix granules (B) containing the drug 400 mg (■), theoretical release curve expected from a MU of A and B (...Δ...) and actual (empirical) release curve for the MU A and B, ratio 1: 2 (▲).

portions 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 capsule or tablet was 300 mg; representing the contribution from A and B granules.

Encapsulation of the granules

Samples of the A or B granules (drug content 300 mg) or mixtures of A and B in the ratios indicated above were filled manually into plain hard gelatin capsules (drug content 300 mg). The capsules

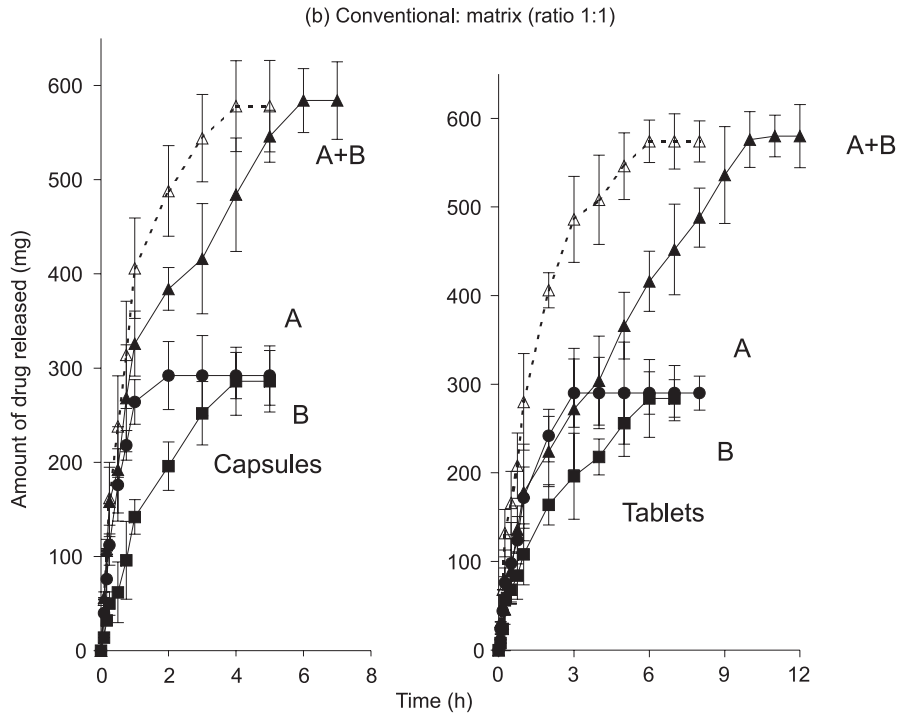


Figure 2b. Cumulative release of theophylline from capsules or tablets of the conventional granules (A) containing the drug 300 mg (●) and the release from capsules or tablets of the matrix granules (B) containing the drug 300 mg (■), theoretical release curve expected from MU of A and B (...△...) and actual (empirical) release curve for the MU A and B, ratio 1: 1 (▲).

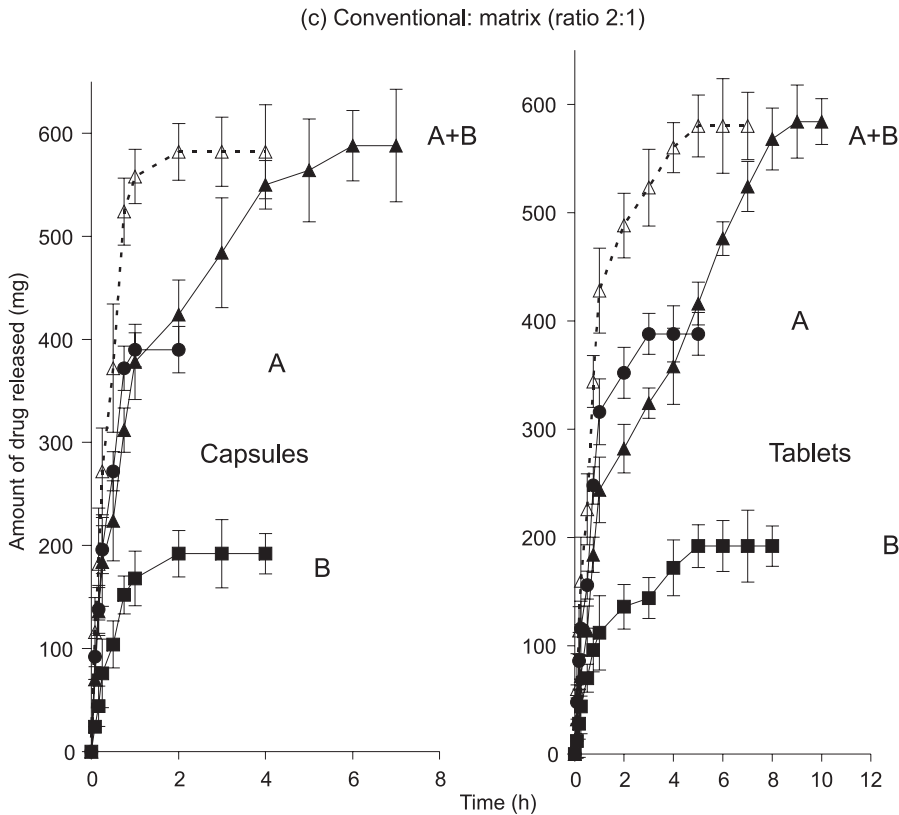


Figure 2c. Cumulative release of theophylline from capsules or tablets of the conventional granules (A) containing the drug 400 mg (●) and the release from capsules or tablets of the matrix granules (B) containing the drug 200 mg (■), theoretical release curve expected from MU of A and B (...△...) and actual (empirical) release curve for the MU A and B, ratio 2: 1 (▲).

Table 3. Drug release parameters (m_p , m_∞ and t_∞) and Higuchi rate constant (k_H) of capsules and tablets of conventional (A) and matrix granules (B).

Dosage forms	Release parameters			
	m_p , (mg)	m_∞ (mg)	t_∞ (h)	k_H (mg h ^{-1/2})
Capsules				
A	420	592	3	28.4
B	228	590	9	18.6
Tablets				
A	348	585	5	16.4
B	156	581	12	9.6

Table 4. A comparison of the empirical and theoretical m_p , and t_∞ values for capsules and tablets of mixtures of A and B.

Evaluation parameters	A : B ratios:					
	1:2		1:1		2:1	
	E	T	E	T	E	T
Capsules (A & B)						
m_p (mg)	272	328	326	406	378	558
t_∞ (h)	7	5	6	4	6	2
Tablets (A & B)						
m_p (mg)	128	198	180	280	240	428
t_∞ (h)	12	8	11	6	9	5

Note: E are empirical while T are theoretical data.

were kept in airtight containers before their use in disintegration and dissolution tests. In another aspect of the study, aliquots of the granules either A or B containing the drug (100, 150 and 200 mg) were filled separately into the capsules.

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 F₃, Poole, England) at a constant load (30 arbitrary units on the load scale) to form flat faced tablets with a diameter of 12.5 mm. The weights of the tablets varied depending on the formulation but the drug content remained 300 mg. In another aspect of the study tablets of A or B only with varied drug content (100, 150 and 200 mg) were separately 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 dessicator, 24 h before their evaluation.

Determination of tablet tensile strength (T)

This is the stress needed to fracture a tablet by diametral compression. It is given by the expression (15):

$$T = 2P/\pi Dt \quad (1)$$

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 (16). The mean values of the fracture loads were used to calculate the T values for various tablets.

Disintegration test

The method described in the British Pharmacopoeia BP (17) was followed using water maintained at 37°C as the disintegration fluid. Six tablets or capsules were used in each determination, which was carried out in triplicate and the mean results are reported.

Dissolution test

The method of Okor (18) was followed. Two capsules or tablets were placed in a cylindrical basket (aperture size 425 μ m, diameter 20 mm; height 30 mm), which was immersed in 800 mL of leaching fluid (0.1 M hydrochloric acid maintained at 37 \pm 2°C). The fluid was stirred at 100 rpm with a single blade Gallenkamp stirrer (Model APP No. 4B 5784A). Samples of the leaching fluid (5 mL) were withdrawn at selected time intervals with a pipette fitted with a cotton wool plug and replacing with an

equal volume of drug-free dissolution fluid. The samples were suitably diluted with blank dissolution fluid and were analyzed for content of theophylline spectrophotometrically at λ max, 272 nm (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 are reported. Individual results were reproducible to $\pm 10\%$ of the mean. The release data were subjected to the Student *t* test $p > 0.05$ to test for significance of difference between paired data.

Determination of rate order kinetics

The dissolution data were analyzed on the basis of zero order, (cumulative amount of drug released vs. time), first order rate (log cumulative amount of drug remaining vs. time) and Higuchi model (cumulative amount of drug released vs. square root of time). These, are the most frequently reported kinetics of drug release from drug particles and their solid dosage forms (18-20). The test rate order equations are:

$$\text{Zero order: } m = k_0 t \quad (2)$$

$$\text{First order: } \log m_1 = \log m_0 - 0.43 k_1 t \quad (3)$$

$$\text{Higuchi } m = k_H t^{1/2} \quad (4)$$

where *m* is the amount of drug released in time *t*; *m*₁ is the residual amount of drug in time *t*; *m*₀ is the initial amount of drug at the beginning of the first order release; *k*₀, *k*₁ and *k*_H are the release rate constants for the zero, first order and the Higuchi models, respectively. The linear correlation coefficient (*R*²) for each rate order was calculated. The dissolution profile was considered to follow a particular rate order if the *R*² value was ≥ 0.95 (9, 21).

RESULTS AND DISCUSSION

Disintegration times of the capsules

The capsule shells disintegrated rapidly (within 2 min) but the matrix granules content did not pass through the 1 mm mesh of the basket, which confirmed matrix property. Capsules filled with the conventional granules disintegrated within 3 min.

Tablet disintegration times, tensile strength and friability

The disintegration times (DT), tensile strengths (T) and friability for the tablets are presented in Table 1. Tablets derived from granules B (i.e. the matrix granules) gave longer disintegration times, higher tensile strengths but lower friability compared with A, indicating that Carnauba wax (matrix former) promotes particle deformation and bonding during tableting as previously reported (14).

Kinetics of drug release from capsules and tablets of conventional (A) and matrix granules (B)

Data of the linear regression coefficient (*R*²) are presented in Table 2 which showed that the drug release was most consistent with the Higuchi square root of time relationship (*R*² = 0.95), indicating that drug release was essentially by a diffusion controlled mechanism (19). Variation in the tablet or capsule formulation did not influence the release mechanism as the *R*² values did not vary significantly ($p > 0.05$).

Drug release profiles of capsules and tablets of granules A or B

The release profiles of capsules and tablets of granules A or B are presented in Figure 1. The matrix granules gave slower release rates and lesser prompt release whereas the conventional granules gave a higher prompt release dose. Tableting further retarded the release and reduced the extent of prompt release (Table 3). Wax granulation followed by tableting increased the time for maximal release from 3 h to 12 h, attributable to the hydrophobic nature of the wax and the compaction of the particles during tableting. On the other hand, the prompt release dose decreased drastically from 420 mg (conventional capsules) to 156 mg (tablets of matrix granules). Based on the conventional adult dose of 200 mg 4 hourly to maximum dose 600 mg per day, the controlled release system should provide a prompt release dose of 200 mg in the first 1 h, while the remaining 400 mg is released over the next 11 h at an average rate of about 35 mg h⁻¹. The capsules of the matrix granules gave a prompt release dose of 228 mg and the maximal release was in 9 h, while the tablets of the matrix granules gave a prompt release dose of 156 mg with maximal release in 12 h. Thus none of the delivery systems met the set target (prompt release dose 200 mg and *t*_∞ 12 h).

Release profiles of the multi-unit dosage forms consisting of A and B

The individual release profile of capsules and tablets of component A or B are presented in Figures 2a, b and c. Figure 2a is the plot of the release data from A (200 mg) and B (400 mg) separately determined, and the mixture of A and B (ratio 1:2). Figure 2b is the plot for the release data from A (300 mg) and B (300 mg) also determined separately, and mixture of A and B (ratio 1:1). Figure 2c is the release data also separately determined from A (400 mg) and B (200 mg) and the mixture A and B (ratio 2:1). The expected release from A and B concomitantly was obtained theoretically by summation of

individual release data from A and B at each time interval. The theoretical release curve expected from the mixture of A and B in the given ratio is represented by the dotted line in each of the plots (Figures 2a-c). The actual (empirically determined) release curve for the mixture (A and B) in the given ratio is also indicated in each plot for comparison with the theoretical curve. The prompt release, as estimated from the theoretical release curve for the mixtures of A and B, were consistently higher than the experimental values, while the theoretical t_{∞} values were consistently and significantly shorter than the empirical t_{∞} values ($p < 0.05$). Thus, the presence of A prolonged the release from B. This explanation is that the rapid leaching from component A decreased the concentration gradient for mass transfer from component B, thus accounting for the increase in t_{∞} values as the proportion of B in the mixture increased (Table 4).

CONCLUSION

The study has shown that wax granulation is an effective approach for retarding drug release from the resultant matrix particles. Tableting rather than encapsulation of the matrix particles is more effective in prolonging the release. The release profile can be best optimized by inclusion of a fast release component A to the slow release component B in the ratio 1:1 (A: B) which gave a prompt release dose (180 mg) and t_{∞} (10 h) against the target prompt release dose (200 mg) and t_{∞} (12 h).

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