

Original Research Article

## Formulation and evaluation of theophylline timed release tablets for chronotherapeutic drug delivery using natural gums

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**Abstract:** This research was done to formulate an optimized Chronotherapeutic Timed Release Tablets (ChrTRTs) containing theophylline, a potent bronchodilator used in the management of asthma in the inner core as a Chronotherapeutic drug delivery system. Theophylline core tablets (TCT) containing *Irvingia gabonensis* gum (2.5 %w/w) as binder and maize starch (15%w/w) as disintegrant were prepared at a compression pressure of 30 units on the arbitrary load scale. ChrTRTs containing the inner core tablet with *Anarcadium occidentale* gum, *Irvingia gabonensis* gum, and Sodium Starch glycolate at varying concentrations (0, 0.5, 1 and 2 % w/w) to achieve a predetermined lag time for chronotherapy were prepared at a compression pressure of 35 units on the arbitrary load scale. The parameters determined were tablet hardness, friability, drug content, disintegration test and *in-vitro* dissolution studies. The release profile showed that all the ChrTRTs tablets exhibited a distinct lag time before burst release of the theophylline. Lag time was dependent on the amount of starch glycolate in the outer shell. The lag time of all formulations was between 0 to 6 h and it decreased with an increase in the amount of starch glycolate in the outer layer. Formulation ChrTRT<sub>2</sub> was considered as the optimized formulation since it yielded a predetermined lag time of 4 h before burst release of theophylline from the ChrTRTs. The indication is that this design can be exploited and utilized to achieve chronotherapeutic drug delivery systems of theophylline for the management of chronic illnesses such as asthma.

**Keywords:** *Irvingia gabonensis* gum, *Anarcadium occidentale* gum, Theophylline, Chronotherapeutic drug delivery systems (ChrDDS), Chronotherapeutic Timed Release Tablets (ChrTRTs), Theophylline Core Tablets (TCTs).

### INTRODUCTION

Asthma is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms such as variable airflow obstruction and bronchospasm. Symptoms include wheezing, coughing, chest tightness and shortness of breath [1]. Asthma is clinically classified according to the frequency of symptoms, force expiratory volume in one second (FEV-1) and peak expiratory flow rate. It may also be classified as atopic (extrinsic) or non-atopic (intrinsic) [2]. It is thought to be caused by a combination of genetic and environmental factors [3]. Asthma symptoms worsen at night, especially late at night and early in the morning. Symptoms of allergy such as running nose, wheezing and sneezing are also most frequent in the morning before breakfast [4]. Treatment of this disease condition occurring in the early hours is not convenient by using conventional immediate release dosage form. Hence, chronotherapeutic drug delivery system (ChrDDS) may be useful for such patients since the drug is released at a predetermined lag time [5].

Chronotherapeutics refers to a treatment method in which *in vivo* drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. It is based on the observation that there is an interdependent relationship between the peak-to-trough rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and pharmacokinetics of many drugs [6]. It is a branch of Pharmacotherapeutics, which follows the treatment approach of attacking the disease, when it is on peak level [7]. Some merits of this delivery system include increased patient adherence to therapy, decreased dosing frequency, reduced toxicity, instantaneous drug level etc. Drugs used in the management of cardiovascular diseases and asthma have been investigated for the chronotherapeutics because these symptoms follow circadian rhythms [8]. Hence, the purpose of this study is to design an optimized chronotherapeutic drug delivery system (ChrDDS) of theophylline using *Irvingia gabonensis* and

*Anacardium occidentale* gums in different ratios with a predetermined lag time.

*Irvingia gabonensis* (IG) gum is a natural polymer obtained from *Irvingia* seeds (*Irvingia gabonensis*) of the Order: Malpighiales, Family: Irvingiaceae and Genus: *Irvingia*. *Irvingia* gum was extracted from the pulverized seeds of IG by processes earlier described by Momoh *et al.*, [9] and was used as binder in this formulation. *Irvingia* gum has been previously used as a matrix former in the formulation of floating drug delivery system [10], binders in tablet formulations, and even as a suspending agent [11]. However, its use as a binder in ChrDDS has not been investigated.

Cashew gum is obtained as exudates from the stem bark of *Anacardium occidentale* L. (family: *Anacardiaceae*), a tree that grows in many tropical and subtropical countries [12-13]. Under certain conditions the bark of cashew exudes a gummy material known in general as cashew gum. It is a complex polysaccharide, comprising 70% galactose, 5% arabinose, 4% rhamnose, 1% mannose and 6% glucuronic acid [14]. Previously, cashew gum has been employed in the formulation of metronidazole tablets, and has been shown to possess excellent binding properties [15-16].

Theophylline also known as dimethylxanthine, is a methyl xanthine drug which acts as a bronchodilator, thus relaxing and opening the air passages to the lungs, increasing the flow of air through them. This explains their use in the treatment and/or prevention of symptoms of bronchial asthma and of reversible bronchospasm associated with chronic bronchitis and emphysema. They are used as muscle relaxants, cardiac muscle and central nervous system stimulants. Conventional preparations are seen as tablets and injectable. It is rapidly and almost completely absorbed after oral administration in solution or tablet with a bioavailability of 96%. It has a half-life of 4.5 h and the usual oral dosage regimen is 60 to 200 mg 4 hourly [17].

The aim of this study was to formulate a ChrTRTs for the management of nocturnal asthma using theophylline as a model drug. The goal was to have a lag time of 4 h i.e., the tablet is to be taken at bedtime (9.00 pm) and is expected to release the active ingredient after a period of 4 h i.e., at 1:00 am. Literature studies show that the time ( $t_{max}$ ) to attain peak plasma concentration of theophylline is approximately 2 h after oral administration [1, 18]. Hence, the therapeutic drug concentration would be at its optimal level, when asthma symptoms are most prevalent, i.e., at 3:00 am.

## MATERIALS AND METHODS

Theophylline (Sigma Chemical Company, St Louis, MO) was a gift from Vitabiotics Nigeria Ltd. Maize starch powder (BDH, Chemical, Poole, UK) was used as a disintegrant in the core tablet. *Irvingia* gum was used as the binder, talc was used as the glidant at a concentration of 1%w/w. IG and AO gums were extracted by methods described earlier (Momoh *et al.*, 2008). All other chemicals were of analytical grades.

### Methods

#### Formulation of an optimised theophylline core tablet (TCT)

Wet granulation method was employed in the formulation of an optimised core tablet of theophylline using 2.5 %w/w concentration of *Irvingia gabonensis* (IG) gum as binder. Appropriate weight of theophylline powder and 15%w/w of maize starch powder (incorporated both intra and extra-granularly) were added and mixed in a mortar. The binder was added to the mixture with continuous mixing to produce a damp mass which was passed through an 850  $\mu$ m aperture sieve, and then oven dried at 60°C for 30 min. The dried granules were subsequently passed through a 710  $\mu$ m aperture sieve. The remaining amount of 15%w/w maize starch (extra-granularly) and 1%w/w talc were added to the dried granules. The resulting granules were compressed into tablets using the single punch tableting machine (Type P3, No: 5L 182, Manesty machines LTD, Liverpool, England) after all the necessary micrometric tests were carried out.

#### Preparation of chronotherapeutic timed-release tablets (CCTRTs)

The IG and AO gums were appropriately weighed as required and mixed together. Sufficient distilled water was used to wet the mass which was passed through an 850  $\mu$ m aperture sieve, and then oven dried at 60°C for 30 min. The dried granules were passed through a 710  $\mu$ m aperture sieve. Sodium starch glycolate was then added to granules. Half the amount of the polymer blend was placed inside the die to make a powder bed. The core tablet was placed at the centre on the polymer bed, while the remaining half of the polymer blend was filled into the die. The contents were compressed using a single punch tableting machine (type-F3 Manesty machine, UK) under a compression force of 35 units to form a biconvex tablet (Table 2).

#### Evaluation of Post-compression Parameters of the TCT and ChrTRTs

##### Hardness test

The hardness of the TCT and ChrTRTs (5 each) was determined by diametrical compression using the Mosanto hardness tester (Mosanto Chemical Company, Liverpool, England). Hardness is defined as force required to fracture a tablet in a diametric compression test [19]. The mean values as well as the

standard deviation of the pressure required to break a tablet placed in the anvil of the hardness tester were recorded.

#### Friability test

The Roche friabilator (Erweka, Germany) was used for this test. Five (5) randomly selected tablets both from the TCT and the ChrTRTs were used. The initial weight of the tablets was determined before they were placed in the friabilator. The friabilator was allowed to operate at 25 rpm after which the final weight of the tablets was determined. These values were used to calculate the percentage friability using equation 1.

$$\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100 \dots\dots (1)$$

#### Disintegration test

Six tablets randomly selected from the TCT batch and the ChrTRTs were individually subjected to the B.P. disintegration test [18]. The mean value of the disintegration time was calculated. The disintegration medium (distilled water) was kept at  $37 \pm 1.5^\circ\text{C}$ .

#### Drug content determination

In order to determine the amount of theophylline present in the TCT and ChrTRT formulations, ten (10) tablets were weighed and crushed to fine powder. The powder equivalent to 100 mg of drug was weighed, transferred to a 100 ml volumetric flask and made up to volume with 0.1 N HCl. The resulting solution was filtered and a dilution of 1 in 100 was made (with 0.1 N HCl). The absorbance of the resulting solution was measured at 272 nm using a UV spectrophotometer (Model Spectronic 21D, Bausch and Lomb, USA) and the percentage drug content was computed.

#### Dissolution test

Six (6) of the ChrTRTs were subjected to *in vitro* drug release studies in two different dissolution media. 900 ml solution of 0.1 N HCl (pH 1.2) was used for the first 2 h and continued in phosphate buffer (pH 6.8) for the next 8 h. The temperature of dissolution medium was kept constant at  $37 \pm 0.2^\circ\text{C}$ . An aliquot of 5 ml was withdrawn at predetermined time intervals and replaced with an equal volume of the fresh dissolution medium. The samples were diluted and analyzed at wavelength of 272 nm for percentage drug release using a UV spectrophotometer (T70, UK). The procedure was conducted in triplicate and the mean value recorded.

## RESULTS AND DISCUSSION

### Flow and packing properties of theophylline granules

The angle of repose for granules of the optimised TCT formulated with 2.5% w/w IG was  $24^\circ$ . This indicates good flowability of the granules which is

very essential in ensuring weight and content uniformity during tableting. The Carr's index value was 17% and this represents the ability of the granules to be compressed upon application of a given stress. Hausner's ratio was 1.2. This is a number also correlated to the flowability of granules. The results of the micromeritic properties indicate that all the granules displayed good flow properties (see Table 1).

### Post Compression Parameters

The TCTs were evaluated for the following parameters; hardness, friability, disintegration time and drug content. The results are presented in Table 3. The hardness value of the optimised TCTs formulated with 2.5% w/w IG was  $3.9 \pm 0.1 \text{ kg/cm}^2$ , while that of the ChrTRTs was  $\leq 12.0 \pm 0.2 \text{ kg/cm}^2$ . Increase in hardness was found to be associated with an increase in binder concentration due to the increased inter-particulate bonding between granules of the tablet. Hardness values are also dependent on the tablet shape, chemical properties as well as pressure applied during compression.

The friability values of the TCT and ChrTRTs were  $0.81 \pm 0.1$  and  $\leq 0.68 \pm 0.1\%$  respectively. Friability is a measure of the ability of the tablets to withstand abrasion during handling, transportation and packaging. It is ideal for tablets to lose not more than 1% of their weight.

The disintegration time for the TCT was 10 min. For the active ingredient to be made bioavailable it is necessary for the tablet to break up into coarse granules and then finer granules before drug dissolution and absorption can occur, hence the time of tablet disintegration is very important. Disintegration time correlates with the amount of disintegrant included in the tablet formulation, hence increase in disintegrant concentration results in reduction in disintegration time and vice versa. There is also a linear relationship between concentration of binder and disintegration time. According to B.P [18] specifications, disintegration time for uncoated tablets should not exceed 15 min. Therefore the disintegration time of the optimised TCT prepared with 2.5% w/w *Irvingia* gum lies within the B.P. specification. The drug content for the TCT and ChrTRTs were 93 and  $\leq 94\%$  respectively and is within the acceptance criteria of 90-110% [20].

### *In vitro* drug release profile of TCT and ChrTRTs

The *in vitro* drug release parameters of the theophylline core tablet in 0.1 N HCl is shown in Figure 1 and the release parameters derived from the curves are presented in Table 4. It was observed that the TCT released 98% of the theophylline in  $< 25$  min which conforms to the BP specification [18] which states that 70% of the drug should be released in 45 min.

The drug release profiles of the ChrTRTs formulations of theophylline are shown in Figure 2. The ChrTRTs (ChrTRT 1, 2, 3 and 4) showed unique lag times before theophylline release. Generally, lag time decreased with increasing concentration of sodium starch glycolate (super disintegrant) from 6 h for ChrTRT<sub>1</sub> (0% sodium starch glycolate) to 0.5 h for ChrTRT<sub>4</sub> (2% sodium starch glycolate). The amount of *Anacardium occidentale* and *Irvingia gabonensis* gums was kept constant in all the ChrTRT formulations in order to produce hard tablets with low brittle fracture tendency. It can also be observed that all the ChrTRT formulations showed characteristic release patterns. Maximum release was observed after 8 h for ChrTRT<sub>1</sub>, 6 h for ChrTRT<sub>2</sub>, 4 h for ChrTRT<sub>3</sub> and 1 h for ChrTRT<sub>4</sub> (See table 2).

Formulation ChrTRT<sub>2</sub> with 0.5% sodium starch glycolate, 400 mg AO and 100 mg IG gums was considered as the optimized formulation since it yielded a predetermined lag time of 4 h before burst release of theophylline from the ChrTRTs. Literature evidence shows that the time ( $t_{max}$ ) to attain peak plasma concentration of theophylline is reached approximately 2 h after oral administration [17]. Thus, if the formulation is administered at bedtime (9:00 pm) and is expected to release the drug after 4 h, peak plasma concentration would be reached approximately 2 h after oral administration. Hence, the drug concentration would be at its maximum level, when asthma attacks are prevalent, i.e. at 3:00 am.

**Table 1: Micromeritic properties of the optimised theophylline granules prepared with 2.5% *Irvingia gabonensis* gum**

Micrometric properties	Bulk volume (ml)	Tapped Volume (ml)	Bulk Density (g/cm <sup>3</sup> )	Tapped Density (g/cm <sup>3</sup> )	Carr's Index (%)	Hausner's Ratio	Angle of Repose (°)
2.5% IG gum	21±0.2	18±0.1	0.52±0.1	0.62±0.1	17±0.1	1.2	24±0.2

**Table 2: Composition of the Chronotherapeutic Timed Release Tablets (ChrTRTs)**

Ingredient	ChrTRT <sub>1</sub>	ChrTRT <sub>2</sub>	ChrTRT <sub>3</sub>	ChrTRT <sub>4</sub>
Sodium starch glycolate (% w/w)	0	0.5	1	2
Irvingia gum (g)	0.10	0.10	0.10	0.10
Anacardium gum (g)	0.40	0.40	0.40	0.40

**Table 3: Physicotechnical properties of theophylline core tablet (TCT) and chronotherapeutic timed released tablets (ChrTRTs).**

Formulations	Friability (%)	Hardness (Kg/cm <sup>2</sup> )	Disintegration time (min)	Drug Content (%)
TCT	1.61±0.1	3.9±0.1	10	98
ChrTRT <sub>1</sub>	0.92±0.2	8.9±0.3	-	97.2
ChrTRT <sub>2</sub>	0.83±0.1	9.3±0.1	-	97.5
ChrTRT <sub>3</sub>	0.75±0.1	11.5±0.2	-	96.8
ChrTRT <sub>4</sub>	0.68±0.1	12.0±0.2	-	97.8

**Table 4: Dissolution parameters of chronotherapeutic timed release tablets (ChrTRTs)**

Dissolution Parameters	ChrTRT <sub>1</sub> (0% S.D)	ChrTRT <sub>2</sub> (0.5% S.D)	ChrTRT <sub>3</sub> (1% S.D)	ChrTRT <sub>4</sub> (2% S.D)
Lag time (h)	6	4	2	0.5
$m_{\infty}$ (%)	98.15	97.85	98.62	98.95
$t_{\infty}$ (h)	8	6	4	1
$m_{\infty}/t_{\infty}$ (% min <sup>-1</sup> )	12.27	16.31	24.655	98.95

Where

$m_{\infty}$  = Maximum release

$t_{\infty}$  = time taken to attain maximum release

ChrTRT = Chronotherapeutic Timed Release tablet

S.D=Super Disintegrant (Sodium starch glycolate)

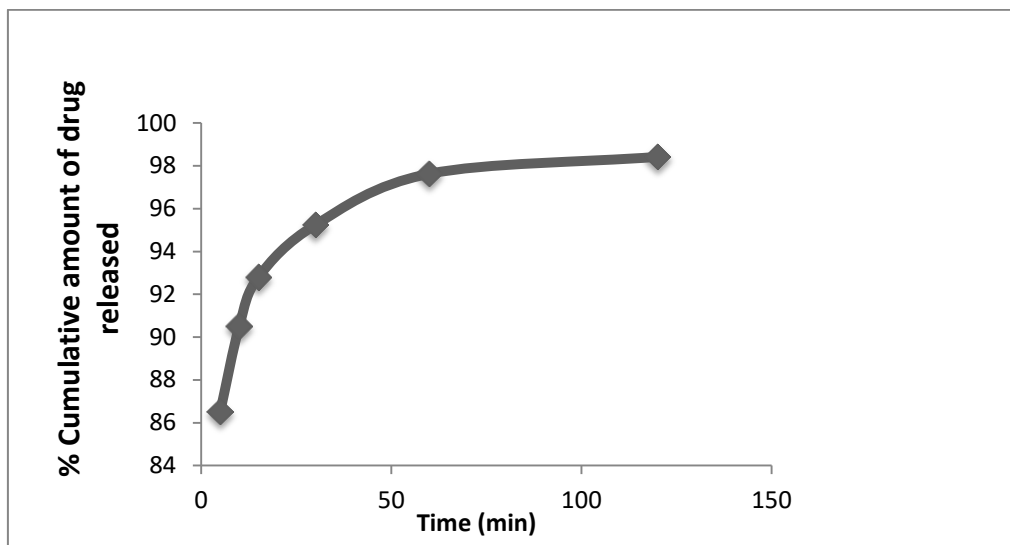


Fig-1: Cumulative theophylline release from TCT formulation in phosphate buffer (pH 6.8), [1]

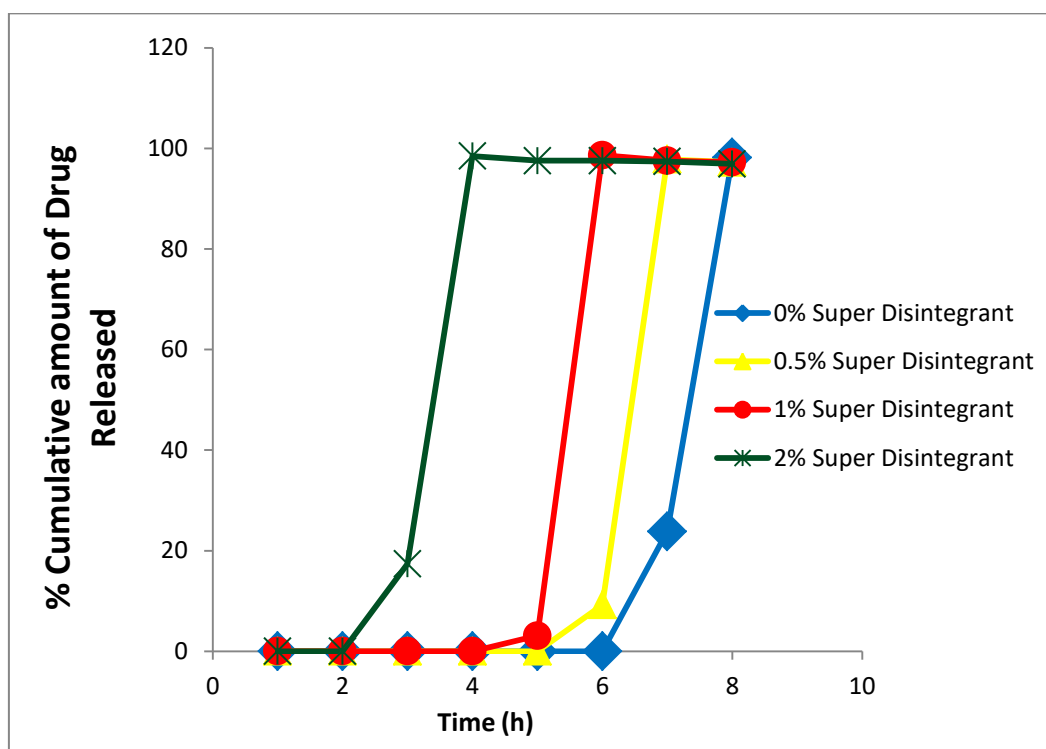


Fig-2: Cumulative theophylline release from CCTRT<sub>1</sub>, CCTRT<sub>2</sub>, CCTRT<sub>3</sub>, CCTRT<sub>4</sub>, and CCTRT<sub>5</sub> tablet formulations in phosphate buffer (pH 6.8) [1].

### CONCLUSION

This design can be exploited to achieve chronopharmaceutical drug delivery system for the treatment of asthma at the time when the symptoms are most aggravated.

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