



Sustained-release Theophylline Matrix Tablet Using Hydrophilic Polymers: Effects of Agitation Rates and pH on Release Kinetics

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Authors' contributions

This work was carried out in collaboration among all authors. Author EIA designed the study and wrote the protocol of the study. Authors GJ and UI carried out the laboratory studies. Authors NIS and UI performed the statistical analysis for the first draft of the manuscript. Authors TOU and DEE managed the analyses of the study, wrote the draft of the manuscript and handled the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background and Objective: Modified-release tablet of theophylline that can increase its usefulness despite narrow therapeutic index and short half-life, is being formulated. However, the rate and extent of release of a sustained-release delivery system can be affected by some factors. This work is aimed at investigating the effect of agitation rates and pH of dissolution medium on release kinetics of sustained-release theophylline tablet formulated using hydrophilic polymers.

Materials and Methods: Theophylline granules was formulated using 3 polymers (HPMC, SCMC and Sodium alginate) to form 3 batches of granule by wet granulation method, using 95% ethanol.

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The granules compacted to batches of sustained-release matrix tablets. The tablet batches were characterized for tablet properties, and dissolution studies carried out using simulated gastric and intestinal fluid separately at different agitation rates. The data from dissolution studies were subsequently fitted into 4 drug release kinetics models.

Results: The swelling of the 3 polymers over time was noteworthy, although there was no significant difference between them. The release kinetic followed the Higuchi model and zero-order releasing more than 90% over 8 hours period, with t_{10} and t_{90} released at 14 minutes and 6.8 hours respectively. The mechanical properties of the tablets were within the acceptable limit.

Conclusion: The agitation rate and pH of the medium had no significant effect on the release of the theophylline from the batches of matrix tablets except in the case of F1 which showed a marginally significant effect.

Keywords: *Theophylline; sustained-release; agitation rate; pH effect; release kinetics; hydrophilic polymer; matrix tablet.*

1. INTRODUCTION

The obvious limitations of conventional oral tablets: the fluctuation in drug plasma concentration, under/over dose of medication, frequency of dosing, poor patient adherence with resultant increased chances of missed doses, necessitate the call for modified tablet formulation. Sustained-delivery systems, a modified delivery, help maintain a near-constant plasma concentration of a drug and enhance clinical efficacy for its intended use [1].

Sustained-release tablets achieve prolonged therapeutic effect by continuously releasing active medication, after a single dose administration, over an extended period, although not at a predetermined rate [2].

Matrix systems are a common means of formulating sustained-release tablets. They are mainly composed of the drug, polymers and other excipients as vehicles for drug delivery [3]. Both hydrophobic polymers and water-soluble hydrophilic materials have been reportedly employed as matrix formers either individually or as polymeric blends [4,5,6]. Some common matrix formers are hydroxy propyl methyl cellulose (HPMC), Sodium carboxy methyl cellulose (SCMC) and Sodium alginate.

Hydroxy propyl methyl cellulose (HPMC), is a hydrophilic polymer that has great functionality in drug delivery. It is a product of chemical modification of cellulose, soluble in both aqueous and non-aqueous solvents [7]. It slowly undergoes dissolution to form a viscous mixture, hence can affect polymer's diffusion pathway. These properties make it a good candidate as matrix former to sustain the release of drugs. The design of a delivery system made from HPMC can influence its general drug release mechanism.

Sodium alginate is a natural hydrophilic polysaccharide salt of alginic acid obtained from brown algae. Its biocompatibility and biodegradability make it useful in delivery systems for controlled release [8]. Unlike HPMC, Sodium alginate quickly forms viscous solutions and gels once in aqueous medium giving its liquid-gel behaviours [9].

Sodium carboxy methyl cellulose (SCMC) is a cellulose derivative polymer, used as a thickener in pharmaceutical preparations and as a matrix former. It is used in concentrations of 0.25 % for suspending powders in parenteral, oral and external products. When this polymer is employed as a binder, granules formed have better compressibility, and give moderately hard tablets. Also, due to its hygroscopic nature, it can absorb a large amount of water (about 50%) at conditions of high relative humidity [10].

Theophylline, a 1, 3 –dimethyl xanthine and drug of choice, for this study is still one of the most widely prescribed drugs for the treatment of asthma and chronic obstructive pulmonary disease (COPD) worldwide because of availability and being less expensive [11]. Its use (as oral tablet or injectable) in airway dilation is directly proportional to its serum concentration. With a narrow therapeutic window of 10-20mg/L and a short half-life, its dosing frequency is about 2-3 times daily [11]. But, theophylline is rapidly and completely absorbed on administration, and shows large inter-individual variation in renal clearance, hence its sustained-release tablet will help modify its release kinetics to maintain a near-constant plasma therapeutic concentration [11,12]. Also, since theophylline toxicity is usually at a concentration above 20 mg/L and its serum

concentration fluctuations can result in variability in clinical response, a sustained-release delivery will maintain therapeutic serum levels for up to 24 hours after once or twice daily dose administration [13]. Several published works abound on the formulation of theophylline as sustained and controlled release preparations using different technologies (matrix tablet system, microbeads, floating tablets [5,6,12,13]. It is important to investigate conditions that can affect or change theophylline release kinetics even from sustained-release matrix tablets. Thus, this work was to formulate theophylline SR matrix tablets using 3 different hydrophilic polymers (Alginate, HPMC, SCMC) respectively and then evaluate its release in different dissolution media. The objective was to assess the effect of pH of medium and stirring rates on the release kinetics of the drug.

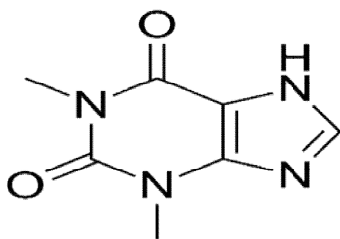


Fig. 1. Chemical structure of theophylline [12]

2. MATERIALS AND METHODS

2.1 Materials

Theophylline anhydrous (Sigma-Aldrich, UK), hydroxyl propyl methyl cellulose (HPMC) (William Ranson & Son Limited, Hitchin Hertfordshire England, Batch No: 639462), sodium alginate(SA), sodium carboxy methylcellulose (SCMC), microcrystalline cellulose (MCC) (Sherman chemical Ltd, Sunderland and Sandy, England), aerosil, 95 % ethanol (Fisher Scientific, UK).

2.2 Methods

2.2.1 Study area

The study was carried out at the pharmaceuticals laboratory, tableting unit and the dosage form evaluation unit, all in the department of pharmaceuticals and pharmaceutical technology, faculty of pharmacy, University of Uyo, a tertiary institution in the South-South region of Nigeria,

between the period of August 2019 and March 2020.

2.2.2 Preparation of granules

The granules were prepared using the wet granulation method. Three batches of the granules were prepared using a polymer for each batch but at the same concentration. The quantities of ingredients in the batches of compacts are reflected in Table 1. The ingredients were weighed accurately and thoroughly mixed in a porcelain mortar. Granulation was done in 95 % ethanol. The wet masses were passed through a 2 mm sieve and the resulting granules dried in a laboratory-sized hot air oven (Techmel & Techmel USA TT-9053) at 60°C for 2hours. The dried granules were then passed through a 1 mm sieve to obtain granules of uniform size.

2.3 Granules Evaluation

The methods of granule evaluation using densities and micromeritics were carried out as described in literature [14].

2.3.1 Densities, Hausner's ratio and compressibility index

Exactly 20 g of the dried granules was weighed and transferred into a 100 mL graduated cylinder. The untapped volume (V_0) was noted. The granule-filled cylinder was tapped for about a hundred times to obtain a constant volume. The new volume (V_{100}) was noted. This procedure was repeated three times and the mean value determined. The bulk density was taken as ratio of mass to untapped volume (V_0) occupied by granule while the tapped density was the ratio of mass of granule to its tapped volume (V_{100}).

For granule density, the fluid displacement method using a 25 mL pycnometer was employed with xylene as the non-solvent [15]. The Hausner's ratio and compressibility indices were determined for the granules by methods previously used [15].

2.3.2 Determination of packing fraction and granule porosity

The packing fraction and the porosity of the batches of granules also were determined as in literature [14].

Table 1. Composition of the theophylline tablet

Ingredients/Batch code	F 1	F 2	F 3
Theophylline (mg)	200	200	200
SCMC (%w/w)	20	-	-
Sodium Alginate (%w/w)	-	20	-
HPMC (%w/w)	-	-	20
Talc (%)	1	1	1
Aerosil (%)	1	1	1
Microcrystalline cellulose to (mg)	400	400	400

KEY: F1: Theophylline + 20% w/w SCMC

F2: Theophylline + 20% w/w Sodium Alginate

F3: Theophylline + 20% w/w HPMC

Hydroxy propyl methyl cellulose (HPMC) Sodium carboxy methyl cellulose (SCMC)

2.3.3 Angle of repose and flow rate

The angle of repose was determined using the fixed height method. Specifically, 20 g of granule of a batch was allowed to flow through a funnel fixed to a retort stand at a height of 4 cm to form a cone heap on a flat horizontal surface. The heap height, diameter of the cone base, and the time taken for all the granule to flow through the funnel were noted. The flow rate was calculated as the ratio of weight of granule to the time taken for it to flow through funnel. The angle of repose was obtained using the equation 1 as described below [16].

$$\text{Angle of Repose}(\theta) = \tan^{-1}\left(\frac{h}{r}\right) \quad (1)$$

Where, h= height of the heap, r = radius of the base of the powder cone

2.4 Compression of Theophylline Tablets

The prepared granules were lubricated with 1 % each of talc and aerosil, then compressed into solid compacts using a single punch tableting press fitted with 12.5 mm flat faced punches (Cadmach, India) at a constant compression force of 15 KN.

2.5 Evaluation of Tablets

2.5.1 Crushing strength and friability

The crushing strength of the tablets was determined using the Monsanto hardness tester (Rolex, Chandigarh). Ten (10) tablets from each batch were selected at random, placed diametrically on the tester and crushed. The crushing strength value as read on the hardness tester was noted and the mean determined. For the friability, five (5) tablets were used in a Roche

friabilator (UNID 056830 Campbell Electronic, Mumbai, India). The tablets were dusted, weighed (W_0), and then placed in the friabilator, operated for 4 minutes at 25 revolutions per minute (rpm). The tablets were then removed from the chamber, dusted and reweighed (W_1). The friability was then calculated from equation 2 below [6]:

$$F = \frac{W_0 - W_1}{W_0} \times 100 \quad (2)$$

Where, W_0 = initial weight of tablets, W_1 = final weight of tablets on removal from friabilator.

2.6 Tablet Dimensions

The dimensions of the tablets (thickness and diameter) were determined using the micrometer screw gauge (KFW Scientific Industries Ambala Cantt, India). Ten (10) tablet randomly selected from each batch were measured and the mean values determined.

2.7 Tablet Porosity

The tablet porosity was determined using the equation 3 below¹² as modified;

$$\text{Tablet porosity} (\varepsilon) = 100 \left[1 - \frac{m}{\rho_t \pi r^2 h} \right] \quad (3)$$

Where, m = mean weight of tablets, ρ_t = particle density, r = mean tablet radius, h = tablet thickness

2.8 Swelling Index

Three (3) tablets from each batch were weighed before placing them in a petri-dish containing 0.1 N HCl for 2 hours. At 30 minute intervals, the swollen tablets were taken out and weighed after

mopping off the fluid medium from the swollen tablets using a tissue paper. The swelling index of the tablet was calculated from equation 4 as stated [17]:

$$S.I = \frac{W_t - W_o}{W_o} \times 100 \quad (4)$$

Where, S.I = swelling index, W_t = weight of tablet at time t, W_o = initial weight of tablet

2.9 Weight Uniformity and Content Uniformity

For weight uniformity, exactly twenty (20) tablets, selected randomly from each batch were weighed using an electronic balance (Ohaus, Galaxy). The mean, standard deviation and coefficient of variation were then determined.

Content uniformity was carried out using 10 tablets from each batch. These tablets were weighed, then crushed in a mortar. A powdered quantity equivalent of 200 mg theophylline was weighed out and dissolved in 100 mL of 0.1 N HCl in a volumetric flask. The solution was filtered using a Whatman filter paper no.1. About 0.1 mL of the filtrate was then diluted to 10 mL with 0.1 N HCl and analyzed using a spectrophotometer (UV-2100 PC, Shanghai, China) at 271 nm and 0.1 N HCl as the blank. The standard calibration curve of theophylline was used to determine the amount of the drug in the filtrate.

2.10 In-vitro Dissolution Test

The USP 1 (basket) method was used for the drug release study. The agitation rates for dissolution were varied for each batch each time at 25, 50 and 100 revolutions per minute (rpm) in a 900 mL medium in dissolution apparatus (RCZ-6C3, China). Two dissolution media were used: the simulated gastric fluid and the simulated intestinal fluid, maintained at a temperature of $36 \pm 0.5^\circ\text{C}$. About 10 mL aliquots were withdrawn at 30 minutes interval for up to 8 hours. Withdrawn samples were quickly replaced with an equal volume of the blank medium maintained at the same temperature. The withdrawn samples were filtered with a Whatman filter paper no.2, diluted appropriately and then analyzed using UNICO-spectrophotometer (UV-2100PC Shanghai Instruments Co. Ltd., China) at a wavelength of 271 nm. The cumulative percentage drug release was also calculated.

2.11 Standard Calibration Curve

A 10 mg quantity of theophylline powder was dissolved in 10 mL of the medium (simulated gastric fluid) respectively. The resultant solution was prepared as serial dilutions of 10 $\mu\text{g/mL}$, 20 $\mu\text{g/mL}$, 30 $\mu\text{g/mL}$, 40 $\mu\text{g/mL}$, and 50 $\mu\text{g/mL}$, and the absorbance read in a UV- spectrophotometer (UNICO-spectrophotometer, UV-2100 PC, Shanghai instrument Co., China) at a wavelength of 271 nm using 0.1HCl as the blank. The graph of absorbance versus concentration was plotted to obtain a calibration curves of theophylline in media.

In vitro Release profile and mechanism of the tablets: The data obtained from *in vitro* dissolution studies were fitted into 4 kinetic models: Zero-order ($Q_0 - Q_t = k t$), First-order ($\ln Q_t = \ln Q_0 - k t$), Higuchi ($Q_t = k t^{1/2}$) and Korsmeyer-Peppas model equation ($Q_t / Q_\infty = k t^n$) [6]. The model with the highest correlation coefficient (R^2) was considered to be the best fit for the designated kinetic release. The mechanism of drug release was also determined by using the Korsmeyer-Peppas model equation and its release exponent co-efficient (n) used to arrive at the release mechanism. The values of Q_0 , Q_t , and Q_∞ are the initial amount of drug, drug released at time, t, and cumulative drug released respectively. K and t refers to the rate constant and the time of release respectively.

2.12 Statistical Analysis

All experiments were done in triplicates and results presented as mean \pm standard deviation. The results data obtained for swelling index and drug release were subjected to statistical analysis. The one-way Analysis of variance (ANOVA) was for the swelling index but a two-way ANOVA for the release pattern in different dissolution medium at different rates of agitation. At a 95% confidence interval, the probability (p) value at $p \leq 0.05$ was considered significant.

3. RESULTS AND DISCUSSION

The result of the micromeritics and particle arrangement of granules is presented in Tables 2 and 3.

The micromeritics and packing geometry results as presented in Tables 2 and 3 show that the granules of theophylline prepared had angle of repose (range from $30-35^\circ$), Hausner's ratio

(range 1.07-1.11) and Carr's index (range 6-10%). They showed good to excellent flowability. All the batches of granules had low value for packing fraction (0.28- 0.30) but high porosity (70-72%). This packing geometry of the granule gives an insight to the ease of flow seen. Such particle arrangement allows for poor interparticle cohesion so that a little vibration could trigger particle movement. Little wonder all batches on tapping gave higher values of tapped densities when compared with the bulk densities. These observations were expected in the granules since granulation improves flowability of particles while tapping causes particle rearrangement to reduce the volume occupied by granules [14]. There was also no significant difference ($p > 0.05$) in the granule density, granule porosity, packing fraction, and tablet hardness in the different polymers used. Microcrystalline cellulose in the formulation was to improve the ease of compaction and tablet formation of the sustained-release matrix tablet [18].

The physical and mechanical properties of the theophylline sustained released tablets are shown on Table 4 while the chemical structure of theophylline, swelling index of matrix tablet and calibration curve are seen in Figs. 1, 2 and 3 respectively.

From Table 4, the crushing strength (or hardness) of the tablets (range of 6.9 - 8.9 Kg F) and friability (range 0.72-0.84 %) are seen. The values reveal that the formulated tablets are neither too hard to resist breakage nor too weak to crumble during transportation. The weight uniformity of the different batches of tablet are also presented. The International Pharmacopoeia specifies that for tablets ≥ 250 mg, not less than 18 tablets must equal $\pm 5\%$ mean weight deviation, but not more than 2 tablets should be $\pm 10\%$ mean weight deviation, for a 20 randomly selected tablets. A good range for hardness is satisfactory while friability must be $\leq 1\%$. The values for friability and weight uniformity meet these official compendia range of

values [12,19,20]. The drug content of all the sustained release matrix formulations were in the range of 92.50% to 95.10%. A good percentage of the drug is present within the tablet matrix and is in the range of acceptable limits given in the compendium for extended release theophylline capsules (90-110%) [20]. This indicates proper mixing and flow of granules during processing of all the three batches. Also the weights of tablets of batches F1, F2 and F3 were not significantly different ($p > 0.05$).

The chemical structure of theophylline (as seen in Fig. 1) shows that the drug has a purine base and is a ketone, no wonder it is also called Purine-2, 6-dione [20]. Fig. 2 shows results of the tablet swelling in 0.1 N HCl. The values range between 65-72% with F3 having the highest, followed by batch F1 with the swelling index of 70% while batch F2 had the lowest swelling index of 65%. However, there was no statistically significant difference ($p > 0.05$) in the swelling index of the tablets made from the different polymer types (SCMC, sodium alginate and HPMC) as used in the sustained-released formulation. Swelling refers to increase in size or weight of tablet while maintaining its integrity, consequent on uptake of a medium (for example water). The swelling index points to the extent of hydration of the tablet formulated with different polymers and how this in turn influences the swelling behavior and drug release kinetics [12, 17]. In this work, we intended to see the degree of swelling in the initial period with consequent initial drug release, hence the swelling study was for 2 hours only.

In Fig. 3, the calibration curve of theophylline (absorbance against concentration) was plotted, giving a correlation coefficient (R^2) of approximately 0.9901 over the concentration range studied (0.06–0.6 mg mL⁻¹). The representative linear equation was $y = 0.0278x - 0.0151$.

Table 2. Micromeritics and flow properties of theophylline granules

Batch code	Bulk density(g/mL) Mean \pm SD	Tapped density (g/mL) Mean \pm SD	Carr's Index (%) Mean \pm SD	Hausner's Ratio Mean \pm SD	Angle of repose (θ) Mean \pm SD	Flow rate (g/s) Mean \pm SD
F1	0.39 \pm 0.01	0.42 \pm 0.01	7.14 \pm 2.57	1.07 \pm 0.02	32.00 \pm 0.82	2.58 \pm 0.01
F2	0.40 \pm 0.01	0.43 \pm 0.01	6.97 \pm 3.06	1.08 \pm 0.02	35.00 \pm 0.82	7.87 \pm 0.01
F3	0.35 \pm 0.00	0.39 \pm 0.01	10.26 \pm 2.29	1.11 \pm 0.04	31.00 \pm 0.82	4.23 \pm 0.01

Keys: F1: Theophylline + 20% w/w SCMC
F2: Theophylline + 20% w/w Sodium Alginate
F3: Theophylline + 20% w/w HPMC

Table 3. Particle densities and other related properties of theophylline granules and tablets

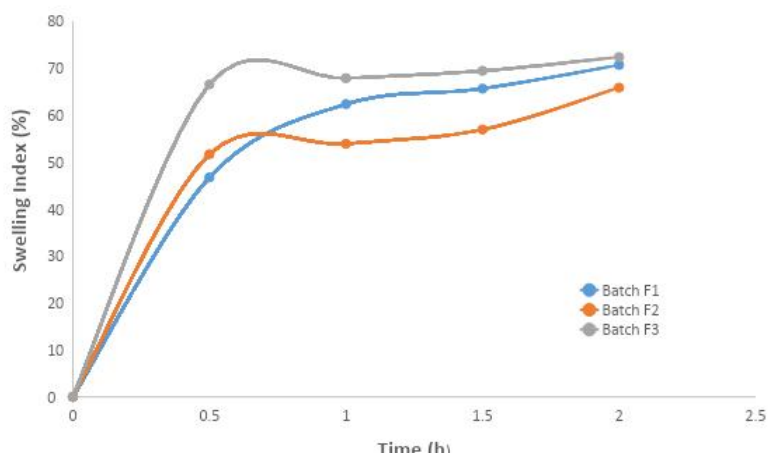
Batch code	Granule density (g/mL)	Granule porosity (%)	Packing fraction	Tablet porosity (%)
F1	1.34±0.01	71	0.29±0.01	9.10
F2	1.34±0.00	70	0.30±0.01	4.50
F3	1.26±0.01	72	0.28±0.00	3.10

Keys: F1: Theophylline + 20% w/w SCMC
 F2: Theophylline + 20% w/w Sodium Alginate
 F3: Theophylline + 20% w/w HPMC

Table 4. Tablet properties of theophylline tablets

Batch code	Weight uniformity (g) mean ±SD n=20	Thickness (mm) Mean ±SD n=10	Diameter (mm) Mean ±SD n=10	Hardness (KgF) mean ±SD n=10	Friability (%) n=10	Drug content (%)
F1	0.40±0.01 (3.52)	2.62±0.17	12.56±0.11	7.10±1.50	0.73	93.20
F2	0.41±0.01 (3.50)	2.60±0.15	12.52±0.02	8.90±1.08	0.84	92.50
F3	0.41±0.01 (2.90)	2.49±0.23	12.54±0.02	6.95±2.09	0.72	95.10

*values in bracket represent coefficient of variation (%).
 Keys: F1: Theophylline + 20% w/w SCMC
 F2: Theophylline + 20% w/w Sodium Alginate
 F3: Theophylline + 20% w/w HPMC

**Fig. 2. Swelling profile of theophylline tablet in 0.1 N HCl**

The Figs. 4-9 show the drug release profiles of the sustained-release tablets at different agitation rates in different dissolution media whereas Tables 5-10 reveal the correlation coefficient values of the kinetic data as fitted into the 4 different drug kinetic models.

The release profile of the drug from the matrix-forming polymers is shown in Figs. 4-9. All the batches of the tablet sustained (extended) the

release of the drug for the 8 hours [20]. This means that the polymers can hold the drug, releasing it over such a duration. The initial release at 30 minutes, in all batches at different conditions, range from 21-43% of the drug content. It is noteworthy though that that initial drug release at 30 minutes was generally lowest in F3 in all the experimental conditions but highest in F1 in most conditions. Also the cumulative percentage of drug released from all

the polymers at the 8th hour, range from 90 - 99%, implying that almost all the drug content was released at this time. The lowest percentage drug release at the 8th hour was obtained with F3 (tablet with HPMC) in SIF at 25rpm agitation whereas highest percentage release was seen with F2 (tablet with Sodium alginate) in SGF at 100rpm. Sustaining the release of a drug over time is a function of the drug's solubility, carrier polymer type, force of compaction and dosage form design [6,16,21,22]. Insoluble polymers have been reported to sustain drug release for 15-24 hours [21]. The polymers used in this work are hydrophilic but their rate of uptake of dissolution media differs and the theophylline is only slightly water soluble, hence such release of almost all the drug content in 8 hours.

These lowest value for both the initial and percentage cumulative drug release seen in F3 in all experimental conditions could be attributed to the delay in swelling time of polymer, viscosity of gel formed and subsequent drug release. HPMC, the polymer in F3 delays in swelling over time [15,23]. This will mean it will likely take longer for HPMC to be completely wetted, eroding the surface, allowing dissolution fluid through the interstices to form a gel, dissolve the drug within the matrix before releasing it through similar pathway. On the other hand, matrix formers of the other two batches (F1 and F2) are sodium salt forms hence will have better wetting and release.

Tables 5-10 also reveal the kinetic model that best describes the drug release pattern. It

appears the medium of dissolution and agitation rates influenced the kinetic model of release that best describes the release kinetics. Generally, the batches, as matrices of hydrophilic polymers, are best described by the Higuchi kinetic model and the zero-order [24]. Specifically, all batches in both media (SIF and SGF) at agitation rates of 50 and 100 rpm followed the Higuchi kinetic model of drug release except F3 in SIF at 50rpm that followed the zero-order. At 25rpm, all batches studied in both SIF and SGF followed Higuchi model but F1 in SIF that is best described by the zero-order kinetics. Batches best fitted into the zero-order, have a constant drug release that is independent of the initial amount of the drug in the tablet matrix. Thus, drug release in such batches depended mainly on matrix erosion and polymer relaxation [24]. The batches, in the given experimental conditions, best described by the Higuchi model release drug depending on the square root of time, meaning that the drug release from the matrix is predominantly controlled by diffusion through the tablet matrices [6,12]. The Higuchi model have been used to describe drug dissolution from matrix tablet [21,25]. Other works had reported theophylline matrix tablets to follow similar kinetic models [6,12,21,23,25]. The release exponents obtained from Korsmeyer-Peppas kinetic equation corroborate the release mechanism for the F1 at 25 rpm indicating that released content is characterized by case II and super case II ($n > 0.89$) which is by erosion mainly and does not depend on amount of drug in matrix [4].

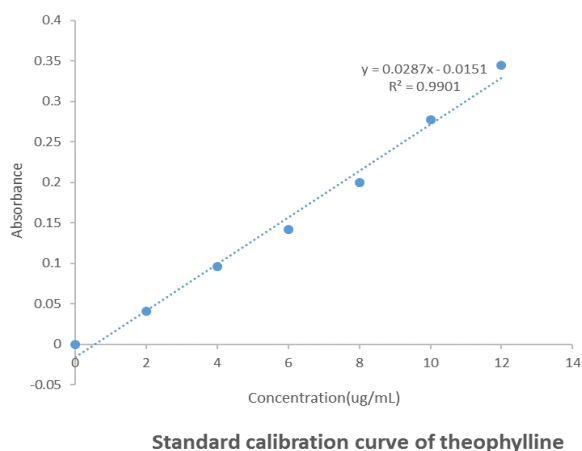


Fig. 3. Standard calibration curve for theophylline

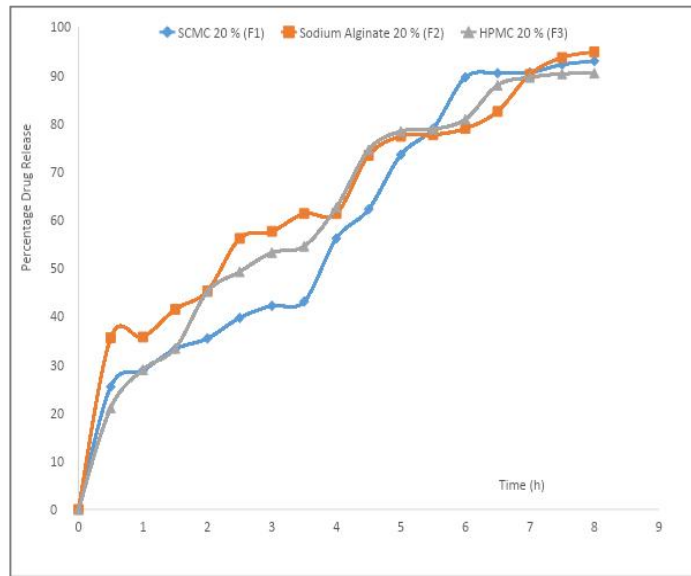


Fig. 4. Release profile of theophylline in SIF at 25rpm

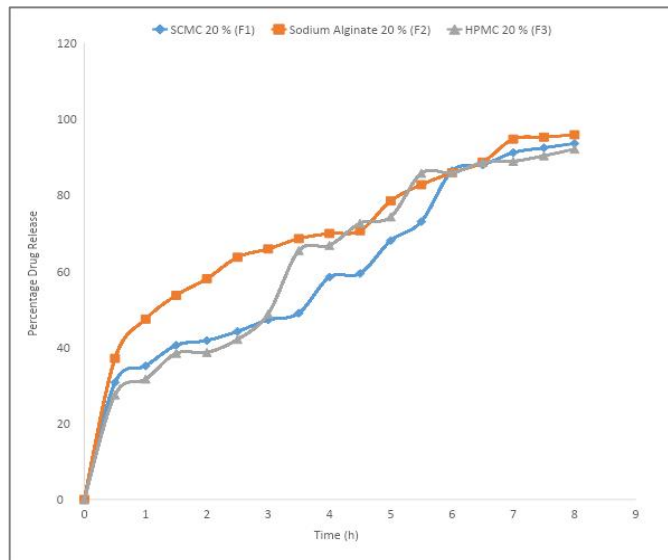


Fig. 5. Release profile of theophylline in SGF at 25 rpm

Table 5. Release kinetics of theophylline tablet in SIF AT 25 rpm

Batch code	R ²				Diffusion exponent (n)
	Zero order	First order	Higuchi model	Korsemeyer model	
F1	0.953*	0.127	0.931	0.487	0.91
F2	0.913	0.096	0.980*	0.383	0.83
F3	0.937	0.084	0.984*	0.497	0.93

Key: F1: Theophylline + 20% w/w SCMC
 F2: Theophylline + 20 % w/w Sodium Alginate
 F3: Theophylline + 20 % w/w HPMC
 *Represents highest correlation coefficient for batch

Table 6. Release kinetics for theophylline tablets in SGF at 25 rpm

Batch code	R ²				Diffusion exponent (n)
	Zero order	First order	Higuchi model	Korsemeyer model	
F1	0.941	0.102	0.945*	0.414	0.83
F2	0.849	0.150	0.971*	0.335	0.75
F3	0.929	0.103	0.969*	0.455	0.88

KEY: F1: Theophylline + 20% w/w SCMC
 F2: Theophylline + 20 % w/w Sodium Alginate
 F3: Theophylline + 20 % w/w HPMC
 *Represents highest correlation coefficient for batch

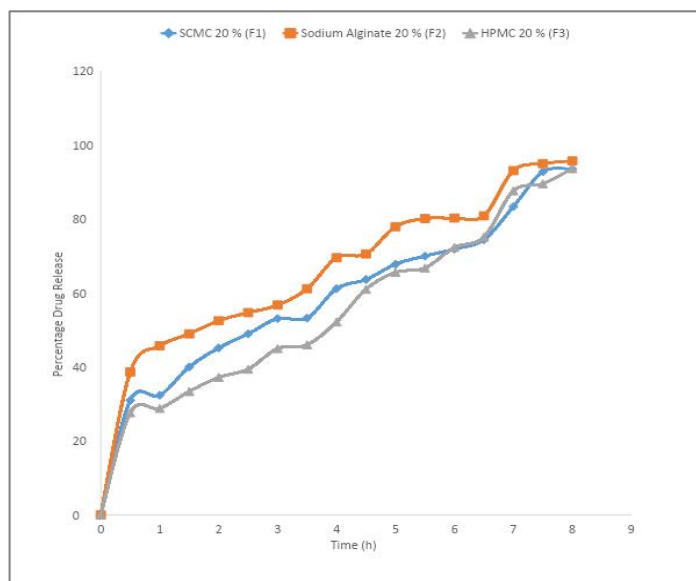


Fig. 6. Release profile of theophylline tablet in SIF at 50rpm

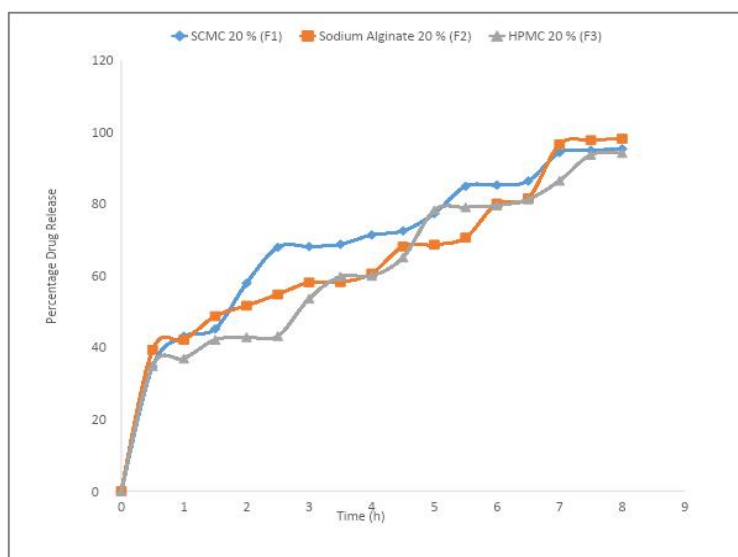


Fig. 7. Release profile of theophylline tablet in SGF at 50rpm

Table 7. Release kinetics of theophylline tablet in SIF at 50 rpm

Batch code	R ²				Diffusion exponent (n)
	Zero order	First order	Higuchi model	Korsemeyer model	
F1	0.927	0.004	0.972*	0.364	0.76
F2	0.880	0.114	0.966*	0.338	0.75
F3	0.963*	0.051	0.949	0.449	0.85

KEY: F1: Theophylline + 20% w/w SCMC
 F2: Theophylline + 20% w/w Sodium Alginate
 F3: Theophylline + 20% w/w HPMC
 *Represents highest correlation coefficient for batch

Table 8. Release kinetics of theophylline tablets in SGF at 50rpm

Batch code	R ²				Diffusion exponent (n)
	Zero order	First order	Higuchi model	Korsemeyer model	
F1	0.851	0.138	0.973*	0.360	0.78
F2	0.886	0.173	0.939*	0.339	0.74
F3	0.925	0.082	0.966*	0.387	0.79

KEY: F1: Theophylline + 20 % w/w SCMC
 F2: Theophylline + 20 % w/w Sodium Alginate
 F3: Theophylline + 20 % w/w HPMC
 *Represents highest correlation coefficient for batch

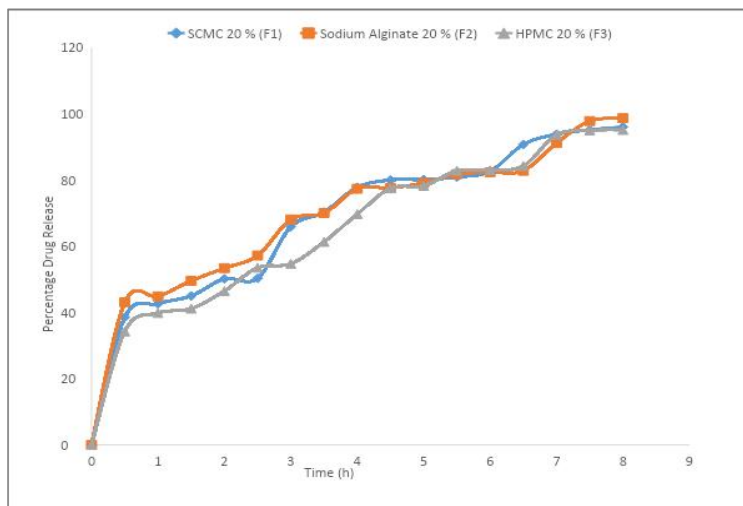


Fig. 8. Release profile of theophylline tablet in SIF at 100 rpm

Table 9. Release kinetics of theophylline tablets in SIF at 100rpm

Batch code	R ²				Diffusion exponent (n)
	Zero order	First order	Higuchi model	Korsemeyer model	
F1	0.915	0.165	0.971*	0.362	0.78
F2	0.848	0.142	0.963*	0.328	0.74
F3	0.874	0.185	0.981*	0.390	0.81

KEY: F1: Theophylline + 20% w/w SCMC
 F2: Theophylline + 20 % w/w Sodium Alginate
 F3: Theophylline + 20 % w/w HPMC

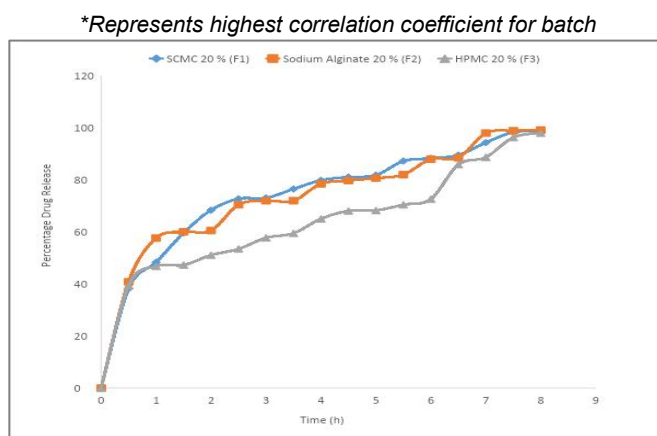


Fig. 9. Release kinetics of theophylline tablets in SGF at 100 rpm

Table 10. Release kinetics of theophylline tablets in SGF at 100rpm

Batch Code	R ²				Diffusion exponent (n)
	Zero Order	First Order	Higuchi Model	Korsemeyer Model	
F1	0.786	0.119	0.945*	0.321	0.74
F2	0.775	0.244	0.939*	0.301	0.71
F3	0.872	0.281	0.939*	0.326	0.73

Key: F1: Theophylline + 20 % w/w SCMC
 F2: Theophylline + 20 % w/w Sodium Alginate
 F3: Theophylline + 20 % w/w HPMC
 *Represents highest correlation coefficient for batch

Table 11 reveals the specific parameters used to characterize each drug release kinetics at different media and agitation rate. It shows the time it takes for 10% of drug to be released as well as for 90% of the drug to be released from the tablet matrix.

The release parameters that characterize the sustained-release matrix tablets, as obtained from the plots, are presented in Table 11. Two parameters (t_{10} and t_{90}) are used to characteristically describe the release pattern: the time for 10% of the drug to be released (t_{10}) and the time for 90% drug release (t_{90}). The t_{10}

range from 0.08 hour - 0.2 hour whereas t_{90} covers range of 6.0-7.7 hours. The high values for the t_{90} is a reflection of the sustainability of drug release by the matrix-formers. There was no noticeable difference in the t_{10} in the three batches in all conditions except in F2 at 25rpm in simulated intestinal fluid. Also, the t_{90} of F3 in all the conditions was highest. This means that of the 3 polymers, HPMC sustained release slightly longer. This is likely because of the delay in its hydration and swelling [15,22]. This value (t_{90}) is similar to that obtained in our earlier work using HPMC at same composition for floating tablet of theophylline [12].

Table 11. Release parameters of theophylline matrix tablet

Batch Code	SIF 25rpm		SGF 25rpm		SIF 50rpm		SGF 50rpm		SIF 100 rpm		SGF 100 rpm	
	t_{10} (h)	t_{90} (h)	t_{10} (h)	t_{90} (h)	t_{10} (h)	t_{90} (h)	t_{10} (h)	t_{90} (h)	t_{10} (h)	t_{90} (h)	t_{10} (h)	t_{90} (h)
F1	0.10	6.00	0.20	6.80	0.20	7.40	0.12	6.70	0.15	6.40	0.10	6.60
F2	0.08	7.00	0.20	6.60	0.20	6.90	0.12	6.80	0.15	7.00	0.10	6.60
F3	0.12	7.20	0.20	7.50	0.20	7.70	0.12	7.30	0.15	6.80	0.10	7.10

KEY: F1: Theophylline + 20 % w/w SCMC; F2: Theophylline + 20 % w/w Sodium Alginate; F3: Theophylline + 20 % w/w HPMC; SIF: Simulated intestinal fluid; SGF: Simulated Gastric fluid

For batch F1 formulated with the polymer SCMC, the effect of the different pH on drug release was non-significant ($P>0.05$). However, the effect of agitation rate on drug release was significant, although marginally ($P= .055$). This means that an increase in the stirring rate resulted in an increase in drug release at each time interval. The interaction effect of the stirring rate and pH of medium on drug release was non-significant ($P>0.05$). For batches F2 and F3 formulated with sodium alginate and HPMC respectively, the effect of the different pH on drug release property was non-significant ($P>0.05$) just as the effect of the stirring rate ($P>0.05$). The effect of interaction of the stirring rate and pH of medium on drug release was equally non-significant ($P>0.05$). These observations are consistent with the non-ionic nature of HPMC but alginate affected mainly by polyvalent cations [24].

Comparatively, using only the p values obtained for inferential deduction; $p= .1633$, $p= .440$ and $p=.610$, for F1, F2 and F3 respectively, batch F1 formulated with SCMC ($p=0.1633$) was likely the most affected by the pH of the medium. The agitation rate effect was also most significant for sodium alginate formulated tablet, with a $p=.055$ compared with p values of .337 and .484 respectively.

The implication of this observation is that the concerns had when there is a need for co-administration of a pH-altering drug (or food) or gastric motility-modifying drug (or food) together with a sustained-release theophylline may be reconsidered after all, as this study finds no significant effect of agitation rate and pH conditions on the release of theophylline. It must be emphasized however that a limitation in this study is that this is an *in-vitro* study and opens up opportunity for an *in-vivo* corroboration using commercial brands of sustained-release theophylline tablets.

4. CONCLUSION

While the three polymers sustained drug release from the matrix tablet for 8 hours, there was no significant difference between the release kinetics at different agitation rates and different dissolution medium except for F1. Thus at a higher stirring rate, the release kinetics is increased. Generally, the release model is Higuchi model showing that drug release depends on the square root of time.

SIGNIFICANT STATEMENT

This study discovers that agitation rate and pH have no significant effect on the release kinetic of sustained-release theophylline matrix tablet formulated from 3 selected hydrophilic polymers. This study sheds light on the likely implication of co-administration of theophylline sustained-release tablet and a gastrointestinal motility-influencing drug (e.g., hyoscine) or pH-altering medicines (e.g. omeprazole). It also opens up another area that will help researchers investigate the *in-vitro* release for longer time as well as *in-vivo* release.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Karna S, Chaturvedi S, Agrawal V, Alim M. Formulation approaches for sustained release dosage forms: a review". Asian Journal of Pharmaceutical and Clinical Research. 2015;8:34-41. Available:<https://innovareacademics.in/journals/index.php/ajpcr/article/view/7185>
2. Mayur Karvekar, Arshad Bashir Khan. A brief review on sustained-release matrix type drug delivery system. Journal of Pharmaceutical Research. 2017;16:282. DOI: 10.18579/jpcrkc/2017/16/3/118769s
3. Raslan H, Maswadeh H. *In vitro* dissolution Kinetic Study of Theophylline from mixed controlled release matrix tablets containing hydroxy propyl methylcellulose and Glycerylbehenate. Indian Journal of Pharmaceutical Sciences. 2006;68:308-312. DOI: 10.4103/0250-474X.26658
4. Kendre PN, Lateef SN, Godge RK, Chaudhari PD, Fernandes SL, Vibhute SK. Oral sustained delivery of theophylline floating matrix tablets- formulation and *In-vitro* evaluation. International Journal of PharmTech Research. 2010;2:130-139.

- Available:<https://www.researchgate.net/publication/285940418>
5. Nagaswamy VD, Sangeetha S, Samantha MK, Sanka S, Suresh B. Design and evaluation of Ethyl cellulose Sustained release matrix tablet of theophylline International journal of Pharmaceutical Science and Nanotechnology. 2008;1:60-63.
Available:<https://www.ijpsnonline.com>
 6. El-Bagory I, Barakat N, Ibrahim MA, El-Enazi F. Formulation and in vitro evaluation of theophylline matrix tablets prepared by direct compression: Effect of polymer blends. Saudi Pharmaceutical Journal. 2012;20:229-238.
DOI: 10.1016/j.jsps.2011.11.007
 7. Deshmukh K, Chidambaram K, Sadasivuni KK, Ponnamma D, AlMaadeed MA. Biopolymer composites with high dielectric performance: Interface engineering in electronics in: Biopolymer Composites in Electronics. 2017;27-128.
Available:<https://doi.org/10.1016/B978-0-12-809261-3.00003-6>
 8. Maiti S, Dey P, Kaity S, Ray S, Maiji S, Sa B. Investigation on processing variables for the preparation of fluconazole-loaded ethyl cellulose microspheres by modified multiple emulsion technique. AAPS Pharm SciTech. 2009;1(10):703-715.
DOI: 10.1208/s12249-009-9257-7
 9. Kuen Yong Leea, David J. Mooneyd. Alginate: Properties and biomedical applications. Progress in Polymer Science. 2012;37:106–126.
DOI:10.1016/j.progpolymsci.2011.06.003
 10. Thomas Dürig Kapish Karan. Binders in wet granulation in: Handbook of pharmaceutical wet granulation theory and Practice in a Quality by Design Paradigm. 2019;317-349.
DOI:10.1016/B978-0-12-810460-6.00010-5
 11. Banes PJ. Theophylline. American Journal of Respiratory and Critical Care Medicine. 2013;188(8):901–906.
DOI: 10.1164/rccm.201302-0388PP
 12. Akpabio EI, Effiong DE, Uwah TO, Sunday NI. Formulation and *in-vitro* evaluation of theophylline hydrochloride effervescent floating tablets: Effect of polymer concentration on tablet buoyancy. International J of Pharm. Pharm. Sci. 2020;12(1):59-65.
DOI: 10.22159/ijpps.2020v12i1.35055
 13. Okunlola A, Adewusi SA. Development of *Theophylline microbeads* using pregelatinized breadfruit starch (*Artocarpus altilis*) as a novel co-polymer for controlled release. Advanced Pharmaceutical Bulletin. 2019;9(1).
DOI: 10.15171/apb.2019.0
 14. Aulton ME. Powder flow in: Aulton ME, Taylor KMG, Aulton's Pharmaceuticals: The design and manufacture of medicines (5th ed.). Churchill Livingstone Elsevier. 2018; 189-198.
Available:<https://www.inkling.com/store/book/aulton-aultons-pharmaceutics-5e/>
 15. Akpabio EI, Effiong DE, Uwah TO, Godwin J. Evaluating Hydrocolloids of *Sida acuta* in sustained-release matrix tablet of Ibuprofen. Global Journal of Medical research. 2020;20(1):1-8
Available:https://globaljournals.org/GJMR_Volume20/3-Evaluating-Hydrocolloids-of-Sida-Acuta.pdf
 16. Ofori-Kwakye K, Mfoafo KA, Kipo SL, Kuntworbe N, El Boakye-Gyasi M. Development and evaluation of natural gum-based extended release matrix tablets of two model drugs of different water solubilities by direct compression. Saudi Pharmaceutical Journal. 2006;24: 82-91
Available:<http://dx.doi.org/10.1016/j.jsps.2015.03.005>
 17. Uwah Timma O, Akpabio EI, Effiong DE, Akpabio AE, Jacob G. Preliminary Investigations into The Physicochemical and Compaction Characteristics of Modified Starch of *Discorea alata* Using Diclofenac sodium tablet. International Journal of Pharmacy and Pharmaceutical Sciences. 2018;10(7):66-74.
DOI: 10.22159/ijpps.2018v10i7.23730
 18. Thoorens G, Krier F, Leclercq B, Carlin B, Evrard B. Microcrystalline cellulose, a direct compression binder in a quality by design environment – A review. Int. J. Pharm. 2014;473(1-2):64–72.
DOI: 10.1016/j.ijpharm.2014.06.055
 19. International Pharmacopoeia. WHO Department of Essential Medicines and Health Products; 2019.
Available:<https://apps.who.int/phint/pdf/b/7.5.3.5.2-Uniformity-of-mass-for-single-dose-preparations.pdf>
 20. Pharmacopoeia, United States. The United States Pharmacopoeia 29, The National

- Formulary 24. United States Pharmacopeial Convention. 2006;2110. Available:http://ftp.uspbpep.com/v29240/usp29nf24s0_m82190.html
21. Ahmad M, Akhtar N, Murtaza G, Hussain SW. Formulation development and *in-vitro* evaluation of theophylline microcapsules Pak. J. Pharm. Sci. 2012;5(1):15-19. Available:<https://www.ncbi.nlm.nih.gov/pubmed/22186304>
22. Obeidat WM, Price JC. Viscosity of polymer solution phase and other factors controlling the dissolution of theophylline microspheres prepared by the emulsion solvent evaporation method. J. Microencapsul. 2003;20:57-65. Available:<https://www.ncbi.nlm.nih.gov/pubmed/12519702>
23. Chakraborty S, Khandai M, Sharma A, Niranjana Patra CH, Jagannath Patro V, Kumar Sen K. Effects of drug solubility on the release kinetics of water soluble and insoluble drugs from HPMC based matrix formulations. Acta Pharm. 2009;59:313-323. Available:<http://dx.doi.org/10.2478/v10007-009-0025-8>
24. Ali Nokhodchi, Shaista Raja, Pryia Patel, and Kofi Asare-Addo. The role of oral controlled release matrix tablets in drug delivery systems. Bioimpacts. 2012;2(4): 175-187. DOI: 10.5681/bi.2012.027
25. Evelyn Ojoe; Edna Mitie Miyauchi; Tais Cobo Viviani; Vladi Olga Consiglieri. Formulation and *in vitro* evaluation of theophylline-Eudragit® sustained-release tablets. Rev. Bras. Cienc. Farm. 2005;41 (3). DOI: 10.1590/S1516-93322005000300011

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