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Design and Evaluation of Drug Release Kinetics of Theophylline from Co-processed *Colocasia esculenta* Gum.

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ABSTRACT

Adjuvants are co-formulated in dosage forms to modify, improve or control the release rate of active pharmaceutical ingredients to achieve optimal drug concentration in the plasma or the site of action, modify onset of action and or duration of action. One such adjuvant is the gummy polysaccharide obtained from *Colocosia esculenta.* The aim of this study is to investigate the release kinetics of Theophylline from the dispersion made from *Colocosia esculenta* co-processed polymer matrix. The polysaccharide gum from *Colocosia esculenta* was extracted with water and precipitated with acetone. The purified polymer isolated was investigated for its drug release properties using Theophylline in form of Theophylline – *Colocosia esculenta* polysaccharide gum matrix. Theophylline interaction with the gum was investigated using Fourier Transform Infra Red (FT-IR) studies. Various concentrations of dispersion of Theophylline was prepared (1.0, 2.5, 5.0 and 7.5, labelled A,B,C and D respectively) in the polymer matrix and were evaluated for drug release using dissolution studies. The FT-IR results indicate no strong chemical interaction between theophylline and *Colocasia esculenta* gum. The dissolution rate of Theophylline in A, B and C follow the first order release model with coefficient of correlation (r^2) of 0.9153, 0.91 and 0.9679 respectively while release kinetics of theophylline from batch D best fits Higuchi model with r^2 of 0.9849 and Hixson Corwel model,with r^2 of 0.9785. The drug release mechanism of batches A, B, and C,are directly proportional to the concentration theophylline in the matrix. The theophylline release from batch D is indicative of control-release matrix that releases drug mainly by diffusion from matrix, and is dependent on the volume of exposed dosage surface. Thus, higher concentration of *Colocasia esculenta* gum in theophylline-gum matrix led to controlled or modified release of Theophylline.

Keywords: Drug release kinetics, control release, *Colocosia esculenta, Polysaccharides, Dissolution studies*

INTRODUCTION

Dosage form is a compounded formulation of drug active and selected adjuncts for wholesome and safe drug administration in biological systems. Adjuncts are mainly chemically inert, and aid in drug compounding, protection, wholesome carriage, and safe delivery at the administration site, and effective release of drug active in biological site. There are different adjuncts that can be selected to achieve these properties and other dosage requirements. After wholesome administration of dosage form, it is important that the required concentration and form of drug-active get to the target site, cell or organ to achieve the intended therapeutic response. Drug concentration at the intended biological site should be above the minimal effective concentration (MEC) and below the minimal toxic concentration (MTC) for appropriate and safe therapy (Perrie and Rades, 2012). The drug released from dosage form should be in a way and manner that meet therapeutic efficacy and safety requirement. Depending on the excipients and process of formulating the dosage form, drug release can be immediate or modified. Immediate-release system releases drug active immediately after administration, in a single action, and give fast onset of drug action. Modified-release, on the other hand, are designed differently, to increase drug stability, safety and efficacy, and or improve patient compliance. Modified-release system releases drug active sometime after dosage administration (delayed release), or for a prolonged time (extended release) or to a specific target in the body (targeted release). Delayed release of drug can be used to protect the drug from degradation in low pH environment in the stomach or to protect the stomach from irritation of the drug or to deliver drug, away from the stomach, at other gastrointestinal sites for local or for systemic action (Tozer and Rowland, 2006). Delayed-release system can be made with polymer adjuncts that dissolve as a function of pH. The prolonged time it takes for extended-release system can be used to reduce the frequency of dosing, and improve patience compliance. Extended-release can be divided into sustained-release and controlled release (Perrie and Rades, 2012).

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Sustained release maintains the rate of drug release for a sustained period, such as throughout the entire gastrointestinal tract. Sustained release systems are often limited to oral dosage forms. Controlled release systems are designed to give predictably constant plasma concentration of drug, independent on the biological environment of the administration site. In contrast to sustained-release, the controlled-release system actually controls the concentration of drug in the body and not just the release of drug from dosage form. Controlled-release systems are used for variety of administration routes like vaginal, transdermal and oral administration. The rate of drug release from controlled-release dosage form is often the rate-determination step for drug absorption, concentration of drug in the plasma and site of action. Controlled release systems do not exclusively deliver drug to target sites, and are not target release systems. Targeted release systems holds on the drug active and releases it only at specifically targeted site. Targeted release system makes use of drug carrier and drug target to control distribution of drug. Mathematical application of correlation of coefficient value from Zero order, First order, Higuchi, Korsmeyer Peppas or Hixson-Crowel release models can be used to determine drug release kinetics. Immediate release system often follow first order release kinetic model (Rescigno, 2003). The controlled-release kinetics is often zero order as a function of time from a reservoir system, or linear release as a function of square root of time from a matrix system (Dash *et al*., 2010).

Zero-order release kinetics is the constant release of drug from dosage form. The drug level in blood remains constant throughout the zero-order release. The zero order release data is obtained from a plot of cumulative drug release over time;

$C_t = C_o + K_o$…… equation 1
Where C_t = is the cumulative amount of drug released,
C_o = the initial concentration of drug which is constant.
K_o = the zero-order rate constant, t = release time (Guoda *et al*., 2017).

Here dissolution rate dependence is t which is actually t^n, but since n value is 1, it is t, and the diffusion mechanism is Case II transport of Zero order model. Other values of n give different diffusion mechanism of other release kinetics with constant concentration (Jeevanandham *et al*., 2010). First-order release kinetics is the release of drug at a rate that is directly proportional to the concentration of drug undergoing reaction. The rate release of drug is dependent on drug concentration and slows down with time. The first-order release kinetic is obtained from a plot of Log of cumulative % of drug release against time, according to the following equation;

$\log C = \log C_o - K_1 t/2.303$ …… equation 2
Where C_o = initial concentration of the drug,
C = present concentration of drug remaining at given time t,
K_1 = first order rate equation expressed in $time^{-1}$ (Guoda *et al*., 2017).

Higuchi model is the release of drug from drug delivery that involves diffusion and dissolution. The data for simple Higuchi model is obtained from cumulative drug release over square root of time;

$Q = K_H * t^{1/2}$ …… equation 3
Where Q = cumulative amount of drug released in time t per unit area,
K_H = Higuchi dissolution constant,
and $t^{1/2}$ = square root of time.
Here n is 0.5 of and dissolution rate dependence is t^n and Higushi model is $t^{1/2}$, and diffusion mechanism is by Fickian diffusion (Subal, 2006).

Korsmeyer-Peppas model follows after confirmation of Higuchi model. It defines the type of diffusion of Higuchi model. Korsmeyer-Peppas model is obtained by a plot of log cumulative % drug release against log time;

$\log(Mt/M0\infty) = \log K_{kp} + n\log t$ … equation 4
Where Mt = amount of drug released in time t.
$M\infty$ = amount of drug released after time ∞,
$\log(Mt/M\infty)$ = log of cumulative drug released,
K_{kp} = Korsmeyer release rate constant,
n = drug release diffusion exponent,
t = time of release (Guoda *et al*. 2017) .
The rate dependence is t^{n-1} and if n>1.0 it is super case II transport, and if 0.5<n>1.0 it is anomalous diffusion (Jeevanandham *et al*., 2010).

Hixson-Crowel is a cube root law that describes the release of drug system where the surface area and diameter of the particle or tablet is changing. It is obtained by a plot of the cube root of drug percentage remaining in matrix *versus* time;

$W_o^{1/3} - W_1^{1/3} = K_{HC}t$ …… equation 5
Where $W_o^{1/3}$ = initial amount of drug in the dosage form,
W_1 = remaining amount of drug in the dosage form at time t,
K_{HC} = Hixson-Crowell constant describing surface volume relationship (Singhvi and Singh, 2011).

The plant *Colocasia esculenta*, Family Aracea, is cultivated in rivers, lakes, and humid tropics,

mainly for its edible gummy corm and medicinal leaves (Wei *et al.*, 2011; Alalor *et al*., 2014). Theophylline hydrate is a white or almost white, odourless, crystalline powder. It is slightly soluble in water, more soluble in hot water, sparingly soluble in alcohol, freely soluble in solutions of alkali hydroxides and in ammonia. Theophylline is a xanthine used to relax bronchial smooth muscle, relieve bronchospasm, and stimulate respiration. It stimulates the myocardium and CNS, decrease peripheral resistance and venous pressure. It is administered as intravenous infusion, orally as an immediate release preparation, as prolonged release tablet. The oral dose is 300 – 1000 mg daily. Initially low dose of about 300 mg is given for up to 3 days and adjusted to 400 mg for 3 days and then to 600 mg. The conventional tablet, capsule or liquid dosage form of theophylline is given every 6 – 8 hrs (Martindale, 2009). The modified release theophylline tablet comes in 175mg to 350 mg for children, taken every 12 hr, and 250 - 500 mg for adults taken every 12 hr. It also comes in modified release capsule of 250 – 500 mg for adults and 60 – 120 mg for children (BNF, 2012., EMDEX, 2013)

MATERIALS AND METHODS

Fresh tubers of *Colocasia esculenta* rhizomes were harvested from Department of Pharmacognosy Farm, Igbinedion University, Okada, Nigeria. Theophylline anhydrous was obtained from Sigma (Local Representative in Nigeria). The other reagents or ingredients used were of analytical grade.

Collection and Identification of *Colocasia esculenta* Gum.

Mr Amodu Emmanuel, The Curator, Paxherbal Clinic and Research Laboratories Herbarium, Ewu, Edo State, did the taxonomical identification of *Colocasia esculenta* plant from Department of Pharmacognosy, College of Pharmacy, Igbinedion University, Okada Farm, and prepared voucher specimen with Herbarium number PAX/H/2053 and preserved for future references.

Extraction of *Colocasia esculenta* Gum

The extraction of the gum was carried out using a slightly modified method of Alalor *et al*., (2014), briefly, fresh rhizomes from one year old *Colocasia esculenta* plants were harvested, sorted and washed. The tubers were peeled, washed and cut into small pieces, and soaked for 6 hr and grated with Model GM Knife Mill Grindomix grinder (Retsh GMBH, Harmburg, Germany). The grated mucilage was then filled to twice its volume with water, stirred vigorously and allowed to stand for 1 hr. The supernatant was carefully poured off and fresh water, twice the volume of the precipitate added, stirred, allowed to stand for 1 hr, and the supernatant decanted. This process of washing the precipitated mucilage was repeated three more times. The precipitated mucilage suspension was then heated to 70 ℃ with constant stirring at 5 min intervals for 30 min to obtain a gummy mucilage. The gummy paste obtained was allowed to stand to cool to 30 ℃. Acetone that is three times the volume of the gummy mucilage was then added with constant stirring, and immediately refluxed until all the gum separates as coarcervates. The fluffy gum coarcervate was then washed and refluxed one more time with acetone, and the solid gum mass separated out using Centaur 2 MSE Centrifuge. The solid gum mass was then dried using Model DHG-9053A Ocean Medical (England) hot air oven. The gum obtained was pulverized, passed through a 0.22 mm stainless steel sieve and packed for further use.

Chemical Compatibility Evaluation of Theophylline - *Colocasia esculenta* Gum solid dispersion

The fusion method reported by Leuner and Dressman (2002) was employed to evaluate chemical compatibility using a Fourier Transform InfraRed Spectrophotometer (FT-IR). Theophylline 2 mg, *colocasia esculenta* gum and 1:1 solid dispersion of theophylline- *Colocasia esculenta* gum were weighed separately. Each sample was made up to 200 mg with potassium bromide (KBr) to produce 1 % solid dispersion in KBr. The mixture was then pulverized and dried in an oven at 110 ℃ for 2 h. The dried mixture was allowed to cool and 80 mg of the dried mixture was fed into a 13 mm diameter pellet-forming die. This was compressed by a press-gauge at 8 tons to produce 80 mg pellet. Plain KBr pellet was used to standardize (blank) the background for spectrophotometer reading. The FT-IR absorbance, at different wavelength, of the different sample pellets were taken using a Schimadzu FT-IR 8400S Fourier transform Infrared Spectrophotometer. The FT-IR readings obtained were analysed for transmission peak interference at critical wave numbers (Table 1) and analysed using Jacox (2013) electronic and vibrational modelling.

Co-processing Theophylline and *Colocasia esculenta* Gum into a Drug-Gum dispersion

A modified form of SeemanchalaRath *et al.*, (2012) method for microencapsulating actives by non-solvent was adopted to co-processing the theophylline- *colocasia esculenta* gum solid dispersion using physico-mechanical technique. 10 g of *colocasia esculenta* gum was made up to 100 ml with water and heated to 80 ℃ with constant stirring for 5 min. The slurry was allowed to stand and swell for 1 hr. Then, 50 ml of hot water was

added to the swell and stirred for 15 min at 50 ℃. 1 g of theophylline was made up to 10 ml with water, stirred to ensure full dispersion, and poured into the 50 ℃ slurry. The resultant mixture was stirred for 15 min at 500 r.p.m. Then 10 ml of 20 % sodium sulphate anti-aggregation solution was added drop-wise for 10 min into the mixture and stirred slowly. With constant stirring, 5 ml of 17 % formaldehyde was added to the mixture and stirred for extra 5 min. The mixture was then spray dried at 140 ℃ inlet, 75 ℃ outlet at 30 mbar of vacuum. The dried granules recovered was labelled as Batch A. Using this same process, but with 2.5, 5 and 7.5 g theophylline, three other batches were prepared and labelled as batches B, C and D respectively. Then 440 mg, 200 mg, 120 mg, and 93.3 mg granules from batches A, B, C and D respectively, equivalent to 40 mg theophylline, were weighed and filled into hard capsule gelatine shells.

In-Vitro Drug Dissolution Test for Theophylline Capsules

A dissolution medium of 1000 ml of 0.1 M HC1 was placed in a 1.1 L dissolution flask set at 37 ℃ in the dissolution apparatus II (Dissolution Machine, Caleva Company Limited, England). The speed was set at 100 rpm. One capsule from each batch was placed in the basket of this machine. The basket was immersed in the dissolution medium and the machine was operated, then 5 ml of the dissolution medium was withdrawn with a syringe at intervals of 0.25, 0.5, 1, 2, 4, 8, 16 and 36 hr and filtered. Then 1 ml of the filtrate was made up to 10 ml with 0.1 M HCl and the absorbance measured in a UV spectrophotometer and recorded at the wavelengths of 271 nm for theophylline. Every 5 ml dissolution medium removed for analysis was replaced with a fresh dissolution medium kept at the same temperature of 37 ℃. The concentration of drug release was determined from the Beer's Lambert plot generated for theophylline. The dissolution reading was used to calculate percentage drug released, plot a dissolution rate graph, and used in a mathematical model to determine drug release kinetics model.

RESULTS

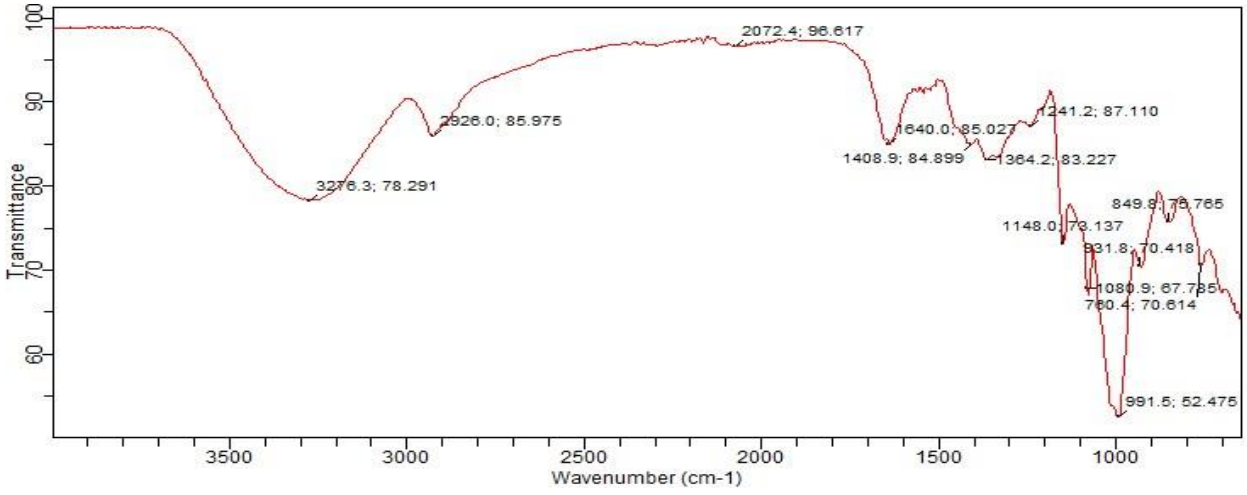

Figure 1: FT-IR Spectrum for *Colocasia esculenta* gum (alone)

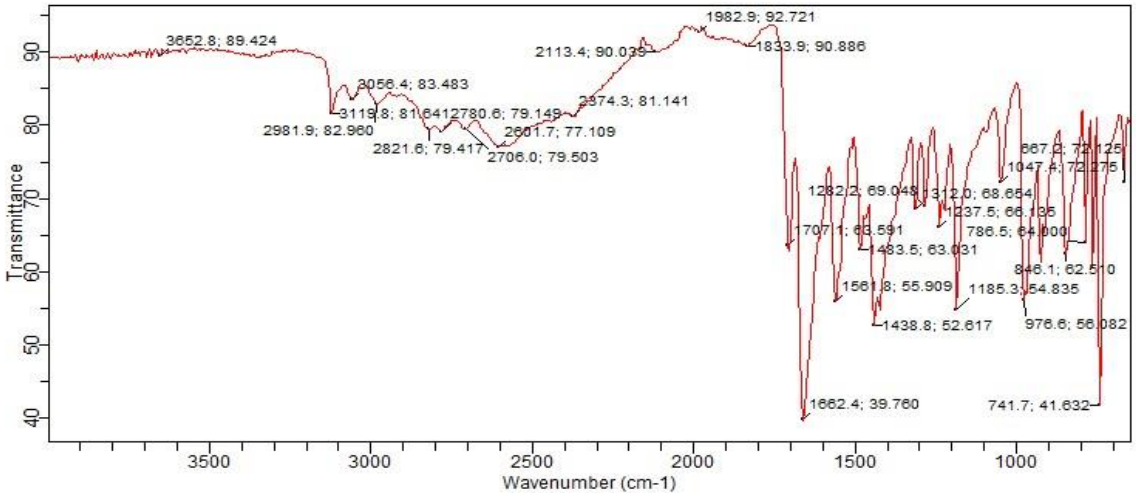

Figure 2: FT-IR Spectrum for Theophylline (Pure Active)

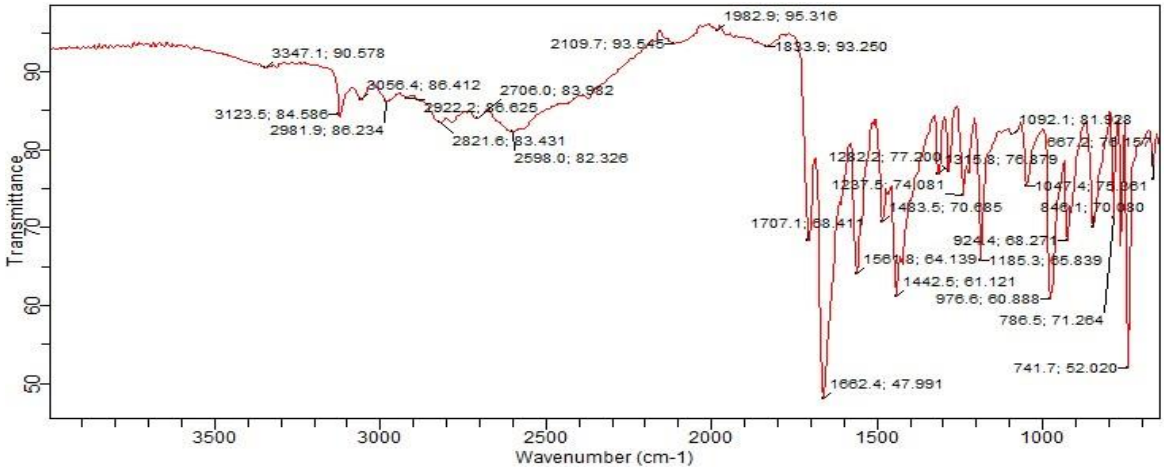

Figure 3: FT-IR Spectrum for Theophylline-*Colocasia esculenta* gum 1:1 Solid Dispersion.

Table 1 : FT-IR analysis of Theophylline, Gum and Theophylline-Gum matrix for possible chemical interaction (Peaks in wavenumber cm^{-1})

PEAK	GUM	THEOPHYLLINE	GUM-THEOPHYLLINE	COMMENTS
1	3216	3119	3123	O-H, N-H stretch
2	-	3056	3056	O-H stretch (bonded)
3	2926	2981	2981	C-H stretch
4	-	1707	1707	C=O, C=N(Theophylline)
5	1640	1662	1662	C=C, C=N(Theophylline)
6	1408	1438	1442	
7	991	976	976	Fingerprint

*Transmission peaks in wave number for Theophylline largely unaffected in the matrix

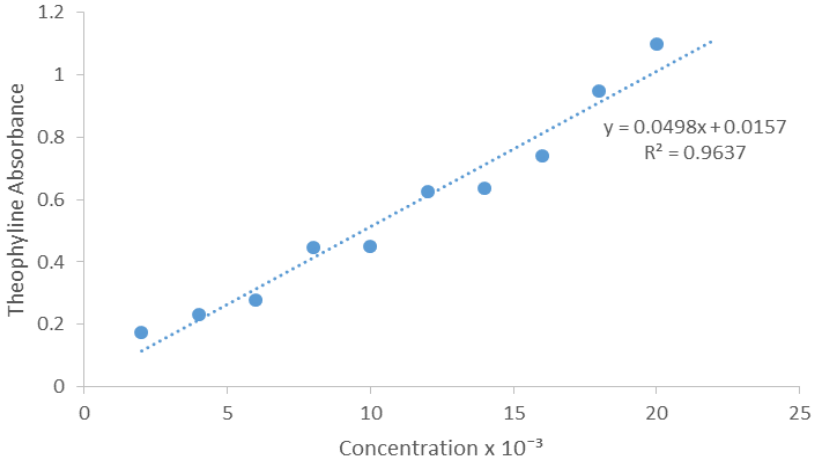

Figure 4: Beer-Lambert Plot of Sample Theophylline.

Table 2: Absorbance of Theophylline Dissolved from Tablet in 10^3 Dissolution Medium

Time (hr)→ Batch ↓	0.25	0.5	1	2	4	8	16	36
A	0.396	0.597	0.633	1.028	1.53	1.562	1.78	1.887
B	0.074	0.096	0.094	0.11	0.164	0.116	0.587	0.637
C	0.068	0.091	0.096	0.21	0.212	0.231	0.617	0.785
D	0.047	0.076	0.096	0.183	0.198	0.369	0.586	0.729

Table 3: Extrapolated Concentration of the Theophylline Dissolve from the Absorbance Readings

Time (hr)→ Batch ↓	0.25	0.5	1	2	4	8	16	36
A	7.94	11.97	12.70	20.63	30.71	31.35	35.73	37.88
B	1.47	1.91	1.87	2.19	3.28	2.31	11.77	12.78
C	1.35	1.81	1.91	4.20	4.24	4.62	12.37	15.75
D	0.93	1.51	1.91	3.66	3.96	7.39	11.75	14.62

Table 4: Calculated Percentage Theophylline Dissolved from Theophylline Batches

Time (hr)→ Batch ↓	0.25	0.5	1	2	4	8	16	36
A	19.84	29.93	31.74	51.57	76.77	78.37	89.32	94.69
B	3.68	4.78	4.68	5.48	8.19	5.78	29.43	31.94
C	3.37	4.53	4.78	10.50	10.60	11.56	30.93	39.37
D	2.32	3.78	4.78	9.15	9.90	18.48	29.38	36.56

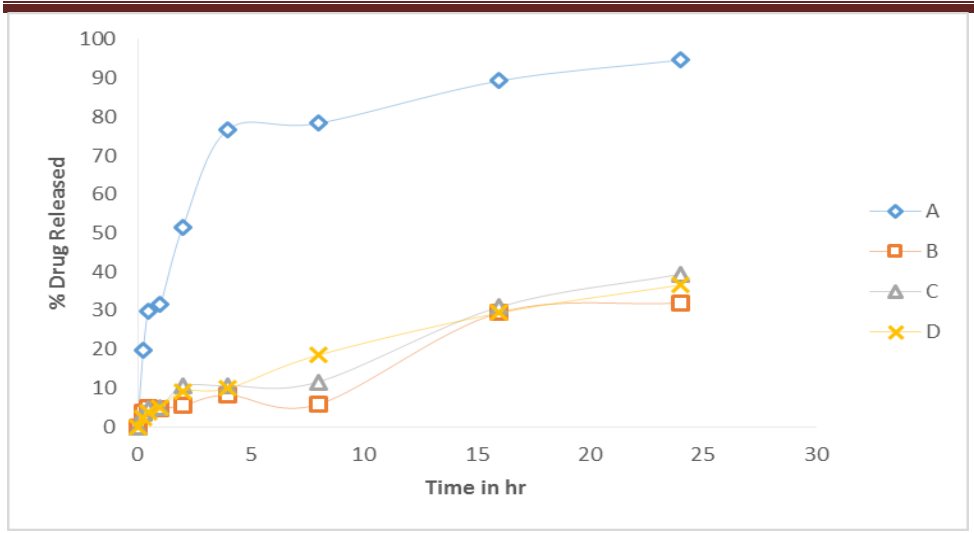

Figure 5: Drug Release Profile for All the Batches

Table 5: R^2- Values of Different Mathematical Models of Theophylline Batches

Batch → Model ↓	A	B	C	D
Zero Order (% hr^{-1})	0.6642	0.9069	0.9612	0.9672
First Order (hr^{-1})	0.9153	0.91	0.9679	0.9833
Higuchi (% $hr^{1/2}$)	0.871	0.8431	0.9273	0.9849
Kormeyer Peppas (hr^{-n})	0.318	0.593	0.6944	0.7866
Hixson Crowel ($hr^{-1/3}$)	0.8374	0.9091	0.9663	0.9785

Table 6: Slope and Dissolution Rate Constant of Different Mathematical Models of Theophylline Batches

Batch →	A		B		C		D	
Model ↓	K	n	k	N	K	N	k	N
Zero Order	32.269	3.2612	2.2811	1.317	3.3405	1.551	3.4765	1.4899
First Order	0.8324	-0.0497	1.9917	-0.007	1.9883	-0.0086	1.9804	-0.0081
Higuchi	16.019	18.91	-1.9556	6.4305	-2.0219	7.7145	-1.969	7.627
Kormeyer Peppas	1.3233	0.5196	0.6106	0.5182	0.662	0.602	0.614	0.6742
Hixson Crowel	0.583	0.1101	0.0321	0.0233	0.0452	0.0282	0.0508	0.0267

DISCUSSION

The FT-IR spectra for *Colocasia esculenta* gum (fig. 1), theophylline (fig. 2) and the theophylline-*colocasia esculenta* gum dispersion (fig. 3) showed no significant difference when evaluated using the Jacox (2013) interpretation. Theophylline show characteristic Infra Red (IR) spectra C=O stretching at 1662 and 1312 cm^{-1}, C=C stretching at 1561cm^{-1} and some fingerprint absorption at 976 and 741 cm^{-1}(Fig.1). These bands were largely unaffected by the IR spectral band contribution of the *Colocosia* gum showing broad O-H stretching at 3276 and 2926 cm^{-1} (Fig.2). The major peaks identifying theophylline were all present in the IR spectra of the Theophylline-*Colocosia gum* blend (Fig.3). This indicate that there was no chemical interaction when the drug and gum were blended. The percentage theophylline dissolved (Table 4) was calculated from the concentration readings (Table 3) calculated too from absorbance readings (Table 2) in reference to theophylline Beer's plot (Table 1, and fig. 4). Using Table 4, but from 0.25 to 16 hr as 4 x 6 contingency table for statistical analysis, in a one-way ANOVA, the F-ratio of 18.2 was obtained, which is higher than F-value of 2.9, and the null hypothesis is rejected. Table 5 shows that the batches A, B and C of 0.1:1, 0.25:1, and 0.5:1 were best fit at the first order kinetic model with highest correlation coefficients in comparison with correlation coefficients of other release kinetics. This interprets that the dissolution of batches A, B and C are concentration dependent.

Increasing the concentration of *colocasia esculenta* gum to 0.75:1 in D alters the theophylline release kinetics. The release kinetics best fits the Higuchi model of diffusion and dispersion, and correlates with the Hixson-Crowel release kinetics at over 0.89 seen in Table 6. At 75 % *colocasia esculenta* gum, a control release matrix that is dependent on diffusion and surface volume of the particles in test capsules.

CONCLUSION

The *colocasia esculenta* gum is chemically inert and does not react with theophylline active. The concentration of *colocasia esculenta* gum in theophylline-gum dispersion significantly affect the rate of drug release ($p > 0.5$). The ratio 0.1:1 dispersion of theophylline in the gum gave the highest and fastest dissolution rate profile. This 0.1:1 dispersion and the 0.25:1, 0.5:1 dispersions all release drug in first order model that is concentration dependent. The 0.75:1 ratio of theophylline gave Higuchi and Hixson-Crowel models of dispersion that is independent of drug active concentration, but on the volume of exposed surface area. High proportion of 75 % *colocasia esculenta* gum can be used to prepare controlled drug release matrix.

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