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Original Research

Mechanisms of theophylline release from encapsulated sustained release theophylline granules formulated with *Abelmoschus esculentus* gum.

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This paper attempts to quantitatively describe the mechanism of drug release from a sustained action theophylline granules formulated with a newly derived polysaccharide gum from *Abelmoschus esculentus.*The drug release rates revealed that gelatin based granules released theophlline fastest while Okro gum had the least drug release. The sustained release granules further delayed drug release at 20%w/w polymer concentration. The mechanism of the theophylline release from the sustained release granules was of mixed order. The first order mechanism was dominant at the lower concentration (10%w/w) while the Higuchi diffusion mechanism predominated at the higher concentration (20%w/w) of the polymers in the granules.

Key Words*:* *Abelmoschus esculentus* gum, Sustained release granules, Drug release mechanism

Introduction

The basic concept underlying the design of oral sustained release formulations is to maintain a steady state therapeutic drug level over a prolonged period of 12 to24 hours. The major advantages of such systems include; convenient dose regimes, better patient compliance, better efficacy, reduced toxic effects and extended shelf life of the product (1). One type of prolonged action formulation can be prepared by compressing a mixture of hydrophilic polymer and drug (2). In contact with moisture, the tablet swells effecting release of the drug. Many researchers have proposed that the drug release is controlled both by drug diffusion through and attrition of the gel sheath formed around the tablet (3–7). Higuchi equations have been widely employed to provide a quantitative interpretation of the exact mechanism of release (8-10).

This paper attempts to quantitatively describe the mechanism of drug release from a sustained action theophylline granules formulated with a newly derived polysaccharide gum, from *Abelmoschus esculentus.*

Materials

The following materials were used as procured from their manufacturers; lactose, gelatin (Merck, Germany); theophylline, ethyl cellulose (Fluka Switzerland).

Methods

Processing of *Abelmoschus esculentus* (okro) gum

The processing of *Abelmoschus esculentus* gum was carried out in our laboratory using standard methods (11). Fresh okro fruits was washed and sliced to small pieces. Then 1.5 kg of the cut okro was macerated in water (2 L) and allowed to hydrate for 6 h. The mucilage was strained to remove the solids using a muslin cloth. Okro gum was precipitated from the mucilage using acetone. A ratio of 3:1 (three parts of acetone and one part of okro mucilage) completely precipitated the gum. The precipitated gum was immersed in acetone to ensure to ensure complete removal of water. The removal of the acetone was accomplished by filtration in vacuo. The gum was dried in a desicator containing anhydrous calcium chloride, ground, sieved (250 µm sieve) and weighed.

Formulation of sustained release granules

Formulations of sustained release theophylline monohydrate granules were accomplished using Abelmoschus gum, ethyl cellulose or gelatin at 10 %w/w and 20 %w/w concentrations. The granules were produced using the wet granulation method. The specified quantities (Table 1) of theophylline and lactose were mixed thoroughly for 5 min. The binder solution was added to the powder mixture and thoroughly blended for 10 min to produce a moist mass. The moist mass was forced through sieve 1.7 mm and was dried at 60 °C for 1 h. The dry granules were subsequently passed through a 1.00 mm stainless steel sieve. The granules were stored in clean dry amber colored and tightly closed bottles. The granules were hand filled into hard gelatin capsules (350 mg capacity) to a target weight of 300 mg per capsule. A total of 200 capsules per batch were produced.

Table 1: Formula for the formulation of sustained release theophylline granules

Drug/Excipient	Wt. Per tablet
Theophylline	50 mg
*Binder	10 & 20 %w/w
Lactose	q.s
Magnesium stearate	1 %w/w

* Okro gum, ethyl cellulose and gelatin

Content Uniformity of the capsules

The contents of twenty capsules were ground to a fine powder. A 300 mg sample of the powder was weighed and transferred to a 100 ml conical flask. The drug content was dissolved with 50 ml of 0.1 HCl. The mixture was filtered into a volumetric flask and the filtrate made up to 100 ml with 0.1 N HCl. A 5 ml aliquot was withdrawn, appropriately diluted and its absorbance read at 272 nm in an SP6-450 UV/VIS spectrophotometer (Pye-Unicam). The average absorbance for triplicate determinations was recorded. The theophylline content was calculated from a standard calibration plot.

Release rate of the theophylline capsules

The BP 1988 method was employed using 100 ml of 0.1 N HCl maintained at 37 ± 0.5 °C as the dissolution medium. One capsule was placed in the basket of the Erweka dissolution apparatus (model DT-D) rotating at 100 rpm. At predetermined time intervals, 5 ml portions of the dissolution medium were withdrawn and the solution assayed at 272 nm for the drug. An equivalent fresh dissolution medium was used to replace each 5 ml withdrawn.

Drug Release profile of the sustained release capsules.

The release profile of theophylline from the sustained release capsules formulation with 10% polymer is shown in Fig.1. The $T_{90\%}$ values of Okro gum, ethyl cellulose and gelatin based matrices were 240 min, 180 min and 90 min respectively, while $T_{70\%}$ was attained at 130 min, 90 min and 60 min, for Okro, ethyl cellulose and gelatin based granules respectively. The drug release rates revealed that gelatin based granules released theophylline fastest while Okro gum had the least drug release.

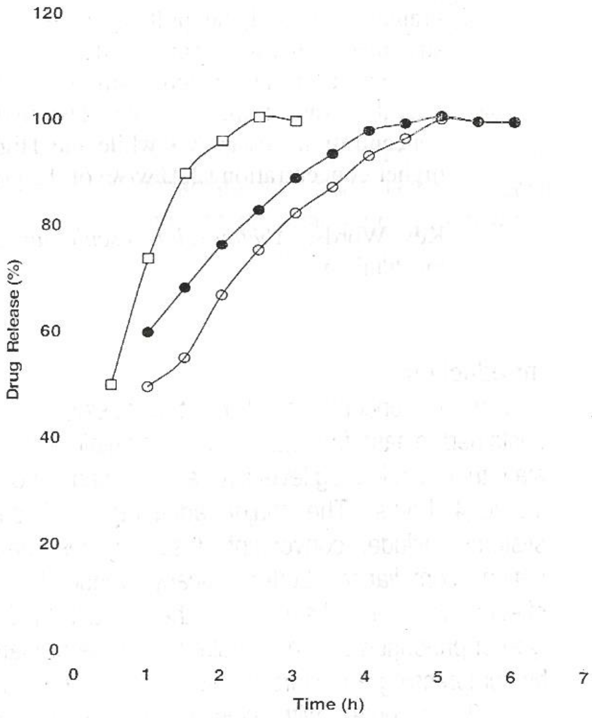

Fig.1. Release profiles of theophylline from encapsulated sustained release granules formulated with 10%w/w binder.

—○— Okro —●— Ethylcellulose —□— Gelatin

At 20%w/w polymer concentration (Fig.2), the sustained release capsules further delayed drug release with the $T_{90\%}$ values being more prolonged. For instance, the $T_{90\%}$ values for Okro gum, ethyl cellulose and gelatin based matrices were 325 min, 255 min, and 150 min. respectively. Also the $T_{70\%}$ values were Okro (200 min), ethyl cellulose (240 min) and gelatin (100 min). The $T_{50\%}$, $T_{70\%}$ and $T_{90\%}$ values of the encapsulated sustained release theopylline monohydrate capsules are presented in Table 2.

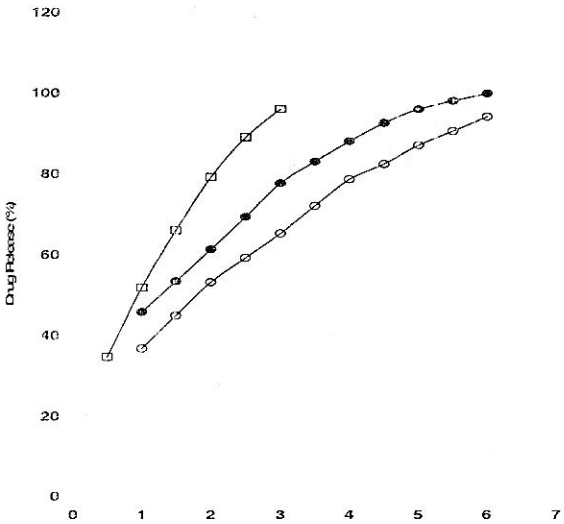

Fig.2. Release Profiles of theophylline from encapsulated sustained release granules formulated with 20%w/w binder.

Table 2: $T_{50\%}$, $T_{70\%}$ and $T_{90\%}$ values of encapsulated sustained release theophylline monohydrate granules formulated with 10 – 20%w/w binder

Matrix formulation	$T_{50\%}$ (min)	$T_{70\%}$(min)	$T_{90\%}$ (min)
10%w/w			
Okro	60	130	235
Ethylcellulose	50	95	180
Gelatin	30	57	90
20%w/w			
Okro	110	205	325
Ethylcellulose	70	140	255
Gelatin	60	100	150

Mechanisms of drug Release from the sustained Release Capsules.

The Higuchi plots of theophylline monohydrate capsules formulated with 10 %w/w concentrations of the polymers are presented in Fig. 3. The experimental points were subjected to a regress ional analysis using a linear equation in order to determine the line of best fit. Linear plots were obtained with high coefficient of correlation values. However, the plots of log Q vs. log t (Table 3) all had slopes of below 0.5 and hence did not confirm diffusion controlled release mechanism as predominant at this concentration. Moreover, the first order plots (Fig.4) produced straight lines with higher degrees of linearity than the Higuchi plots. The rate of drug release plots (Table3) according to the first order model also showed higher degree of linearity than those of Higuchi drug release model perhaps confirming the first order drug release as predominant at this concentration.

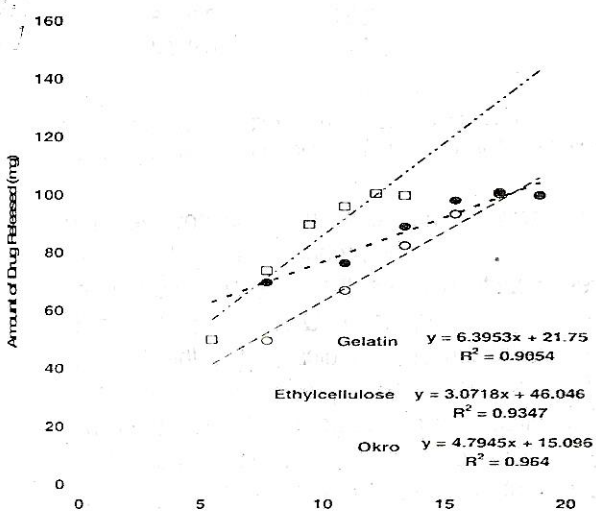

Fig.3.Higuchi plots of theophylline released from encapsulated sustained release granules formulated with 10% w/w binder.

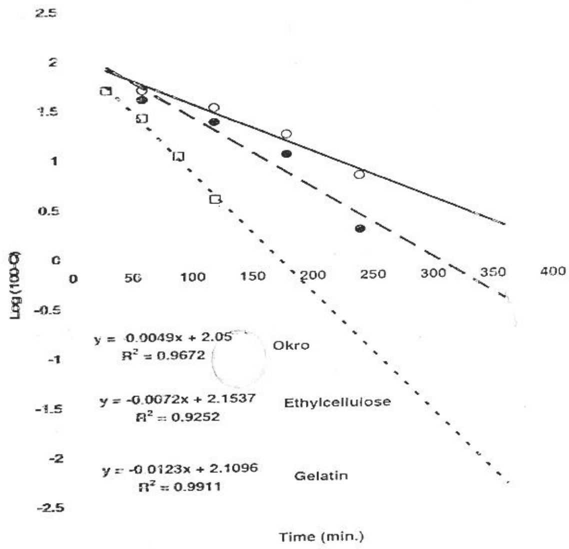

Fig.4. First order plots of theophylline released from encapsulated sustained release granules formulated with 10 %w/w binder.

□ Gelatin ● Ethylcellulose
○ Okro - - - Linear (Gelatin)
-- Linear (Ethylcellulose) —— Linear (Okro)

Table 3: Regression Analysis Data of encapsulated theophylline monohydrate granules formulated with 10 %w/w binder.

Polymer	Q vs $T^{1/2}$	LogQ vs LogT	Log (100-Q) vsT	Q/T vs 1/Q	Q/T vs Q
Okro					
R^2	0.9640	0.9797	0.9672	0.8063	0.8600
R	0.9818	0.9897	0.9835	0.8979	0.9274
N	0.413				
Ethyl cellulose					
R^2	0.9347	0.9597	0.9252	0.9773	0.9683
R	0.9668	0.9796	0.9619	0.9886	0.9840
n	0.3049				
Gelatin					
R^2	0.9054	0.9378	0.9911	0.8137	0.8664
R	0.9515	0.9684	0.9955	0.9021	0.9308
n	0.4023				

n-mechanism of drug release (n = 0.5 – Higuchi controlled release, n>0.5<1 – anomalous behavior). R – correlation coefficient.
Q- quantity of drug released R^2 – square of correlation coefficient T – time of drug release.

At 20 %w/w polymer concentrations however, the Higuchi plots (Fig. 5) produced straight lines of higher linearity degrees than the first order plots (Table 4). Moreover, the log Q vs. log t plots (Fig 6) had slopes of almost 0.5, indicating that the diffusion mechanism is now predominant at this concentration. The rate of drug release plots (Table 4) did also confirm that diffusion control is predominant because the Q/t vs. 1/Q plots had higher linearity degrees than the Q/t vs Q plots, for the 3 polymers at this concentration.

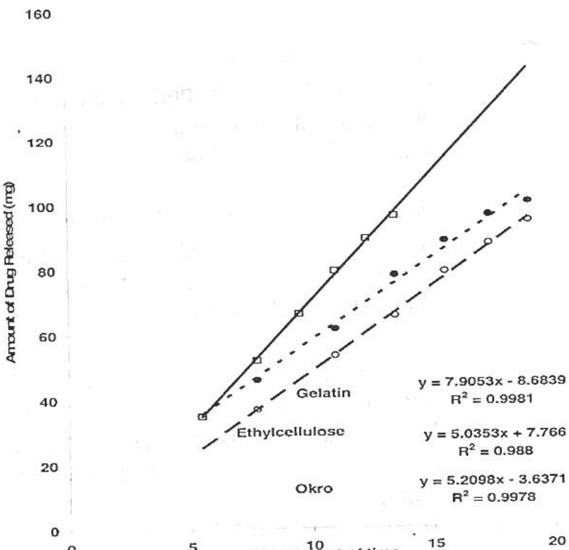

Fig.5. Higuchi plots of theophylline released from encapsulated sustained release granules formulated with 20 %w/w binder.

o Okro • Ethylcellulose
□ Gelatin ——— Linear (Gelatin)
- - - Linear (Ethylcellulose) — — Linear (Okro)

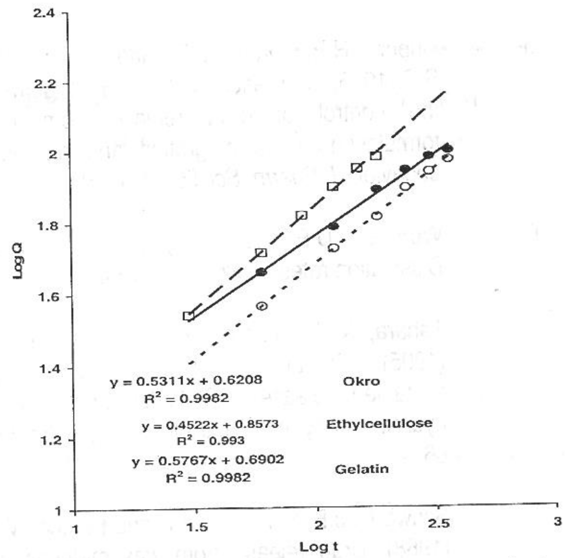

Fig.6. Plots of log theophylline released from sustained release granules formulated with 20 %w/w binder.

□ Gelatin O Okro
• Ethylcellulose — — Linear (Gelatin)
——— Linear (Ethylcellulose) - - - Linear (Okro)

Table 4: Regression Analysis Data of encapsulated sustained release theophylline monohydrate granules formulated with 20%w/w binder.

Polymer	Q vs $T^{1/2}$	LogQ vs LogT	Log (100-Q) vsT	Q/T vs 1/Q	Q/T vs Q
Okro					
R^2	0.9978	0.9982	0.9659	0.9963	0.9358
R	0.9989	0.9991	0.9828	0.9981	0.9674
n	0.5311				
Ethyl cellulose					
R^2	0.9880	0.9930	0.9850	0.9852	0.9422
R	0.9939	0.9643	0.9770	0.9926	0.9707
n	0.4522				
Gelatin					
R^2	0.9981	0.9981	0.9479	0.9932	0.9500
R	0.9990	0.9991	0.9736	0.9966	0.9707
n	0.5767				

n-mechanism of drug release (n = 0.5 – Higuchi controlled release, n>0.5<1 – anomalous behavior). R – correlation coefficient.
Q- quantity of drug released R^2 – square of correlation coefficient T – time of drug release.

Conclusion

It might be said that the mechanism of theophylline release from the sustained release capsules is of mixed order. However, the first order mechanism was predominant at the lower concentration (10%w/w) of the polymers, while the Higuchi diffusion control predominated at the higher concentration (20%w/w) of the polymer in the capsule matrices.

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