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SOME PHYSICAL PROPERTIES OF THEOPHYLLINE MONOHYDRATE SUSTAINED RELEASE TABLETS FORMULATED WITH ABELMOSCHUS ESCULENTUS GUM AS A HYDROPHILIC MATRIX

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ABSTRACT

Abelmoschus esculentus (okro) gum remarkably prolonged/delayed the release of theophylline monohydrate from the sustained release tablets. It performed better than ethyl cellulose and much better than gelatin as a sustained release drug matrix. It is very effective at low concentrations. The kinetics of drug release changed from first order to Higuchi diffusion controlled as the polymer concentrations increased from 2-10% w/w.

KEYWORDS: Sustained release, *Abelmoschus esculentus*, Hydrophilic matrix

INTRODUCTION

Matrix tablets consist essentially of a drug dispersed in a retardant material which effectively delays the passage of the drug from the matrix to dissolution medium, which might result in a sustained drug availability from the dosage form (Tahara et al, 1995; Higuchi, 1963; Cheng-Hsiung et al, 1995; Huet et al, 1991). Drug/retardant blends could be granulated prior to compression. The hydrophilic retardant material swells on absorption of water (dissolution medium) to form a gel, which serves as a barrier, to drug diffusion (Wang et al, 1991; Mashiro, et al 1983; Gumma, et al, 1972).

Abelmoschus esculentus gum swells in water to form very viscous suspension. It has been reported to produce tablets with high hardness values and prolonged disintegration times when used as a tablet binder (Onunkwo and Mba, 1996).

This paper reports the application of *Abelmoschus esculentus* gum in theophylline monohydrate sustained release formulations.

EXPERIMENTAL MATERIALS

The following materials were utilized as supplied by their manufacturers; lactose, theophylline monohydrate (BDH), ethyl cellulose (Fluka), gelatin (M & B) and magnesium stearate (Sigma).

Abelmoschus esculentus (okro) gum was processed in our laboratory.

METHODS

Beers Plot of Theophylline Monohydrate

A 0.1% w/v stock solution of theophylline monohydrate was prepared using 0.1N HCl. Serial dilution of this solution was done to yield 0.1- 0.001% w/v solutions for the construction of a Beers plot (Table1). The absorbance of the solutions was read off at 272 nm using a spectrophotometer SP8-560 (Pye Unicam, England).

Formulation of Sustained Release Theophylline Monohydrate Granules

Formulations of sustained release theophylline monohydrate granules were performed using okro gum, ethyl cellulose or gelatin at low concentrations. The binders were employed at a concentration range of 2-10% w/w, as sustained release matrices. The formula for the preparation of the tablets is shown in Table 2. The granules were produced using the wet granulation method. The specified quantities of theophylline monohydrate and lactose were blended for 5 min. Adding the binder solution to the powder mixture gradually with thorough mixing for 10 min produced a damp mass. The damp mass was forced through 1.7-mm sieve and was dried at 60°C for 1 h. The dry 1.7 mm granules were subsequently passed through a 1.00 mm sieve. The granules were stored in clean, dry, amber colored and tightly closed bottles.

Evaluation of Tablet Properties.

Uniformity of Tablet Weight

An electronic balance (Satorius) was used for the determination of tablet weight uniformity. Twenty tablets selected at random from the batch were weighed individually and collectively. The mean, standard deviation and coefficient of variation were calculated.

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Table 1. Absorbance of graded concentrations of theophylline

Conc.(mg %)	Absorbance	K
0.4	0.21	0.53
0.8	0.42	
1.2	0.64	
1.6	0.85	
2.0	1.06	

Table 2: Formula for the formulation of sustained release theophylline monohydrate granules and tablets.

Drug/Excipient	Wt. Per tablet
Theophylline monohydrate	50 mg
*Binder	2-30% w/w
Lactose	q.s
Magnesium stearate	1% w/w

* - Okro gum, ethyl cellulose and gelatin.

Crushing Strength and Friability:

The crushing strength (hardness) of ten tablets (selected at random from each of the tablet batches after equilibrating for 24h.) was determined in an automatic hardness tester (Erweka). The mean crushing strength was calculated.

The tablet friability was determined by weighing 20 tablets (selected from each batch at random) collectively as initial weight (Wa). The tablets were placed in a friabilator (Erweka) and set to rotate at 25 r.p.m. for 4 min. At the end of the run, the tablets were dedusted and weighed (Wb). Friability was calculated from the expression:

$$F = \frac{Wa - Wb}{Wa} \times \frac{100}{1} \quad \text{-------Eq. I}$$

Content Uniformity

Twenty tablets were crushed to a fine powder. A 300 mg sample of powder was weighed out, transferred to a 100 ml volumetric flask and dissolved in 50 ml of 0.1N HCl. The solution was filtered and made up to 100 ml with 0.11N HCl. An aliquot was withdrawn, diluted and its absorbance read off at 272 nm in a spectrophotometer (SP6-450, UV/VIS, Pye-Unicam, England).

Table 3: $T_{50\%}$, $T_{70\%}$ and $T_{90\%}$ values of sustained release theophylline monohydrate tablets formulated with 2-10% w/w binder.

Matrix formulation	$T_{50\%}$ (Min.)	$T_{70\%}$ (Min.)	$T_{90\%}$ (Min.)
2% w/w			
Okro	37	58	120
Ethyl cellulose	35	50	100
Gelatin	30	45	60
4% w/w			
Okro	60	100	205
Ethyl cellulose	45	75	170
Gelatin	35	50	90
6% w/w			
Okro	70	140	250
Ethyl cellulose	55	100	220
Gelatin	41	65	95
8% w/w			
Okro	90	170	300
Ethyl cellulose	70	135	250
Gelatin	48	75	130
10% w/w			
Okro	100	195	345
Ethyl cellulose	80	150	300
Gelatin	50	95	150

Dissolution Rate

The B.P. 1980 method (Anonymous, 1980) was adopted. The dissolution medium was 1000 ml of 0.1N HCl maintained at 37 ± 0.5°C. One tablet was placed in the basket of the Erweka dissolution apparatus and rotated at 100 r.p.m. At predetermined time intervals, 5-ml portions of the dissolution medium were withdrawn using a pipette fitted with a non-absorbent cotton wool. The solution was assayed for the drug at 272 nm using an SP6-450 UV/VIS Spectrophotometer (Pye-Unicam). Each 5 ml withdrawn was replaced by an equivalent fresh dissolution medium, maintained at 37 ± 0.5°C.

RESULTS AND DISCUSSION

Drug Release Profile

The drug release profiles of the sustained release theophylline monohydrate tablets formulated with 2 – 10% w/w polymer are shown in Figs. 1 – 5. It can be seen that matrix tablets containing formulations with okro gum recorded the lowest drug release rates. The time for the release of 50%, 70% and 90% of theophylline from the matrix tablets are shown in Table 3.

The matrices containing 2% w/w okro gum and ethyl cellulose released all the theophylline during the 360 min. dissolution period while gelatin based matrices recorded 100% drug release at about 120 min. Ethyl cellulose and okro gum based matrices showed similar drug release profiles (with okro gum being lower). For instance, the $T_{50\%}$ and $T_{90\%}$ were 50 and 100 min. for ethyl cellulose and 58 and 120 min. for okro gum respectively. However, the release of theophylline was gradually prolonged as the matrix concentrations of the polymers increased. For instance at 6% w/w polymer concentration, gelatin based matrices recorded 100% drug release at about 180 min. while 100% drug release was not attained for ethyl cellulose and okro gum based matrices at the end of the dissolution period. The release of theophylline was much more retarded at 10% w/w polymer matrix concentration. At this concentration, the $T_{70\%}$ for gelatin, ethyl cellulose and okro based matrices were 95, 150 and 195 min. respectively, which are about twice the T70% values at 4% w/w polymer concentration.

Mechanism of Drug Release from the Matrices

The slopes of logQ Vs logT plots (Table 4) were all well below 0.5, for the theophylline matrix tablets formulated with 2% w/w okro gum, ethyl cellulose and gelatin respectively. For instance, the slope for matrix tablets containing okro was 0.12, ethyl cellulose

Table 4: Regression Analysis Data of the Sustained Release Theophylline Monohydrate Tablets.

Polymer Conc. (%w/w)	Q Vs $\sqrt{T}$ (a)	Log Q Vs T (b)	Log (100-Q) Vs T (c)	Q/T Vs 1/Q (d)	Q/T Vs Q (e)
2					
Okro					
R^2	0.9254	0.9474	0.9311	0.9855	0.9834
R	0.9620	0.9733	0.9649	0.9927	0.9917
n		0.1202			
Ethyl cellulose					
R^2	0.8788	0.9424	0.9899	0.9449	0.9954
R	0.9374	0.9708	0.9949	0.9721	0.9977
n		0.1014			
Gelatin					
R^2	0.7466	0.8100	0.9356	0.6783	0.767
R	0.8641	0.9000	0.9673	0.8236	0.8758
n		0.3300			
4					
Okro					
R^2	0.9353	0.9615	0.9897	0.9562	0.9805
R	0.9353	0.9806	0.9948	0.9782	0.9902
n		0.3546			
Ethyl cellulose					
R^2	0.9192	0.9629	0.9659	0.9834	0.9959
R	0.9587	0.9813	0.9828	0.9917	0.9979
n		0.2473			
Gelatin					
R^2	0.8659	0.9123	0.9788	0.8432	0.9299
R	0.9305	0.9551	0.9893	0.9183	0.9643
n		0.3753			

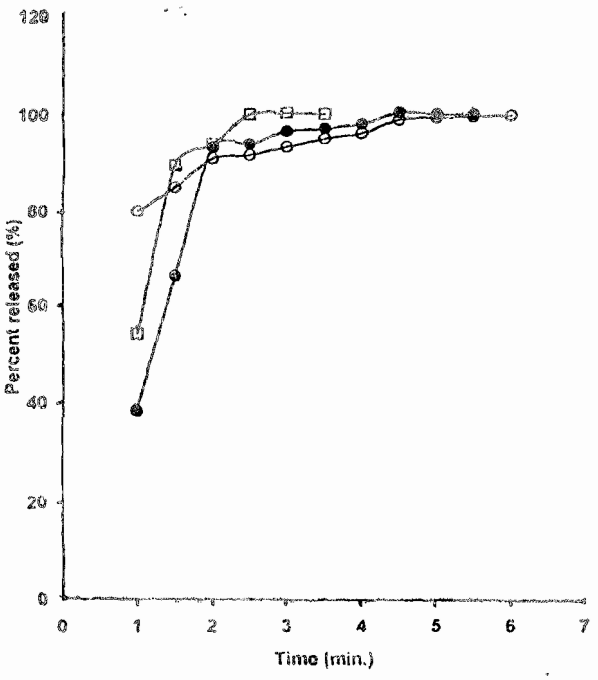

Fig.1. Release profile of theophylline from matrix tablets formulated with 2% w/w binder.

—⊖— Okro —⊖— Ethyl cellulose —⊟— Gelatin

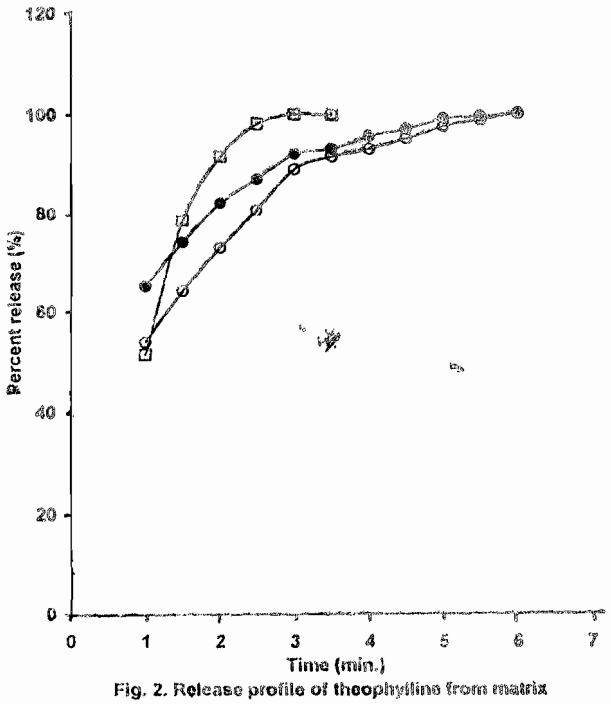

Fig. 2. Release profile of theophylline from matrix tablets formulated with 4 %w/w binder.

—⊖— Okro —⊖— Ethylcellulose —⊟— Gelatin

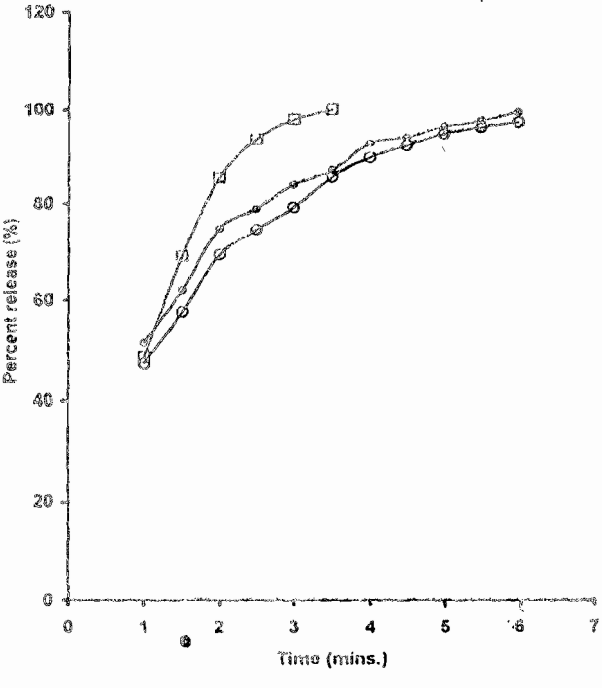

Fig. 3. Release profile of theophylline from matrix tablets formulated with 6 %w/w binder.

—⊖— Okro —⊖— Ethylcellulose —⊟— Gelatin

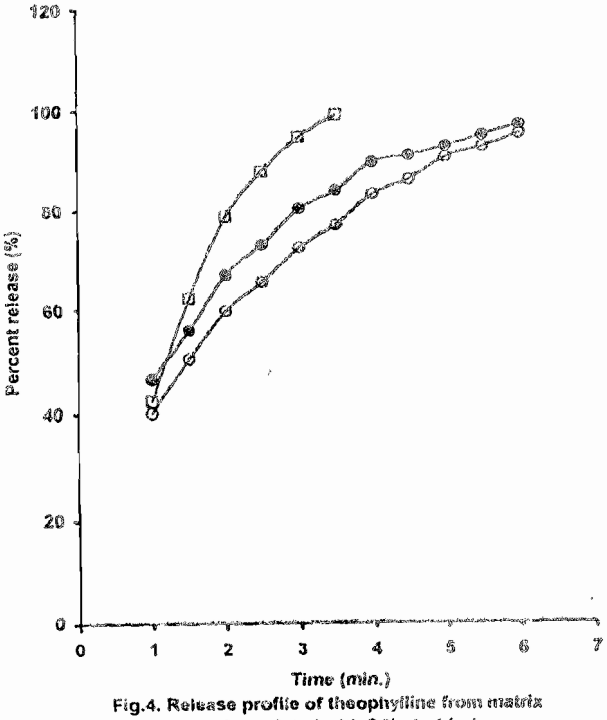

Fig.4. Release profile of theophylline from matrix tablets formulated with 8 %w/w binder.

—⊖— Okro —⊖— Ethylcellulose —⊟— Gelatin

0.1 and gelatin 0.33. Since a slope of 0.5 confirms diffusion controlled release, it means that diffusion controlled release is not dominant at this concentration. Also the linearity of the Q plots (Table 4) was higher than those of 1/Q plots indicating that the first order mechanism of drug release (dissolution controlled) is predominant due perhaps to the low concentration of polymer in the matrix tablets.

At 4% w/w polymer concentration, the first order plots were more linear than the Higuchi plots based on the coefficient of correlation values. Also the slopes of the logQ Vs logT plots were still below 0.5, indicating that the 1st order release mechanism is still dominant. Moreover, the rate of drug release plots based on first order release mechanism were more linear than those based on the Higuchi plots confirming the dominance of the first order mechanism even though the entire drug release mechanism is of mixed order.

The Higuchi plots (Fig. 6) at 6% w/w polymer concentration had higher linearity degree than those of 4% w/w polymer. The slopes were

Table 5: Regression Analysis Data of the Sustained Release Theophylline Monohydrate Tablets

Polymer Conc. (% $^{w}/_{w}$)	Q Vs $\sqrt{T}$ (a)	Log Q Vs Log T (b)	Log (100-Q) Vs T (c)	Q/T Vs 1/Q (d)	Q/T Vs Q (e)
6					
Okro					
R^2	0.9715	0.9860	0.9914	0.9807	0.9635
R	0.9856	0.9930	0.9957	0.9904	0.9816
n		0.4299			
Ethyl cellulose					
R^2	0.9593	0.9774	0.9368	0.9641	0.9924
R	0.9794	0.9886	0.9679	0.9819	0.9964
n		0.3761			
Gelatin					
R^2	0.9486	0.9827	0.9776	0.9529	0.9839
R	0.9486	0.9913	0.9827	0.9762	0.9919
n		0.4416			
8					
Okro					
R^2	0.9893	0.9921	0.9837	0.9521	0.9687
R	0.9946	0.9960	0.9918	0.9758	0.9842
n		0.4764			
Gelatin					
R^2	0.9796	0.9793	0.9108	0.9659	0.9907
R	0.9897	0.9896	0.9543	0.9828	0.9953
n		0.4764			
10					
Okro					
R^2	0.9465	0.9967	0.9781	0.9936	0.9647
R	0.9729	0.9983	0/9890	0.9968	0.9822
n		0.5017			
Ethyl cellulose					
R^2	0.9659	0.8750	0.9935	0.9268	0.9962
R	0.9828	0.9354	0.9968	0.9627	0.9981
n		0.4475			
Gelatin					
R^2	0.7533	0.9988	0.9104	0.9927	0.9336
R	0.8679	0.9994	0.9541	0.9963	0.9662
n		0.5668			

n- mechanism of drug release(**n**<0.5-first order dominant, **n**=0.5- Higuchi diffusion controlled dominant)
R-correlation coefficient
R^2-square of correlation coefficient
Q-amount of drug released
T-time of drug release

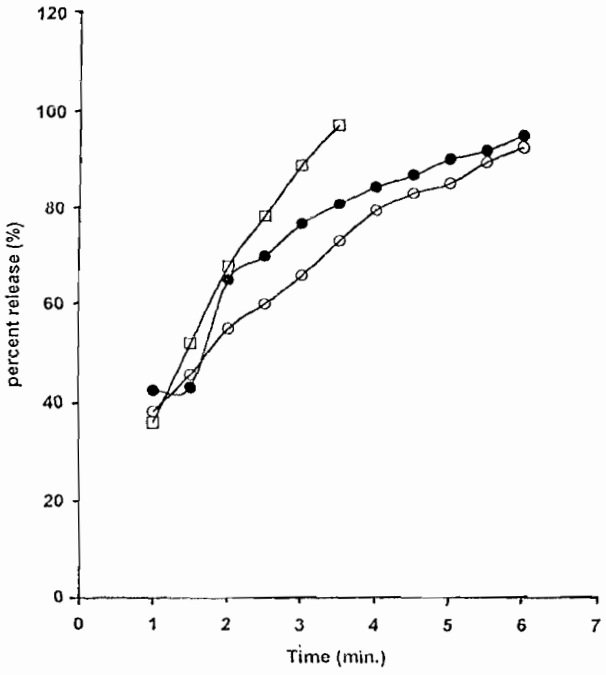

Fig.5. Release profile of theophylline from matrix tablets formulated with 10 %w/w binder.

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

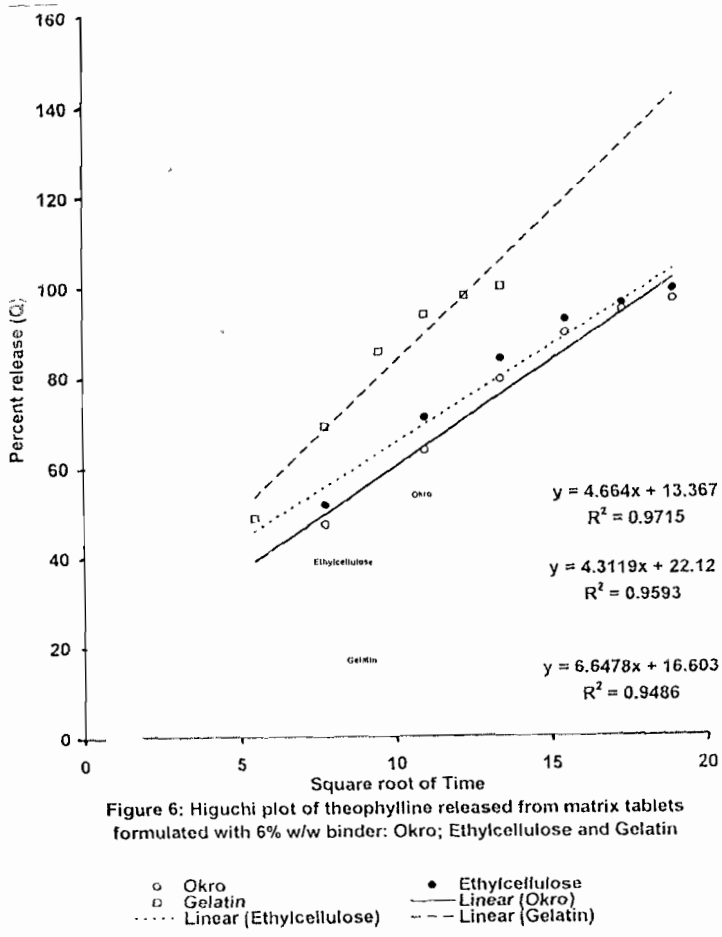

Figure 6: Higuchi plot of theophylline released from matrix tablets formulated with 6% w/w binder: Okro; Ethylcellulose and Gelatin

○ Okro
□ Gelatin
····· Linear (Ethylcellulose)
● Ethylcellulose
—— Linear (Okro)
– – – Linear (Gelatin)

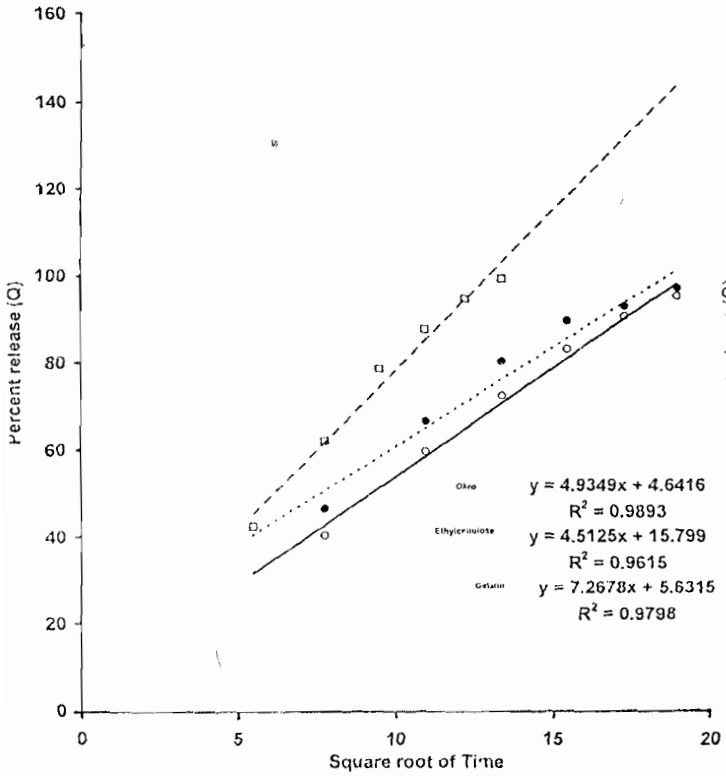

Figure 7: Higuchi Plots of theophylline released from matrix tablets formulated with 8% w/w binder: Okro; Ethylcellulose and Gelatin

○ Okro
□ Gelatin
····· Linear (Ethylcellulose)
● Ethylcellulose
—— Linear (Okro)
– – – Linear (Gelatin)

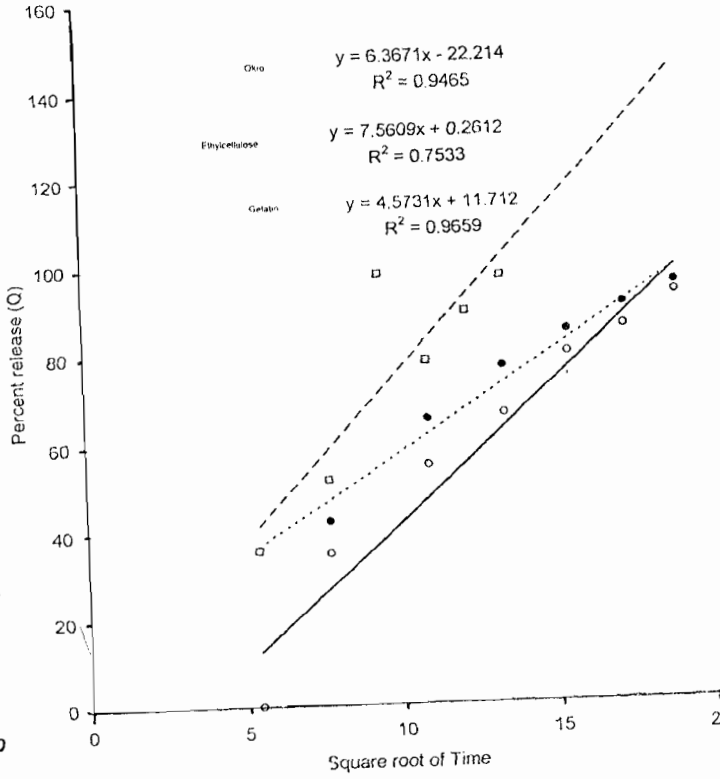

Figure 8 Higuchi plots of theophylline release from matrix tablets formulated with 10% w/w binder: Okro, Ethylcellulose and gelatin

○ Okro
□ Gelatin
····· Linear (Ethylcellulose)
● Ethylcellulose
—— Linear (Okro)
– – – Linear (Gelatin)

also higher than those of 4% w/w polymer and were gradually approaching 0.5, indicating may be that the diffusion controlled release mechanism is becoming significant. However, from the slopes of the first order plots (Table 5) and the rate of drug release plots (Table 5), it might still be that the first order release mechanism are still dominant at this concentration. However, okro is an exception since the coefficient of correlation value for the rate of drug release plots based on Higuchi diffusion control is slightly higher, implying perhaps that the drug release mechanism for okro matrices is approaching a transition.

At 8% w/w polymer concentrations, the Higuchi plots (Fig. 7) produced more linear plots than those of 6% w/w polymer concentration. The slopes of log Q Vs log T plots were almost 0.5 (with exception of ethyl cellulose), indicating probably that the diffusion mechanism is now the controlling process of drug release. The first order plots had lower degrees of linearity than those of Higuchi plots, with exception of ethyl cellulose matrices. However, the rate of drug release plots favored first order release mechanism. It could be that both mechanisms of drug release are now of the same magnitude.

The Higuchi plots (Fig. 8) at 10% w/w polymer concentration were linear. Also, the slopes of log Q Vs log T plots were close to 0.5. Matrix tablets containing gelatin had a slope of 0.57, ethyl cellulose, 0.45 and okro 0.50. Moreover the rate of drug release plots now favor diffusion controlled release as the predominant release mechanism, since the degree of linearity of the 1/Q plots were higher than Q plots,

Hardness and Friability

The hardness and friability profiles of the sustained release theophylline tablets are presented in Figs. 9 and 10. The plots show that the hardness values increased with an increase in binder concentration. Friability behaved in the opposite direction. Friability decreased gradually as the binder concentration increased. Okro gum had the highest hardness-friability ratios.

This observation imply that okro gum may have a higher capacity for adhesive bonding of the tablets when compared with gelatin and ethyl cellulose. It perhaps forms strong adhesive bonds, which accounts for the high hardness values and low friability. This strong adhesive bond could considerably retard tablet wetting and the penetration of dissolution medium into a tablet

Table 6: Content and Weight uniformity of sustained release theophylline monohydrate tablets formulated using different matrices (2-10% w/w)

Matrix Conc. (% w/w)	Content Uniformity Av. Drug Content (mg)	Weight Uniformity (mg)
Gelatin		
2	50.00	310.20 (1/99)
4	49.63	331.80 (2.54)
6	49.91	310.65 (1.87)
8	50.19	338.50 (2.21)
10	50.47	289.90 (2.69)
Ethyl cellulose		
2	50.00	305.25 (2.31)
4	49.63	300.10 (2.47)
6	49.81	306.45 (1.67)
8	50.19	310.15 (2.16)
10	50.47	297.35 (2.23)
Okro		
2	49.81	292.35 (1.98)
4	50.10	294.25 (2.61)
6	49.81	309.55 (2.14)
8	50.00	293.25 (3.35)
10	50.38	309.80 (2.09)

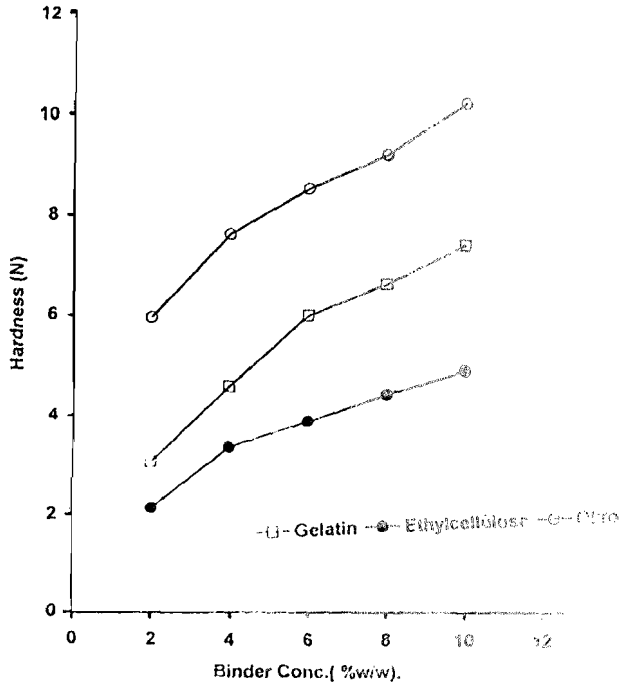

Fig. 9.Hardness plots of theophylline matrix tablets formulated with different binders(2-10 %w/w).

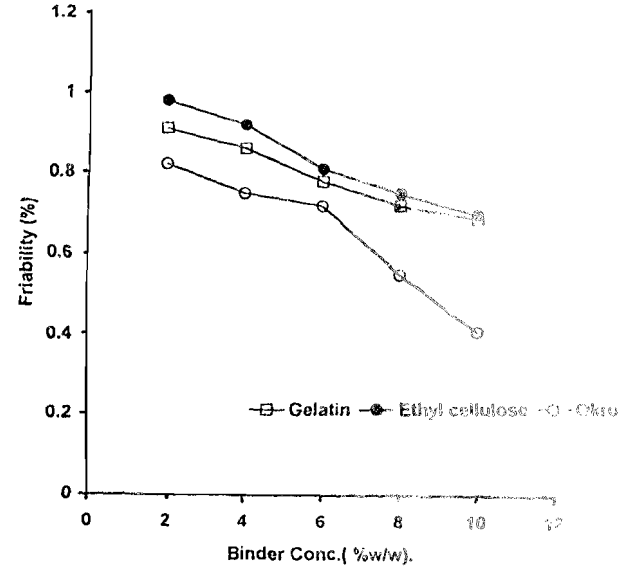

Fig. 10. Friability plots of theophylline matrix tablets formulated with different binders (2-10 %w/w).

(Wang, 1991; Onunkwo and Mba, 1996; Nasipuri, et al 1996). Delayed wetting of tablets and dissolution of the drug may prolong dissolution rates.

Weight and Content Uniformity

The weight uniformity of the sustained release tablets was good as shown from the low values of the standard deviations (Table 6). This perhaps resulted in the satisfactory content uniformity. The average content uniformity of the batches was all within the range of 90-110% of the labeled tablet potency. Good content uniformity might ensure a prompt attainment of desired bioavailability and therapeutic goals. It can also eliminate erratic drug plasma peaks and therapeutic failure.

CONCLUSION

In general, it might be said that the diffusion-controlled mechanism was more predominant as polymer concentration in the matrices increased. First order release mechanism was however dominant at lower concentrations of the polymers. As the polymers concentrations increased, the drug release kinetics became more of mixed order until diffusion release mechanism became dominant. *Abelmoschus esculentus* (okro) gum could be successfully applied in the formulation of sustained release theophylline monohydrate tablets as a hydrophilic matrix since it remarkably delayed the release of theophylline monohydrate from the matrix tablets.

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