Mechanisms of Drug Release from Theophylline Monohydrate Sustained Release Tablet Matrices formulated with Okro Gum

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Abstract

The mechanisms of theophylline monohydrate release from sustained release tablet matrices formulated with okro gum were studied. Okro gum was employed at high concentrations (15-30 %w/w) in order to investigate the mechanism of drug release at these concentrations. Gelatin and ethyl cellulose were employed as standard polymers for comparison. Wet granulation method was used to formulate the tablets. The matrix tablets formulated with gelatin recorded the highest drug release rates while okro gum based matrices showed the lowest rate of drug release among the three polymers. The rate and extent of drug release were much lower at 25 – 30 % w/w polymer concentrations. For instance at 30 % w/w, the matrix tablets containing Gelatin did not record up to 90 % drug release in 180 min while matrix tablets containing okro gum did not release up to 70 % of theophylline within 360 min. The drug release mechanism of the polymers at 15 – 30 % w/w concentrations showed an anomalous behaviour, since the slope indicative of mechanism of drug release were all in the range of 0.5 to 1.0. This perhaps shows that the mechanism of drug release is changing from diffusion controlled to zero order.

Keywords: Okro gum, Matrix tablets, Drug release

Introduction

A basic property of sustained release delivery systems is that they release drugs *in vivo* according to a predictable rate (1-2). It is possible to predict the rate of drug release only when the mechanism of drug release is well defined and the rate can be regulated by known physicochemical principles (3-5). Drug release from sustained release systems could occur as a square root of time (diffusion controlled) or as first order with declining release profiles. Diffusion controlled release of drugs dispersed in solid matrices have been studied by Higuchi (6) and Desai et al (7). For diffusion-controlled mechanism, the rate of drug release will be inversely proportional to the total amount of drug released (Q) according to the following equation (8):

$$Q^1 = \frac{Q}{S} = K.t^{1/2} \quad \ldots\ldots\ldots\ldots\ldots\ldots 1$$

Where Q^1 is the total amount of drug released per surface area, S, of the matrix. Equation 1 can be expressed as:

$$Q^1 = K.S.t^{1/2} \quad \ldots\ldots\ldots\ldots\ldots\ldots 2$$

By differentiation and substitution (8) it becomes

$$\frac{dQ}{dt} = \frac{K^2S^2}{2Q} = K.t^{1/2} \quad \ldots\ldots\ldots\ldots\ldots\ldots 3$$

This is the basis for the rate of release plot according to the Higuchi model (9). The rate predicted by first order kinetics is given by

$$\frac{dQ}{dt} = K.A_o - K_Q \quad \ldots\ldots\ldots\ldots\ldots\ldots 4$$

where A_o is the initial amount of the drug in the product. The amount of the drug (A), remaining in the product is given by:

$$A = A_o - Q^1 \quad \ldots\ldots\ldots\ldots\ldots\ldots 5$$

This indicates that the rate of drug release is proportional to Q^1 rather than inversely proportional as predicted by the diffusion model (10). Also a plot of drug released (Q) will give a straight line with a negative slope. A confirmation of the Higuchi diffusion model is provided by the logarithmic form of Equation 2:

$$\text{Log } Q = \text{Log } K^1 + 1/2 \text{ log } t \quad \ldots\ldots\ldots\ldots 6.$$

A plot of log Q against log t is linear with a slope of 0.5 confirming the diffusion model (8). Equation 6 is similar to the logarithmic form of an empirical equation given by Ritger and Peppas (11).

$$\frac{Mt}{Mo} = K.t^n \quad \ldots\ldots\ldots\ldots\ldots\ldots 7$$

where Mt/Mo is the fraction of drug released up to time t; K is a constant incorporating structural and geometric characteristics of the tablet and n is the diffusional exponent of the mechanism of release. The Fickian diffusion (or Case I) occurs when n = 0.5 and the zero order mechanism (or Case II) occurs when n=1. In this paper, the mechanisms of drug release from theophylline monohydrate sustained release tablets formulated with different polymers were evaluated.

Materials and Methods

The following materials were used as supplied by their manufacturers; lactose, Gelatin (Merck, Germany), theophylline, ethyl cellulose (Fluka, Switzerland).

Processing of *Abelmoschus esculentus* (Okro) gum; Fresh okro fruits were washed and sliced to small pieces. Then 2.0 kg of the cut okro was macerated in water (2L) and allowed to stand 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 gm was immersed in acetone to ensure complete removal of water. The removal of the acetone was accomplished by filtration in vacuum. The gum was dried in a desiccator containing anhydrous calcium chloride, ground, sieved (250 um sieve) and weighed.

Formulation of sustained release tablets: Formulations of sustained release theophylline monohydrate granules were carried out using okro gum, ethyl cellulose or gelatin at high concentrations. The binders were employed at a concentration range of 15-30 % w/w as sustained release matrices. The formula for the preparations of the tablets is shown in Table I.

Table 1: Formula for the formulation of sustained release theophylline monohydrate tablets

Drug/Excipient	Wt. Per tablet
Theophylline monohydrate	50 mg
Binder*	15-30 % w/w
Lactose	q.s
Magnesium stearate	1 % w/w

** - Okro gum, ethyl cellulose and gelatin*

The granules were produced using the wet granulation method. The specified quantities of theophylline monohydrate and lactose were blended thoroughly for 5 min. Adding the binder solution to the powder mixture with thorough mixing for 10 min produced a damp mass. The damp mass was forced through sieve 1.7 mm 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 coloured and lightly closed bottles. The different granule batches were mixed thoroughly with specified quantities of magnesium stearate for 5 min. The granules were compressed in an F-3 tabletting machine (Manesty, England), set at a machine pressure of
50 units. The tabletting machine was fitted with 9.5 mm concave faced punches and its die set at an adequate fill volume to produce 300 mg tablets.

Evaluation of tablet properties

Weight uniformity: An electronic balance (model 404/48, Sauter) was used for the determination of tablet weight uniformity. Twenty tablets selected at random from every batch were weighed individually and collectively. The mean, standard deviation and coefficient of variation were calculated.

Content uniformity; Twenty tablets were crushed to fine powder. A 300 mg sample of powder was weighed out, transferred to a 100 ml volumetric flask and dissolved in 50 mls of 0.1 N HCl. The solution was filtered and made up to 100 ml with 0.1 N HCl. A 5 ml aliquot was withdrawn, diluted and its absorbance read at 272 nm in an Sp6-450 UV/VIS spectrophotometer (Pye-Unicam). The average of triplicate determinations was recorded. The theophylline monohydrate content of a given tablet was calculated from the titre of the Beers plot.

Dissolution rate; The BP. Method (7) was adopted. The dissolution medium was 100 ml of 0.1 N HCl maintained at 37 ± 0.5 °C. One tablet was placed n the basket of the Erweka (model DT-D) dissolution apparatus rotating 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 with an equivalent fresh dilutions medium maintained at 37 ± 0.5 °C.

Results and Discussion

Drug release profile from the tablet matrices: Figs. 1-4, present the drug release profiles of the sustained release theophylline monohydrate tablets formulated with 15-30 % w/w of the binders.

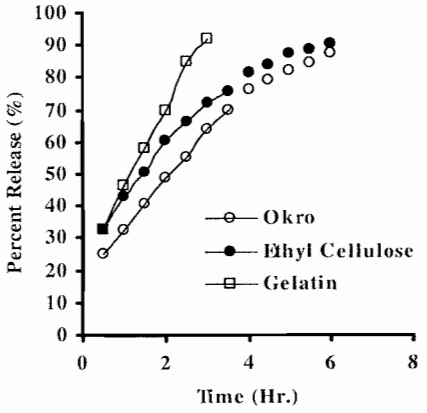

Fig. 1. Release profiles of theophylline from matrix tablets formulated with 15 %w/w binder.

The matrix tablets formulated with gelatin recorded the highest drug release rates with $T_{50\ \%}$ and $T_{70\ \%}$ of 7 and 120 min. at 15 % w/w and 91 and 143 min. at 20 % w/w polymer concentrations. The matrix tablets formulated with either ethyl cellulose or okro gum had lower $T_{50\ \%}$ and $T_{70\ \%}$ values. Okro gum based matrices showed the lowest rate of drug release recorded among the three polymers. At 20 % w/w polymer concentrations,
matrices containing ethyl cellulose and okro gum had less than 90 % of drug release after 360 min.

The rate and extent of drug release from the matrix tablets were much lower at 25-30 % w/w polymer concentrations. Also, the matrix tablets containing gelatin did not record up to 90 % drug release in 180 min., while matrix tablets containing okro gum did not release up to 70 % of theophylline within 360 min. The $T_{50\ \%}$, $T_{70\ \%}$ and $T_{90\ \%}$ values of the sustained release theophylline monohydrate tablets are presented in Table 2.

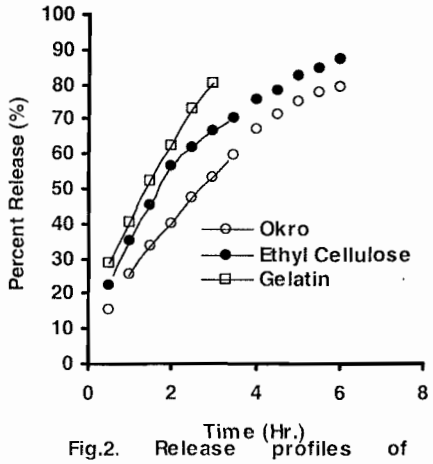

Fig.2. Release profiles of theophylline from matrix tablets formulated with 20 %w/w binder.

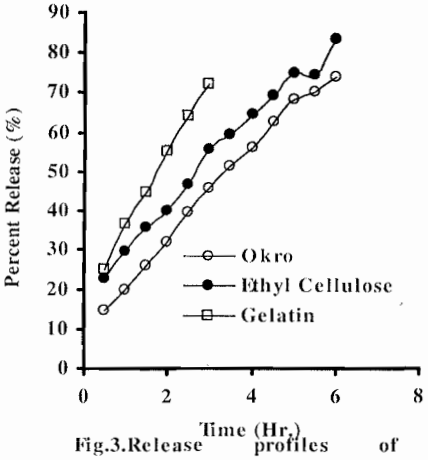

Fig.3.Release profiles of theophylline from matrix tablets formulated with 25 %w/w binder.

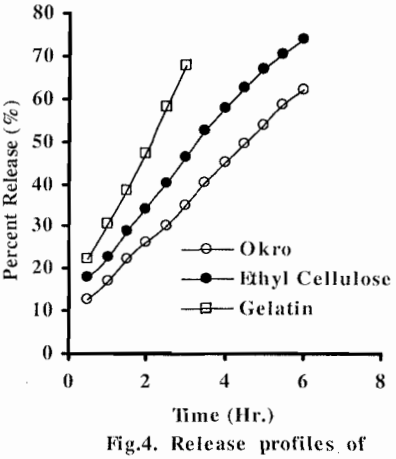

Fig.4. Release profiles of theophylline from matrix tablets formulated with 30 %w/w binder.

Table 2: $T_{50\ \%}$, $T_{70\ \%}$ and $T_{90\ \%}$ values of sustained release theophylline monohydrate tablets formulated with 15-30 % w/w binder

Matrix formulation	$T_{50\%}$ (Min.)	$T_{70\%}$ (Min.)	$T_{90\%}$ (Min.)
15 % w/w			
Okro	125	207	>360
Ethyl cellulose	90	165	350
Gelatin	70	120	172
20 % w/w			
Okro	165	270	>360
Ethyl cellulose	83	175	>360
Gelatin	87	143	>360
25 % w/w			
Okro	200	315	>360
Ethyl cellulose	160	275	>360
Gelatin	108	155	>180
30 % w/w			
Okro	260	>360	>360
Ethyl cellulose	195	325	>360
Gelatin	124	>180	>180

Mechanisms of drug release from the tablet matrices: The Higuchi plots at 15 % w/w concentration (Fig. 5) were all linear. The log Q vs. log t plots had slopes (Table 3), which slightly exceeded 0.5 for okro (0.56) and gelatin (0.59).

Table 3: Regression Analysis Data of the Sustained Release Theophylline Monohydrate Tablets

Polymer Conc. (% $^{w}/_{w}$)	Q Vs $\sqrt{t}$ (a)	Log φ Vs Log T (b)	Log (100-φ) Vs T (c)	φ/T Vs 1/φ (d)	φ/T Vs φ (e)
15					
Okro					
R^2	0.9934	0.9899	0.9975	0.9562	0.9629
R	0.9967	0.9949	0.9987	0.9779	0.9813
n		0.5646			
Ethyl cellulose					
R^2	0.9803	0.9900	0.9979	0.9864	0.9868
R	0.9901	0.9950	0.9989	0.9932	0.9934
n		0.4287			
Gelatin					
R^2	0.9884	0.9925	0.9446	0.9784	0.8204
R	0.9942	0.9962	0.9719	0.9891	0.9058
n		0.5908			
20					
Okro					
R^2	0.9918	0.9925	0.9945	0.9625	0.9398
R	0.9959	0.9962	0.9972	0.9810	0.9694
n		0.6567			
Ethyl cellulose					
R^2	0.9814	0.5972	0.9979	0.9737	0.9936
R	0.9907	0.7728	0.9989	0.9868	0.9968
n		0.3526			
Gelatin					
R^2	0.9938	0.9951	0.9853	0.9809	0.8433
R	0.9969	0.9975	0.9926	0.9904	0.9183
n		0.5767			

n- mechanism of drug release (n= 0.5-Higuchi controlled release, n>0.5<1-Anomalous behaviour); R-correlation coefficient R^2-Square of correlation coefficient; T-time of drug release

However, ethyl cellulose (0.43) was below 0.5. Ethyl cellulose matrices may be having first order as the major drug release mechanism.

The predominance of the diffusion controlled release mechanism is perhaps confirmed by the rate of drug release plots, which show higher values of correlation coefficients (Table 3) for the plots based on Higuchi diffusion model. This is more pronounced for gelatin at this concentration.

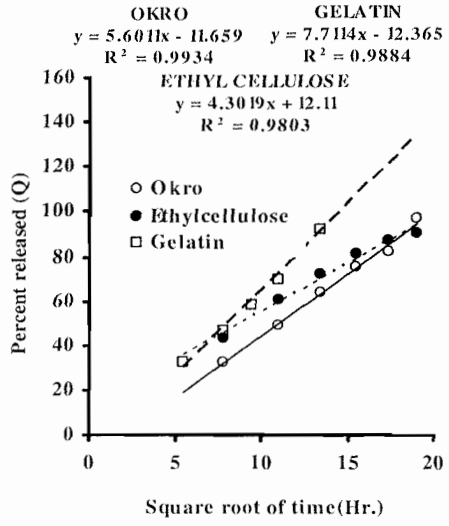

Fig.5: Higuchi plots of theophylline release from matrix tablets formulated with 15% w/w binder: Okro; Ethylcellulose and Gealtin

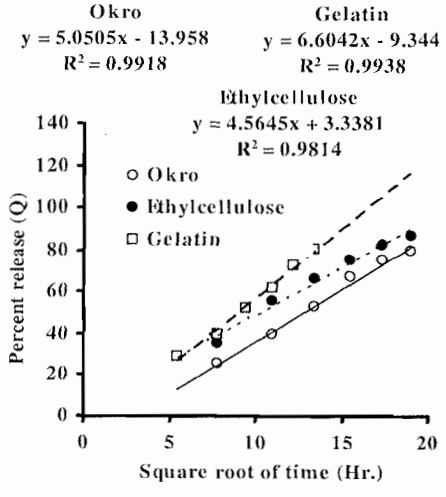

Fig.6: Higuchi plots of theophylline released from matrix tablets formulated with 20% w/w binder: Okro; Ethylcellulose and Gelatin.

The Higuchi plots (Fig. 6) at 20 % w/w polymer is similar to that of 15 % w/w polymer with a high level of linearity. The slopes of the log – log plots of okro, ethyl cellulose and gelatin were 0.66, 0.55 and 0.58 respectively (Table 3). However, the first order plots were also linear for all the polymers thus creating the need for confirmation of the major mechanism of drug release by the rates of drug release plots. The Q/t Vs 1/Q plots had higher linearity degrees than that of Q/t Vs Q plots for okro and gelatin showing may be that the first order release mechanism is becoming minor. However, ethyl cellulose based matrices might still be at the transitional stage since its Q/T Vs Q plots still had higher correlation values.

The increase in the values of the log Q Vs log t plots above 0.5 may suggest an anomalous or non-Fickian release behaviour (13). This anomalous behaviour occurs when the slope indicative of release mechanism is between 0.5 and 1.0. That is the drug release mechanism is changing from diffusion controlled to zero order.

Fig. 7 shows the Higuchi plots for theophylline matrix tablets formulated with 25 % w/w polymer. The plots were linear to a very high degree (correlation coefficients > 0.99). However, the first order plots also showed similar high level of linearity (Table 3). The log per cent release versus log time plots (Table 3) had slopes, which were still increasing with increase in polymer concentration. The slopes for okro, ethyl cellulose and gelatin were 0.75, 0.60 and 0.59 respectively.

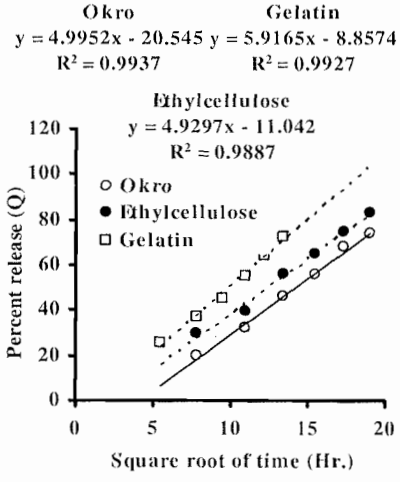

Fig.7: Higuchi plot of theophylline released from matrix tablets formulated with 25% w/w binder: Okro; Ethylcellulose and Gelatin.

The drug release mechanism is still in the anomalous range since the values are still below one. The rate of drug release plots (Table 3) plotted according to Higuchi diffusion model also had higher degree of linearity than that of the first order plots. This may perhaps show the minor rate of the first order drug release at this concentration.

The Higuchi (Fig. 8) and first order (Table 4) plots at 30 % w/w polymer concentration were all very linear, similar to the Higuchi plots at 25 % w/w concentration. The slopes of the log Q Vs log t plots (Table 4) for okro, ethyl cellulose and gelatin based matrices were 0.71, 0.68 and 0.62 respectively.

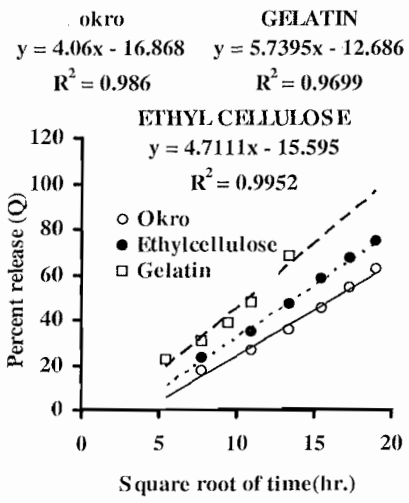

Fig. 8: Higuchi plots of theophylline released from matrix tablets formulated with 30% w/w binders: Okro; Ethylcellulose and Gelatin

This shows that the mechanism of drug release is gradually approaching zero order as the concentration of polymer in the matrices increased especially at high concentrations. The Q/t Vs 1/Q plots (Table 4) were also more linear than the Q/t Vs Q plots (Table 4). This trend is also similar to the rate of drug release plots of 25 % w/w concentrations.

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

Polymer Conc. (% $^{w}/_{w}$)	Q Vs $\sqrt{t}$ (a)	Log φ Vs Log T (b)	Log (100-φ) Vs T (c)	φ/T Vs 1/φ (d)	φ/T Vs φ (e)
25					
Okro					
R^2	0.9937	0.9984	0.9904	0.9666	0.8904
R	0.9968	0.9992	0.9952	0.9832	0.9436
n		0.7481			
Ethyl cellulose					
R^2	0.9887	0.9853	0.9960	0.9863	0.8644
R	0.9943	0.9926	0.9980	0.9931	0.9297
n		0.601			
Gelatin					
R^2	0.9927	0.9961	0.9893	0.9906	0.8586
R	0.9963	0.9980	0.9980	9.9953	0.9250
n		0.5873			
30					
Okro					
R^2	0.9860	0.9968	0.9922	0.9736	0.7694
R	0.9930		0.9961	0.9867	0.8772
n		0.7400			
Ethyl cellulose					
R^2	0.9952	0.9974	0.9960	0.9863	0.8823
R	0.9976		0.9980	0.9931	0.9393
n		0.6798			
Gelatin					
R^2	0.9699	0.9836	0.9699	0.9251	0.6823
R	0.9848		0.9848	09848	0.8260
n		0.6244			

Weight and Content Uniformity: Table 3 shows the weight and content uniformity values of the tablets. The low values of standard deviations indicate good weight uniformity. Also the content uniformity is satisfactory since the average content uniformity of the batches were all within the range of 90-110 % of the labeled tablet potency.

Conclusion: The drug release mechanisms of the polymers at 15-30 % w/w concentrations showed an anomalous behaviour. This is because the slope indicative of mechanism of drug release were all in the range of 0.5 to 1.0; indicating perhaps that the drug release mechanism is changing from diffusion controlled to zero order.

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