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The Effect of Polymer Blends on the Formulation of Sustained Release Ciprofloxacin Matrix Tablets

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: The application of polymers to sustain drug release is increasingly becoming popular and the use of polymer blends provides an alternative method to developing new pharmaceutical raw materials.

Objective: This work aims to study the effect of polymer blends of xanthan gum (X), hydroxypropylmethyl cellulose (HPMC) and *Chrysophyllum albidum* gum (CAG) on the mechanical properties and release rate of ciprofloxacin tablet.

Method: Ciprofloxacin tablets prepared by direct compression was evaluated for weight uniformity, friability and hardness. The time taken for 50 % (T_{50}) and 75 % (T_{75}) drug release were obtained and the in vitro release data were fitted into drug kinetics models to determine the mechanism of drug release.

Result: The tablets showed satisfactory mechanical strength. The rank order of tablet strength for the various blends is CAG-HPMC > CAG-X-HPMC > CAG-X. All the formulations with polymer blends had higher values of T_{50} and T_{75} than formulations containing single polymers. An increase in the proportion of CAG in formulation containing CAG-X (in ratio 2:1) resulted in almost a two- fold sustained drug release with T_{50} and T_{75} values of 4.4 and 7.1 hrs respectively. Generally, a blend of the three polymers resulted in a slower drug release. The proportion of polymers in the blend had no significant ($p>0.05$) effect on drug release rate in formulations containing the three polymers. Higuchi model was the most prominent model while the mechanism for drug release was super case II transport.

Conclusion: This study highlights the potentials of polymer blends in the design and formulation of sustained release ciprofloxacin matrix tablets.

Keywords: Polymer blend, Sustained release, Ciprofloxacin, Xanthan gum, *Chrysophyllum albidum* gum

INTRODUCTION

Sustained release formulations have received considerable attention in recent years because of their numerous advantages over immediate release dosage formulations. These include reduced fluctuations in drug level, improved patient compliance due to reduced dosing frequency, minimal side effects and reduced health cost due to improved therapy. They have revolutionized novel drug delivery systems (Sharada *et. al*., 2012). They are reservoir systems formulated to keep drug plasma concentration within therapeutic level by providing a constant and continuous drug release over a prolonged period of time after administration of a single dose. Various approaches to sustained release of drugs include diffusion sustained release, dissolution, osmotic pump systems, ion exchange systems and pH dependent systems. An example of diffusion system is the use of polymer matrix. The application of polymer to prolong drug release is increasingly becoming popular in recent times (Ibrahim El Belgory *et al.*, 2012). It has been observed that the use of polymer blends provides an alternative method to developing novel pharmaceutical raw materials with desirable properties rather than designing and synthesizing entirely new compounds (Lua *et. al.*,

2007; Ibrahim El Belgory *et al.*, 2012). Thus polymer blending offers a simple and effective means of combining the desirable characteristics of different polymers. A number of polymers such as hydroxypropyl methylcellulose (HPMC), xanthan gum, cashew gum and guar gum have been used to sustain drug delivery. (Amtul *et.al*, 2018, Baviskhar *et. al*., 2013; Manishet *et. al*., 2014, Anirbandeep Bose *et. al.*, 2013)

HPMC is an inert viscoelastic semisynthetic polymer while xanthan gum is a polysacharide produced by *Xanthomonas campestris* bacterium (Vania *et al*., 2013) when it is exposed to aerobic conditions in the presence of maize, sugar cane and their derivatives. It is widely employed as thickening agent in drilling fluids, food and cosmetics (Geremia & Rinaudo, 2005). *Chrysophyllum albidum* gum is a natural gum extracted from the fruit of *Chrysophyllum albidum* or African star apple which is a dominant canopy tree of lowland and mixed rainforests. It belongs to the family Sapotaceae. The fruit is seasonal, spherical in shape and has a slightly pointed tip with 3 to 5 brown hard shiny seeds arranged in a star-shaped pattern in the yellow pulp. The gum extracted from the fruit had been characterized and used as binder and suspending agent (Bakre and Ajakore, 2015; Okoye and Ndiwe, 2016; Bakre *et. al*., 2017). Ciprofloxacin is a broad spectrum fluoroquinolone with activity against both gram-positive and gram-negative bacteria. It is rapidly absorbed following oral administration and it has a serum elimination half-life of 4hours. Due to the short half-life, a more frequent administration of the conventional formulation is required in order to maintain its antimicrobial activity. This often results in poor compliance and consequently development of antibiotic resistance. A sustained release formulation of ciprofloxacin will ensure a constant drug release over a prolonged period of time and reduce the dosing frequency.

This study aims to evaluate the effect of polymer blends of *Chrysophyllum albidum* gum, xanthan gum (X) and hydroxypropylmethyl cellulose (HPMC) on the mechanical and sustained release rate of ciprofloxacin tablet.

MATERIALS AND METHODS

Ciprofloxacin lactate monohydrate was obtained from Dr. Reddy laboratory, India while xanthan gum and hydroxylpropylmethylcellulose (HPMC) E15 premium LV were purchased from Shanghai Blueway Limited and Jiangsu, China respectively. Microcrystalline cellulose (BDH Chemical, UK) was also used. The *Chrysophyllum albidum* gum was prepared at the Department of Pharmaceutics and Pharmaceutical Technology, Olabisi Onabanjo University, Nigeria. All the reagents were of analytical grade and used without further purification.

Preparation of *Chrysophyllum albidum* gum

Chrysophyllum albidum fruits without the seeds were sun-dried for three weeks and thereafter size reduced. The powder was sifted using a sieve of size 250µm. Ten (10) kg of dried powder were extracted exhaustively using 96 % ethanol. The extracted gum was dried in a desiccator and the dried gum was milled into powder.

Preparation of tablets by direct compression

The desired compositions of the powders in Table 1 were weighed and compressed on a Carver hydraulic hand press (Model 38510E, Carver Inc, USA) fitted with a pressure gauge. Five hundred (500) mg batches of ciprofloxacin lactate monohydrate formulation were compressed into tablets using a 12.5 mm die and flat faced punches at compression pressure of 1.0 tonne and a dwell time of 30 seconds. Before each compression, the punches and die were lubricated with 2 % w/v dispersion of magnesium stearate in 96 % ethanol. The tablets were carefully ejected and stored appropriately to avoid absorption of moisture.

Evaluation of Tablet

Determination of friabilty

The initial weight of ten tablets was taken on an electronic balance (Ohaus Corporation, USA). The tablets were placed in a friabilator (Shivani scientific Ind., Mumbai, India) which was operated at 25 revolutions per minute. After four minutes, the tablets were collected, dusted and re-weighed. The percentage weight loss was calculated and taken to represent the friability. Determinations were made in triplicate.

Table 1: Composition of different formulations of ciprofloxacin matrix tablet (~500mg)

Formulation	Ciprofloxacin (mg)	CAG (mg)	Xanthan gum (mg)	HPMC (mg)	MCC (mg)	Magnesium Stearate (mg)
A	100	100	-	-	5	295
B	100	-	100	-	5	295
C	100	-	-	100	5	295
D	100	50	50	-	5	295
E	100	100	50	-	5	245
F	100	150	50	-	5	195
G	100	50	-	50	5	295
H	100	100	-	50	5	245
I	100	150	-	50	5	195
J	100	50	50	50	5	245
K	100	50	50	100	5	195
L	100	100	50	50	5	195

Determination of Crushing Strength

The force required to diametrically fracture the tablet was determined at room temperature using a hardness tester (Ketan, India). Tablets were randomly selected from each batch. Each tablet was held between a fixed anvil and a moving jaw. Pressure was applied by turning the knurled knob just sufficiently to hold the tablet in position. The reading of the pointer was adjusted to zero after which the pressure was gradually increased until the tablet fractured. The value of the load on the gauge at this point gives a measure of the tablet crushing strength. The values were recorded in $kgcm^{-1}$

Determination of Dissolution Rates of Tablets

The dissolution rate test was carried out using a dissolution apparatus (paddle method) (Copley dissolution machine, NE4-COPD, Nottingham, UK). Phosphate buffer (900ml and pH 7.4) was used as the medium and the paddle was rotated at 50 rpm. At specific time interval, 10ml of the sample were withdrawn and replaced with 10ml phosphate buffer and maintained at 37±0.5^{o}C. The withdrawn samples were filtered using a whatman filter paper and analyzed by UV spectrophotometry at 276nm.

Kinetics of Drug Release

The *in vitro* release data were fitted into the following drug kinetics release models (Higuchi, 1963; Ritger and Peppas, 1987; Siepmann and Peppas, 2001)

Higuchi model: $Q = k_H t^{½}$…(1)
Cumulative percentage of drug released versus the square root of time was plotted

First order: $\text{Log } Q = \log Q_0 - K_1 t/2.303$… (2)
Log cumulative percentage of drug released against time was plotted

Zero order: $Q=K_0 t$… (3)
Cumulative amount of drug release was plotted against time was plotted

where Q is the quantity of drug released at time t, Q_0 is the intial concentration of drug, the k_0, k_1 and k_H, represent the release constants for zero-order, first-order and Higuchi models respectively.

Mechanism of Drug release

The first 60% drug release data was fitted into Korsmeyer–Peppas model to get the mechanism of drug release (Korsmeyer et. al., 1983)

$$Q/Q_0 = kt^n \text{ ..... } (4)$$

Where Q/Q_0 is the fraction of drug released at time t, k is the rate constant and n is the release exponent. The drug release pattern was analyzed by plotting log cumulative percentage drug release against log time. The diffusional exponent, n indicates the drug release mechanism. Values of n equals to 0.45 indicates a Fickian diffusion mechanism, $0.45 < n < 0.89$ to non-Fickian transport, $n = 0.89$ to Case II (relaxational) transport, and $n > 0.89$ to super case II transport.

RESULTS AND DISCUSSION

Mechanical properties of ciprofloxacin tablets

An ideal tablet should combine good mechanical strength with adequate drug release profile. The mechanical properties of compressed tablets can be evaluated by the crushing strength and friability. Table 2 shows that the tablets showed satisfactory mechanical strength. The crushing strength of all the formulations range between 4.7-9.83N. The friability values for the ciprofloxacin formulations were below 1 % which conventionally is generally considered acceptable. This shows that the formulations possess

enough strength to withstand mechanical shocks and abrasion during handling. The rank order of tablet strength for the various blends is CAG-HPMC > CAG-X-HPMC > CAG-X.

An increase in the proportion of CAG in formulations with CAG-HPMC blend had little effect on the tablet strength while it resulted in a decrease in tablet hardness and friability in formulations containing CAG-X blend. Formulations containing HPMC were stronger than those without it ($p<0.05$). Formulation containing CAG and X (3:1) had the least strength. The CSF gives an indication of the strength and weakness of tablets; hence the parameter can be used to measure the mechanical strength of the formulations. A higher value of CSF implies a strong tablet. All the formulation had high CSF values. Formulations containing HPMC however had higher values. The weight uniformity test result shows that the weight variation for the formulations was below 5 % which implies consistency of dosage unit during compression while the thickness was between 4.19 - 4.88 mm.

Table 2: Physical Parameters of Ciprofloxacin matrix tablets

Formulation	Weight (mg)	Thickness (mm)	Friability % (F)	Crushing strength(N)	CSF
A	493.3 ± 27.2	4.19 ± 0.10	0.15	6.50 ± 0.50	43.33
B	496.4 ± 11.8	4.36 ± 0.47	0.47	8.80 ± 0.26	18.72
C	486.8 ± 12.3	4.67 ±0.49	0.31	9.83 ± 0.35	31.71
D	480.6 ± 26.0	4.86 ±0.06	0.38	5.66 ± 0.41	14.89
E	496.6 ± 29.3	4.40 ±0.10	0.22	5.40 ± 0.52	24.55
F	486.9 ± 30.4	4.50 ±0.32	0.19	4.70 ± 0.17	24.74
G	498.0 ± 13.5	4.40 ±0.43	0.23	7.00 ± 0.20	30.43
H	482.0 ± 10.0	4.23 ±0.57	0.26	7.00 ± 0.20	26.92
I	485.9 ± 8.8	4.45 ±0.40	0.24	6.46 ± 0.34	26.92
J	497.0 ± 1.5	4.30 ±0.02	0.27	6.93 ± 0.11	25.67
K	484.8 ± 17.4	4.31 ±0.01	0.24	8.23 ± 0.25	34.29
L	492.8 ± 15.4	4.88 ±0.08	0.16	6.41 ± 0.52	40.06

In vitro drug release

The drug release profile is presented in Figures1 and 2. The time taken for 50 % (T_{50}) and 75 % (T_{75}) drug release are important parameters for evaluating drug release in tablet formulations. All the formulations with polymer blends had higher T_{50} and T_{75} than formulations A, B and C which contain single polymers. However, among the formulations with single polymers, the formulation containing CAG exhibited the slowest drug release. CAG has been reported to absorb about twice its weight of water and swell appreciably (Bakre, 2017). The swelling and hydration properties result in the formation of a thick viscous gel which serve as a barrier to diffusion and thereby slows down water penetration into the matrix. This consequently retards drug release.

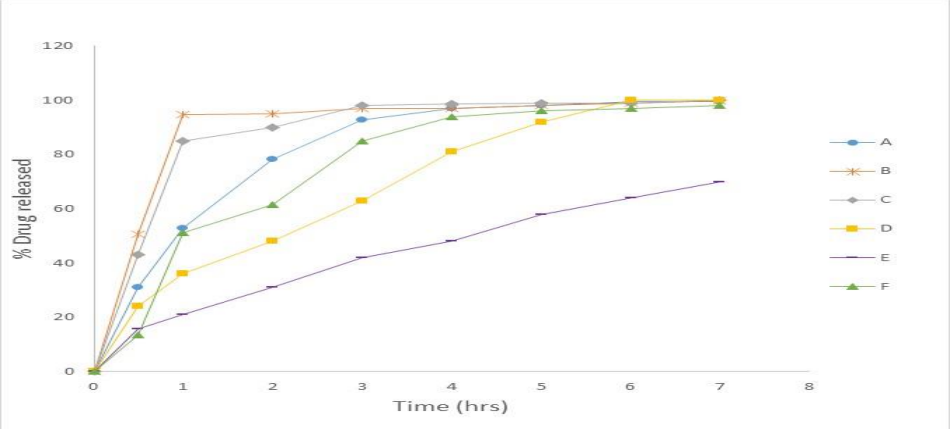

Figure 1: Drug release profile of selected ciprofloxacin matrix tablet formulations

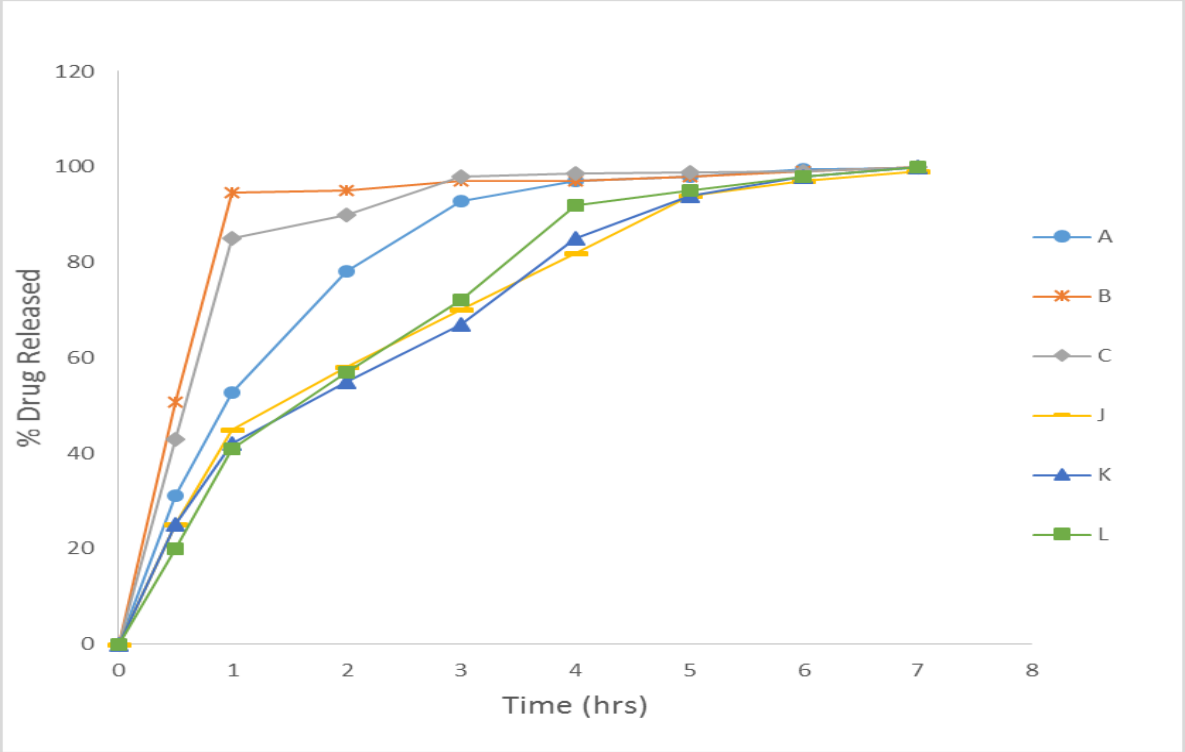

Figure 2: Drug release profile of selected ciprofloxacin matrix tablet formulations

Table 3: Values showing T_{50} and T_{75} for ciprofloxacin matrix tablets

Formulation	T_{50} (hrs)	T_{75} (hrs)	R^2
A	1.4	3.4	0.983
B	0.2	2.6	0.966
C	0.3	2.8	0.991
D	2.6	4.1	0.952
E	4.4	7.1	0.960
F	2.0	3.9	0.945
G	2.8	5.0	0.945
H	1.5	3.6	0.989
I	2.0	3.9	0.995
J	2.2	4.1	0.988
K	2.2	4.1	0.964
L	2.2	4.0	0.960

Formulation D has CAG and X in ratio 1:1. An increase in the proportion of CAG in formulation containing CAG-X (in ratio 2:1) resulted in almost a two- fold sustained release of CAG from the matrix tablet with T_{50} and T_{75} values of 4.4 and 7.1 hrs respectively. The two polymers most likely exhibited a synergistic increase in viscosity probably due to direct interaction between the polymer chains. Similar observation was made when HPMC was combined with sodium carboxymethylcellulose (Walker and Well, 1982). However, a further increase in the amount of CAG to 3- fold in Formulation F led to a faster release of drug from the polymer matrix. This suggests that the threshold

CAG content has been exceeded and the synergistic effect on viscosity becomes less prominent. Formulations containing blends of CAG and HPMC did not exhibit a controlled drug release despite the fact that HPMC is known to retard drug release. The presence of CAG might have reduced the tortuosity of the diffusion path of ciprofloxacin. It has been shown in previous studies that addition of lactose to HPMC led to increased drug release rates of promethazine hydrochloride (Sung et.al., 1996; Gao et. al., 1995). Generally, (except for Formulation E and G), a blend of the three polymers resulted in a slower drug release as observed from the values of T_{50} and T_{90} which was highest for Formulations J, K and L. This probably suggests a rheological synergism between the three polymers. T_{50} and T_{90} were similar for formulations containing a blend of the three polymers regardless of the ratio of combination. This suggest that the ratio/proportion of polymer blend had no significant ($p>0.05$) effect on the release rate of the drug from the matrix tablets formulated with the three polymers.

Kinetics of Drug release

The in vitro release data were fitted into different drug release models to determine the pattern of ciprofloxacin release from the matrix tablets. The mechanism that has the highest correlation coefficient 'r' was taken to be the preferred mechanism for drug release. Formulations A, C and F follow first order kinetics which suggests that drug release from the matrix system is concentration dependent. The Higuchi model is however the most prominent model for all the other formulations. This indicates that drug release is controlled by diffusion through the gel layer and gradual erosion. The value of the diffusional exponent, n, for all the formulations containing polymer blends indicates that drug release is by super case II transport.

Table 4: Release kinetics of ciprofloxacin matrix tablet

	Zero order model		First order model		Higuchi diffusion model		Hixson- crowell		Korsmeyer Peppas model		
Formulation	R^2	K_0	R^2	K_1	R^2	K_H	R^2	K	R^2	K	n
A	0.826	18.405	0.991	0.830	0.966	47.369	0.963	0.702	0.729	1.613	8.80
B	0.507	14.339	0.722	0.693	0.763	41.839	0.634	0.565	0.383	1.777	6.34
C	0.613	15.872	0.928	0.926	0.844	44.335	0.833	0.689	0.500	1.739	7.79
D	0.962	16.976	0.945	0.460	0.985	40.842	0.980	0.489	0.783	1.468	7.79
E	0.961	10.562	0.988	0.160	0.988	25.487	0.983	0.215	0.784	1.267	4.86
F	0.878	19.289	0.982	0.970	0.952	47.785	0.974	0.641	0.823	1.521	9.50
G	0.883	12.850	0.964	0.245	0.987	32.322	0.947	0.302	0.712	1.459	5.87
H	0.823	16.785	0.985	0.620	0.974	43.433	0.969	0.580	0.669	1.659	7.70
I	0.9063	17.386	0.976	0.568	0.992	43.275	0.987	0.559	0.745	1.557	8.02
J	0.919	16.884	0.948	0.499	0.995	41.786	0.979	0.511	0.766	1.525	7.84
K	0.939	17.232	0.951	0.515	0.993	42.151	0.982	0.525	0.775	1.510	7.97
L	0.940	18.597	0.961	0.605	0.984	45.262	0.983	0.594	0.822	1.500	8.85

CONCLUSION

The different polymer blends produced tablets of satisfactory mechanical strength. Formulation containing CAG-X (in ratio 2:1) resulted in a sustained release of ciprofloxacin from the matrix tablet. This study highlights the potentials of polymer blends in the design and formulation of sustained release ciprofloxacin matrix tablets.

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