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Formulation and *In Vitro* Evaluation of Ciprofloxacin Matrix Tablets: Effect of Drug-Polymer Ratio

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ABSTRACT

An ideal tablet should combine good mechanical strength with adequate drug release profile. This work aims to study the effect of drug-polymer ratio on the mechanical properties and release profile of ciprofloxacin tablet. Ciprofloxacin formulations containing drug and the polymers (*Chrysophyllum albidum* gum (CAG), hydroxypropylmethylcellulose (HPMC) and xanthan gum) in ratios of 2:1, 1:1 and 1:2, respectively were prepared by direct compression. The crushing strength, friability and the time taken for 50% (T_{50}) and 90% (T_{90}) drug release were obtained. The mechanism of drug release was also determined. Tablets containing CAG had significantly ($p<0.05$) lower crushing strength than those containing other polymers. In tablets containing xanthan gum and HPMC, there was an increase in crushing strength as the amount of polymer was increased to equal amount with the drug, but a further increase in polymer concentration to twice the amount of the drug resulted in a decrease in strength. T_{50} and T_{90} increased with increase in polymer concentration for formulations containing CAG. Drug release in formulations containing CAG and xanthan gum was by first order kinetics while the zero order model was the most prominent in tablets with HPMC. The first order constant, k_1 decreased with increase in polymer concentration for tablets with CAG while the reverse was the case for xanthan gum. However, irrespective of the drug-polymer ratio, all the formulations exhibited super case transport mechanism. This study suggests that the drug-polymer ratio has a significant influence on the mechanical strength and the release profile of ciprofloxacin tablets.

Keywords: Drug-polymer ratio, *Chrysophyllum albidum* gum, hydroxypropylmethylcellulose, xanthan gum, Ciprofloxacin matrix tablets.

Introduction

Drug delivery systems are engineered technologies, formulations, approaches and systems for delivering a pharmaceutically active compound to elicit the desired therapeutic effect. The use of polymers in drug delivery has received considerable attention in recent years.[1] They have been used as binders, flow controlling agents, film coating and to modify and control drug release. A number of polymers such as hydroxypropylmethylcellulose (HPMC), xanthan gum, cashew gum and guar gum have been used in drug delivery.[2-5] However, there is growing need to device new methods of improving the efficacy of drugs and control their pharmacokinetics. To this end, the effect of the use of different polymer blends on the release properties of drugs had been widely investigated.[6-8] It appears little is known about the effect of drug-polymer ratio on the mechanical and release properties of ciprofloxacin tablets.

Ciprofloxacin is a second-generation fluoroquinolone with a wide range of activity against gram-positive and gram-negative bacteria.[9] It is indicated in the treatment of bone infection, typhoid fever and throat infections. It inhibits DNA gyrase in susceptible organisms and promotes breakage of double-stranded DNA. It binds to serum protein (20 to 40%), has a wide tissue distribution and possesses a serum elimination half-life of 4 hours in patients with normal renal function. Xanthan gum is a polysaccharide composed of repeating units of pentasaccharide,[10] while hydroxypropyl methylcellulose (HPMC) is an inert semi- synthetic viscoelastic polymer used as an excipient in oral drug delivery and it is found in a variety of commercial products.[11] *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.[12-16]

In this present work, the effect of drug-polymer ratio on the mechanical properties and release profile of ciprofloxacin tablets using *Chrysophyllum albidum* gum, xanthan gum and HPMC (hydroxypropylmethylcellulose) of varied ratio was studied.

Materials and Methods

Reagents/chemicals

The materials used include ciprofloxacin lactate monohydrate obtained from Dr. Reddy laboratory, India and microcrystalline cellulose (BDH Chemical, UK). Hydroxylpropylmethylcellulose (HPMC) E15 premium LV and xanthan were purchased from Shanghai Blueway Limited and Jiangsu, China respectively. The *Chrysophyllum albidum* gum was extracted at the Pharmaceutical Technology laboratory, Olabisi Onabanjo University, Nigeria. All the reagents were of analytical grade and used without further purification.

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Extraction of Chrysophyllum albidum gum
Ripe *Chrysophyllum albidum* fruits (authenticated at the Department of Plant Sciences, Olabisi Onabanjo University, Nigeria) without the seeds were sundried for three weeks and thereafter size reduced. The powder was sifted using a sieve of size 250µm. About 10 kg of dried powder was extracted exhaustively using 96 % ethanol. The extracted gum was dried in a desiccator and the dried gum was milled into powder.

Tablet compression
The powders according to the formulation Table 1 were weighed and compressed on a Carver hydraulic hand press (Model 38510E, Carver Inc, USA) fitted with a pressure gauge. Tablets of 500 mg of ciprofloxacin each were compressed at a pressure of 1.0 tonne for 30 seconds with a 12.5 mm die and flat faced punches. A 2% w/v dispersion magnesium stearate in 96 % ethanol was used to lubricate the punches and die prior to each compression. The ejected tablets were stored over silica gel in order to allow for elastic recovery.

Tablet evaluation
Ten (10) tablets whose weight had been taken were placed in a friabilator (Shivani Scientific Ind., Mumbai, India) and operated at 25 revolutions per minute for four minutes. The tablets were collected, de dusted and re-weighed. The percentage weight loss was taken as the friability and determinations were made in triplicate. The mean force required to break each of the randomly selected tablets was recorded in $kgcm^{-1}$ as the crushing strength.[6]

Determination of Dissolution Rates of Tablets
Copley dissolution machine, NE4-COPD, Nottingham, UK was used for the study. The medium and the speed of rotation were 900 ml of phosphate buffer pH 7.4 and 50 rpm respectively. Ten (10 ml) of the sample was withdrawn at specific intervals and replaced with an equal amount of phosphate buffer maintained at 37±0.5ºC. The amount of drug in the withdrawn samples were analyzed by UV spectrophotometry at 276 nm.

Kinetics of Drug Release
The drug release data were fitted into the following kinetics models.[17-19]

Zero order: $Q=K_0 t$… (1)
Cumulative amount of drug release against 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
Higuchi model: $Q = k_H t^{½}$ … (3)
Cumulative percentage of drug released versus the square root of 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.

Drug release mechanism
The mechanism of drug release was obtained by fitting the first 60% drug release data into Korsmeyer–Peppas model.[20]

$Q/Q_0 = kt^n$ …….. (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. A plot of log cumulative percentage drug release against log time was made and the diffusional exponent, n indicates the drug release mechanism. Values of n equal to 0.45 indicate 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.[6]

Results and Discussion

Evaluation of tablet properties
The tablet weight variation was observed to be below 5% while the thickness ranged between 3.18-2.77. All the formulations formed strong tablets. Tablets containing CAG had significantly ($p<0.05$) lower crushing strength than those containing other polymers. The rank order of tablet strength was HPMC> xanthan> CAG. In tablets containing xanthan gum and HPMC, there was an increase in crushing strength as the amount of polymer was increased to equal amount with the drug 1:1 but a further increase in polymer concentration to twice the amount of the drug resulted in a decrease in strength. Formulations containing ciprofloxacin: HPMC (1:1) were the hardest. Friability is another parameter that describe the mechanical properties of tablet formulations because they are often subjected to abrasion during transportation, storage and patient handling. Formulations containing CAG had friability values less than 1% which is generally considered acceptable.[6] Tablets containing HPMC and xanthan gum however had values above 1%. Friability decreased with an increase in amount of polymer in formulations containing CAG and HPMC. The reverse was the case for tablets containing xanthan gum. Crushing strength- friabilty ratio, CSF has been described as a better index of tablet quality because it measures simultaneously the strength and weakness of tablets.[21] Higher values indicate strong tablets. Table 2 shows that with the exception of tablets containing HPMC, formulations containing drug: polymer ratio (1:2) formed stronger tablets.

Drug release kinetics
Figure 1 shows representative plots of the dissolution profile of ciprofloxacin matrix tablets while Table 4 presents T_{50} and T_{90} (time taken for 50% and 90% of the drug release respectively). These two dissolution parameters have been used to describe the release behaviour of drug formulations.[20] Formulations containing CAG had the slowest drug release. CAG has been reported to absorb about twice its weight of water and swell appreciably.[14] The swelling and hydration properties result in the formation of a viscous gel which serves as a barrier to diffusion and thereby slows down water penetration into the matrix. This consequently retards drug release. T_{50} and T_{90} increase with increase in polymer concentration for formulations containing CAG. It took almost 15 minutes more for 50 % of the drug to be released when the polymer concentration was increased two-fold. However, for formulations containing xanthan and HPMC, a polymer: drug ratio of 1:1 resulted in faster drug release than ratio 1:2. A further increase to 2:1 resulted in a retardation of ciprofloxacin release. The retardation might be because at higher polymer content, the gel layer becomes stronger which results in a higher resistance to diffusion and matrix erosion as reported by Kiatissak *et al*.[23]

Kinetics of drug release
The drug release data were fitted into various kinetics models. The model that had the highest correlation coefficient 'R' was taken to be the preferred model for drug release. The result in Table 4 suggests that drug release from formulations containing CAG and xanthan gum was by first order while the zero-order model was the most prominent in tablets formulated with HPMC. In addition, the first order constant, k_1 decreased with increase in polymer concentration for tablets formulated with CAG while the reverse was the case for formulations containing xanthan gum. However, the zero-order constant, k_0 decreased with increased polymer concentration in formulations containing HPMC. In order to determine the mechanism of drug release the dissolution data were studied with the Korsmeyer–Peppas equation. The result showed that irrespective of the drug-polymer ratio, all the formulations had values of the release exponent n> 0.89 which suggests a super case transport mechanism.

Conclusion

The crushing strength and friability of ciprofloxacin matrix tablets was observed to be dependent on the ratio of the drug and polymer in the formulations. In addition, drug release was fastest in formulations containing equal proportion of the drug and the polymer. Thus, the present study has shown that the drug-polymer ratio has a significant influence on the mechanical strength and the release profile of ciprofloxacin matrix tablets.

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Table 1: Formulations table of ciprofloxacin matrix tablet (~500mg).

Formulations	Ciprofloxacin (mg)	CAG (mg)	Xanthan gum (mg)	HPMC (mg)	MCC (mg)	Magnesium stearate (mg)
F1	100	50	-	-	345	5
F2	100	100	-	-	295	5
F3	100	200	-	-	195	5
F4	100	-	50	-	345	5
F5	100	-	100	-	295	5
F6	100	-	200	-	195	5
F7	100	-	-	50	345	5
F8	100	-	-	100	295	5
F9	100	-	-	200	195	5

Table 2: Physical properties of ciprofloxacin matrix tablet.

Formulations	Thickness (mm)	Weight (mg)	Crushing strength (CS) (kg/cm)	Friability (F) (%)	CS-F
F1	3.59 ± 0.55	487.3 ± 13.1	5.3 ± 0.32	0.98 ± 0.04	5.41
F2	3.25 ± 0.10	489.5 ± 8.7	4.4 ± 0.35	0.96 ± 0.10	4.58
F3	3.43 ± 0.07	489.9 ± 16.6	5.8 ± 0.44	0.95 ± 0.16	6.37
F4	3.29 ± 0.07	482.5 ± 23.5	9.1 ± 0.36	2.37 ± 0.95	3.84
F5	3.17 ± 0.05	486.2 ± 10.5	9.2 ± 0.67	3.67 ± 0.96	2.51
F6	3.16 ± 0.03	488.2 ± 15.9	9.0 ± 0.90	2.12 ± 0.19	4.25
F7	3.15 ± 0.08	488.3 ± 15.8	10.9 ± 0.80	2.16 ± 0.60	5.05
F8	3.77 ± 0.91	480.6 ± 11.4	11.4 ± 0.79	1.72 ± 0.35	6.63
F9	3.27 ± 0.09	482.5 ± 12.9	9.4 ± 1.04	1.60 ± 0.40	5.88

Table 3: Dissolution parameters of ciprofloxacin matrix tablets.

Formulation	T_{50} (min)	T_{90} (min)	R^2
F1	41.9	79.86	0.9597
F2	54.12	100.34	0.9874
F3	59.8	108.25	0.9818
F4	39.67	75.48	0.9585
F5	28.30	54.22	0.9762
F6	49.68	92.77	0.9724
F7	36.0	67.74	0.9853
F8	28.30	58.22	0.9762
F9	65.11	125.70	0.9118

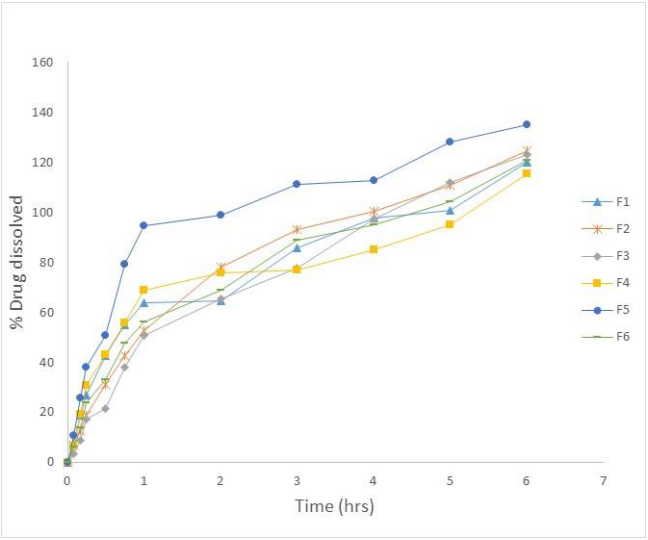

Figure 1: Representative plot of dissolution profile of ciprofloxacin tablet formulation.

Table 4: Release kinetics parameters for ciprofloxacin formulations.

Formulation	Zero order model		First order model		Higuchi diffusion model		Hixson- crowell		Korsmeyer Peppas model		
	R^2	K_0	R^2	K_1	R^2	K_H	R^2	K	R^2	K	n
F1	0.9605	63.206	0.9952	1.0159	0.9749	68.302	0.9874	1.3331	0.2445	42.304	28.12
F2	0.9876	51.866	0.9991	0.7383	0.9621	54.906	0.9976	1.0123	0.2585	33.264	23.40
F3	0.9818	49.73	0.9737	0.6863	0.9066	51.254	0.9785	0.9511	0.2933	30.031	23.97
F4	0.9593	67.026	0.9913	1.1288	0.9673	72.192	0.9867	1.4548	0.2525	44.554	30.33
F5	0.9768	92.571	0.9853	1.7101	0.9571	98.279	0.9733	2.7634	0.2519	59.854	41.46
F6	0.9727	55.715	0.9926	1.8213	0.9615	59.411	0.9887	1.1121	0.2599	36.242	25.40
F7	0.9855	79.655	0.9871	1.4251	0.9620	80.174	0.9963	1.7587	0.2617	48.596	34.38
F8	0.9836	75.792	0.9207	1.7048	0.9401	83.671	0.9561	1.9943	0.2586	50.328	36.08
F9	0.9925	39.545	0.9113	0.5274	0.9887	44.138	0.9396	0.7404	0.1607	28.679	14.63

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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