

CHARACTERISATION AND CONTROLLED RELEASE PROPERTIES OF *ENTANDOPHRAGMA ANGOLENSE* GUM IN IBUPROFEN MATRIX TABLETS

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Abstract

A novel hydrophilic polymer, *Entandophragma angolense* gum (ENTA), was characterized and incorporated as excipient in Ibuprofen tablet matrices prepared by direct compression. Comparisons were made with formulations incorporating Gelatin or Hydroxypropylcellulose. The gum was analysed by X-ray Diffraction and drug-polymer interactions were assessed by Fourier-Transform Infrared (FTIR) spectrometric studies. Mechanical properties of matrices were assessed using crushing strength (CS) and friability (F). *In vitro* drug release studies were conducted for 24 hours at 37 °C in phosphate buffer pH 7.2 dissolution medium. The results were fitted into kinetic models to determine the drug release mechanism. There were no interactions between Ibuprofen and ENTA. Increased polymer content led to an increase in CS and a decrease in F values. The ranking of the CS was Hydroxypropylcellulose > ENTA > Gelatin, while the ranking was reversed for F. The ranking of the time for 25% drug release, at 80%w/w polymer concentration was ENTA > Hydroxypropylcellulose > Gelatin. The release kinetics determined using the Akaike criterion Index indicate Korsmeyer supercase II model at high concentrations of the gum. Incorporation of *Entandophragma angolense* gum enhanced the mechanical properties of Ibuprofen matrix tablets and also the controlled drug release.

Rezumat

Guma *Entandophragma angolense* (ENTA), un nou polimer hidrofili, a fost caracterizată și încorporată ca excipient în tablete matriceale cu Ibuprofen, preparate prin comprimare directă. Au fost făcute comparații cu formulări ce au încorporat gelatina sau hidroxipropilceluloza. Guma *Entandophragma angolense* a fost analizată prin difracție cu raze X și interacțiunile medicament-polimer au fost evaluate prin studii spectrometrice cu transformata Fourier în infraroșu (FTIR). Proprietățile mecanice ale matricelor au fost evaluate cu ajutorul testelor de rezistență (CS) și friabilitate (F). Au fost efectuate studii *in vitro* de eliberare a substanței active timp de 24 ore la 37 °C în tampon fosfat pH 7,2 ca mediu de dizolvare. Rezultatele au fost fitate în modele cinetice pentru a determina mecanismul de eliberare al medicamentului. Nu au existat interacțiuni între Ibuprofen și ENTA. Conținutul crescut de polimer a condus la creșterea CS în ordinea hidroxipropilceluloză > ENTA > gelatină și scăderea valorilor F. Cinetica de eliberare determinată folosind criteriul Akaike Index indică modelul Korsmeyer supercase II, la concentrații ridicate de gumă. Încorporarea gumei *Entandophragma angolense* consolidează proprietățile mecanice ale comprimatelor matriceale cu Ibuprofen și eliberarea controlată a medicamentului din forma farmaceutică.

Keywords: *Entandophragma angolense* gum, controlled release, Ibuprofen, matrix tablets, direct compression

Introduction

Controlled release (CR) dosage forms are designed to modify the rate or the place at which active ingredients are released in the body. Possible therapeutic benefits of a properly designed CR dosage form include lack of toxicity, low cost, improved efficacy, simple processing, flexibility in terms of range of release profiles attainable, increased convenience and improved patient compliance [1]. There are a number of methods available for the formulation of CR dosage forms; however, the preparation of hydrophilic matrix tablets by direct compression is one of the least complicated approaches from a practical point [1, 2]. Drug release from these matrices has been found to be dependent on polymer wetting, polymer

hydration and polymer dissolution. Many variables influence the mechanisms by which the drug is released from tablets, such as the rate of dissolution/diffusion of soluble excipients or drug out of the tablet and the rate at which the insoluble excipients or drug in the polymer/ excipient/drug complex erodes or dissolves [3].

Natural polymers such as cissus gum, okra gum, xanthan gum and cedrela gum have been investigated for their use as excipients in tablet formulations [4, 5, 6, 7]. *Entandophragma angolense* gum (Family: *Meliaceae*) derived from the incised trunk of the tree is a natural hydrophilic polymer that is widely available throughout the whole year in tropical Africa [8]. *Entandophragma angolense* gum has been demonstrated to be non-

toxic and to exhibit a good potential as a suspending agent [9]. On contact with water, the gum swells to form a viscous gel when left standing for about 30 minutes. When used as a binding agent, Ibuprofen formulations containing *Entandophragma angolense* gum showed slower disintegration and dissolution times when compared with those prepared using Gelatin, indicating the possibility to be used as a controlled release agent [2].

This study was designed to characterize and evaluate the mechanical and *in vitro* controlled release properties of Ibuprofen matrix tablets containing *Entandophragma angolense* gum. The matrices were compared with those containing official Gelatin and Hydroxypropylcellulose. The crushing strength and friability of the tablets were evaluated, and effects of the polymer type and concentration on the release kinetics of the matrix formulations were also investigated. The data obtained from the dissolution tests were fitted into release kinetic models to determine the drug release type.

Materials and Methods

Materials

The materials used were Ibuprofen powder BP, (Sigma Chemicals, St. Louis, MO), Gelatin and Hydroxypropylcellulose (HPC) (Aqualon, Hercules Incorporated, USA), all supplied by Bond Pharmaceuticals Limited, Nigeria. The gum was obtained from the early morning exudates of the trunk of *Entandophragma angolense* (family: *Meliaceae*), available as a tree crop in the Botanical Gardens of the University of Ibadan, Ibadan, Nigeria, and authenticated at the Forest Herbarium, Ibadan, Nigeria (FHI No: 108883).

Methods

Collection and Purification of Gum

Entandophragma angolense tree was incised and the exudates were allowed to harden, after which it was collected and dried in the oven at 50 °C for about 10 hours. The gum was pulverized after drying with an Osterizer blender (Model 857, Willamette Industries, Bowling Green, Kentucky, USA) to produce a powdered form of the gum. The gum was extracted and purified according to established procedures [2, 7].

Fourier Transform Infrared (FTIR) Determination

Spectra were obtained for the *Entandophragma angolense* gum, Gelatin or HPC and the model drug (Ibuprofen) using a Magna-IR, 560 spectrometer (Perkin Elmer, USA). A quantity (5 mg) of each of the completely dried powdered samples was weighed and then dispersed in 200 mg potassium bromide (pellet procedure). Signal averages were obtained at a resolution of 4 cm⁻¹ [6].

X-ray powder Diffraction

The X-ray diffraction pattern was recorded with a copper anode X-ray tube (Cu K_{α1} and K_β radiation) using a XPERT-PRO PW3064/60 diffractometer (Stoe and Cie GmbH, Darmstadt, Germany). The polymers were tightly packed in sample holders and exposed to the X-ray spinning beam at a generator setting of 40 kV and 30 mA. The scanning diffraction angle (2θ) was 5.01°-99.07° at a continuous scan step time of 6.35 sec.

Preparation of Ibuprofen Matrix Tablets

Ibuprofen tablet matrices containing *Entandophragma angolense* gum (Gelatin or Hydroxypropylcellulose; 400 mg ± 5 mg) were prepared by direct compression at a compression force and compression time of 1 tone and 30 seconds, respectively, using a Carver hydraulic hand press (model C, Carver Inc, Menomonee falls, Wisconsin, U.S.A) to determine the effect of polymer concentration on the matrix tablets. The hydrophilic matrices were formulated to contain 10, 20, 30 and 40 % of Ibuprofen and 90, 80, 70 and 60 % respectively of the polymers.

Crushing Strength (CS) Measurement

Crushing strength measurements were determined using the Erweka Hardness Tester (Model TBH 28, Apparatebau, GMBH, Germany). Measurements were made in quadruplicate on individual tablets and the results of the crushing strength test were accepted only if the tablets split cleanly into two halves.

Friability Test

The friability test of the tablets was performed using the Veego tablet friability testing apparatus (Veego Scientific Devices, Mumbai, Maharashtra, India). To achieve this, ten tablets were randomly selected, weighed together and then placed in the friabilator, and the apparatus was operated at 25 rpm for 4 min (100rpm). The tablets were collected, dusted and weighed again. Determinations were made in quadruplicate and the percentage weight loss was calculated.

In Vitro Drug Release Studies

In vitro drug release studies from the matrix tablets were conducted for 24 hours at 37 ± 0.5 °C in a dissolution medium with a rotating basket providing agitation of 100 rpm (USP-XXII dissolution apparatus 2). The dissolution media contained 900mL of pH 7.2 phosphate buffer. The pre-weighed tablet matrices were introduced into the dissolution medium and at different time intervals, 10 mL of the sample were withdrawn and replaced with 10 mL of fresh medium. Samples (10 mL) that were removed at designated intervals were subjected to UV spectrometric analysis of drug content at 221 nm. The absorbance of the removed samples was measured and the total concentration of the drug in each medium was determined.

Release Kinetics

The drug release mechanisms of the matrix tablets were fitted into the following kinetic models: Zero-order, First-order, Higuchi, Hixson-Crowell and Korsmeyer. The model with the highest correlation coefficient, r^2 was chosen as the best fit [5]. A system where the drug release rate is independent of its concentration is described as Zero order kinetics [10]; in first order kinetics the release rate is concentration dependent [11], while drug release from an insoluble matrix as a square root of time-dependent process based on Fickian diffusion follows the Higuchi's model [12]. Further, the Hixson-Crowell cube root law describes drug release from systems where there is a change in surface area and diameter of particles or tablets [13]. Hence, in order to determine the mechanism of drug release from the formulation, release data may be fitted in Korsmeyer [14] equation:

$$\text{Log}(M_t/M_f) = \text{Log } k + n \text{Log } t, \quad (1)$$

where, M_t is the amount of drug release at time t , M_f is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the dosage form and n is the diffusional exponent indicative of the mechanism of drug release [15]. The value of $n \leq 0.45$ indicates Fickian (case I) release; > 0.45 but < 0.89 for non-Fickian (anomalous) release; and > 0.89 indicates super case II type of release for a cylinder shaped matrix. Case II mechanism refers to the erosion of the polymer and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled drug release [16]. The differences in the various models were

further established using the Akaike criterion Index (AIC) using DDSolver, an add-in program for Microsoft Excel.

Statistical Analysis

Statistical analysis was performed to compare the mechanical and release properties of Ibuprofen tablet matrices containing *Entandophragma angolense* gum and those of the reference polymers (Gelatin or Hydroxypropylcellulose) using the analysis of variance (ANOVA) on a computer software; Graphpad Prism 5 (Graphpad Software Incorporation, San Diego, USA). Variable multiple comparison tests (quantitative) were used to compare the differences between the effects of the polymers, p values ≤ 0.05 were considered significant.

Results and Discussion

The results of the FTIR spectrum obtained for *Entandophragma angolense* gum alone and for the powdered mixtures of *Entandophragma angolense* gum with Ibuprofen are shown in Figures 1 and 2. The functional group region (4000 to 1300 cm^{-1}) showed sharp peaks at 2926.85 cm^{-1} and 2853.19 cm^{-1} , (Figure 1). These sharp peaks are characteristic of methyl C-H stretching associated with aromatic rings and carboxylic acids. The sharp peaks at 2359.93 and 2341.37 cm^{-1} are indications of asymmetric C-O stretch. The peaks obtained at 1573.69 and 1558.36 showed similar functional groups consisting of strong N=O nitroso and weak C-O stretch.

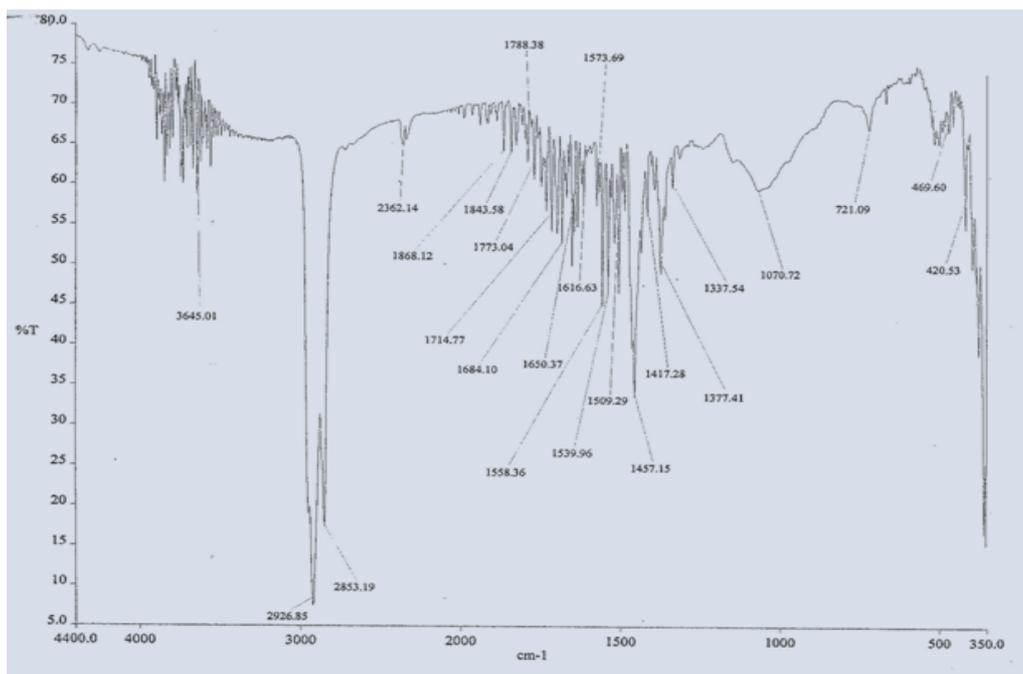


Figure 1.

FTIR Spectroscopy pattern for *Entandophragma angolense* gum

The fingerprint region consists of a characteristic peak at 1070.72 cm^{-1} . This peak confirms the presence of strong aromatic characters consisting of C-O, C=O, C-N and C-F stretches, and weak P-H bending groups, which are present in carbohydrates, starch, and natural polymers [17].

The results revealed the presence of methyl, amine, phosphine and hydroxyl groups, in *Entandophragma angolense* gum, and suggested the absence of a chemical reaction between *Entandophragma angolense* gum and Ibuprofen.

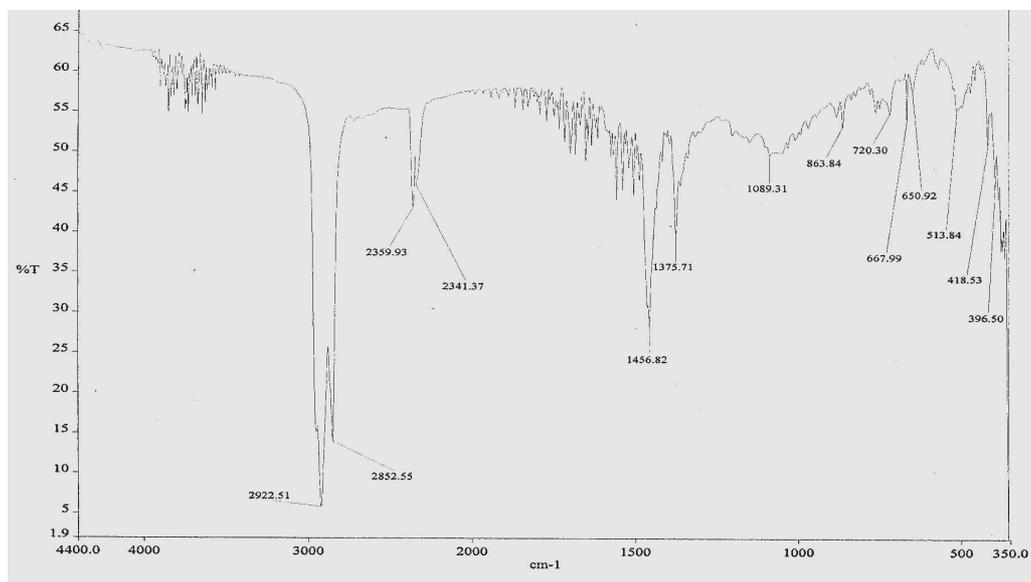


Figure 2.

FTIR spectroscopy pattern for the physical mixture of *Entandophragma angolense* gum and Ibuprofen powders

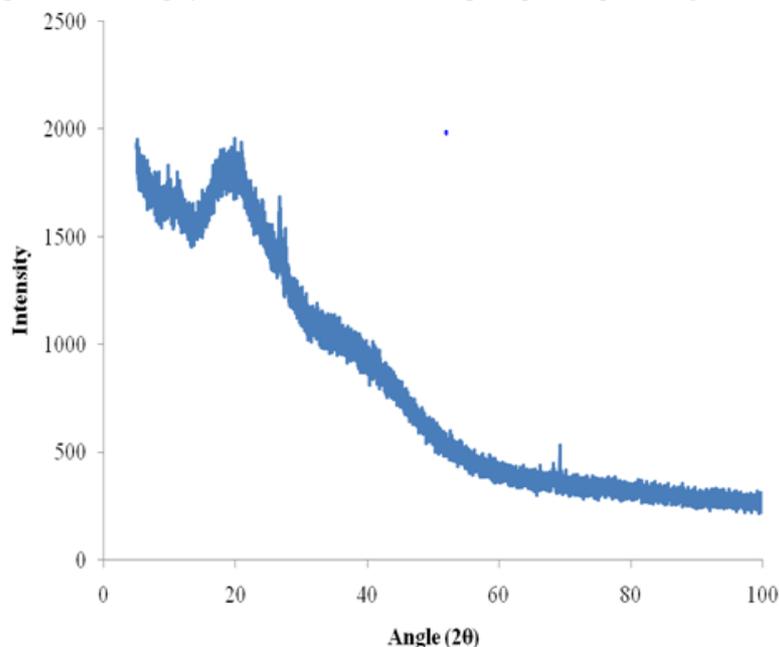


Figure 3.

X-ray diffraction pattern of *Entandophragma angolense* gum

The X-ray diffraction pattern was used to characterize the crystal packing in the *Entandophragma angolense* gum granules. The X-ray diffraction pattern of *Entandophragma angolense* gum is shown in Figure 3 [18]. *Entandophragma angolense* gum showed peaks at 20.99° , 26.68° , 26.73° , 27.59° and 69.21° , all at 2θ .

These patterns of a few peak areas of crystallinity with larger areas demonstrate the amorphous nature of the gum [19]. This indicates that the gum is more amorphous than crystalline.

The values of the crushing strength and friability for each formulation are presented in Table I. The ranking of the crushing strength for the polymers

was in the order Hydroxypropylcellulose > *Entandophragma angolense* > Gelatin. All the polymers gave friability values less than 1%. The mechanical strength of a tablet may be characterized by two properties: bond strength and brittleness [20]. Bond strength has been evaluated by the crushing strength of the tablet [21], while the tendency of a tablet to cap or laminate can be measured by the brittle fracture index (BFI) of the material [22]. The tendency for tablets to undergo capping or lamination increases as a result of an increase in elastic energy, due to axial recovery, and perhaps also to the expansion of entrapped air during decompression and ejection [23, 24]. It was observed that the crushing strength of the tablet matrices increased as the concentration of the

polymers also increased. There was also a decrease in friability values. This could have been due to the fact that polymers are plastoelastic in nature and as the concentration is increased during the process of compression, plastic deformation also increases, leading to the formation of more solid bonds, and consequently, an increase in the crushing strength. The increased resistance of the matrices to fracture and abrasion as the polymer concentration increased could also be attributed to the formation of more solid bonds [25].

Representative plots of the release profiles of Ibuprofen from the matrices containing *Entandophragma angolense* gum or the standard polymers Hydroxypropylcellulose or Gelatin are presented in Figure 4.

Table I

Values of crushing strength and friability obtained from the matrix tablets containing different concentrations of polymer (Mean± SD, n = 4)

Polymer	Polymer Concentration (%w/w)	Crushing Strength (N)	Friability (%)
<i>Entandophragma angolense</i> gum	90	80.13±0.03	0.33±0.04
	80	75.13±0.12	0.44±0.07
	70	71.28±0.06	0.59±0.11
	60	68.93±0.02	0.76±0.02
Hydroxypropylcellulose	90	81.22±0.11	0.31±0.04
	80	79.12±0.23	0.32±0.05
	70	78.11±0.14	0.36±0.02
	60	72.22±0.04	0.47±0.13
Gelatin	90	76.24±0.12	0.67±0.09
	80	73.15±0.13	0.76±0.03
	70	68.43±0.03	0.83±0.05
	60	65.39±0.03	0.88±0.04

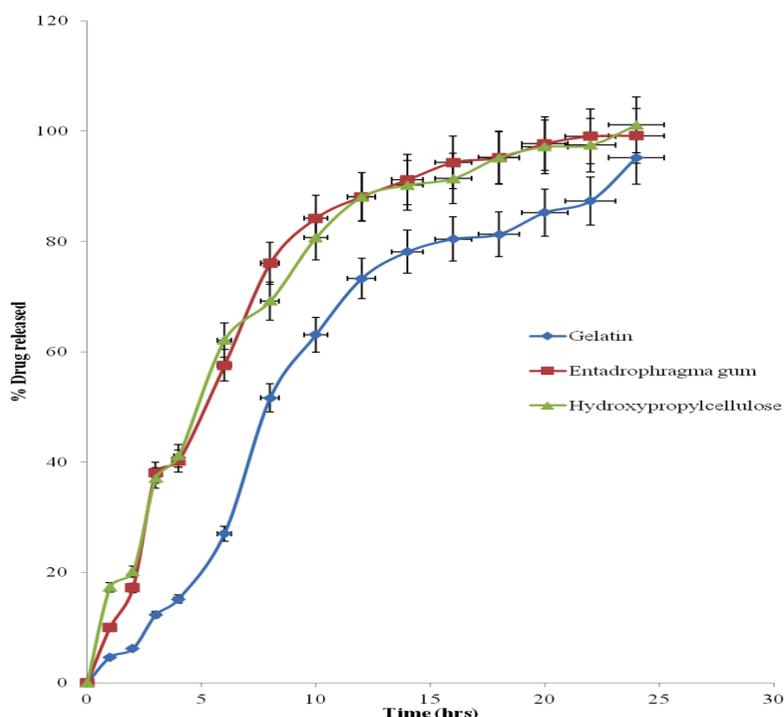


Figure 4.

Release profile of Ibuprofen from matrices containing 80% w/w polymers (mean ± SD, n=3)

The release parameters derived from kinetic modeling are given in Table II. The parameters (regression equations, correlation coefficient (r^2), diffusional release exponents (n) and kinetic constants) were obtained by fitting the data obtained into the different release models (Korsmeyer, Higuchi, Zero-order and Hixson-Crowell). The highest correlation coefficient (0.963) was observed in the zero-order model for the matrix containing 10%w/w *Entandophragma angolense* gum, thus indicating non Fickian

diffusion. However, a further fitting using the using the Akaike criterion Index (AIC) to compare the different models yielded the lowest values for the Korsmeyer model. This suggests that the Korsmeyer model would better describe the release mechanism from the matrix tablets rather than the zero order model. The release was found to be super case II type at the higher concentration of the experimental gum. This indicates a combination of both diffusion and erosion controlled drug release.

Table II*In-vitro* release kinetics of Ibuprofen from the matrix tablets

Formulation code	Zero-order		First-order		Higuchi		Hixson-Crowell		Korsmeyer			AIC
	r^2	k	r^2	k	r^2	k	r^2	k	r^2	k	n	
10% w/w Ibuprofen in ENTA	0.963	4.146	0.918	0.053	0.757	12.419	0.935	0.016	0.959	2.279	1.254	69.8
10% w/w Ibuprofen in HPC	0.885	3.461	0.896	0.043	0.775	10.568	0.896	0.013	0.866	4.118	0.926	91.2
10% w/w Ibuprofen in Gelatin	0.873	3.231	0.877	0.041	0.761	10.471	0.861	0.014	0.838	1.726	0.778	91.1
20% w/w Ibuprofen in ENTA	0.885	3.467	0.896	0.043	0.776	10.589	0.896	0.013	0.867	4.147	0.923	90.2
20% w/w Ibuprofen in HPC	0.887	3.691	0.909	0.047	0.808	11.345	0.906	0.015	0.874	5.166	0.856	97.6
20% w/w Ibuprofen in Gelatin	0.865	3.713	0.911	0.051	0.803	11.311	0.854	0.027	0.854	2.256	0.749	87.4
40% w/w Ibuprofen in ENTA	0.863	4.124	0.914	0.055	0.859	12.817	0.904	0.017	0.878	7.696	0.732	90.6
40% w/w Ibuprofen in HPC	0.899	4.116	0.850	0.052	0.815	12.908	0.900	0.022	0.885	10.982	0.870	97.2
40%w/w Ibuprofen in Gelatin	0.895	3.815	0.849	0.051	0.809	12.911	0.887	0.034	0.825	4.993	0.813	96.9

Release of drug from polymeric matrices occurs when a matrix is placed in contact with a compatible solvent. Progressive swelling of the polymer particles is observed, leading to considerable structural changes. These include changes in the mobility of the macromolecular chains, macromolecular relaxations, and changes of the porous structure including alteration of the shape and size distribution of the pores [26]. These will change the porosity and tortuosity of the polymer during swelling and diffusional release

[27]. The results of the release profiles of Ibuprofen from the polymer matrices showed an increase in the release rate of the drug as the concentration of the polymer decreased. Generally, when a natural gum comes in contact with the dissolution medium, the polymer absorbs water, swells and becomes a hydrated gel [28]. The decrease in the release rate of the drug as a result of an increase in polymer concentration may therefore be accounted for the reduction in the number of low microviscosity pores.

Table III

Dissolution parameters of Ibuprofen matrix tablets

Formulation code	$t_{25}\%$ (hr)	$t_{50}\%$ (hr)	$t_{75}\%$ (hr)
10% w/w Ibuprofen in ENTA	6.95	14.73	22.79
10% w/w Ibuprofen in HPC	7.02	14.84	22.99
10% w/w Ibuprofen in Gelatin	6.23	13.79	22.36
20% w/w Ibuprofen in ENTA	6.79	11.82	22.71
20% w/w Ibuprofen in HPC	6.31	11.18	22.77
20% w/w Ibuprofen in Gelatin	6.12	11.44	22.11
40% w/w Ibuprofen in ENTA	6.00	11.69	22.44
40% w/w Ibuprofen in HPC	5.58	8.71	19.10
40% w/w Ibuprofen in Gelatin	6.08	9.13	22.09

ENTA: *Entandophragma angolense* gum, HPC: Hydroxypropylcellulose

The increase in the release rate of the matrices containing 80 %w/w polymers may be due to the weakening of the matrix lattice due to the high concentration of the Ibuprofen, which provides a diffusion pathway for erosion/disintegration of the matrix. The reduction in the bond strength of the matrix was a result of the formation of the gel phase, and increased permeability of solvent in the swollen region [18]. The release rate of the drugs

decreased as the concentration of the polymers increased as shown in Figure 3. This could be due to an increase in the extent of viscous gel formation which is more likely to be resistant to drug diffusion and erosion [29, 30]. The ranking of t_{25} , which is the time taken for 25% of the drug to be released, was *Entandophragma angolense* gum > Gelatin > Hydroxypropylcellulose, while the ranking of t_{75} was Gelatin > *Entandophragma*

angolense > Hydroxypropylcellulose (Table III). There was no significant difference between the drug released from the tablet matrices containing *Entandophragma angolense* gum and Gelatin ($p > 0.05$).

The release kinetics fitted the zero-order model, thus indicating that the release of the drug from the matrix was concentration independent. The real dissolution of a drug substance (intrinsic dissolution rate) undergoes a zero order reaction, if its surface is kept temporarily constant. The release parameters derived from the Korsmeyer's model show an anomalous transport mechanism; with n (release exponent related to the mechanism of release) values decreasing as the polymer concentration was decreased. The values of n , however, indicate that the release of the drug is at least, partially controlled by the viscoelastic relaxation of the matrix during solvent penetration.

Conclusions

The mechanical properties of the Ibuprofen matrices were dependent on the concentration of polymers present in the formulation. *Entandophragma angolense* gum formulations had better mechanical properties than Gelatin formulations, and exhibited comparable properties with Hydroxypropylcellulose matrices. *Entandophragma angolense* gum was able to effectively control the release of Ibuprofen from the matrices for 24 hours. Diffusion and erosion might be responsible for the release of the drug from the matrices. Drug release is dependent on the polymer concentration, and the release kinetics fitted the Korsmeyer super case II release model. *Entandophragma angolense* gum had comparable sustained release properties with Hydroxylpropylcellulose in Ibuprofen matrix tablet formulations and should be further investigated as a substitute in such formulations.

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