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Article

Evaluation of *Cedrela* gum as a binder and bioadhesive component in ibuprofen tablet formulations

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The compressional, mechanical and bioadhesive properties of tablet formulations incorporating a new gum obtained from the incised trunk of the *Cedrela odorata* tree were evaluated and compared with those containing hydroxypropylmethylcellulose (HPMC). Compressional properties were evaluated using Hausner's ratio, Carr's Index, the angle of repose, and Heckel, Kawakita and Gurnham plots. Ibuprofen tablets were prepared using the wet granulation method. Bioadhesive studies were carried out using the rotating cylinder method in either phosphate buffer pH 6.8 or 0.1 M hydrochloric acid media. The gum is a low viscosity polymer (48 cPs), and Fourier transform infrared spectroscopy revealed the presence of a hydroxyl group. P_y and P_k values, which are measures of plasticity, showed the gum to be significantly ($p<0.05$) more plastic than HPMC, and plasticity increased with polymer concentration. All tablet formulations were non-friable (<1.0%), and the formulations containing the gum had a higher crushing strength (130.95 N) than those containing HPMC (117.85 N) at 2.0% w/w binder. Formulations incorporating the gum were non-disintegrating and had a significantly longer drug release time than those containing HPMC. At the highest binder concentration, *Cedrela* gum formulations adhered to incised pig ileum longer than those containing HPMC. *Cedrela* gum exhibited better compressive, flow and binding properties than HPMC and is suitable as a bioadhesive and for sustained release of drugs.

Uniterms: *Cedrela* gum/evaluation/compression properties. *Cedrela* gum/bioadhesive component. Tablet formulations. Hydroxypropylmethylcellulose. Ibuprofen tablets/bioadhesive studies. Bioadhesion.

Propriedades de compressão, mecânicas e de formulações de comprimidos bioadesivos, que incorporam nova goma de mascar obtidas a partir de incisão de tronco da árvore de *Cedrela odorata,* foram avaliadas e comparadas com aquelas contendo hidroxipropilmetilcelulose (HPMC). Propriedades de compressão foram avaliadas usando a razão de Hausner, índice de Carr, ângulo de repouso e os gráficos de Heckel, Kawakita e Gurnham. Prepararam-se comprimidos de ibuprofeno utilizando o método de granulação a úmido. Realizaram-se estudos de bioadesividade utilizando o método de cilindro rotativo em tampão fosfato pH 6,8, ou meio ácido com 0,1 M de ácido clorídrico. A goma é um polímero de baixa viscosidade (48 cPs) e a espectroscopia no infravermelho por Transformada de Fourier (FTIR) revelou a presença de um grupo hidroxila. Valores de Py e Pk, que são medidas de plasticidade, mostraram que a goma é significativamente ($p <0,05$) mais plástica do que HPMC e que a plasticidade aumenta com a concentração de polímero. Todas as formulações de comprimidos mostraram-se não-friáveis (<1,0%) e aquelas contendo a goma apresentaram maior resistência ao esmagamento (130.95N) do que aquelas contendo HPMC (117.85N) em 2,0% (p/p) do ligante. As formulações que incorporaram a goma eram não-desintegrantes e apesentaram tempo de liberação significativamente maior do que aquelas contendo HPMC. As formulações de goma de *Cedrela* aderiram à incisão de íleo de porco por tempo maior do que aquelas contendo HPMC com a maior concentração de ligante. A goma *Cedrela* apresentou melhor fluxo, compressão e propriedades de ligação do que HPMC e é adequada como bioadesivo e para a liberação sustentada de fármacos.

Unitermos: *Cedrela* goma/avaliação/propriedades de compressão. *Cedrela* goma/componente microadesivo. Formulações de comprimidos. Hidroxipropilmetilcelulose. Ibuprofeno/estudos bioadesivos. Bioadesão.

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INTRODUCTION

As a result of the inability of most drug powders to be made into satisfactory tablets, it is often necessary to incorporate excipients, which provide adequate compressive characteristics. These excipients include diluents, binders, glidants and lubricants. Binders provide adequate mechanical properties to pharmaceutical tablet formulations by promoting the bonding properties between the different components of the powder mixture (Joneja *et al,* 1999). They bind powders and granules together in the wet granulation and compression processes, respectively. Binders are now being investigated for their bioadhesive properties in drug formulation.

Different compaction parameters such as measurement of ejection forces, die wall friction, axial to radial load transmission, compressibility, and deformation characteristics are used in assessing the compaction behaviour of powders and formulations. The Heckel and Kawakita equations have been found to be useful in studying the powder behaviour during compression (Odeniyi, Jaiyeoba, 2007). The mathematical equations of Heckel, Kawakita and Gurnham (Zhao *et al*., 2006) are used in assessing tablet properties, while the Kitazawa equation is also used to analyse the release characteristics of tablet formulations.

Many synthetic polymers, such as polyacrylic acid (PAA), polymethacrylic acid, cellulose derivatives, and polyethylene oxide, have been used as mucoadhesive drug carriers. However, these synthetic polymers are associated with undesirable mucosal irritation and, hence, the need for the development of natural polymers as bioadhesive drug delivery systems (Ameye *et al*., 2005).

Cedrela odorata, the most common species among the *Cedrela*, is widespread in seasonally dry tropical and subtropical forests. It is an important timber tree and has become naturalised in Africa and southeast Asia. While many plant gums, such as gum acacia, gum karaya, gum terminalia (Kumar *et al*., 2008), okra gum (Kalu *et al*., 2007), *Delonix regia* seed gum (Adetogun, Alebiowu, 2009) and Cissus gum (Adeleye *et al.*, 2010), have been investigated, the gummy exudate of *Cedrela odorata* tree bark has not been studied as a binder and mucoadhesive component in pharmaceutical formulations. This study was therefore designed to determine the compressive, mechanical, bioadhesive and release properties of tablet formulations incorporating a new gum obtained from the incised trunk of the *Cedrela odorata* tree.

The formulations were compared with those containing hydroxypropylmethylcellulose (HPMC). Ibuprofen, a non-steroidal anti-inflammatory drug widely used to reduce pain, inflammation and stiffness caused by osteoarthritis, rheumatoid arthritis, ankylosing spondylitis or abdominal cramps associated with menstruation, has fewer side effects than similar drugs (Simon, 1997; Ong *et al.*, 2007) and was used as the model formulation drug.

MATERIAL AND METHODS

Material

The materials used were ibuprofen powder (Sigma Chemicals, St. Louis, MO), lactose BP (DVM Veghel, Holland), HPMC (Benecel K35M, Aqualon, Hercules Inc. USA), magnesium stearate BP, (Aqualon, Hercules Inc. USA), and *Cedrela* gum from the incised trunk of the *Cedrela odorata* tree (Botanical garden, Department of Botany, University of Ibadan, Ibadan, Nigeria).

Preparation of gum

Cedrela gum was extracted from the incised trunk of a *Cedrela odorata* tree from the Botanical Garden at the University of Ibadan (Ibadan, Nigeria) and purified using the established methods (Berressem, 1999). Briefly, the exudate was hydrated in 0.5: 95.5 (v/v) $CHCl_3$/water mixture for five days with intermittent stirring; extraneous materials were removed by straining through a muslin cloth. The gum was precipitated from solution using absolute ethanol. The precipitated gum was filtered, washed with diethyl ether, and then dried in a hot air oven at 40 °C for 18 hours. The gum was pulverised using a laboratory blender and sieved, and the size fraction < 170 µm was used for this study.

Physicochemical properties

The viscosity of 1% w/v *Cedrela* gum dispersed in distilled water at 25 °C was determined using a Brookfield DV-11+Pro viscometer (Brookfield Engineering Laboratories, Middleboro, MA, USA). The Fourier transform infrared (FTIR) spectrum of *Cedrela* gum was obtained on an IR spectrometer (Perkin-Elmer, 2000, USA) using the KBr disk (2 mg sample in 200 mg KBr). The scanning range was 400 to 4,000 cm^{-1}.

Preparation of granules

An 80 g batch of ibuprofen (50%), cornstarch (10%), and lactose (40%) was prepared by dry-mixing the powders for 5 minutes using a mortar and pestle; the mixed powder was transferred into an Erweka AR400

planetary mixer, mixed for another 5 minutes, and then moistened with distilled water. Mixing was continued for 5 minutes, and the wet mass was granulated by manually passing it through a number 14 mesh sieve (1250 µm). The granules were then dried in a hot oven (Gallenkamp oven) for 24 hours at 60 °C. The same procedure was used in the preparation of granules using varying concentrations of HPMC, and this was repeated for batches of granules containing *Cedrela* gum. Varying concentrations of the binders (0.5%, 1%, 2%, 3%, and 4%) were used as gum mucilage to moisten the dry-mixes instead of distilled water. The granules were stored in airtight containers.

Compressional properties of the granules

The bulk density of each formulation at zero pressure (loose density) was determined by pouring the granules into a 50 ml glass measuring cylinder with a diameter of 24 mm through a funnel at an angle of 45°. Determinations were made in triplicate. The relative density (D) of each formulation was obtained from the ratio of the loose density to its particle density.

The angle of repose of the granules was determined by the fixed funnel method (Panda *et al*., 2008). The bulk and tapped densities were determined by weighing 2 g (W) of granules into a 10-mL measuring cylinder. After the initial volume (V_o) was measured and the cylinder was tapped on a hard surface until no further change in volume was observed, the tapped volume (V_T) was noted. The bulk density (BD) and the tapped density (TD) were calculated using the following formula:

$$BD = W/V_o \quad (1)$$

$$TD = W/V_T \quad (2)$$

The compressibility index of the granules was determined by Carr's compressibility index

$$\text{Carr's Index (\%)} = \frac{TD - BD}{TD} \times 100 \quad (3)$$

Hausner's ratio was calculated from the ratio of the tapped density to the bulk density.

Preparation of tablets

Equal quantities (400 mg) of each of the formulation granules were accurately weighed on a Mettler Balance PC440 and compressed into tablets, using a Carver Hydraulic tablet press (Model C, Carver Inc, Menomonee Falls, Wisconsin, USA), with nine predetermined pressures between 28 and 226 MNm^{-2}. The 10.5-mm die and flat-faced punches were lubricated with a 2% w/v dispersion of magnesium stearate in ether–ethanol (1:1) prior to each compression. Tablets obtained were stored over silica gel for 24 h to allow for elastic recovery and to prevent falsely low yield values. The tablets' weights and dimensions were determined to within ± 1 mg and 0.01 mm, respectively, and their relative densities (D) were calculated using the equation

$$D = {}^{w}\!/_{V_t \cdot \rho_s}, \quad (4)$$

where V_t is the volume of tablet (cm^3), and ρ_s is the particle density of the solid material (g/cm^3).

Mechanical properties

The friability test was performed on the tablets using a DKB Friability 5026/6 (England). The crushing strength of the tablets was determined by diametral compression (Adeleye et al., 2010) using a tablet crushing strength tester made by Karnara Industrial Cooperation, Bombay. The results were taken only from tablets that split cleanly into two halves without any sign of lamination.

Compression properties of tablets

Heckel plots of ln (1/ (1-D)) against the applied pressure (p) were plotted for each of the binder granulations. Values of K and A were obtained from the slope and intercept, respectively. Kawakita plots of P/C against the applied pressure, p, were plotted for each binder granulation. Values of a and b were obtained from the slope and intercept, respectively. Gurnham (Gurnham *et al.*, 1946) plots of ln P versus porosity were made for the formulations. Values of *c,* which give a measure of material plasticity, were obtained from the slopes.

Mucoadhesive properties of tablet formulations

This is a modification of the method described by Kafedjiiski et al. (2005). A porcine intestinal segment was fixed, using an elastic rubber band, onto a stainless steel cylinder with the basolateral side facing the cylinder. The tablets containing the different concentrations of the gum were pressed on the apical side, and the cylinder was put into 500 mL of a buffer medium, pH 6.8 (prepared by dissolving 6.8 g of sodium dihydrogen orthophosphate in sufficient distilled water to produce 1000 mL and pH-adjusted using 10% sodium hydroxide solution on a pH meter).

The rotation speed was set at 50 rpm. The elapsed time when the tablet detached from the mucosa was observed and recorded. The same procedure was repeated using 0.1 M hydrochloric acid. The phosphate buffer and HCl were used to simulate alkaline and acidic conditions in the small intestine and stomach, respectively. The study was carried out in triplicate.

Histopathological evaluation of mucosa

The histopathological evaluations of tissues immersed in either phosphate buffer (pH 6.8) or 0.1 N HCl were compared with those of tissues before adhesion. Tissue was fixed in 10% buffered formalin, routinely processed and embedded in paraffin. Sections were cut onto glass slides and stained with hematoxylin and eosin. Sections were examined under a light microscope to detect any damage to the tissue.

Disintegration and release properties of tablets

The disintegration times of the different tablets were determined using a BP of Manesty disintegration unit (Manesty Machines Ltd, Liverpool, U.K.).

In vitro drug release studies from the prepared tablets containing *Cedrela* gum or HPMC as binder were conducted at 37 °C in a dissolution basket at 100 rpm. The basket containing the tablets was immersed in 900 mL of phosphate buffer at pH 7.4. Samples of 5 mL were withdrawn and replaced with fresh medium. The amount of ibuprofen released was determined using a UV spectrophotometer (Unico, UV2102 PC) at a wavelength of 221 nm. The amount of drug dissolved at specific time points was plotted as percent released versus time.

Statistical analysis

Statistical analysis was performed to compare the effect of the binders on the tablet properties using ANOVA and a t-test. At 95% confidence interval, p values of ≤ 0.05 were considered significant.

RESULTS AND DISCUSSION

Cedrela gum is a low viscosity polymer (48 cPs). FTIR revealed the presence of a hydroxyl group at 3000–3500 cm^{-1}. The angle of repose is a measure of the frictional forces between the particles of a loose powder (Emery *et al.*, 2009). It indicates powder flow, and values less than 30° represent materials with good flow properties. The values were found to be in the range of 24-27° for both the *Cedrela* gum and HPMC formulations. Carr's index and Hausner's ratio are based on bulk and tap densities and indicate the flow properties of the materials. Granules containing the gum had similar values of Carr's index and Hausner's ratio of generally less than 17% and 1.2%, respectively (Table I). Generally, materials with Carr's index of up to 16% are known to show good flow behaviour, while those above 28% indicate poor powder flow. These results show that *Cedrela* gum is of similar grade with HPMC in terms of good flow behaviour.

Heckel plots for the formulations showed initial curves at low pressures, which is an indication of rearrangement and particle fragmentation (Figures 1 and 2). At the later stages of compression, linearity was obtained; this indicates that the materials deform plastically. The mean yield pressure (P_y) value, calculated from the slope of the curve, is an inverse plasticity parameter (Matsson, 2000) and a measure of the onset of plasticity, which indicates granule plasticity. Lower P_y values were obtained for formulations containing *Cedrela* gum than for those containing HPMC. This suggests faster onset of plastic deformation in the *Cedrela* gum formulations (Table II).

The Kawakita equation is used to depict the softness of materials and is frequently used to investigate pharmaceutical powders (Denny, 2002). A linear relationship with a correlation coefficient of >0.999 was obtained at all binder concentrations (Figure 3). This indicates that the equation can be used to determine the deformation mechanism of the materials. P_k (also an inverse plasticity parameter) is the pressure required to reduce the bed by 50% (Shivannand, Sprockel, 1992); it indicates the total amount of plastic deformation occurring in the mate-

TABLE I - Granule and flow properties of ibuprofen formulations containing *Cedrela* gum and HPMC as binders at 3% w/v

Binder	Mean Granule size (μm)	Bulk density (gcm^{-3})	Tapped density Bulk density (gcm^{-3})	Angle of Repose (°)	Hausner's Ratio	Carr's Index
Cedrela gum	902.16	0.24 ± 0.02	0.72 ± 0.04	25.16 ± 1.12	1.14 ± 0.06	12.54 ± 5.11
HPMC	721.29	0.23 ± 0.03	0.77 ± 0.01	25.52 ± 2.37	1.10 ± 0.01	9.34 ± 0.61

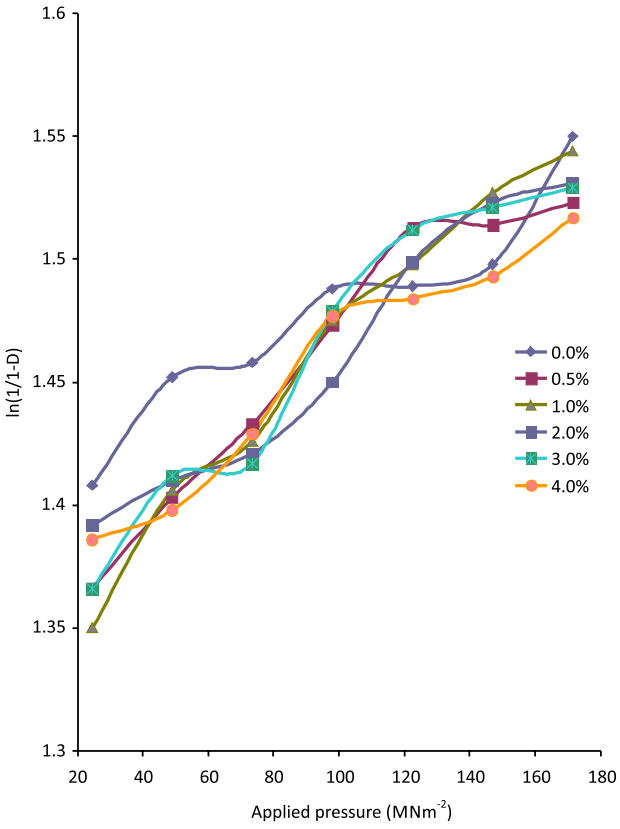

FIGURE 1 - Heckel plots for ibuprofen formulations with *Cedrela* gum as the binder.

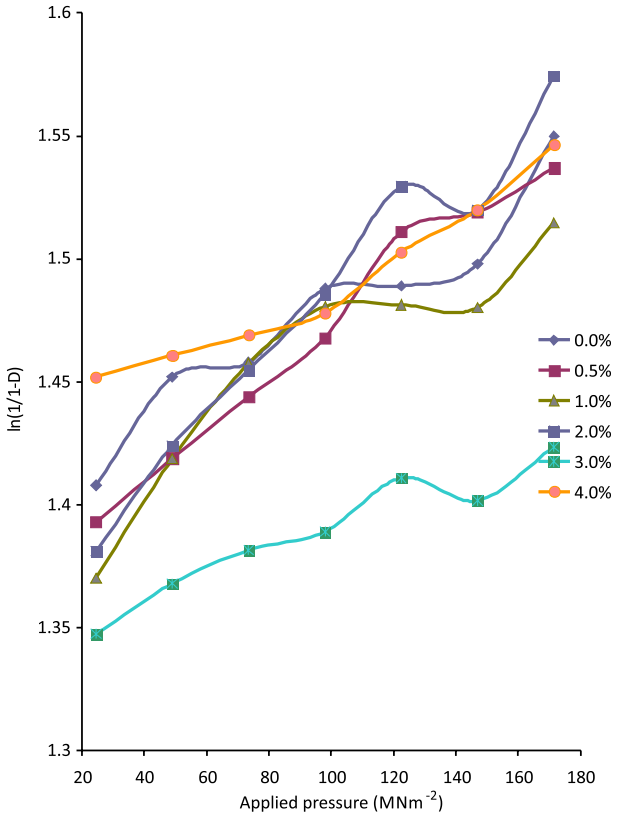

FIGURE 2 - Heckel plots for ibuprofen tablets containing hydroxypropylmethylcellulose as the binder.

rial. Lower values of P_k were obtained with increasing concentrations in the tablet formulations. It is possible to obtain more information in the deformation profile of a material from the combined use of P_y and P_k to obtain conditions for optimum plasticity (Ayorinde, Itiola, 2010). Materials with low values for both P_y and P_k would not be expected to give any appreciable problems on any type of tableting machine during compression. P_y indicates

TABLE II - Values of parameters obtained from the Heckel, Kawakita and Gurnham plots

Type of binder	Concentration of binder (% w/w)	Mean yield pressure P_y (MN/m^2)	Relative density at zero pressure (D_o)	Initial relative density (D_i)	Pressure required to reduce powder bed by 50%_P_k (MN/m^2)	Effect of pressure on compact porosity c
HPMC	0.5	10.010	0.205	0.021	9.79	0.020
	1	12.063	0.191	0.019	0	0.023
	2	8.278	0.183	0.018	9.81	0.016
	3	21.552	0.162	0.017	9.83	0.021
	4	16.103	0.168	0.016	0	0.010
Cedrela gum	0.5	9.042	0.194	0.155	59.10	0.021
	1	7.813	0.187	0.019	29.42	0.016
	2	9.709	0.184	0.018	39.26	0.020
	3	8.757	0.180	0.019	9.81	0.009
	4	10.977	0.162	0.017	9.83	0.010

the onset of plastic determination, while P_k indicates the ability to deform plastically under pressure. The D_i value is a measure of the packed initial relative density with the application of small pressures or tapping (Adetunji *et al*., 2006). Low values were recorded for all of the formulations. The D_i values generally decreased with increasing binder concentrations for all formulations. The values of D_i are much lower than those of D_o, which shows that the reduction in volume is a result of compression and that the gum impacts the plasticity of the material (Table II).

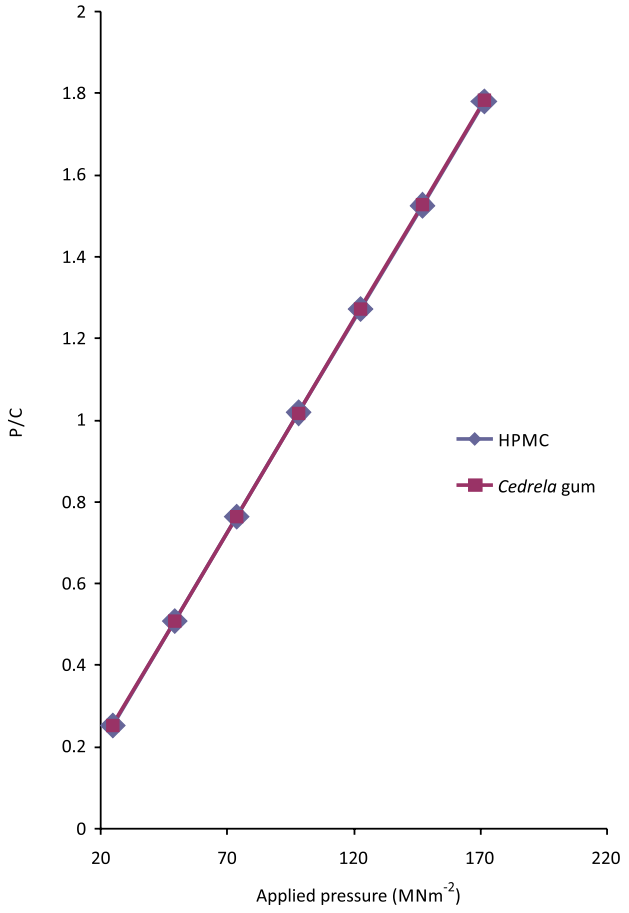

FIGURE 3 - Representative Kawakita plots for ibuprofen formulations at 3% w/w binder concentration.

The Gurnham equation has been investigated to study the compression process in pharmaceutical powders (Zhao *et al.*, 2006). The equation was first introduced in chemical engineering to describe the expression of liquids from fibrous materials (Gurnham, Masson, 1946). It was proposed that any increase in pressure, expressed as a fractional increase over the existing pressure, results in a proportional increase in the apparent density of the mass:

$$dP/P = AdD, \quad (5)$$

where p is pressure, D is the apparent density (bulk density), and A is a constant.

The equation describes volume reduction of dry fibrous materials. Compression processes in tableting could be studied using this equation (Zhao *et al.*, 2006):

$$E = 1\text{-}D/D_{T,} \quad (6)$$

where E is the porosity, D_T is the particle density, and D is the bulk density.

Replacing density with porosity in the equation changes it as follows:

$$E = -c\ LN\ (P) + d. \quad (7)$$

Plots of ln P versus porosity give a linear relationship for powder compression. Constant *c* (slope) is an expression of the effect of pressure on compact porosity. A high value of c is an indication of a strong volume reduction ability of the material as the pressure increases. A linear relationship was observed for the binders at the early stage of compression (Figure 4). This highlights the possible limitations of the equation for plasto-elastic materials such as gums.

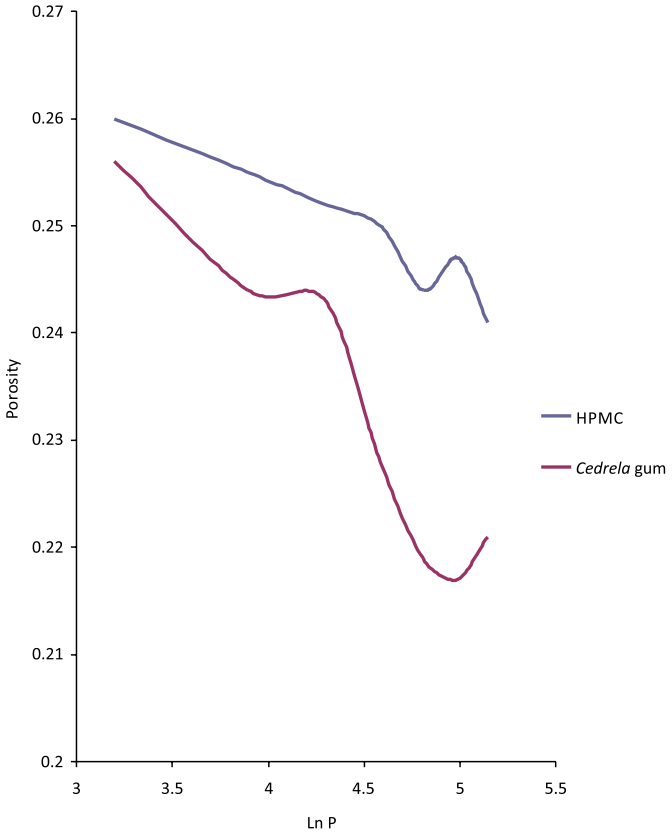

FIGURE 4 - Representative Gurnham plots for ibuprofen tablet formulations at 3% w/w binder concentration.

Plots of ln P against porosity, using the Gurnham equation, gave a linear relationship only at the initial stages of compression (Figure 4). The regression coefficient values for the compression stages were observed to be low. The c values obtained for formulations containing *Cedrela* gum and HPMC were not significantly different and were generally low, within the range of 0.01 – 0.02. The Gurnham equation has been used to characterise crystalline pharmaceutical powders (Zhao *et al.*, 2006), but the results obtained from this study showed that the equation has limitations when considering amorphous materials that are plasto-elastic in nature. This most likely account for the low values of c obtained for both *Cedrela* gum and HPMC despite the good flow and compressibility properties indicated by the Carr's index, Hausner's ratio, and the Heckel and Kawakita equations, which have been used to characterise different types of pharmaceutical powders.

Mechanical property

Friability values for all the formulations were found to be less than 1.0%. One of the mechanical properties used in assessing the usefulness of a new binder in a formulation is the crushing strength. This is a measure of the bond strength and ability of the tablets to withstand the stress of packaging, transportation and handling. Formulations containing *Cedrela* gum were found to have significantly ($p < 0.05$) higher values of tensile strength than those containing HPMC. There was positive correlation between crushing strength and binder concentration (Figure 5). The concentration and type of binder have been shown to affect the tensile strength of tablets (Itiola, 1991; Ayorinde *et al.*, 2011). The effect of binder concentration can be due to the plasto-elastic property of the binding agent; the heat produced during compaction causes melting of asperities and of the binder, which, on cooling, solidifies to form strong solid bonds between the particles. The binding agent also undergoes plastic deformation and is forced into the interparticulate spaces, thereby increasing the area of contact between the particles and forming solid bonds (Odeniyi, Jaiyeoba, 2009).

Dissolution profile

Dissolution of a drug is a prerequisite for absorption of the drug into the body and is directly related to its bioavailability. It is a standardised method for measuring the rate of drug release from a dosage form. The therapeutic effect of different formulations of the same drug depends on the rates at which the drug is released (Banakar, 1996).

The release profile of ibuprofen from the *Cedrela* gum tablets is shown in Figure 6 and that of the tablets incorporating HPMC is shown in Figure 7. The drug release was assessed for over 5 hours with *Cedrela* gum, while the release assessment of HPMC took 3 hours because the HPMC tablets dissolved faster than those incorporating the gum. Dissolution time was higher for the gum formulations than for HPMC tablets at all binder concentrations. Dissolution time increased with increasing binder concentrations, that is, the rate of release is slower at higher concentrations of both formulations. This increase in dissolution time with increasing binder concentrations could be due to the formation of a thick film of gum mucilage as the tablet comes into contact with the dissolution fluid. This film would be converted into a mucilaginous viscous barrier, which would hinder the release of drug molecules (Adetogun, Alebiowu, 2009). The release behaviour was non-linear in nature with the decreasing release rate, most likely due to diffusional resistance. The decrease in drug release rate could also be due to higher bond formation as a result of increasing binder concentrations (Odeniyi, Jaiyeoba, 2007). An increase in the hardness value of the tablets is usually accompanied by a decrease in the drug release rate due to a decrease in the porosity of the tablets. (Tabandeh *et al.*, 2003).

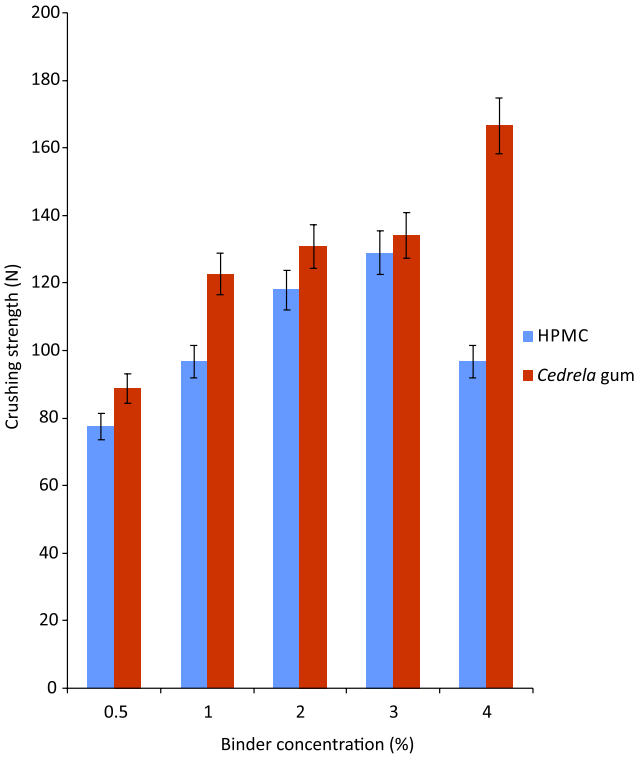

FIGURE 5 - Effect of the binder concentration on the crushing strength of ibuprofen tablet formulations.

The release mechanism of a drug would depend on

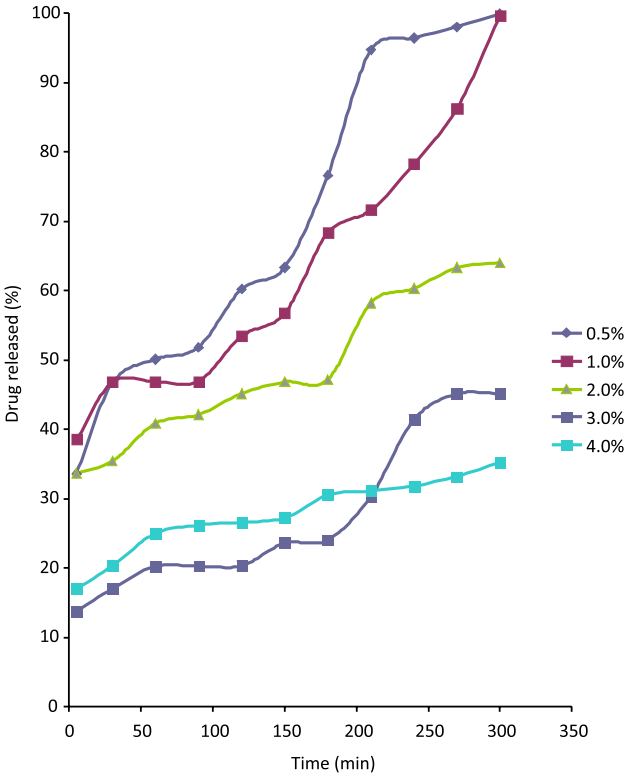

FIGURE 6 - Dissolution plot for ibuprofen released vs. time for tablets containing *Cedrela* gum as the binder in phosphate buffer, pH 7.4.

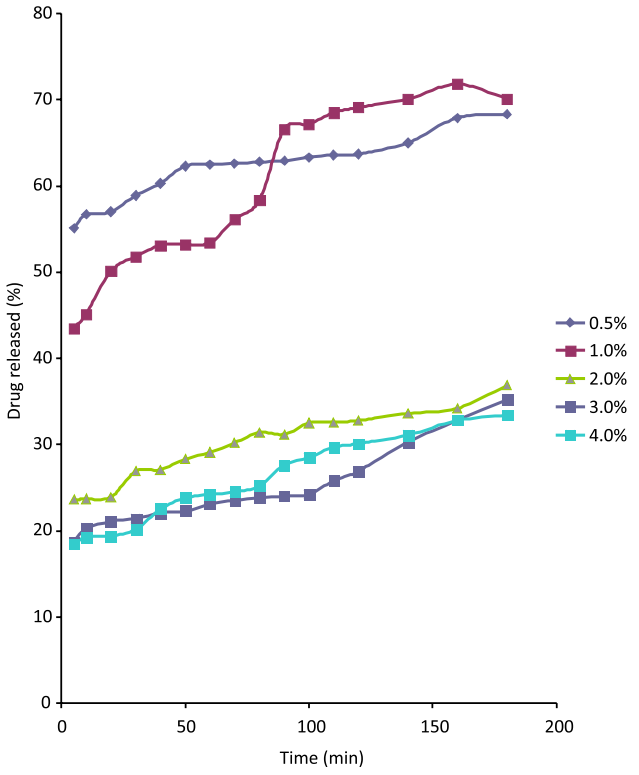

FIGURE 7 - Dissolution plot for ibuprofen released vs. time for tablets containing HPMC as the binder in phosphate buffer, pH 7.4.

the dosage form selected, pH, nature of the drug and the polymer used. The disparity in the release rate of different classes of drugs can be attributed to the differences in their physical and chemical properties, particularly on their solubility profile (Kalu *et al.*, 2007). The high swelling capacity of the gum and the slow rate of the *Cedrela* gum tablets dissolution suggest the possible use of the gum in a sustained release tablet dosage form. The data obtained from the dissolution process was further subjected to the Kitazawa *et al*. analysis (1975), which involves the integrated form of the Noyes-Whitney equation (1897) written as follows:

$$\ln\left[Cs/(Cs-C)\right] = kt,$$

where C_s is the concentration of the solute at saturation, C is the concentration at time t, and k is the dissolution rate constant. Values of In $[C_s/(C_s\text{-}C)]$ were plotted versus t and shown for tablets containing *Cedrela* gum or HPMC as binders. The data obtained are shown in Table III.

The Kitazawa plots (Figure 8) generally showed two straight regression lines of slopes k_1 and k_2 for the non-disintegrating tablets incorporating *Cedrela* gum while showing a third regression line k_3 for tablets incorporating HPMC. The times at which the lines intersect are denoted t_1 and t_2. The values of k_1, k_2, k_3, t_1 and t_2 for the relevant samples are presented in Table III. The table shows k_1 to be lower than k_2 for all the formulations, implying that the dissolution rate of the drug was faster after t_1. It would appear that changes in the surface area of the dissolving particles brought about by the disintegration in the HPMC tablets and possible erosion in the *Cedrela* gum tablets and de-aggregation of the tablets were manifested in the increase in dissolution rate after t_1. The values of t_1, k_1 and k_2 for all the formulations were not significantly different.

There was no significant difference between the two polymers in adhesion time values in both media (Table IV). However, there was a general increase in adhesion time with increasing binder concentration for both polymers. This could be attributed to an increase in viscosity with increasing polymer concentrations as well as swelling properties of the incorporated binders (Bottenberg *et al*., 1991). The formulation containing 4.0% w/w *Cedrela* gum exhibited the highest adhesion time (Figure 9). It has been shown that at low concentrations of some polymers, the number of penetrating polymer chains per unit volume of the mucus is small and the interaction between polymer and mucus is unstable. A more concentrated polymer leads

TABLE III - Dissolution characteristics of ibuprofen tablets (Mean ± SD, N=3)

Polymer	Binder conc. (% w/w)	t_1 (min)	t_2 (min)	k_1	k_2	k_3
Cedrela gum	0.5	150.0 ± 2.24		0.004 ± 0.001	0.025 ± 0.021	
	1.0	270.0 ± 1.24		0.004 ± 0.012	0.067 ± 0.012	
	2.0			0.061 ± 0.014		
	3.0			0.047 ± 0.003		
	4.0			0.022 ± 0.008		
HPMC	0.5	50.0 ± 1.14	120.0 ± 4.14	0.004 ± 0.001	0.001 ± 0.005	0.003 ± 0.001
	1.0	70.0 ± 3.85	110.0 ± 3.18	0.004 ± 0.003	0.011 ± 0.001	0.002 ± 0.004
	2.0	100.0 ± 2.75		0.001 ± 0.001	0.002 ± 0.001	
	3.0	90.0 ± 2.98		0.002 ± 0.015	0.000 ± 0.010	
	4.0	80.0 ± 3.17		0.001 ± 0.001	0.001 ± 0.004	

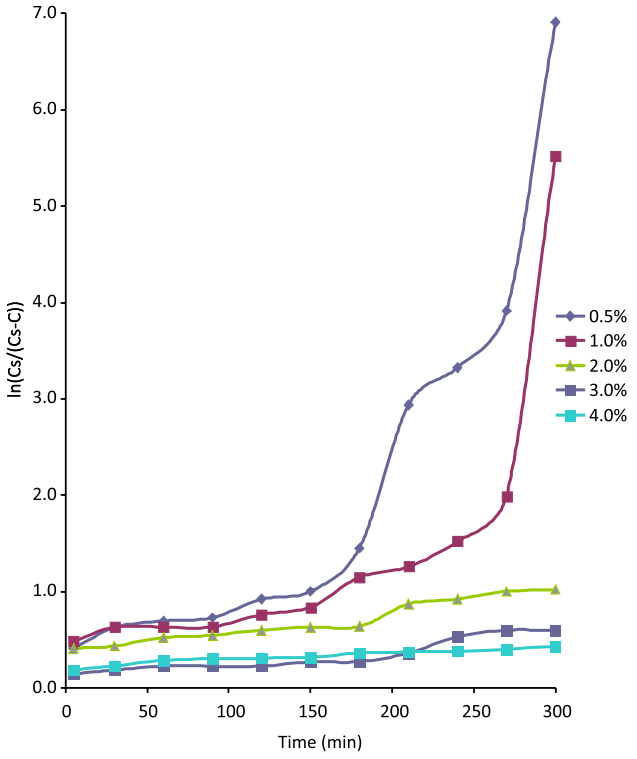

FIGURE 8 - Kitazawa plots for ibuprofen tablets containing *Cedrela* gum as the binder.

to longer penetrating chain length and better adhesion. Increased concentration of a bioadhesive polymer usually increases its binding potential (Park and Robinson, 1984). Further, at this concentration, *Cedrela* gum formulations showed a higher adhesion time in pH 6.8 phosphate buffer due to a possible increase in hydrogen bonding effects. This indicates the potential use of the gum to target the intestine (Odeniyi *et al.,* 2011).

TABLE IV - Adhesion time for formulations containing HPMC or *Cedrela* gum in 0.1 M HCl or pH 6.8 phosphate buffer (n=3)

Binder	Concentration of binder (%w/w)	Adhesion time (min)	
		0.1 M HCl	Phosphate buffer, pH 6.8
	0.0	0.11 ± 0.01	0.14 ± 0.06
HPMC	0.5	0.16 ± 0.03	2.05 ±0.04
	1.0	4.30 ± 0.13	3.09 ±0.02
	2.0	3.21 ± 0.19	8.03 ± 1.16
	3.0	13.12 ± 1.22	9.15 ± 1.03
	4.0	20.08 ± 1.16	12.13 ±1.55
Cedrela gum	0.5	0.13 ± 0.05	1.31 ± 0.02
	1.0	0.25 ± 0.02	2.04 ± 1.31
	2.0	11.01 ±1.12	11.02 ± 2.72
	3.0	16.08 ± 1.41	15.42 ± 1.42
	4.0	24.31 ± 2.31	150.08 ± 6.82

Histopathological evaluation

Pictures of light micrographs of the intestinal mucosa prior to adhesion and after detachment of the tablets are shown in Figures 10. No damage was observed to the tissue after adhesion when examined under a light microscope. This suggests that the ibuprofen tablet formulation containing *Cedrela* gum has no adverse effect on the mucosal lining, making it suitable for *in-vivo* application.

CONCLUSION

Cedrela gum was found to be hydrophilic. The low values of P_y and P_k indicated that formulations with *Cedre-*

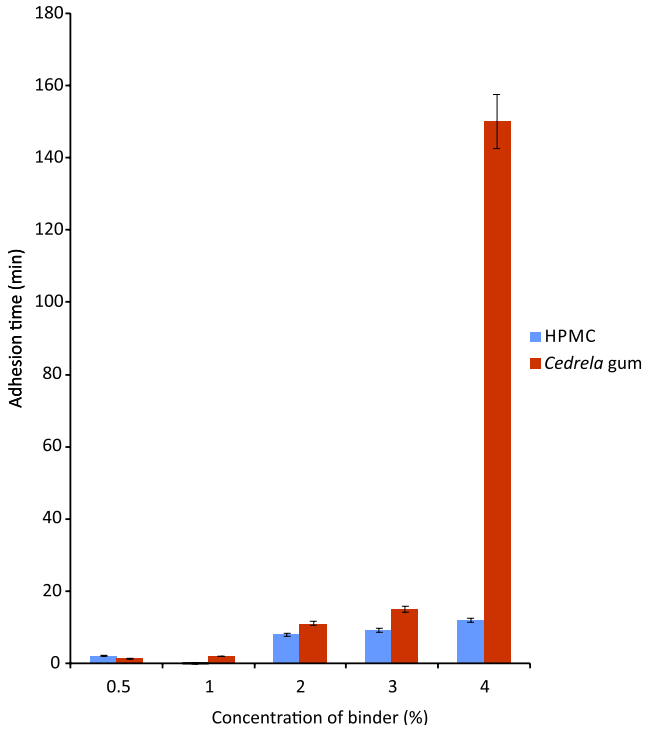

FIGURE 9 - Adhesion time on incised pig mucosa for HPMC and *Cedrela* gum formulations in pH 6.8 phosphate buffer (n=3)

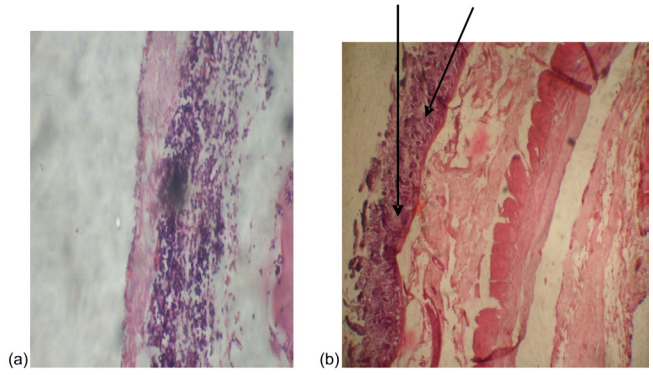

FIGURE 10 - Light micrographs of the intestinal mucosa (a) prior to application of the oral tablets and (b) after the detachment of the oral tablets. The arrows show points of attachment of the tablets.

la gum had a fast onset of plastic deformation and readily deformed plastically under pressure. The Gurnham equation was found to have limitations in characterising plasto-elastic materials such as gums. *Cedrela* gum was found to possess a better mucoadhesive property with a prolonged adhesion time than hydroxypropylmethylcellulose at the highest polymer concentration and had no deleterious effect on the intestinal mucosa. The gum showed a slower release property as indicated by a slower dissolution rate than HPMC, indicating its potential usefulness in sustained release tablet formulations. *Cedrela* gum has been found to be a suitable material as a binder in tablet formulations and bioadhesive component in the dosage form.

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