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RELEASE AND MUCOADHESION PROPERTIES OF DICLOFENAC MATRIX TABLETS FROM NATURAL AND SYNTHETIC POLYMER BLENDS

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Abstract: The delayed release and mucoadhesive properties of Cedrela gum and hydroxypropylmethylcellulose blend in diclofenac sodium tablet formulations were evaluated. Tablets were prepared by direct compression and the crushing strength and detachment force were found to increase from 74.49 ± 1.22 to 147.25 ± 2.57 N and 0.302 ± 0.36 to 1.141 ± 0.05 N from low to high level of polymers, respectively. The release kinetics followed Korsmeyer-Peppas release and the *n* varied between 0.834 and 1.273, indicating that the release mechanism shifts from Fickian to super case I (anomalous release). The drug release profile fits a pulsatile-release pattern characterized by a lag time followed by a more or less rapid and complete drug release. The Cedrela gum-hydroxypropylmethylcelluse blend tablets delayed diclofenac release for 2 h and sustained the release for 12 h. The polymer blend delayed drug release in the 0.1 M HCl simulating gastric environment and subsequent release pH 6.8 phosphate buffer.

Keywords: Cedrela gum, delayed release, mucoadhesion matrix, polymer blend, release mechanism

Mucoadhesion has been defined as interfacial force interactions between polymeric materials and mucosal tissues. Significant attention has been paid to the design of novel drug delivery systems with ability to prolong the residence time of dosage forms as well as sustain drug release and consequent bioavailability (1-4). Various routes of administration such as ocular, nasal, buccal, vaginal and rectal, make mucoadhesive drug delivery systems an attractive and flexible dosage form.

While several synthetic and natural polymers have been investigated extensively for this purpose (2, 5), the use of natural polymers for pharmaceutical applications is attractive because they are readily available and economical, non-toxic, potentially biodegradable and with few exceptions, also biocompatible. Also, plant resources, if cultivated or harvested in a sustainable manner, can provide a renewable supply of raw materials. Natural polymers have been successfully employed to formulate solid, liquid and semi-solid dosage forms and are specifically useful in the design of modified release drug delivery systems (5, 6).

Many synthetic polymers such as polyacrylic acid (PAA), polymethacrylic acid, cellulose derivatives, polyethylene oxide have been used as mucoadhesive drug carriers. However, these are associated with undesirable mucosal irritation and hence, the need for the development of natural polymers as bioadhesive drug delivery systems (7, 8). Controlled release drug delivery technology minimizes the frequency of administration by keeping the drug in therapeutic window for a longer period, improves patient compliance and reduces drug wastage by optimizing the efficacy of drugs (9, 10). However, controlled release technology generally is inadequate and incapable of increasing gastric resident time of drugs (11, 12).

Cedrela odorata (Meliaceae) is a widely distributed tropical plant and produces a clear gum. The polysaccharide isolated from the *C. odorata*, contains galactose, arabinose and rhamnose as neutral sugars and uronic acid residues. These sugar acids are represented by glucuronic acid and its 4-*O*-methyl derivative. The cationic composition of the ash showed the presence of calcium and magnesium predominantly (13). The flow behavior of *C. odorata* dispersion under steady shear is highly non-Newtonian and is characterized by the lack of a low-shear limiting Newtonian viscosity plateau even at very low shear rates (14).

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Cedrela gum has been found to be effective as a suspending agent (15), a carrier for theophiline in microcapsule formulation (16) and as a binder in tablet formulations at relatively low concentrations with potential bioadhesive properties (17). Cedrela gum hydrates quickly and hence cannot form a strong gel to retard drug release, while hydroxypropyl methylcellulose forms firm gel but do not hydrate quickly (18, 19). Further, while the mucoadhesive properties of HPMC have been found to be only moderate, the gum displays significant adhesive potential in a tablet formulation (17). Hence, a blend of HPMC and Cedrela gum is being investigated in order to overcome the limitations of the individual polymers. The initial drug burst release observed with formulations incorporating HPMC would be controlled by the strong binding properties of the natural gum while the subsequent drug release and matrix integrity maintained by the firm gel formed by HPMC.

Diclofenac sodium (DS), a widely used non-steroidal anti-inflammatory drug that exhibits anti-rheumatic, analgesic, osteoarthritis, and anti-pyretic activities, was chosen as the model drug. It has a short half-life in plasma of one to two hours.

MATERIALS AND METHODS

Materials used in this study include diclofenac sodium (Unique Chemicals, Gujarat, India), Cedrela gum (obtained from the incised trunk of *Cedrela odorata* (Meliaceae) tree, Botanical Gardens, University of Ibadan, Ibadan, Nigeria, hydroxypropyl methylcellulose (Methocel® K100M, Colorcon, UK), Tablettose (Meggle Pharma, Germany), Aerosil (Uitgest, Holland), magnesium stearate (R&M Chemicals, Essex, UK). Materials were used as received. Other reagents were of analytical grade.

Preparation of gum

Cedrela gum was extracted from the incised trunk of *Cedrela odorata* from the Botanical Garden, University of Ibadan (Ibadan, Nigeria) and authenticated at the Department of Botany Herbarium, University of Ibadan (UIH-22378), and purified using previous methods (17). 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 with absolute ethanol. The precipitated gum was filtered, washed with diethyl ether, and then dried in hot air oven at 40°C for 18 h. The gum was pulverized using a laboratory blender, sieved and the size fraction < 170 µm was used for the study.

Formulation design and matrix tablet preparation

The formulation design for the matrix tablets is given in Table 1. Cedrela gum was evaluated at 10, 30 and 50 mg while HPMC K100M was evaluated at 10, 20 and 30 mg in the tablet formulations.

Study of interaction between Cedrela gum and diclofenac sodium

Fourier transform infrared (FTIR) spectroscopy (on Model 2000 Perkin Elmer Spectroscopy, USA apparatus) was carried out to check the compatibility of the drug and excipients in the final formulation. The IR spectra of the samples were obtained using KBr discs that were prepared with hydraulic press after careful grinding of a small amount of each sample with KBr. The spectral width was 400–4,000 cm^{-1}. Each spectrum was acquired by performing 32 scans.

Preparation of matrix tablets

Matrix tablets were produced by weighting, screening, and mixing the excipients through a 40-

Table 1. Formulation design for diclofenac sodium matrix tablets (in mg).

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diclofenac sodium	200	200	200	200	200	200	200	200	200
Cedrela gum	10	30	50	10	30	50	10	30	50
HPMC	10	10	10	20	20	20	30	30	30
Tabletosse	176	156	136	166	146	126	156	136	116
Aerosil	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total (mg)	400	400	400	400	400	400	400	400	400

mesh sieve, to which the active ingredient was added and mixed thoroughly. Bulk density and tapped density of the powder blend was determined with graduated cylinders according to USP guidelines. Hausner ratio and Carr's index were determined to assess the flow property and compressibility of the powder blend (20). The powders were compressed using a tabletting machine (Manesty Machine Ltd., England) fitted with round, concave faced, 10 mm diameter punches and dies. The compression force was 1 tonne.

Evaluation of tablets

Twenty tablets were powdered individually and a quantity equivalent to 100 mg of diclofenac sodium was accurately weighed and extracted with a suitable volume of pH 6.8 phosphate buffer. Each extract was filtered through Whatman filter paper No. 41 (Whatman Paper Limited, UK) and analyzed spectrophotometrically (Hitachi U2000, Tokyo, Japan) at 276 nm after sufficient dilution.

The matrix tablets were also evaluated for crushing strength using a hardness tester (Erwerka Aapparatebau GmbH, Germany), friability (Erweka Aapparatebau GmbH, Germany), weight variation using analytical balance (Citizen CY 200), and thickness using digital micrometer gauge (Mitutoyo, Japan).

Determination of *ex vivo* mucoadhesive strength

Mucoadhesion testing was conducted *ex vivo* using freshly incised cow intestine from a slaughter house. Measurements were made with a Texture Analyser (TA-XT2i, Stable Micro Systems, Surrey, UK). Each tablet was attached to the base of an aluminium probe (using double-sided adhesive tape) fixed to the mobile arm of the texture analyzer. The tablet was lowered at a rate of 0.1 mm/s until contact with the intestine was made. A contact force of 0.25 N was maintained for 5 min, after which the probe was withdrawn from the intestine at a rate of 0.1 m/s. The peak detachment force (N) was recorded as a measure of bioadhesion (21, 22). Triplicate determinations were made with typically a coefficient of variation (cv) of < 5 %.

Drug release

The *in vitro* drug dissolution study was carried out in 900 mL of 0.1 M HCl at 37.0 ± 0.5°C for the first one hour and pH 6.8 phosphate buffer for 11 h,

Table 2. Micromeritic properties of powder blends of the various formulations.

	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk density (g/cm^3)	0.476	0.435	0.455	0.417	0.455	0.385	0.385	0.370	0.385
Tapped density (g/cm^3)	0.625	0.588	0.625	0.625	0.556	0.526	0.556	0.526	0.556
Carr's index (%)	23.810	26.087	27.273	33.333	18.182	26.923	30.769	29.630	30.769
Hausner's ratio	1.313	1.353	1.375	1.500	1.222	1.368	1.444	1.421	1.444

Table 3. Physical characteristics and bioadhesive properties of matrix tablets.

Formulation code	Diameter (mm)	Thickness (mm)	Crushing strength (N)	Friability (%)	Drug content (%)	Peak detachment force (N)
F1	10.0 ± 0.05	5.26 ± 0.03	74.49 ± 1.22	0.12 ± 0.01	98.42 ± 1.63	0.304 ± 0.24
F2	10.0 ± 0.03	5.27 ± 0.01	85.31 ± 1.43	0.01 ± 0.03	98.03 ± 1.54	0.302 ± 0.36
F3	10.0 ± 0.04	5.20 ± 0.06	113.29 ± 2.21	0.01 ± 0.01	98.51 ± 2.39	1.236 ± 0.13
F4	10.0 ± 0.01	5.30 ± 0.04	90.65 ± 0.14	0.01 ± 0.01	98.45 ± 2.18	0.740 ± 0.04
F5	10.0 ± 0.05	5.28 ± 0.03	147.25 ± 2.57	0.01 ± 0.01	98.83 ± 1.39	1.017 ± 0.08
F6	10.0 ± 0.03	5.28 ± 0.01	109.76 ± 1.32	0.01 ± 0.01	99.26 ± 1.17	0.499 ± 0.05
F7	10.0 ± 0.01	5.29 ± 0.02	97.12 ± 1.54	0.01 ± 0.02	99.62 ± 1.54	0.963 ± 0.02
F8	10.0 ± 0.05	5.28 ± 0.01	103.93 ± 2.11	0.00 ± 0.01	98.58 ± 2.23	0.989 ± 0.03
F9	10.0 ± 0.01	5.21 ± 0.02	132.01 ± 3.27	0.00 ± 0.01	98.79 ± 1.93	1.141 ± 0.05

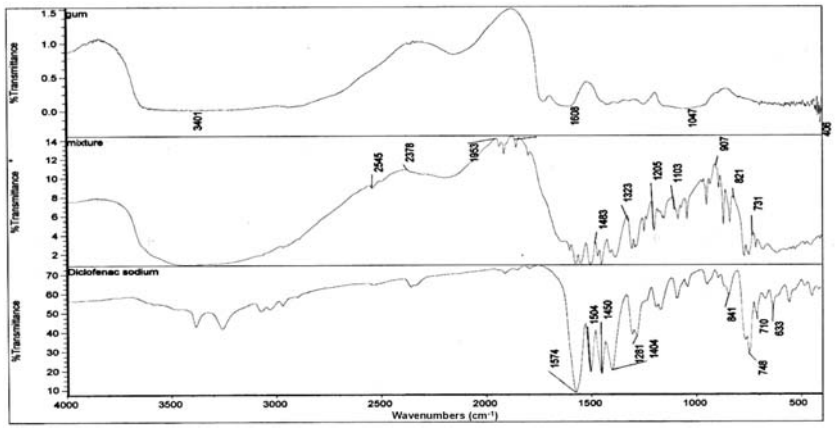

Figure 1. FTIR spectra of Cedrela gum, diclofenac sodium and physical mixture of gum and drug

using USP basket method at a stirring speed of 100 rpm. Samples were withdrawn and immediately replaced with an equal volume of fresh dissolution medium at predetermined intervals. The samples were filtered using a 0.45 µm membrane filter and the amount of drug released was determined using UV spectrophotometer (Hitachi U2000, Tokyo, Japan) at 276 nm.

Mechanism of drug release

Drug release from tablet formulations may follow either zero order kinetics which describes the systems where the drug release rate is independent of its concentration (23), first order kinetics where the release rate is concentration dependent (24), or Higuchi's model in which the release of drugs from insoluble matrix as a square root of time-dependent process based on Fickian diffusion (25). The Hixson-Crowell cube root law describes the release from systems where there is a change in surface area and diameter of particles or tablets (26). However, in order to determine the mechanism of drug release from the formulation, release data may be fitted in Korsmeyer et al. (27) equation (Equation 1):

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

This equation describes drug release behavior from polymeric systems. 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 (27, 28). For a cylinder shaped matrix the value of n = 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. 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 (29).

The mean dissolution time (MDT), was proposed by Möckel and Lippold (30), as providing a more accurate drug release rate that the t_x%. The equation is used to characterize drug release rate from the dosage form and the retarding efficiency of the polymer. Values of MDT can be calculated from dissolution data using the equation:

$$MDT = (n/n + 1)k^{-1/n} \quad (2)$$

where n is the release exponent and k is release rate constant. A higher value of MDT indicates a higher drug retaining ability of the polymer (31).

Statistical analysis

Statistical analysis was carried out using Students' *t*-test and ANOVA, p value lower or equal to 0.05 was considered the limit of significance.

RESULTS AND DISCUSSION

No significant shifts or reduction in the intensity of FTIR bands of diclofenac sodium was observed in the physical mixture with the gum. Characteristic peaks present in the FT-IR spectrum of Cedrela gum and HPMC K100M appeared in the spectra of the physical mixture with diclofenac sodium indicating the absence of any chemical interaction between the drug and the excipients (Fig. 1).

The micromeritic properties of the formulations are given in Table 2. There was no substantial difference in the bulk and tapped densities of all the

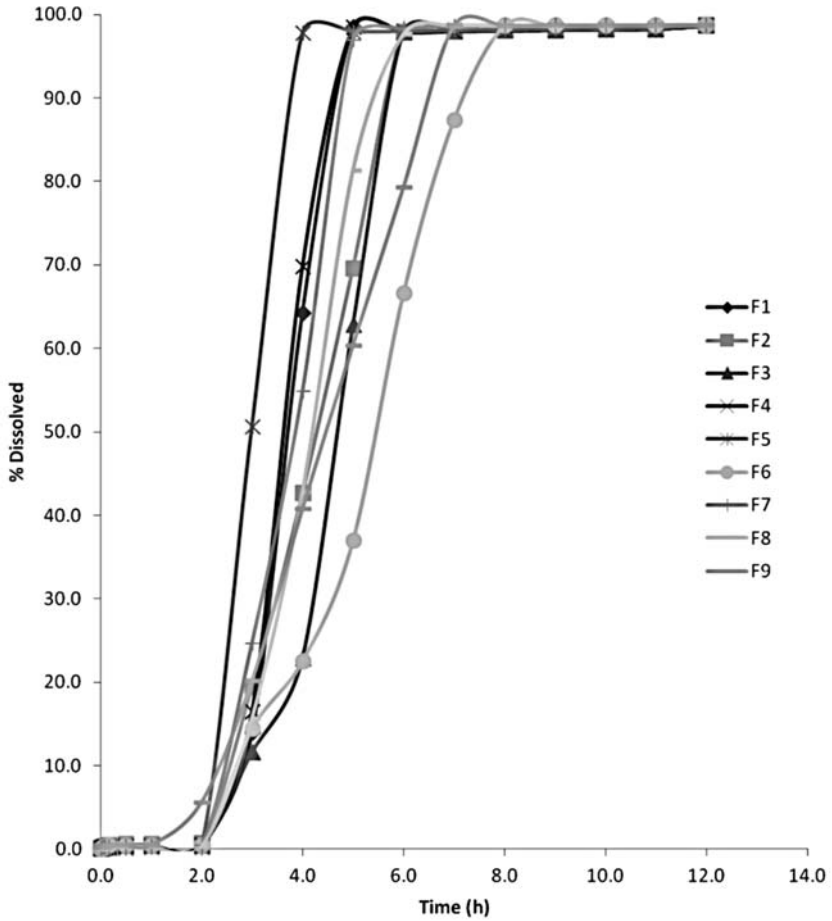

Figure 2. Cumulative release of diclofenac sodium from batches F1 to F9. Each point represents the mean ± SD (n = 3)

formulations. Table 2 shows that compressibility index was highest for batch F4 (containing Cedrela gum/HPMC at ratio 1 : 2) and lowest for F5 (containing Cedrela gum/HPMC at ratio 3 : 2). The flow property was determined by Hausner ratio (1.22-1.50) and Carr's index (18.18-33.33%). Carr's compressibility index is an indication of the compressibility and flowability of a powder, and is also a direct measure of the propensity of a powder to consolidate when undergoing vibration, shipping and handling (6). Also, Hausner's ratio, presented in Table 2, is an indication of the flowability of powders. Formulation F5 had the lowest value (1.2) and hence the highest flowability, while F4 (1.5) had poor flow properties.

The tablets produced from the powder blends had uniform thickness, low friability and a high degree of content uniformity (Table 3). This indicates that the direct compression method is suitable for preparing matrix tablets of DS. The assayed content of DS in the various formulations varied between 98.03 and 99.62% (mean 98.83%) while the friability of the batches complied with British Pharmacopoeia (Table 3).

The crushing strength values, a measure of the hardness of tablets, are presented in Table 3. The hardness of the tablets increased proportionally with the amount of polymers in the formulation due to their binding properties. Formulations containing higher amounts of the natural gum contributed a greater effect to the crushing strength of the matrix tablets than HPMC ($p < 0.001$). This agrees with the previous study by Odeniyi et al. (17) using Cedrela gum as a binder in ibuprofen tablet formulations by wet granulation process. The results show that the bond forming property of the gum is not dependent on process of tablet formulation but increases with availability of binding surfaces provided with increasing polymer concentration. An additive effect could further be observed, as formulation F9

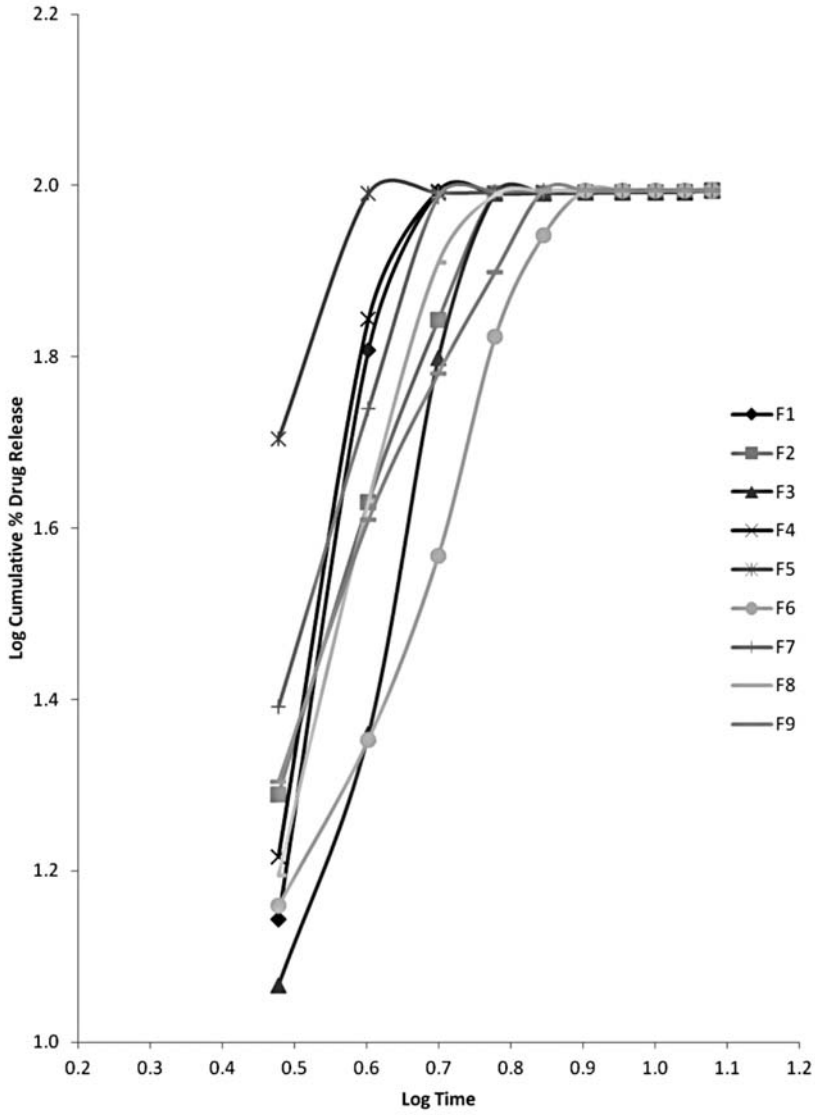

Figure 3. Korsmeyer-Peppas model for mechanism of drug release from matrix tablets

incorporating the highest concentration of both Cedrela gum and HPMC had the highest crushing strength values. Polymer type and amount in a formulation have been demonstrated to affect the crushing strength of tablets (32). This effect has been attributed to the plasto-elastic property of both polymers in the formulation. Cedrela gum was shown to undergo plastic deformation and thereby forced into the interparticulate spaces between the drug particles. This causes an increase in the contact area between the particles thereby forming solid bonds (17, 33).

Dissolution studies results are presented in Figure 2. A lag time of about 2 h was observed for the formulations. This was due to the fact that the first hour of dissolution was conducted in 0.1 M HCl, simulating the stomach. The drug release profile fits a pulsatile-release pattern which is characterized by a lag time followed by a more or less rapid and complete drug release (34). Drug release into the acidic stomach medium is avoided and release into the intestine or colon can therefore be achieved due to the apparent pH-dependent swelling and drug release of the Cedrela gum-HPMC blend. Further, the time taken for 25% (t_{25}), 50% (t_{50}), 75% (t_{75}) and 90% (t_{90}) drug release were obtained from the dissolution plot (Table 4). The lag times obtained from the dissolution curve generally increased with

Table 4. Dissolution parameters of matrix tablets.

Formulation code	t_{25}% (h)	t_{50}% (h)	t_{75}% (h)	t_{90}% (h)	MDT (h)	Lag time (h)
F1	3.358	3.818	4.116	4.257	3.739	2.000
F2	3.023	3.487	5.297	7.585	4.186	2.313
F3	4.000	4.045	4.797	6.893	4.537	2.878
F4	4.000	4.000	4.000	4.010	3.653	2.000
F5	3.000	3.000	3.000	3.134	3.031	1.346
F6	3.425	4.874	7.169	8.936	5.183	2.917
F7	3.000	3.080	4.051	6.343	3.710	2.000
F8	4.000	4.000	4.108	5.446	4.091	2.345
F9	2.014	4.473	7.137	8.806	4.411	2.529

Table 5. *In vitro* release kinetics of matrix tablets.

Formulation code	Zero-order		First-order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
	r^2	k_0	r^2	k_1	r^2	K_H	r^2	K_{HC}	N	r^2	K
F1	0.825	10.736	0.866	0.270	0.908	37.716	0.894	0.076	0.012	**0.994**	97.047
F2	0.883	10.408	0.885	0.239	0.946	37.447	0.916	0.067	0.265	**0.970**	60.078
F3	0.875	10.199	0.848	0.220	0.933	38.879	0.882	0.063	0.141	**0.980**	77.441
F4	0.820	10.784	0.869	0.277	0.907	37.924	0.897	0.078	0.017	**0.991**	97.439
F5	0.762	11.110	0.887	0.333	0.876	36.946	0.910	0.094	0.021	**0.999**	93.847
F6	0.923	9.634	0.860	0.188	**0.960**	36.675	0.896	0.054	0.527	0.958	34.867
F7	0.840	10.756	0.881	0.271	0.923	37.770	0.910	0.076	0.158	**0.976**	74.401
F8	0.868	10.512	0.874	0.245	0.935	37.990	0.906	0.069	0.070	**0.989**	87.699
F9	0.918	10.207	0.903	0.224	0.965	37.356	0.934	0.063	0.867	**0.994**	13.663

polymer concentration. Higher values were observed to correlate with increase proportion of the polymers in the formulations. At higher polymer loading, the viscosity of the polymer gel increases and this results in ineffective diffusion of the drug (35). Cedrela gum at highest concentration (formulation F6) modulated the release profile giving a sigmoidal curve when compared with other formulations. With further increase in HPMC concentration, a thicker gel is formed, which inhibits water penetration and resulting in significant increase in t_x values.

MDT values are also given in Table 4. They ranged between 3.03 – 5.18 h and increased with polymer loading. A positive correlation was observed (0.873) between MDT and t_{90}.

The dissolution data were best fitted to the Korsmeyer-Peppas equation (Fig. 3) with correlation coefficient of 0.96 – 0.99. The *n* values for all the formulations ranged from 0.01 to 0.87 (Table 5). This shows that the release mechanism for all the formulations, except F6 and F9, was Fickian (case I) release. Solute diffusion, polymeric matrix swelling and material degradation have been suggested to be the main driving forces for solute transport from drug containing polymeric matrices. Fickian diffusion, based on Fick's law of diffusion, refers to the solute transport process in which the polymer relaxation time is much greater than the characteristic solvent diffusion time. This mechanism is associated with solute concentration gradient, the diffusion distance, and degree of swelling (36). It has been shown that the presence of monovalent ions like Na^+ or K^+ tend to reduce swelling and increase rate of drug release from matrix tablets (36). However, for formulations incorporating the high amounts of Cedrela gum and high and intermediate amounts of HPMC K100M (F6 and F9) (Table 5), the *n* values were > 0.45 but < 0.89 indicating anomalous transport (non-Fickian) which is a combination of both diffusion and erosion controlled drug release (29).

The values of peak detachment force, which is a measure of mucoadhesive strength, of the tablet formulations are presented in Table 3. The values range from 0.302 to 1.141 N. Mucoadhesive strength was observed to increase with amount of polymer in the tablet formulations ($p < 0.05$). The highest value was observed in the formulation F9 incorporating the highest levels of the two polymers. Increasing the amount of polymers provided more adhesive sites and polymer chains for interpenetration with mucin. This will consequently increase the adhesion strength of the formulations (37). The high adhesion value obtained with the polymers in this case could be due to increase in hydrogen bonding effects (38).

CONCLUSION

Mucoadhesive and delayed release matrix tablets of diclofenac sodium were obtained by using a blend of Cedrela gum and hydroxypropyl methylcellulose (Methocel® K100M). The inclusion of hydroxypropyl methylcellulose, in the matrix tablets of diclofenac sodium led to increase in the mechanical, release retarding and mucoadhesive properties of Cedrela gum in the matrix tablets. Drug release was pulsatile-like and was dependent on the amount and type of matrixing agent The kinetics of drug release was explained by Korsmeyer-Peppas model. A blend of polymers by varying the proportions of Cedrela gum and hydroxypropyl methylcellulose could be used to formulate targeted and delayed release tablets.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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