JPP Journal of Pharmacy and Pharmacology

JPP 2004, 56: 1365–1370

Received May 25, 2004
Accepted July 28, 2004
DOI 10.1211/0022357044652
ISSN 0022-3573

Evaluation of khaya gum as a directly compressible matrix system for controlled release

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Abstract

Khaya gum has been evaluated as a controlled release agent in modified release matrices in comparison with hydroxypropylmethylcellulose (HPMC) using paracetamol (water soluble) and indometacin (water insoluble) as model drugs. Tablets were produced by direct compression and the in-vitro drug release was assessed in conditions mimicking the gastrointestinal system. Khaya gum matrices provided a controlled release of paracetamol for up to 5 h. The release of paracetamol from khaya gum matrices followed time-independent kinetics ($n = 1.042$) and release rates were dependent on the concentration of the drug present in the matrix. The addition of tablet excipients not only improved the mechanical properties of the tablet, but also altered the dissolution profile, except for dicalcium phosphate where the profile remained unchanged. HPMC could be used to control the drug release rates from khaya gum matrices and a combination of khaya gum and HPMC gave zero-order time-independent release kinetics. Indometacin exhibited a lag time in excess of 2 h, due to its insolubility at low pH, before the zero-order release was observed. Thus khaya gum matrices could be useful in the formulation of sustained release tablets for up to 5 h and the appropriate combination of khaya gum and HPMC could be used to provide a time-independent release for longer periods.

Introduction

Hydrophilic matrices have been used extensively to provide controlled release oral drug delivery. A number of natural and modified polysaccharides, such as xanthan gum, guar gum and karaya gum, alginates and carrageenan, have been shown to be useful for controlled release due to their hydrophilic properties (Bamba et al 1979; Talukdar & Kinget 1995; Sujja-areevath et al 1996; Cox et al 1999). The potential use of these inexpensive devices for the release of drugs at controlled and perhaps time-independent rates is of particular interest.

In this work, khaya gum, obtained from the incised trunk of the tree *Khaya grandifoliola* C.D.C (Meliaceae), a typical West African mahogany tree, is evaluated as a controlled release agent in modified release matrices. It is known to contain highly branched polysaccharides consisting of D-galactose, L-rhamnose, D-galacturonic acid and 4-*O*-methyl-D-glucoronic acid (Aspinall & Bhattacharjee 1970). Khaya gum has been developed as a binding agent in tablet formulations and has been shown to be useful as an alternative binding agent to produce tablets with particular mechanical strength and drug release profiles (Odeku & Itiola 1996, 1998, 2003). Further work has shown that khaya gum possesses the ability to destroy microorganisms during tabletting in a similar manner to standard binders (Odeku et al 1999a). Khaya gum is a hydrophilic polymer and has been shown to possess emulsifying properties comparable with acacia gum (Odeku et al 1997, 1999b). The fact that the gum is naturally available, inexpensive and non-toxic has also fostered the interest in developing the gum for pharmaceutical use.

The aim of this study was to evaluate khaya gum for sustained release purposes as a directly compressed matrix tablet. The swelling behaviour of khaya gum and the compression properties of khaya gum were evaluated. The properties of the tablets and drug release from the hydrophilic matrix were studied using paracetamol (a water-soluble drug) and indometacin (a poorly soluble drug) as the model drugs. Hydroxypropylmethylcellulose (HPMC) was used as a hydrophilic matrix for

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Funding: We wish to acknowledge the MacArthur Foundations – University of Ibadan for the Staff Development Grant awarded to O. A. Odeku.

comparative purposes. Controlled release of drug from hydrophilic matrices is achieved by two mechanisms: water-soluble drugs are released by diffusion out of the gelatinous layer and by erosion of the gel, whereas poorly soluble drugs are released solely by erosion (Ford et al 1987). An attempt is made to determine the release mechanism and to evaluate the effect of some tablet excipients on the release properties from khaya gum matrix tablets.

Materials and Methods

Materials

Paracetamol and indometacin were supplied by Sigma Chemical Company (USA). Lactose and magnesium stearate were obtained from BDH Chemicals Ltd (UK). Hydroxypropylmethylcellulose (HPMC) was obtained as Methocel E4M Premium grade from Colorcon Ltd (UK). Microcrystalline cellulose was received as Avicel PH 102 from FMC International (Ireland). Dicalcium phosphate was supplied as Encompress by Mendell Co. Ltd (UK). Hydrochloric acid with a specific gravity of 1.16 was supplied by Fisher Scientific (Loughborough, UK). Potassium dihydrogen orthophosphate and disodium orthophosphate were general purpose reagents obtained from BDH Chemicals Ltd (UK). Khaya gum was obtained from *Khaya grandifoliola* (also known as *K. grandilolia*) at the Botanical garden, University of Ibadan, Nigeria. The description of the collection and purification of khaya gum has been given elsewhere (Odeku & Itiola 1998, 2003); the size fraction $< 170\,\mu$m was used.

Characterisation of khaya gum

The pH and viscosity of 1% w/v khaya gum was determined using a Microprocessor pH meter (pH 210, UK) and an Ostwald U-tube Viscometer made from borosilicate glass (Technico, UK), respectively. The Swelling Index (SI) of the polymer was determined by the European Pharmacopoeia method (Ph. Eur. Method 2.8.4) and calculated from the expression:

$$\mathrm{SI} = \frac{\text{volume of polymer at time t} - \text{initial volume}}{\text{Initial volume}} \times 100 \quad (1)$$

Preparation of matrix tablets

Khaya gum matrix tablets (500 mg) were prepared by direct compression of the polymer at various compression forces with 12.5 mm flat-faced punches using a hydraulic press (Beckman, model 16, UK). The die and punches were lubricated with a 1% dispersion of magnesium stearate in dichloromethane. The breaking load, friability and the disintegration times of the tablets were determined using the hardness tester (Type C50, Engineering Systems, UK), Roche Friabilator (Type TAR 100, Copley Scientific Ltd, UK) and disintegration tester (Type ZT 31 Copley Scientific Ltd, UK), respectively.

Matrix tablets (final weight 500 mg) were prepared as described above under a compression force of 4000 kg with the following modifications: effect of drug concentration — matrix tablets containing 5, 10, 20, and 40% w/w paracetamol; effect of excipients — matrix tablets containing Avicel, lactose and dicalcium phosphate, respectively, in the drug–khaya gum–excipient ratio of 1:3:1; effect of HPMC — khaya gum matrix tablets containing HPMC in the drug–khaya gum–HPMC ratios of 2:7:1, 2:6:2, 2:5:3, 2:4:4 and 2:0:8; effect of drug solubility — matrix tablets containing indometacin in the drug–polymer ratio of 1:9.

Dissolution testing

The dissolution test was carried out using the USP XXIII basket method (Erweka Dissolution Tester, Type DT 700; Copley Scientific Ltd, UK) rotated at 50 rev min^{-1} with 900 mL medium maintained at a constant temperature of $37 \pm 0.5^{\circ}$C. The media used were 0.1 M HCl, pH 1.2, for the first 2 h and then Sorensen's phosphate buffer, pH 7.4, for 3 h to simulate the gastrointestinal environment. Samples of 5 mL were withdrawn and replaced with fresh medium at fixed time intervals. The sample was diluted and the amount of paracetamol and indometacin released was determined using a UV spectrophotometer (Cecil CE 1020; Cecil Instrument Ltd, UK) at wavelengths 243 and 304 nm, respectively. The results are the means of three determinations.

Erosion studies

The method used for the erosion studies was similar to the method for determining the dissolution profile as described above. The tablets were placed in wire mesh baskets and then weighed accurately. During the dissolution process, a basket containing the remnant of the matrix tablet was removed every hour for 5 h and dried at 60°C for 24 h. After cooling at room temperature, the baskets were re-weighed and the percentage loss in weight calculated.

Data analysis

The dissolution data were fitted according to the Korsmeyer equation (Korsmeyer et al 1983), which is often used to describe drug release behaviour from polymeric systems:

$$M_t/M_\infty = Kt^n \quad (2)$$

where M_t/M_∞ is the fraction of drug released at time t, k is the kinetic constant (with unit t^{-n}) incorporating the properties of the polymeric system and the drug and n is the release exponent, which indicates the mechanism of release. This equation can be used to analyse the first 60% of a release curve where the release is linearly related to t^n, regardless of the geometric shape. Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical exponential gradient while the

Case-II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers, which swell in water or biological fluids. This term also includes polymer disentanglement and erosion (Sinclair & Peppas 1984; Cox et al 1999).

Statistical analysis

Results from the various gum and polymer combinations were analysed with the SPSS statistical package using an analysis of variance to assess any significant ($P < 0.05$) differences.

Results and Discussion

Gums are generally macromolecular acids and good buffers and hence the liquid penetrating the tablet on forming a gel will attain a fairly constant pH in the gel, regardless of its original pH (Bamba et al 1979). The polymer swelled rapidly over the first hour to about 250% of its initial volume with a maximum increase of approximately 320% achieved after 8 h. This shows that khaya gum is hydrophilic. It hydrates and swells in cold water, forming a viscous colloidal dispersion or gel. The pH of a 1% w/w solution at 21°C is 3.83 and the viscosity is 1.15 cP.

Khaya gum on its own was highly compressible and formed intact tablets at low compression forces (≈ 1000 kg) although the tablets were highly friable. Khaya gum compressed alone at compression force of 4000 kg produced tablets with a breaking load of 6.43 ± 0.12 kg, friability of 3.24% and disintegration time of 10.89 ± 0.15 min.

Effect of drug concentration

The release profiles of paracetamol from khaya gum matrix tablets are presented in Figure 1. Paracetamol was released in a controlled manner over 5 h when present in low concentrations of 5–20% w/w with no significant ($P > 0.05$) effect of drug concentration on release, but at 40% w/w the release was immediate, dissolving completely in 1 h. The increased dissolution rate in tablets containing 40% w/w of paracetamol may be due to the weakening of the matrix lattice due to the high concentration of the water-soluble drug, which provides a diffusion pathway for erosion/disintegration of the matrix.

The release parameters derived from the Korsmeyer equation (equation 2) are presented in Table 1. The high values of the coefficient of linear regression confirm that the data treatment may be used successfully for khaya gum matrices. The release mechanism for 5 and 10% drug concentration was anomalous (non-Fickian), but approaches Case II transport with n values of 0.641 and 0.668, respectively. Khaya gum matrix tablets containing 20% paracetamol showed time-independent release kinetics with $n = 1.042$. Khaya gum, when in contact with the dissolution medium, hydrates and forms a gel, which is gradually eroded. On the other hand, HPMC matrices containing 10% of paracetamol showed a Case I release mechanism

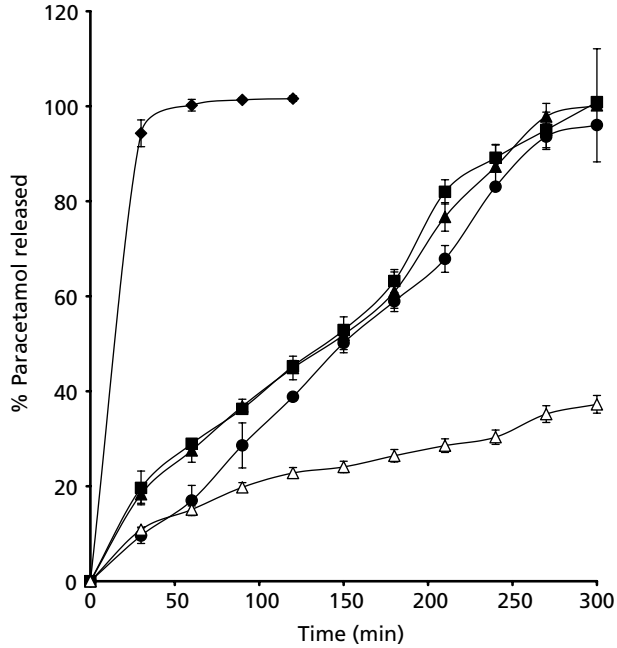

Figure 1 Release profile of paracetamol from khaya gum (closed symbols) and HPMC (open symbols) matrices (mean ± s.d., n = 3). ■, 5%; ▲, 10%; ●, 20% and ◆, 40% drug concentration.

Table 1 Release parameters derived using equation 2 for khaya gum matrices containing various concentration of paracetamol

Drug concn (% w/w)	Release exponent (n)	Kinetic constant (k) (min^{-n})×10^3	Correlation coefficient (r^2)
5	0.64 ± 0.08	21.4 ± 2.2	0.991
10	0.67 ± 0.08	18.4 ± 3.2	0.997
20	1.04 ± 0.05	2.6 ± 1.9	0.994
40	0.09 ± 0.06	700.2 ± 12	1
10[a]	0.51 ± 0.10	19.5 ± 2.3	0.992

[a]HPMC matrix.

with n = 0.506. The release rates from HPMC matrices were much lower than those from khaya gum matrices. Moreover there was an initial burst followed by a decrease in the release rate with increasing time, which is typical of Case I diffusion behaviour. Alderman (1984) described the prolonged release from HPMC as being due to the formation of a strong viscous gel when the polymer hydrates on contact with water. However, the major disadvantage of HPMC is that the drug release does not follow time-independent kinetics (Ford et al 1985; Rao & Devi 1988; Shah et al 1993; Talukdar et al 1996).

Effect of excipients

Although khaya gum matrix tablets containing up to 20% of the drug were able to release paracetamol in a controlled manner over 5 h, the tablets showed high friability

(14.99%) and low breaking loads (3.18 ± 0.21 kg) indicating its lack of ability to withstand the rigors of shipping and handling. The addition of directly compressible excipients has been used not only to alter the tablet size but also to improve the compaction and mechanical properties of the tablet (Cox et al 1999). Thus, Avicel (microcrystalline cellulose, water insoluble), lactose (freely water soluble) and dicalcium phosphate (Emcompress water insoluble) were used in the ratio of drug–khaya gum–excipient of 1:3:1. The excipients reduce the friability of the tablets to less than 1% and increase the breaking load to 6–8 kg. The release profiles of khaya gum matrix tablets containing the excipients are shown in Figure 2. The results show that the addition of the excipients not only improved the hardness and friability but also altered the release profile.

Matrix tablets containing lactose and Avicel release the drug rapidly with t_{50} values of 20.20 ± 1.20 and 18.55 ± 2.06 min, respectively. On the other hand, tablets containing dicalcium phosphate showed a significantly ($P < 0.05$) slower controlled release over 5 h with a t_{50} value of 150.02 ± 3.36 min. The release parameters, using the Korsmeyer equation (Korsmeyer et al 1983) to derive the release exponent (n) and kinetic constant (k), are presented in Table 2.

Khaya gum, when in contact with the dissolution medium, absorbs water, swells and becomes a hydrated gel. At the same time, lactose being freely water-soluble will dissolve and provide a pathway for diffusion of the drug and erosion of the matrix, leading to a fast release of the drug from the matrix tablet. Although Avicel and dicalcium phosphate are water-insoluble, Avicel has disintegrating properties that promote the disintegration of the matrix and therefore the matrix will be easier to erode compared with dicalcium phosphate (Khan & Zhu 1999). In addition, tablets of dicalcium phosphate do not disintegrate readily (Fischer 1992; Cox et al 1999). Therefore matrices containing dicalcium phosphate would have less tendency to erode compared with Avicel, consequently showing a slower release profile. These results are in agreement with those of Cox et al (1999) for xanthan gum mini-matrices. Lapidus & Lordi (1968) indicated that the presence of larger levels of insoluble diluents (e.g. tricalcium phosphate) reduced release rates by increasing the tortuosity of the matrix, whereas the addition of a soluble diluent (e.g. lactose) merely reduced the tortuosity of the matrix thereby increasing the rates.

Table 2 Release parameters derived using equation 2 for khaya gum matrices containing various tablet excipients

Composition (drug–khaya gum–excipient)	Release exponent (n)	Kinetic constant (k) (min^{-n})	Correlation coefficient (r^2)
1:3:1 Avicel	0.24 ± 0.05	347.1 ± 26.1	0.996
1:3:1 Lactose	0.39 ± 0.07	190.0 ± 15.6	0.909
1:3:1 Dicalcium phosphate	0.77 ± 0.09	11.4 ± 0.7	0.988

The release parameters presented in Table 2 show that the release mechanism from matrix tablets containing dicalcium phosphate approaches time-independent release kinetics ($n = 0.771$) and the amount released after 5 h was $93.93 \pm 2.88\%$. Thus, in addition to improving the mechanical properties of the tablet, dicalcium phosphate did not alter or destroy the ability of khaya gum to release the drug in a controlled time-independent manner.

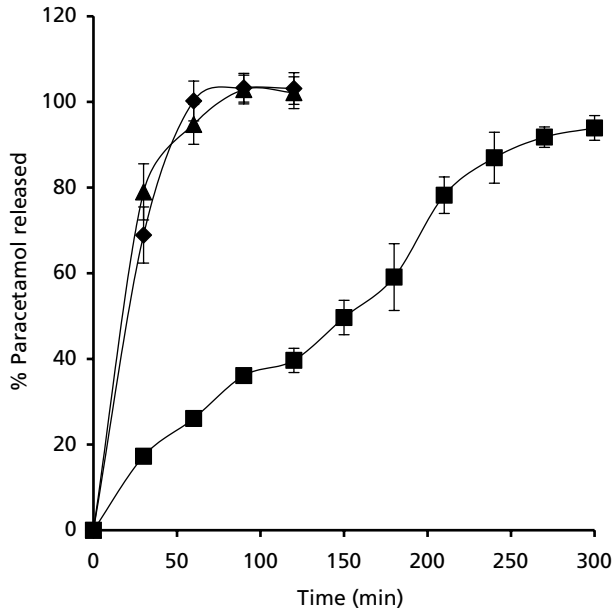

Figure 2 Release profile of paracetamol from khaya gum matrices containing the excipients in the ratio drug–khaya gum–excipient of 1:3:1 (mean ± s.d., n = 3). ◆, Lactose; ▲, Avicel; ■, dicalcium phosphate.

Effect of HPMC

One of the methods of achieving controlled time-independent release is by using a mixture of polymers to achieve sustained release over the desired length of time. If the two polymers are carefully chosen and used in the right proportions, it should be possible to obtain a polymer system that exhibits a time-independent release. Thus HPMC, which forms strong viscous gels, was used to replace part of the khaya gum in the matrix with the aim of achieving a longer dissolution time (i.e. more than 5 h). The release profiles of the tablets are shown in Figure 3, and the parameters derived using equation 2 and the amount of drug released after 5 h are presented in Table 3. The release rate of paracetamol from the matrix tablets decreased significantly ($P < 0.05$) with an increase in concentration of HPMC. As the amount of HPMC increases, there is an increase in the resistance of the gel layer to erosion and the high viscosity of the gel serves to retard the diffusion of the drug at the early stage of release. The results of the erosion studies (Figure 4) show that khaya gum matrices showed the greatest degree of erosion while HPMC matrices showed the lowest after 5 h. Tablet

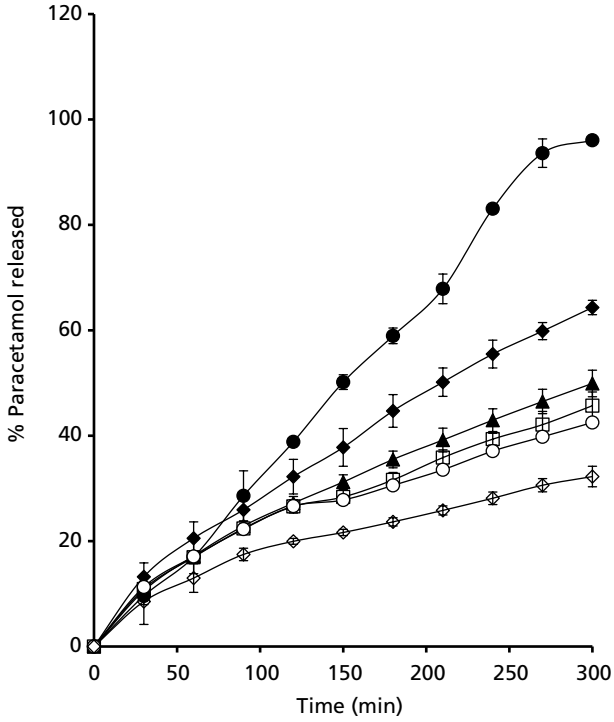

Figure 3 Release profile of paracetamol from khaya gum matrices containing drug–khaya gum–HPMC (mean ± s.d., n = 3). ●, 2:8:0; ♦, 2:7:1; ▲, 2:6:2; □, 2:5:3; ○, 2:4:4; ◇, 2:0:8.

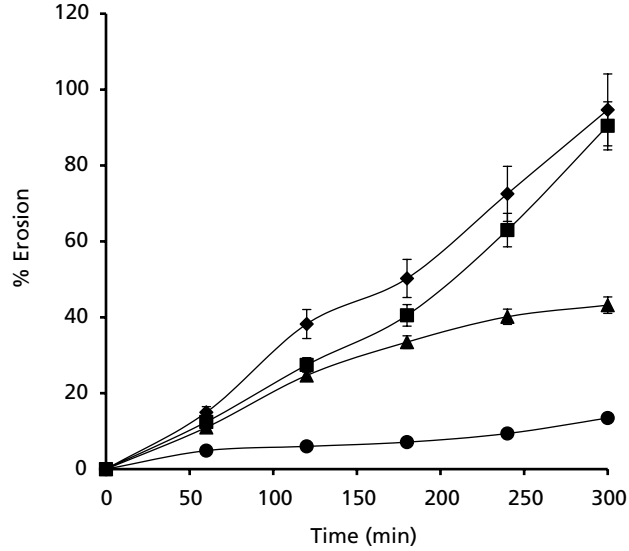

Figure 4 The percentage erosion against time (min) from khaya gum matrices (mean ± s.d., n = 3). ♦, drug–khaya gum 1:4; ■, drug–khaya gum–dicalcium phosphate 1:3:1; ▲, drug–khaya gum–HPMC 1:3:1; ●, drug–HPMC 1:4.

erosion increases the drug dissolution rate (Sujja-areevath et al 1998) and this is true for khaya gum matrices. The rate of erosion is slower for tablets containing dicalcium phosphate probably because the insolubility of the excipient increases its resistance to erosion. Khaya gum–HPMC matrices showed a lower degree of erosion after 5 h (40%) indicating that the addition of HPMC into khaya gum matrices increased the resistance of the tablet to erosion.

The n values for HPMC matrices (Table 3) show that the release mechanism from the matrix approaches the Case I or Fickian diffusion mechanism while formulations made with a combination of the two polymers approach time-independent release. The exponent n decreased with an increase in the content of HPMC. Thus manipulating the proportion of khaya gum and HPMC can be used to obtain the desired release rate.

Effect of drug solubility

A considerable lag time in excess of 2 h was observed with indometacin due to the insolubility of indometacin in acidic pH. The release observed after 2 h is due to the increased solubility of indometacin in basic pH, which will lead to erosion/diffusion of the drug from the matrix (Alderman 1984). Khaya gum matrices showed significantly ($P < 0.05$) higher release rates than HPMC matrices. The release mechanism was time independent with $n = 1.023 \pm 0.320$ for khaya gum matrices and Fickian diffusion with $n = 0.507 \pm 0.02$ for HPMC matrices.

Conclusions

Khaya gum matrices showed time-independent release kinetics of paracetamol up to 5 h. The release rates and mechanism was dependent on the concentration of the drug present in the matrix tablet. Khaya gum showed good compaction properties when compressed directly but the

Table 3 Release parameters derived using equation 2 for khaya gum matrices containing HPMC

Composition drug–(khaya gum–HPMC)	Release exponent (n)	Kinetic constant (k) $(min^{-n}) \times 10^{-3}$	Correlation coefficient (r^2)	% Drug released after 5 h
2:8:0	1.04 ± 0.05	2.64 ± 0.2	0.994	98.96 ± 4.40
2:7:1	0.70 ± 0.03	11.7 ± 1.2	0.997	64.32 ± 1.36
2:6:2	0.67 ± 0.15	11.9 ± 0.9	0.999	49.91 ± 2.51
2:5:3	0.61 ± 0.10	14.0 ± 1.1	0.997	45.69 ± 2.61
2:4:4	0.56 ± 0.09	17.2 ± 1.2	0.995	42.50 ± 0.42
2:0:8	0.56 ± 0.06	13.0 ± 0.7	0.995	32.25 ± 1.95

tablets had high friability values. The addition of lactose, Avicel and dicalcium phosphate improved the mechanical properties of the tablets but also altered the release rates and kinetics except for formulation containing dicalcium phosphate, which remained unchanged. The addition of HPMC to khaya gum matrices further extended the release of paracetamol (>5 h), providing a release mechanism which approaches time-independent release. The rate of release decreased with an increase in HPMC content, with formulations containing HPMC alone showing a Case I or Fickian transport and the lowest release rates. The release of indometacin from the khaya gum matrices showed a lag time in excess of 2 h before time-independent kinetics was obeyed. Thus khaya gum could be useful in the formulation of matrix tablets for sustained release of drugs for up to 5 h and the appropriate combination of khaya gum and HPMC could be used to provide a time-independent release for longer periods.

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