Original Paper

Grewia polysaccharide as a pharmaceutical excipient in matrix tablets.

Elijah I. Nep[1*], Barbara R. Conway[2]

[1*]Department of Pharmaceutics and Pharm. Technology, University of Jos, Nigeria
[2]Pharmacy, School of Applied Sciences, University of Huddersfield, Huddersfield, HD1 3DH

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ABSTRACT

Matrix-based tablets using different concentrations of grewia gum, and the model drug ibuprofen, were prepared using a wet granulation technique. Similar formulations were also prepared using HPMC, guar gum or ethyl cellulose as the polymer matrix. In addition to tablet properties, swelling and erosion of tablets and kinetics of drug release were also investigated. *In vitro* drug release studies, in phosphate buffer (pH 7.2) using USP type II apparatus, revealed that grewia gum at concentrations of 16%, 32% and 48% can sustain the release of ibuprofen tablets for up to 24 hours. Release profiles were similar to those tablets containing ethyl cellulose as the matrix former. Swelling and erosion of grewia gum matrices occurred simultaneously, and ibuprofen release was by anomalous diffusion in accordance with the Korsmeyer-Peppas model. There was evidence suggesting synergism between grewia gum and guar gum in sustaining the release of ibuprofen from tablets when used in the ratio 2:1. Grewia gum may therefore prove a useful excipient, when used on its own, or in combination with other polymers, to modify drug release.

KEY WORDS: Ibuprofen, swelling, erosion, drug release, release profile, controlled delivery

INTRODUCTION

The aim of controlled delivery of drugs is to deliver the active ingredient at a controlled rate over the desired period of time. The primary objectives are, therefore, to ensure safety and to improve efficacy of drugs, as well as to improve patient compliance. A number of approaches have been used to obtain controlled drug release, but hydrophilic matrices are recognized as the simplest and are the most widely used.

Drug release from hydrophilic matrix tablets initially results from swelling upon ingestion which causes a gel layer to form on the tablet surface. This gel layer retards further ingress of fluid and subsequent drug release. Sujjaareevath *et al.*, (1) have shown that in the case of hydrophilic matrices, swelling and erosion of the polymer occurs simultaneously, and both of them contribute to the overall drug release rate. It is well documented that drug release from hydrophilic matrices show a typical time-dependent profile (i.e. decreased drug release with time because of increased diffusional path length) (2, 3). Many controlled-release products (including hydrophyllic and hydrophobic matrices) are designed on the principle of embedding the drug in a porous matrix. Liquid penetrates the matrix and dissolves the drug, which then diffuses into the exterior liquid (4). The hydrophilic matrices form a gel through which the drug must diffuse, while

* Corresponding author: Department of Pharmaceutics and Pharm. Technology, University of Jos, Nigeria Tel.: +(234) 8166116714, E-mail: nepeli2000@yahoo.com

hydrophobic matrices like ethyl cellulose, show little or no swelling. The release of drug from the matrices is controlled by a network of tortuous capillaries or channels which develop as the drug is dissolved and released.

Polysaccharide gums are often used for oral controlled delivery of medicines. Their ability to hydrate and swell in aqueous media renders them a viable platform as hydrophilic matrices for time-dependent release of soluble or insoluble drugs. Hydrophilic matrices from natural polysaccharide gums such as xanthan gum (5-8), guar gum (9-11) and karaya gum (12) have been shown to provide varying degrees of control over the release of medicines. These natural hydrophilic colloids are widely used in pharmaceutical dosage forms because of their biocompatibility, low cost and relatively abundant availability (13).

Grewia polysaccharide gum is obtained by extraction from the inner stem bark of the plant *Grewia mollis* (Fam. Tiliaceae). The plant grows abundantly, wild or cultivated, in the middle belt region of Nigeria and forms part of the delicacies of the inhabitants of the region (14). Aqueous dispersions of the pulverised inner stem bark of grewia gum hydrates and swell to form a highly viscous dispersion. This property of the plant has kindled a lot of interest into the potential application of the gum as a matrix for oral controlled delivery of medicines. The gum has been isolated and some physicochemical (15-17), binding (18), rheological (19) and mechanical properties of aqueous based grewia gum films (20, 21) have been evaluated.

In this study matrix tablets of ibuprofen were formulated by wet granulation using 16%, 32% or 48% w/w of grewia gum. The tablet properties and drug release from the tablets were compared with corresponding tablets made with hydrophilic matrix formers HPMC or guar gum (reference polymers). The grewia matrix tablets were also compared with similar formulations using the more hydrophobic ethyl cellulose. To evaluate synergism between grewia gum and the reference polymers, binary composite matrices of grewia gum and the reference polymers were also prepared and studied at total polymer concentration of 16% w/w and polymer ratios of 1:1 (8% grewia gum + 8% reference polymer), 1:2 (5.33% grewia gum + 10.67% reference polymer) and 2:1 (10.67% grewia gum + 5.33%w reference polymer).

MATERIALS AND METHODS

Materials

Ibuprofen BP was donated by GSK Consumer Health. Ethyl cellulose (Ethocel® - standard 100FP Premium, solution viscosity - 90-110 cP, Molecular weight 880,000) was a gift from Colorcon, UK. HPMC (Metolose® - 90SH-100SR, viscosity 100 mPa.s, substitution type-2208, Molecular weight 230,000) was a gift from R.W. Unwin, UK and colloidal silicon dioxide (Aerosil 200®) was a gift from Evonik, UK. Lactose monohydrate USP (Pharmatose®, grade DCL14) was a gift from DMV-International, UK. Guar gum (Molecular weight 250,000), and magnesium stearate (grade Puriss.) were purchased from Sigma, UK. Grewia gum (Pullulan equivalent average molecular weight- 5925 KDa) was extracted in our laboratory as detailed previously (17).

Extraction of grewia gum

Grewia polysaccharide gum was extracted as detailed previously (17). Briefly, the dried and pulverized inner stem bark of the plant was dispersed in 0.1% w/v sodium metabisulphite and hydrated for 48 hours. It was then passed through a muslin bag. The filtrate was treated with 0.1N NaOH and centrifuged (Miww centrifuge, UK) at 3,000 rpm for 10 minutes. The supernatant was then treated with acidified ethanol containing 0.1N HCl and centrifuged again as described previously. Absolute ethanol was used to precipitate the supernatant and the resultant precipitate repeatedly washed with absolute ethanol until clear absolute ethanol was recovered. The precipitate was wet-milled

using a BL440 blender (Kenwood, UK) and then passed through a muslin bag to remove excess ethanol before air-drying the product. The air-dried product was dry-milled before further drying at 50°C in a size 2 fan-assisted drying oven (Gallenkamp, UK) for 48 hours.

Preparation and analysis of tablets

Single polymer matrix granules of polymer, lactose and ibuprofen were prepared using wet granulation. All powders were passed through a 250 μm sieve before wet granulation. Briefly, appropriate amount of polymer to provide 16%, 32% or 48% (w/w of ibuprofen) were mixed with lactose monohydrate USP and ibuprofen (Table 1) and the powder mass was wetted with just enough distilled water to give a damp and coherent, but loose, powder mass. Mixing was carried out using a KMC560 mixer (Kenwood, UK) at speed setting 3 rev/min. Granulations using ethyl cellulose, HPMC or guar gum were also prepared for comparison. The moist mass was passed through a 710 μm sieve to form granules which were dried at 50°C overnight in an oven (Gallenkamp, UK). Thereupon, particle-size analysis of the dried granules was determined as outlined in next section. Granule sizes of <250 μm were discarded. The granule sizes between 355-710 μm were then blended with magnesium stearate and colloidal silicon dioxide, before comp-ression on a single station press, Minipress MII (RIVA, Germany) operated at a speed of 50 tablets per min.

Flat-faced tablets of 832 mg weight, 13 mm diameter and hardness of 70.3 ± 8.9 N were made. The compressed tablets were stored in air-tight containers prior to evaluation of tablet properties.

Table 1 Per tablet formula for Monolithic matrix tablets of ibuprofen

Ingredients	I	II	III
Ibuprofen (mg)	500	500	500
Polymer (mg)	80	160	240
Lactose monohydrate (mg)	220	140	60
Magnesium stearate (mg)	8	8	8
Colloidal silicon dioxide (mg)	24	24	24

Similarly, binary composite matrix tablets of ibuprofen containing 16% w/w total polymer concentration of grewia gum and guar, grewia gum and ethyl cellulose or grewia gum and HPMC in the ratio 1:1, 1:2 or 2:1 were made by wet granulation. The amounts of ibuprofen, lactose and polymers, as shown in Table 2, were mixed and moistened with distilled water, and the granules were prepared by wet granulation as outlined above.

Characterization of granules

Moisture content of the granules was determined using a Sartorius moisture balance (Sartorius, Germany). Angle of repose was determined

Table 2 Per tablet formula for binary composite matrix tablets of ibuprofen

	I	II	III	IV	V	VI	VII	VIII	IX
Ibuprofen (mg)	500	500	500	500	500	500	500	500	500
Grewia (mg)	40	40	40	26.7	26.7	26.7	53.3	53.3	53.3
Ethyl cellulose (mg)	40	-	-	53.3	-	-	26.7	-	-
HPMC (mg)	-	40	-	-	53.3	-	-	26.7	-
Guar (mg)	-	-	40	-	-	53.3	-	-	26.7
Lactose (mg)	220	220	220	220	220	220	220	220	220
Colloidal silicon dioxide (mg)	24	24	24	24	24	24	24	24	24
Magnesium stearate (mg)	8	8	8	8	8	8	8	8	8

by weighing accurately the granules into a funnel. The height of the funnel was adjusted so that it just touched the apex of the heap of granules. The granules were allowed to flow through the funnel freely onto a flat surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$$Tan\ \theta = h/r \qquad \text{Eq. 1}$$

Where, h and r are the height and radius of the powder cone.

Bulk and tapped density were determined using a USP tap density tester (Sotax TD2, Switzerland). The compressibility index of the granules was determined according to Carr's compressibility index percentage.

Granule size analysis was carried out by accurately weighing and transferring 30 g of granules into the arrangement of sieve sizes 710, 500, 355 and 250 μm respectively. The sieves were arranged such that the largest size (710 μm) is on top and the smallest (250 μm) sitting on top of the collector. The sieve analyzer (Fritsch Analysette 3 SPARTAN, Germany) was set to 12 minutes with amplitude of 1.0 mm. At the end of the run time the granules on top of each sieve was collected and weighed. Granules <250 μm were discarded.

Characterization of tablets

Crushing strength, friability, uniformity of weight and content of the tablets were evaluated. Tablet crushing strength was tested with a model 6D tablet tester (Schleuniger Pharmatron, Manchester, NH). Friability was tested using friability testing apparatus (Roche type). The uniformity of weight test (20 tablets) was carried out on an analytical balance. Uniformity of content test (10 tablets) was carried out on all batches of matrix tablets in phosphate buffer (pH 7.2) and UV absorbance read at 265 nm on a Mattson Galaxy 3020 UV spectrophotometer (Unicam, UK). The calibration curve gave a regression coefficient of 0.9984 and the standard error of the slope was 0.0198.

In vitro drug release studies

The release of drug from the matrix tablets of ibuprofen was studied in 900 ml of 0.1M phosphate buffer (pH 7.2) using USP II (paddle method) at 100 rpm and 37 ± 1°C equipped with a 40 mesh sinker (DT 600, Erweka, Germany). A 4 ml sample was taken at time intervals of 15 minutes, 30 minutes and thereafter every 1 hour for 12 hours for both single polymer and binary systems. Further samples from the single polymer systems were taken after 24, 25 and 26 hours. The samples were filtered through syringe filters (pore size = 0.45 μm) before assaying for drug content using the UV-spectrophotometer at 265 nm. After each sample was removed, it was replaced with an equal volume (4 ml) of fresh buffer solution at the same temperature. All experiments were run in triplicate.

Water uptake and erosion studies

Water uptake and erosion studies were also carried out using the DT 600 dissolution apparatus. The matrix tablets, in a sinker, were placed in 900 ml of phosphate buffer (pH 7.2) equilibrated at 37 ± 1°C and the paddle was rotated at 100 rpm. The tablets were allowed to hydrate, swell and erode for a range of durations. Two tablets were used per time point. At predetermined intervals (0, 30 minutes, 1, 2, 4 or 8 hours), the tablets were removed from the dissolution vessel and lightly patted with tissue paper to remove excess water. The wet weight of the tablets was determined and they were then dried at 50°C until a constant weight was obtained. This remaining dry weight was recorded. Water uptake and erosion were determined gravimetrically according to the following equations:

$$\text{Water uptake}(\%) = \frac{\text{wet weight} - \text{remaining dry weight}}{\text{remaining dry weight}} = \text{x } 100 \qquad \text{Eq. 2}$$

$$\text{Erosion (\%)} = \frac{\text{original weight} - \text{remaining dry weight}}{\text{original weight}} = \text{x } 100 \quad \text{Eq. 3}$$

Kinetic analysis of dissolution data

The mechanism of drug release from the tablet matrices was studied by fitting the release data into the zero-order, first-order and Higuchi kinetic equations (22):

Zero order: $Q_t = Q_0 + K_0^t$ Eq. 4
First order: $\ln Q_t = \ln Q_0 + K_1^t$ Eq. 5
Higuchi: $Q_t = K_H^{t^{1/2}}$ Eq. 6

These models fail to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore, the dissolution data was also fitted to the well-known exponential equation (Korsmeyer equation), which is often used to describe drug release behaviour from polymeric systems (23):

$$Log\ (M_t/M_\beta) = Log\ k + n\ Log\ t \quad \text{Eq. 7}$$

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 tablet, and n is the diffusion exponent indicative of the mechanism of drug release.

To determine the release exponent, the log value of percentage drug dissolved was plotted against log time for each batch according to the equation. A value of $n = 0.45$ indicates Fickian (case I) release; $0.45 < n < 0.89$ indicates non-Fickian (anomalous) release; and >0.89 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain, and anomalous transport (non-Fickian) refers to a combination of both diffusion and erosion controlled drug release (24).

The similarity factor f_2 as proposed by Moore and Flanner (33) was used to compare dissolution between the test polymer and the reference polymers.

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{n-1}^{n}\left(\left[R_t - T_t\right]^2\right)\right]^{-0.5} \times 100\right\} \quad \text{Eq. 8}$$

Where, n = number of observations made, R_t = average percentage drug dissolved from reference formulation at time t and T_t = average percentage drug dissolved from test formulation at time t.

Statistical Analysis

The data were analysed using one-way ANOVA (Instat software, GraphPad, San Diego, CA).

RESULTS AND DISCUSSION

Granule properties

The granules of single polymer matrix tablets and binary composite matrix tablets were prepared according to the formulae in Tables 1 and 2 respectively. Angle of repose was between 27° and 33° for all the batches of granules indicating 'good' to 'passable' flow behaviour while the values for Carr's compressibility indicate poor flow (25, 26). Consequently, the flow of all batches of granules was improved by the use of colloidal silicon dioxide.

The particle size and size analysis of single polymer and binary composite granules are presented in Figures 1a and 1b respectively. The particle-size distribution of the granules show that single polymer granules of grewia (16%, 32%), guar (16%, 32%, 48%), and HPMC (48%) predominantly consist of smaller particle sizes (fines) of <250μm. Inter-particulate attraction tends to be higher in fine particles and are therefore more cohesive and less free flowing. Granules made of binary composites all predominantly consisted of particles of <250 μm, except granules consisting of grewia/ethyl cellulose (1:2 and 1:1). To improve flow, granules <250 μm were discarded.

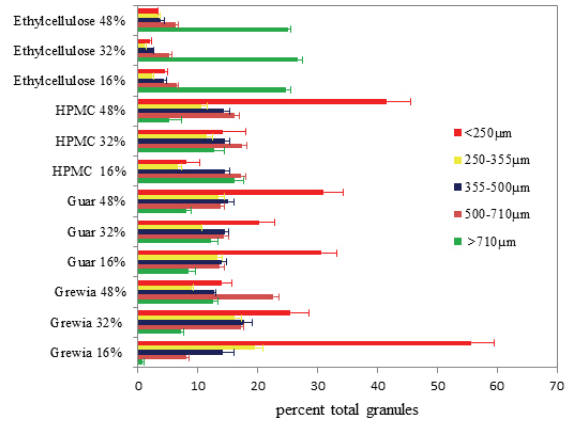

Figure 1 (a) Particle-size distribution of granules for monolithic tablets of ibuprofen (n=3, mean±s.d.)

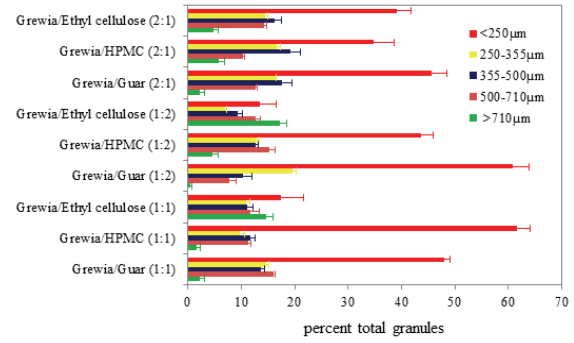

Figure 1 (b) Particle-size distribution of granules for binary composite matrices of ibuprofen (n=3, mean ± s.d.)

Tablet properties

All formulations passed the uniformity of weight test with no single tablet deviating from the mean (n = 20) weight by >5%. There was a high degree of chipping of guar gum in both singular and binary composite matrices accounting for high friability values with the exception of grewia/guar (2:1) matrices. Capping was seen in grewia/ethyl cellulose (1:1) matrices. Drug content was between 94.0%-96.5% for all the formulations. All other formulations demonstrated satisfactory tablet properties including friability (<1.0 %) and a crushing strength of 70.3 ± 8.9 N and 72.8 ± 10.1 N for the single polymer matrices and binary composite matrices respectively.

In vitro release of ibuprofen from tablets

Effect of polymer type and concentration on drug release from single polymer matrices

Drug release profiles for ibuprofen from single polymer matrix tablets containing 16 %, 32 % or 48 %w/w of grewia, guar, HPMC or ethyl cellulose are shown in Figures 2 a-c.

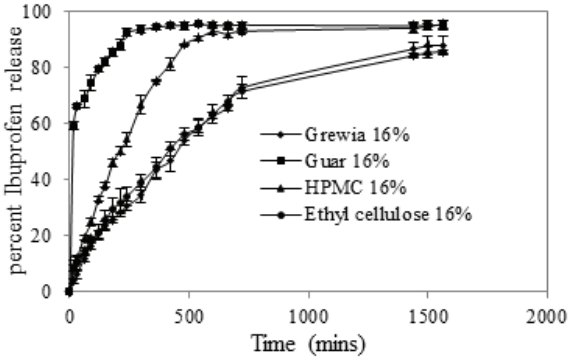

Figure 2 (a) Release profiles of ibuprofen from the matrices containing 16% w/w of grewia, guar, HPMC or ethyl cellulose in phosphate buffer solution at 37± 1°C (n=3, mean ± s.d.)

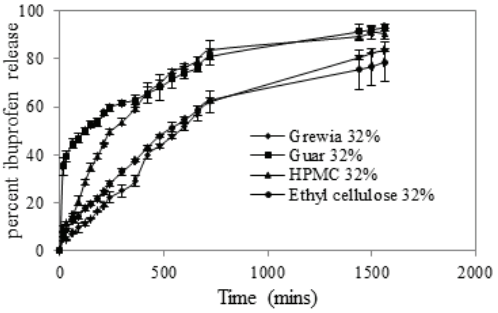

Figure 2 (b) Release profiles of ibuprofen from the matrices containing 32% w/w of grewia, guar, HPMC, or ethyl cellulose in phosphate buffer solution at 37± 1°C (n=3, mean ± s.d.)

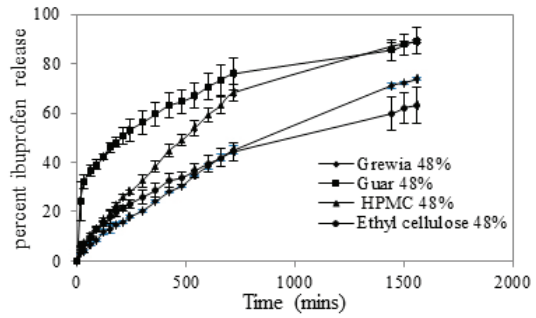

Figure 2 (c) Release profiles of ibuprofen from the matrices containing 48% w/w of grewia, guar, HPMC, or ethyl cellulose in phosphate buffer solution at 37± 1°C (n=3, ± s.d.)

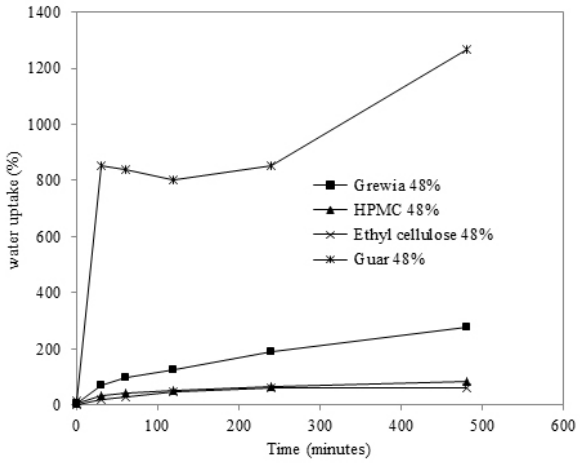

Figure. 3 (**a**) Water uptake with time of single polymer matrices (48%), (n=2).

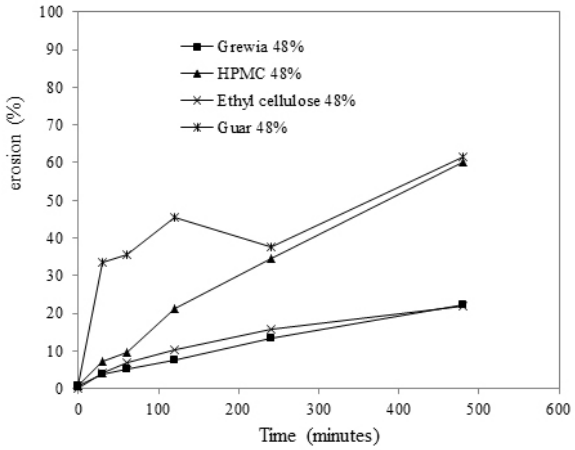

Figure 3 (**b**) erosion with time of single polymer matrices (48%), (n=2).

There was no initial burst release from the grewia, HPMC and ethyl cellulose matrices (defined as more than 30% drug release in the first hour indicating the likelihood of dose dumping (27)). However, differences between these polymers in the initial release could be seen. Figure 2a shows that more than 48% of drug was released within the first hour for matrix tablets prepared using 16% w/w guar gum. At 32% and 48% w/w (Figures 2 b and c), tablets prepared using guar gum also resulted in a burst effect which can be attributed to surface erosion or initial disaggregation of the matrix tablet prior to gel layer formation around the tablet core (28). This is also confirmed by the water uptake and erosion with time profiles for these polymer matrices (shown in Figures 3a and 3b respectively). The absence of burst effect with ethyl cellulose matrices is attributable to the hydrophobic nature of ethyl cellulose which causes reduction in the penetration of the solvent molecules into the matrix (27).

The difference in the mechanism of drug release between hydrophilic and hydrophobic matrices is attributable to the observed differences in drug release profiles of the polymer matrices. The hydrophobic ethyl cellulose matrices do not swell or form gels. The water repellent nature of polymer reduces water ingress into the polymer matrix and drug release from the matrices is primarily controlled by network of tortuous capillaries or channels which develop as the drug is dissolved and released (27). Consequently, ethyl cellulose matrices were more effective than the hydrophilic matrices of grewia gum, guar gum and HPMC in delaying the release of drug. The hydrophilic matrices swell and form a gel across which the drug must diffuse. The ability to delay release is controlled by the lengths of the diffusion path across the matrix core at any given time. The ability of grewia gum to delay the release of the drug was second only to ethyl cellulose. Although grewia gum is hydrophilic in nature it is only slightly soluble in water (17) compared to guar gum which is soluble in water. This low solubility of grewia gum implies that drug release from the matrix core of grewia matrices may occur in a similar manner as ethyl cellulose matrices, the rate and extent of diffusion across the matrix being reduced by the insoluble matrix core.

Table 3 shows the time for 50% drug released (t_{50}) from the single polymer matrices. The results show very rapid release of ibuprofen from guar gum matrices closely followed by HPMC matrices. At 16%, 32% and 48% w/w polymer concentration, there was no significant difference ($P>0.05$) in the t_{50} between grewia polysaccharide gum and ethyl cellulose, both matrices providing a more sustained release of ibuprofen than HPMC ($P<0.001$) at 48% w/w

Table 3 Time for 50% ibuprofen release (t_{50}) and

% ibuprofen release from single polymer matrices after 24 hours in phosphate buffer (pH 7.2), (n=3, mean ± s.d.)

Formulation	t_{50} (min)	% release (24h)
Grewia 16%	440.0 ± 21.2	86.6 ± 2.5
Grewia 32%	574.6 ± 22.1	80.6 ± 0.8
Grewia 48%	806.6 ± 90.1	71.1 ± 1.1
Guar 16%	13.3 ± 2.9	94.7 ± 1.0
Guar 32%	130.0 ± 17.3	91.3 ± 3.2
Guar 48%	220.0 ± 34.6	85.5 ± 4.2
HPMC 16%	213.3 ± 15.3	94.0 ± 1.8
HPMC 32%	320.0 ± 138.6	89.4 ± 3.9
HPMC 48%	496.7 ± 28.9	68.3 ± 2.0
Ethyl cellulose 16%	413.3 ± 30.6	84.2 ± 1.0
Ethyl cellulose 32%	520.0 ± 26.5	75.6 ± 8.3
Ethyl cellulose 48%	920.0 ± 346.3	59.8 ± 7.0

polymer concentration or guar gum at all polymer concentrations ($P<0.001$). The results also show that the ability to delay the release of ibuprofen from the polymeric matrix tablets increases with an increase in the concentration of the polymer from 16% to 48% w/w.

Drug release from binary matrices

Release profiles for ibuprofen from polymer binary composites are presented in Figures 4 a-c. There was no burst effect with any batches of matrix tablets containing grewia and HPMC or ethyl cellulose (1:1, 1:2 and 2:1) and this is probably due to the low surface erosion of grewia gum. However, at a 1: 2 ratio of grewia to guar gums, this low surface erosion was offset by the high surface erosion of guar with >48 % drug release in the first 15 minutes (Figure 4a).

The delay in release of ibuprofen was highest for composite matrix tablets of grewia/guar (2:1), closely followed by grewia/HPMC (2:1) (Table 4).

There is a significant improvement in the ability of grewia gum or guar gum (2:1) to delay the

Table 4 Time for 50% ibuprofen release (t_{50}) and % ibuprofen release from binary matrices after 12 hours in phosphate buffer (pH 7.2), (n=3, mean ± s.d.)

Formulation	t50 (min)	% release (12 h)
Grewia/Guar (1:2)	13.3±1.5	97.3±2.8
Grewia/Guar (1:1)	306.0±15.1	74.3±0.8
Grewia/Guar (2:1)	557.7±18.0	60.6±1.8
Grewia/HPMC (1:2)	185.7±23.1	88.5±0.9
Grewia/HPMC (1:1)	235.3±35.6	80.6±5.1
Grewia/HPMC (2:1)	405.0±8.7	68.6±1.4
Grewia/Ethyl cellulose (1:2)	273.3±25.2	82.5±3.3
Grewia/Ethyl cellulose (1:1)	206.7±35.1	98.0±2.7
Grewia/Ethyl cellulose (2:1)	316.0±14.2	79.6±1.7

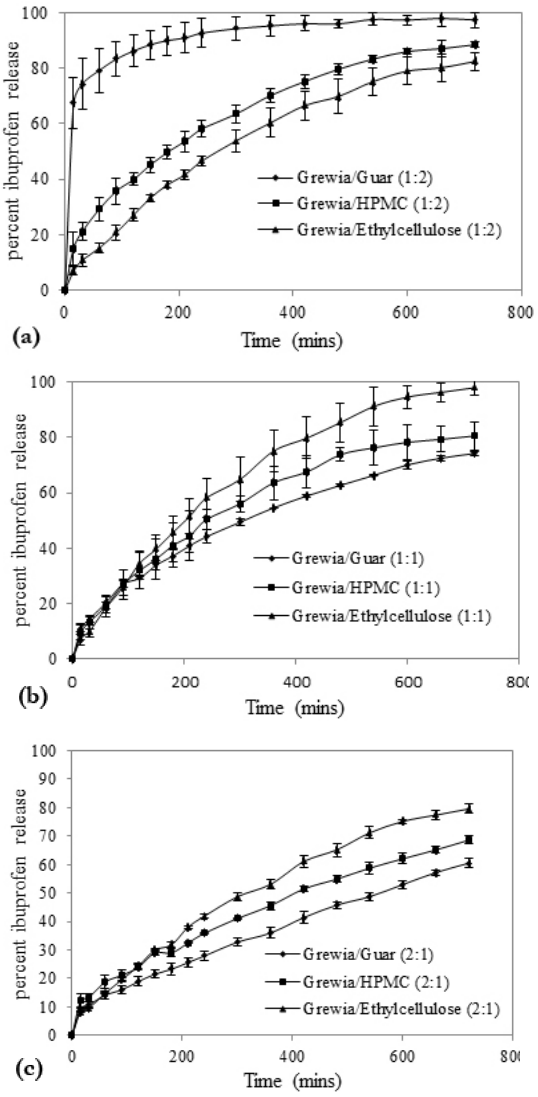

Figure 4 Release profiles of ibuprofen from the composite matrices containing 16% w/w of grewia and guar, HPMC, or ethyl cellulose in the ratio **(a)** 12, **(b)** 11 and **(c)**. 21, in phosphate buffer solution at 37± 1°C (n=3, mean ± s.d.)

release of ibuprofen when used as composite matrices, rather than as a single polymer matrix. The t_{50} of either grewia or guar gum single polymer matrices (16% w/w total polymer concentration) were 440.0 ± 21.2 and 13.3 ± 2.9 minutes respectively, but when combined in the ratio 2:1 (10.67% grewia gum + 5.33% guar gum), the t_{50} was extended to 557.7 ± 18.0 minutes. This represents a significant improvement ($P<0.001$) in the ability of the binary composite to delay ibuprofen release. The increase in the ability of the matrices to delay release of drug may be attributed to the higher proportion of grewia gum in the grewia/guar (2:1) binary composite matrices. The synergy between grewia and guar gum may be attributed to interaction between the two gums. The binary composite of grewia and HPMC (2:1) does not present a significant improvement in sustained release of ibuprofen when compared to grewia 16% single polymer matrices ($P>0.05$). This was however significant when compared with guar 16% single polymer matrix tablets ($P<0.001$). All other binary composites of the polymer matrix tablets of ibuprofen gave t_{50} values which were less than the corresponding single polymer (16%) matrix tablets.

The results also show that increasing the concentration of grewia gum in the binary composite formulations enhances the ability of the matrices to delay the release of the drug (Figures 4 a-c). At all concentrations the ability to delay release of drug from the binary matrices was in the order: grewia/ethyl cellulose > grewia/HPMC > grewia/guar.

Swelling and erosion

Both swelling and erosion occur simultaneously in the tablet matrices but to varying extents (Figures 4 a-b shows the results for 48% w/w matrices as an example). Consequently a constant release rate of drug can be expected from the single polymer matrices (29) as the increase in diffusion path length, which occurs due to swelling, is compensated for by the simultaneous erosion of the matrix (30). The very low water uptake by ethyl cellulose matrices may be attributed to the hydrophobic nature of the ethyl cellulose matrices.

The water uptake and erosion plots selected for binary composite matrices (1:2 and 2:1) are shown in Figures 5a-d. The results show that erosion and water uptake occur simultaneously for all batches. The complete erosion of grewia/guar (1:2) tablet matrices occurred within 2 hours probably due to low mechanical strength of the tablets resulting in the inability of this polymer combination to sustain the release of ibuprofen from the matrix tablets. The predominant effect of grewia gum is shown by the reduction in the erosion of grewia/guar (2:1) matrices (Figure 5d) as against grewia/guar (1:2) matrices (Figure 5b). This result supports the dissolution results and show that grewia gum reduces the rate and extent of erosion of guar gum matrices with a consequent enhancement of the ability of binary matrices (grewia/guar (2:1)) to delay the release of drug from the matrices.

Release mechanism and kinetics

The kinetic data for all the single polymer matrices and binary composite matrices are shown in Table 5. Drug release data from grewia single polymer matrices (16%, 32% and 48% w/w) all showed highest correlation with the Korsmeyer-Peppas kinetic models. The 16% w/w grewia single polymer matrix tablets show linearity with Higuchi and Korsmeyer-Peppas kinetic models ($P>0.05$). In addition, grewia 48% w/w single polymer matrix tablets show good correlation with Korsmeyer-Peppas kinetic model. The value of *n* for all the grewia single polymer matrices ranged between 0.7 to 0.8 and since there is no significant difference ($P>0.05$) between the correlation coefficient of the zero order kinetics and Korsmeyer-Peppas model, it can be concluded that drug release was by anomalous transport and always approximately zero order for a significant part of the total release time (31). The release exponent for all HPMC matrix tablets indicate

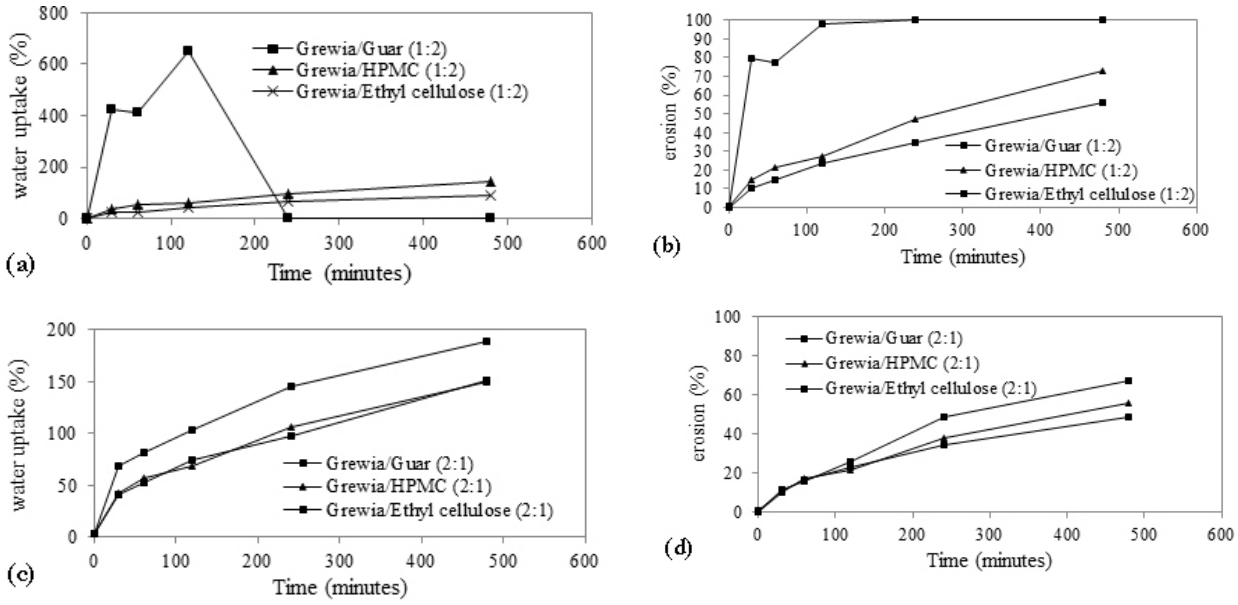

Figure 5 (a) Water uptake with time and **(b)** erosion with time of binary composite matrices (ratio 12), **(c)** water uptake with time and **(d)** erosion with time of binary composite matrices (ratio 21), (n=2).

Table 5 The release kinetics of single polymer matrix tablets of ibuprofen (n=3, mean ± s.d.)

Formulation	Diffusion exponent (n)	Korsmeyer-Peppas (r^2)	Zero order (r^2)	First-order(r^2)	Higuchi (r^2)	Similarity factor (f_2)
Grewia 16%	0.8 ± 0.08	0.99 ± 0.00	0.98 ± 0.00	0.782 ± 0.03	0.98 ± 0.01	-
Grewia 32%	0.7 ± 0.04	0.95 ± 0.02	0.99 ± 0.01	0.886 ± 0.05	0.94 ± 0.01	-
Grewia 48%	0.7 ± 0.03	0.99 ± 0.00	0.99 ± 0.00	0.85 ± 0.01	0.97 ± 0.00	-
Guar 16%	N/A	N/A	0.68 ± 0.03	0.64 ± 0.04	0.84 ± 0.02	16.2 ± 0.4
Guar 32%	0.2 ± 0.04	0.96 ± 0.02	0.93 ± 0.05	0.87 ± 0.08	0.98 ± 0.02	26.1 ± 0.6
Guar 48%	0.3 ± 0.07	0.97 ± 0.02	0.93 ± 0.02	0.82 ± 0.07	0.98 ± 0.01	25.9 ± 1.5
HPMC 16%	0.7 ± 0.06	0.99 ± 0.01	0.92 ± 0.01	0.76 ± 0.02	0.98 ± 0.00	32.8 ± 0.3
HPMC 32%	0.7 ± 0.04	0.98 ± 0.00	0.94 ± 0.02	0.77 ± 0.03	0.99 ± 0.00	34.2 ± 0.9
HPMC 48%	0.8 ± 0.03	0.99 ± 0.00	0.99 ± 0.00	0.82 ± 0.03	0.98 ± 0.00	42.9 ± 2.5
Ethyl cellulose 16%	0.6 ± 0.05	0.98 ± 0.01	0.99 ± 0.01	0.85 ± 0.02	0.99 ± 0.01	70.4 ± 4.1
Ethyl cellulose 32%	0.6 ± 0.03	0.98 ± 0.00	0.99 ± 0.00	0.88 ± 0.00	0.98 ± 0.00	61.9 ± 4.6
Ethyl cellulose 48%	0.6 ± 0.03	0.99 ± 0.00	0.98 ± 0.00	0.84 ± 0.00	0.99 ± 0.00	61.3 ± 5.9
Grewia/Guar (1:1)	0.5 ± 0.04	0.99 ± 0.00	0.95 ± 0.01	0.79 ± 0.02	0.99 ± 0.00	51.4 ± 2.3
Grewia/Guar (1:2)	N/A	N/A	0.69 ± 0.09	0.75 ± 0.04	0.78 ± 0.10	14.5 ± 1.9
Grewia/Guar (2:1)	0.5 ± 0.02	0.96 ± 0.01	0.99 ± 0.00	0.92 ± 0.01	0.98 ± 0.01	61.1 ± 2.1
Grewia/ HPMC (1:1)	0.6 ± 0.05	0.98 ± 0.01	0.92 ± 0.02	0.75 ± 0.04	0.98 ± 0.01	42.7 ± 6.0
Grewia/ HPMC (1:2)	0.5 ± 0.07	0.98 ± 0.01	0.92 ± 0.02	0.76 ± 0.05	0.99 ± 0.01	33.9 ± 1.1
Grewia/ HPMC (2:1)	0.5 ± 0.04	0.98 ± 0.02	0.98 ± 0.00	0.88 ± 0.02	0.99 ± 0.01	65.5 ± 1.7
Grewia/Ethyl cellulose (1:1)	0.7 ± 0.06	0.98 ± 0.00	0.94 ± 0.03	0.73 ± 0.06	0.99 ± 0.01	32.7 ± 4.2
Grewia/Ethyl cellulose (1:2)	0.7 ± 0.04	0.99 ± 0.01	0.95 ± 0.00	0.76 ± 0.04	0.99 ± 0.01	45.8 ± 4.1
Grewia/Ethyl cellulose (2:1)	0.7 ± 0.01	0.99 ± 0.00	0.97 ± 0.00	0.82 ± 0.002	0.99 ± 0.00	52.6 ± 1.9

that drug transport was by a non-Fickian mechanism. There was correlation with more than one release model. HPMC, like other hydrophilic polymers, forms matrices in which the overall release rates of drug from the matrices are controlled by swelling and erosion which occur simultaneously (1, 32). Drug release from ethyl cellulose single polymer matrix tablets also showed linearity with more than one kinetic model. The release exponent

indicated that drug transport was by anomalous or non-Fickian mechanisms.

Drug release from all the binary composite matrices showed linearity with a number of kinetic models (Table 5). The kinetic exponents were all indicative of non-Fickian or anomalous transport although the release exponent *n* could not be calculated for the 16% w/w guar single polymer matrices and grewia/guar (1:2) binary matrices because there were insufficient data points on the release profiles between 10% and 60% release to provide accurate values.

The similarity factor f_2 (33) which was derived from a pair-wise model independent procedure was used to assess the similarity between the dissolution profiles. The test profiles were grewia 16%, 32% and 48% for the single polymer matrices while grewia 16% was the test profile for the binary composite matrices. An f_2 of 100 suggests that the test and reference profiles are identical. As the value decreases, the dissimilarity between the release profiles increases.

Ethyl cellulose formulations were most similar to the grewia-based formulations for drug release (Table 5). The guar gum single polymer matrices were the least similar formulations to grewia single polymer matrices at all concentrations. The hydrophilic matrices control drug release by swelling and diffusion across the gel layer. Ethyl cellulose has water repelling properties and, unlike hydrophilic polymers like HPMC, guar or grewia, its hydrophobic nature repels water from penetrating the tablet matrix and as a result retards drug release from the tablet matrix (34). The similarity between the dissolution profiles of grewia matrices and ethyl cellulose matrices may be attributable to the fact that grewia gum only hydrates and swells in aqueous media but dissolution of the gel does not occur owing to low solubility of the gum in water (17).

The binary composite matrices with the highest f_2 were grewia/guar (2:1), grewia/HPMC (2:1) and grewia/ethyl cellulose (2:1), indicating the highest similarity to grewia alone (16% w/w). At higher levels of grewia gum within the matrix, its properties may be seen to dominate and impact the drug release.

CONCLUSION

The results from this study indicate that grewia polysaccharide gum can provide sustained release of ibuprofen from matrix tablets for up to 24 hours. Physicochemical properties such as high molecular weight, low solubility, high viscosity and long swelling time (17) makes grewia polysaccharide gum a suitable insoluble polymer matrix for the release of active drugs. The release profiles bear greatest similarity to ethyl cellulose. The drug release was by anomalous diffusion and approximates zero order for the most part of the release. The present study also indicates synergism between grewia gum and guar gum (total polymer concentration of 16% w/w) when combined in matrix formulations of ibuprofen in the ratio of 2:1 (10.67% grewia gum +5.33% guar gum). Its relative abundant availability and low cost makes it an economically viable alternative source of excipient for both the food and pharmaceutical industry. When the sustained-release of an API is indicated, grewia may therefore not only have economical advantages over HPMC and guar gum, but may also extend the duration of release.

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