Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

Formulation and *In-vitro* Evaluation of Sustained Release Diclofenac Sodium Matrix Tablets using Blends of Cashew Gum, Xanthan Gum and Hydroxypropylmethylcellulose as Hydrophilic Drug Release Modifiers

K. OFORI-KWAKYE*, E. OBESE, M. E. BOAKYE-GYASI

Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, College of Health Sciences, Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana

ARTICLE DETAILS

Article history:
Received on 18 October 2013
Modified on 25 November 2013
Accepted on 04 December 2013

Keywords:
Natural gums,
Hydrophilic polymers,
Swelling capacity,
In vitro dissolution,
Sustained release

ABSTRACT

Sustained release diclofenac sodium matrix tablets (~100 mg) were prepared by wet granulation using blends of cashew gum, xanthan gum and HPMC as drug release modifiers. The flow properties of diclofenac sodium granules and the physical properties of the compressed matrix tablets namely, weight variation, tablet thickness, crushing strength, friability, drug content and swelling index were evaluated. *In vitro* dissolution studies were performed in phosphate buffer (pH 7.5) using Voltaren Retard® tablet as a reference drug. Kinetic models and difference (f_1) and similarity (f_2) factors were employed to evaluate the drug release data. The granules exhibited good flow properties while the physical properties of tablets generally fell within acceptable limits. Tablet formulations containing 60-100 % xanthan gum exhibited high water absorption capacities in phosphate buffer pH 7.5. Formulations F10, F12, F13 and F15 passed the dissolution test for modified release oral tablets while the rest failed the test. Formulations F7 to F15 appeared similar to the reference drug ($p < 0.05$; $f_1 \leq 10$; $f_2 \geq 60$) and could be used interchangeably. Drug release data fitted well to the Higuchi square root model and the Korsmeyer-Peppas equation, indicating anomalous or non-Fickian drug release. Blends of cashew gum, xanthan gum and HPMC when employed in the appropriate ratios could optimize the sustained release activity of diclofenac sodium matrix tablets.

INTRODUCTION

Matrix tablets as monolithic systems have been designed by various researchers as sustained release drug delivery systems for oral administration [1-7]. Other techniques which can be used in the design of oral sustained release products include the coating of beads, granules and tablets with polymer materials; complex formation; microencapsulation; and extrusion/spheronization. Matrix drug delivery systems may be produced using both hydrophilic (e. g. HPMC, xanthan gum, sodium alginate) and hydrophobic polymers (e. g. ethylcellulose, polyvinyl chloride) and may be divided into lipid matrix systems, inert or insoluble matrix systems and hydrophilic matrix systems or swellable-soluble systems.

*Author for Correspondence:
Email: koforikwakye@yahoo.com

Hydrophilic matrix tablets may be produced by direct compression of the mixture of drug and hydrophilic carriers [8], or from a wet granulation containing the drug and hydrophilic polymer materials.

Cashew gum, xanthan gum and HPMC are hydrophilic polymers which are used in matrix tablet formulations as drug release modifiers for controlled drug delivery [9-12]. Cashew gum is obtained as exudates from the stem bark of the tree *Anacardium occidentale* L. (family: *Anacardiaceae*). It is naturally-occurring, generally non-toxic, biocompatible and readily available in many tropical and sub-tropical countries. Cashew gum is a complex polysaccharide of high molecular mass which upon hydrolysis yields galactose and galacturonic acid. Cashew gum has been utilized as agglutinant for capsules and pills in the pharmaceutical industry and in the food industry as a stabilizer of juices. The binder and drug

release modifying activity of cashew gum has also been demonstrated in tablet formulations [13-14]. Xanthan gum is a high molecular weight anionic natural polysaccharide produced by the fermentation of a carbohydrate source with the bacterium *Xanthomonas campestris*. It is widely used in the food, cosmetic and pharmaceutical industry because of its stability, compatibility and remarkable viscosity properties. HPMC is a semi-synthetic, inert and viscoelastic polysaccharide which is employed extensively in the food industry as an emulsifier, thickener and suspending agent. It is used as a binder and as a component of tablet coatings [15], as well as a drug release modifier in the pharmaceutical industry. The technique of blending different polymers has been employed in tablet formulations to enhance and optimize the physicochemical properties of the resultant polymer such as viscosity, elasticity, hardness, toughness, and drug release-modifying action [16-20]. This study reports the formulation and *in vitro* evaluation of diclofenac sodium matrix tablets using different ratios of cashew gum, xanthan gum and HPMC as hydrophilic drug release modifiers.

MATERIALS AND METHODS

Materials

Crude cashew gum was obtained from the Wenchi cashew plantation (Wenchi, Ghana). Diclofenac sodium powder (HPG Ltd., China), hydroxypropyl methylcellulose (HPMC) (UK Chemicals, Ghana), and microcrystalline cellulose (Amponsah-Effah Pharm. Ltd., Ghana) were used as received. Xanthan gum, talc and magnesium stearate were obtained from the Chemical Store of the Department of Pharmaceutics.

Purification of Cashew Gum

Crude cashew gum was purified and screened as previously reported [14]. The purified cashew gum obtained was used for further evaluation.

Moisture Content and Insoluble Matter of Cashew Gum

The moisture content and insoluble matter of crude and purified cashew gum were determined according to British Pharmacopoeia methods [21].

Viscosity of Gum Dispersions

Aqueous dispersions of xanthan gum (0.5, 0.75, 1 % w/v) and cashew gum (1, 2, 5 and 10 % w/v) were prepared using distilled water. The viscosity of the samples was determined at 25 °C and shear rate of 1 rpm with a Brookfield viscometer (spindle #2) (Brookfield Engineering, USA).

Swelling Capacity of Gums

The swelling capacity of cashew gum and xanthan gum was individually determined in distilled water and phosphate buffer pH 7.5 using a previously reported procedure [22].

Particle size analysis of gums

The particle size and size distribution of cashew gum and xanthan gum powder were determined using the Retsch Mechanical Shaker (Retch Technology GmbH, Haan, Germany). A nest of sieves was arranged from sieve # 8 to sieve # 200 on the mechanical shaker and 120 g of the gum was weighed and placed on the topmost sieve and covered with the lid. The powder was agitated for a period of 15 min at amplitude of vibration of 60° after which the amount of powder retained on each sieve was weighed and recorded. The size range and size distribution of the powder was then determined.

Preparation of granules

Fifteen different formulations of granules comprising of diclofenac sodium (23.8 % w/w), polymer (61.9 % w/w), microcrystalline cellulose (11.3 % w/w) magnesium stearate (1.0 % w/w) and talc (2.0 % w/w) were prepared by the wet granulation technique. The ratio of the release modifying hydrophilic polymers in each formulation is shown in Table 1. Formulation F1, F2 and F3 contained cashew gum, xanthan gum and HPMC, respectively, while formulations F4-F6, F7-F9, F10-F12 and F13-F15 contained cashew gum/HPMC, xanthan gum/HPMC, cashew gum/xanthan gum and cashew gum/xanthan gum/HPMC, respectively. A blend of all the ingredients, except magnesium stearate and talc, was massed in a porcelain mortar using water as granulating fluid. The damp mass was screened through 2.38 mm sieve and dried at 60 °C for 1 h in a hot air oven. The dried granules were thereafter screened through 1.19 mm sieve. The granules were used in further determinations and compression into tablets.

Evaluation of flow Properties of Gums and Granules

Bulk Density

The bulk or fluff density (ρb) was determined by slowly pouring 10 g of the gum or granule into a 100 ml graduated glass cylinder. The bulk density was obtained by dividing the mass of gum or granule by the volume. The mean of three determinations was recorded.

Table 1: Ratios of hydrophilic polymers employed as drug release modifiers in the formulation of diclofenac sodium matrix tablets

Formulation	Composition	Cashew gum (C)	Xanthan gum (X)	HPMC (H)
F1	C_{10}	100	-	-
F2	X_{10}	-	100	-
F3	H_{10}	-	-	100
F4	$C_2 H_8$	20	-	80
F5	$C_4 H_6$	40	-	60
F6	$C_8 H_2$	80	-	20
F7	X_8H_2	-	80	20
F8	X_6H_4	-	60	40
F9	X_2H_8	-	20	80
F10	$C_2 X_8$	20	80	-
F11	$C_4 X_6$	40	60	-
F12	$C_8 X_2$	80	20	-
F13	$C_6X_2H_2$	60	20	20
F14	$C_2X_2H_6$	20	20	60
F15	$C_2X_6H_2$	20	60	20

Tapped Density

The tapped density (ρt) was determined by tapping a graduated glass cylinder containing 10 g of gum or granules from a height of 2 cm, 100 times. The tapped density was obtained by dividing the weight of gum or granule by the minimum volume of gum or granule attained after tapping. The mean of three determinations was recorded.

Hausner Ratio

The Hausner ratio was calculated as the ratio of the tapped density (ρt) to the bulk density (ρb)

i. e. (ρt/ρb).

Carr's Index

The Carr's index [23] (C) or compressibility (%) was calculated as follows:

$C = (\rho t - \rho b) / \rho t \times 100$,

where ρt is tapped density and ρb is bulk density.

Angle of Repose

The angle of repose (θ) was determined using the fixed height method. The gum or granules was allowed to flow freely from a funnel at a fixed height onto a horizontal surface to form a cone. The base of the cone was marked and the height of the orifice of the funnel from the horizontal surface was measured as well as the height of the cone. The angle of repose was calculated from the height of the cone (h) and the radius (r) of its base using the relation, $\theta = \tan^{-1} (h/r)$.

Compression of Matrix Tablets

Fifteen diclofenac sodium matrix tablet formulations, each tablet containing ~100 mg diclofenac sodium with a nominal weight of 420 mg were compressed from the granules produced; using a Single punch tableting machine (DP30 Tablet Press, Pharmao Industries Co. Ltd., China) fitted with concave punch and dies set. Magnesium stearate and talc were employed as lubricant and glidant respectively. The tablets were stored in plastic containers until use.

Physical Properties of Matrix Tablets

The mean tablet weight was determined by weighing twenty (20) randomly sampled tablets individually (Precision balance, Mettler Toledo, USA) and the mean determined. The crushing strength which is the force needed to diametrically fracture a tablet was determined using a Monsanto tablet hardness tester (Type Mht-20, Missouri, USA). The test was repeated twice and the mean recorded. The friability of the tablets was determined with an Erweka Friabilator (TA 20 GmbH, Heusenstamm, Germany). Twenty randomly selected tablets were de-dusted and weighed on a precision balance. The tablets were placed into the transparent drums of the friabilator and set to rotate at 100 revolutions. The tablets were de-dusted after the test, weighed and the difference in weight expressed as a percentage of the initial

weight. Tablet thickness (*n = 10*) was determined with an electronic vernier caliper.

Swelling Profile of Tablets

The swelling capacity of the matrix tablets was determined in phosphate buffer pH 7.5 over 18 h and the percent water absorption calculated as:

$$\% \text{ water absorption} = \frac{(Mt - Mo)}{Mo} \times 100$$

where, Mt = weight of tablet at time t and Mo = weight of tablet at time t = 0.

Assay of Matrix Tablets

Twenty matrix tablets were weighed and powdered. A quantity of powder containing 0.1 g diclofenac sodium was weighed and 70 ml 0.1M NaOH added and shaken for 15 min using a flask shaker. Sufficient quantity of 0.1M NaOH was added to produce 100 ml and filtered using 0.45 µm HA membrane filter. Two milliliters of the filtrate was diluted to 100 ml with 0.1M NaOH and absorbance of the resulting solution measured by UV spectrophotometer (PG Instruments, UK) at 276 nm using 0.1M NaOH as reference. Using the regression data ($y = 336x - 0.071$, R^2 = 0.9969) obtained from a calibration plot of diclofenac sodium (0.75-2.5 mg/ml) in 0.1 M NaOH, the amount of diclofenac sodium in the tablet formulations was determined.

In Vitro **Dissolution Studies**

In vitro dissolution tests were carried out on the matrix tablets using an Erweka dissolution machine (Type DT6, Erweka GmbH, Heusenstamm, Germany) with Voltaren Retard® tablet as a reference sample. The test conditions employed were 900 ml phosphate buffer pH 7.5 dissolution medium, test temperature of 37 ± 0.5 °C, and paddle speed of 50 rpm. At 5, 15, 30 min, 1, 2, 4, 6, 8, 10, 12, 15, 18, 21 and 24 h, 10 ml samples were withdrawn and replaced with an equal amount of fresh dissolution medium pre-warmed at 37 ± 0.5 °C . The withdrawn samples were filtered using 0.45 µm HA membrane filters, diluted appropriately with dissolution medium and analysed by UV spectrophotometer (PG Instruments, UK) at 276 nm using phosphate buffer pH 7.5 as reference. Using the regression data ($y = 334x - 0.069$, R^2 = 0.9986) obtained from a calibration plot of diclofenac sodium (0.75-2.5 mg/ml) in phosphate buffer pH 7.5, the amount of diclofenac sodium in the tablets was determined.

Determination of Difference and Similarity Factors

The drug release data generated from the dissolution studies were fitted into equations to determine the difference (f_1) and similarity (f_2) factors of the tablet formulations compared to the reference drug.

$$f_1 = \{[\Sigma\, t_{=1}^{n} |Rt-Tt|] / [\Sigma\, t_{=1}^{n} Rt]\} \times 100$$

$$f_2 = 50 + \log \{[1+ (1/n) \sum_{t=1} * n (Rt-Tt)^2]^{-0.5} * 100\}$$

where n = time points, Rt = cumulative percentage dissolved at time t for the reference and Tt = cumulative percentage dissolved at time t for the test. Difference and similarity factors are model-independent methods used for dissolution profile comparison when three or more dissolution time points are available [24]. A test batch is considered similar to a reference batch if f_2 of two profiles is between 50 and 100. Also, a difference factor between 0 and 15 indicates a minor difference between two products [25].

Kinetics of Drug Release and Release Mechanism

The drug release data obtained from the dissolution studies was fitted into Zero order, First order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas equations to determine the kinetics of drug release as well as the mechanism of drug release from the matrix tablets in the dissolution medium.

Statistical Analysis

The tablet dissolution and swelling data were subjected to analysis of variance followed by Bonferroni test using GraphPad Prism 5 (GraphPad Software, Inc, USA). Differences between tablet formulations were considered significant when $p < 0.05$.

RESULTS AND DISCUSSION

Table 2 presents the results of some physicochemical properties of cashew and xanthan gum evaluated. The percentage yield of cashew gum after purification was 72.3 % w/w, implying that about 27.7 % w/w of the crude gum consisted of impurities and other extraneous materials. The percentage yield of cashew gum obtained after purification was similar to that obtained in previous studies [14, 26], but higher than that reported in another study [13], using either the same or different purification method. The moisture (%) and insoluble matter (%) content of cashew gum obtained in the study

was within acceptable limits (moisture content <15 %; insoluble matter <0.5 %). Crude cashew gum had higher moisture and insoluble matter content than the purified gum. The purification process therefore removes some moisture and insoluble material from crude gum. The moisture content can have marked effect on the storage conditions, microbiological stability, viscosity and flow properties of the gum [27].

Table 2: Physicochemical properties of purified cashew gum and xanthan gum

Property	Cashew gum	Xanthan gum
Yield (%)	72.3	-
Moisture content (%)	13.84 ± 0.12*	-
	11.14 ± 0.24	-
Insoluble matter (%)	0.45 ± 0.12*	-
	0.26 ± 0.03	-
Viscosity (cPs)		
1 % w/v	5.2	312.3
5 % w/v	25.6	-
Swelling capacity (%)		
Distilled water	3.33	4.38
Phosphate buffer pH 7.5	3.91	5.25
Particle size distribution (%)		
425 – 850 µm	7.7	0
250 – 425 µm	62.1	1.6
180 – 250 µm	26.9	3.7
75 – 180 µm	2.4	79.3
75 µm	0.9	15.4
Flow properties		
Bulk density (g/ml)	0.59	0.50
Tapped density (g/ml)	0.63	0.56
Hausner's ratio	1.07	1.12
Carr's Index (%)	6.35	10.71
Angle of repose (°)	24.7	14.6

* = Crude cashew gum; - = Not determined

A five-fold increase in cashew gum mucilage concentration (1-5 %) produced a proportionate increase in viscosity (5.2-25.6 cPs). However, the viscosity of 1 % w/v cashew gum (5.2 cPs) was sixty times lower than that of xanthan gum (312.3 cPs) of the same concentration. The swelling capacity of cashew gum was lower than that of xanthan gum in distilled water and phosphate buffer pH 7.5. For both cashew and xanthan gum, however, the swelling capacity was higher in phosphate buffer pH 7.5 than in distilled water. This observation confirms the finding that the presence of ions in a medium can enhance the swelling of xanthan gum [28]. Most of the cashew gum powder particles fell within a higher particle size range than xanthan gum powder. The particle size range obtained for both gums were, however, comparable to literature values [29, 30]. Both cashew and xanthan gum powders showed good flow properties characterized by optimal Hausner ratio (1.07 & 1.12), Carr's index (6.35 % &10.71 %) and angle of repose (14.6° & 24.7°).

Table 3 shows the flow properties of diclofenac sodium granules produced. All the 15 formulations of diclofenac sodium granules prepared exhibited good flowability with optimal Hausner ratio (1.04-1.12), Carr's index (4.0-10.7 %) and angle of repose (25.9-35.3°). A Hausner ratio of less than 1.25 is indicative of good flowability of the material, whereas a value of 1.25 or higher suggests a poor flow property [31]. According to Carr [23], a Carr's index of 5-15, 12-16, 18-21, and 23-28 connotes excellent, good, fair, and poor flow properties of the material, respectively. Powders and granules with angle of repose values of 20-35° demonstrate good flowability [31]. The granules produced therefore possessed the requisite flow properties required for compression into tablets.

Table 4 shows the physical properties of the matrix tablets prepared. The average weight of the tablets ranged from 408 ± 9 to 441 ± 12 mg with an average thickness of 5.70 ± 0.40-7.10 ± 0.37 mm. All the tablet formulations passed the crushing strength test (≥ 4 kg), except F3. All the formulations passed the friability test (weight loss ≤ 1 %) except F4 and F10. Friability assesses the ability of the tablet to withstand stress and abrasion associated with handling, packaging and transportation and chipping. The crushing strength-friability ratio (CSFR) is used as an assessment of the mechanical strength of tablets [32-34]. The crushing strength (CS) is indicative of the strength of the tablet, while friability (F) provides a measure of tablet weakness. In general, a high CSFR indicates a strong tablet [35]. The CSFR of the formulations ranged from 3.2 to 42.8. The highest and lowest CSFR values were achieved in F2 and F10, respectively. Sustained-release diclofenac sodium tablets are required to contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of diclofenac sodium [36]. The diclofenac sodium content in the 15 formulations fell in the range 98.7-101.5 % indicating that the tablets produced were of the required potency.

Table 3: Flow properties of diclofenac sodium granules prepared using cashew gum, xanthan gum and HPMC as drug release modifiers

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Hausner's ratio	Carr's Index (%)	Angle of repose (°)
F1	0.56	0.59	1.05	5.1	30.8
F2	0.45	0.48	1.07	6.3	32.4
F3	0.45	0.5	1.11	10.0	28.6
F4	0.50	0.53	1.06	5.7	31.5
F5	0.50	0.56	1.12	10.7	27.1
F6	0.48	0.5	1.04	4.0	35.3
F7	0.45	0.5	1.11	10.0	26.4
F8	0.50	0.56	1.12	10.7	29.6
F9	0.48	0.53	1.10	10.4	31.7
F10	0.53	0.59	1.11	10.2	30.2
F11	0.48	0.53	1.10	9.4	34.9
F12	0.53	0.59	1.11	10.2	25.9
F13	0.53	0.56	1.06	5.3	33.4
F14	0.45	0.5	1.11	10.0	30.7
F15	0.53	0.56	1.06	5.3	32.2

Table 4: Physical properties of diclofenac sodium matrix tablets

Formulation	Tablet weight (mg)	Tablet thickness (mm)	Crushing strength, CS (Kg)	Friability, F (%)	CSFR	Drug content (%)
F1	441 ± 12	5.70 ± 0.40	4.4 ± 1.1	1.00	4.4	101.5 ± 0.4
F2	433 ± 7	5.75 ± 0.40	6.8 ± 1.6	0.16	42.8	98.7 ± 0.5
F3	417 ± 11	6.50 ± 0.39	3.8 ± 0.8	0.64	6.0	99.4 ± 0.2
F4	428 ± 9	6.30 ± 0.51	4.0 ± 0.8	1.10	3.6	99.7 ± 0.5
F5	428 ± 11	6.30 ± 0.40	4.0 ± 0.8	0.79	5.1	99.5 ± 0.2
F6	425 ± 11	6.75 ± 0.40	4.1 ± 1.2	0.47	8.7	100.6 ± 0.6
F7	419 ± 12	6.85 ± 0.39	4.1 ± 0.7	0.16	25.9	99.9 ± 0.2
F8	424 ± 11	7.10 ± 0.37	4.3 ± 0.6	0.80	5.4	99.3 ± 0.2
F9	428 ± 12	6.95 ± 0.42	5.2 ± 1.2	0.63	8.3	98.9 ± 0.2
F10	417 ± 10	6.90 ± 0.44	4.1 ± 0.8	1.29	3.2	99.5 ± 0.2
F11	416 ± 12	6.20 ± 0.40	5.3 ± 1.9	0.81	6.6	99.4 ± 0.2
F12	418 ± 9	6.55 ± 0.42	4.0 ± 0.6	0.16	24.8	99.2 ± 0.2
F13	431 ± 10	5.85 ± 0.39	4.1 ± 0.7	0.16	25.0	99.7 ± 0.5
F14	408 ± 9	6.15 ± 0.45	6.6 ± 1.9	0.65	10.1	99.4 ± 0.1
F15	417 ± 11	6.30 ± 0.46	5.7 ± 1.7	0.66	8.6	100.5 ± 0.5

Figure 1 shows the water absorption profiles of the matrix tablets in phosphate buffer pH 7.5. Most of the tablets hydrated and swelled considerably within the first 2 h after which erosion began leading to a progressive reduction in swelling capacity. However, formulations F2, F7, F10 and F11 showed good swelling behaviour which increased continuously up to 18 h, with minimal observable tablet erosion. Formulation F2 (100 % xanthan gum) showed the greatest water absorption capacity at 18 h (285.7 % w/w) with the lowest exhibited by F3

(100 % HPMC) at 1 h (7.1 % w/w) ($p < 0.05$). Most of the formulations which exhibited good water absorption capacity contained a high amount of xanthan gum (60-100 %).

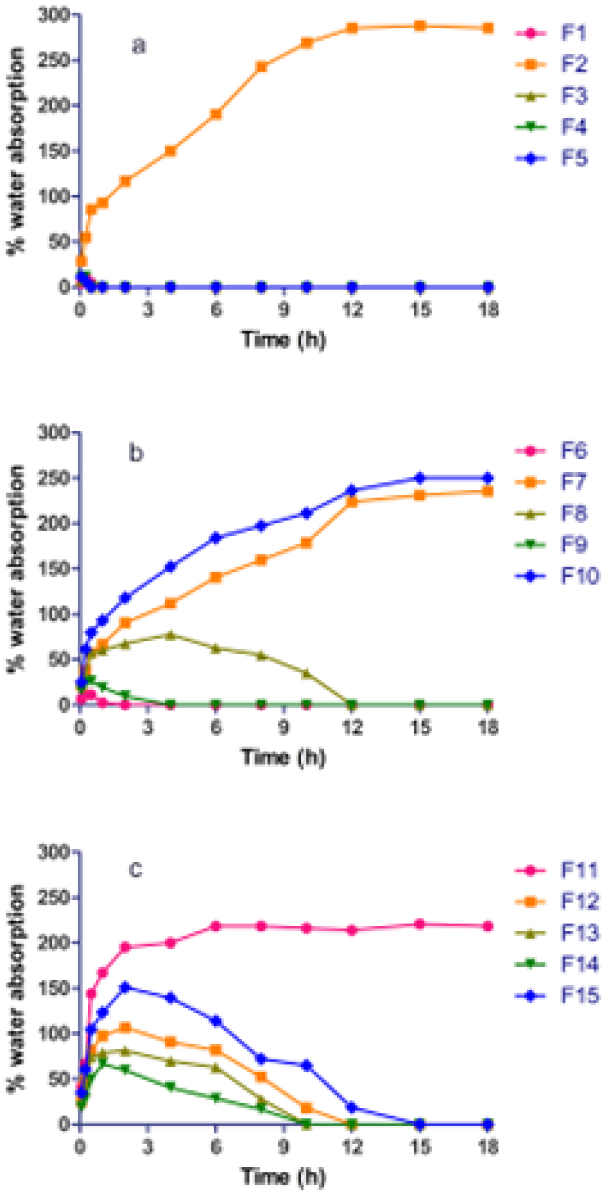

Figure 1: Water absorption profiles of diclofenac sodium matrix tablet formulations in phosphate buffer pH 7.5.

This confirms the finding that xanthan gum achieves good swelling in phosphate buffer pH 7.5 due to the presence of ions [28]. Matrix tablets containing xanthan gum alone (F2) exhibited higher water absorption capacity than tablets containing cashew gum alone (F1) or HPMC alone (F3). Water absorption causes the hydration of tablets which then swells and increases tablet size. In the presence of water the hydrophilic polymers become hydrated, then swells to form a gel within and outside the matrix tablet cores. The gels will form a diffusion barrier within and around the tablet cores, increasing the diffusion path length of drug molecules which causes reduced drug release from the tablets.

Figure 2 shows the release profiles of diclofenac sodium matrix tablets compared to Voltaren Retard® in phosphate buffer pH 7.5. For modified-release solid oral dosage forms, about 20-30 % of drug release should occur within the first 2 h, 50 % release after 8 h and about 80 % release after 24 h of testing [37].

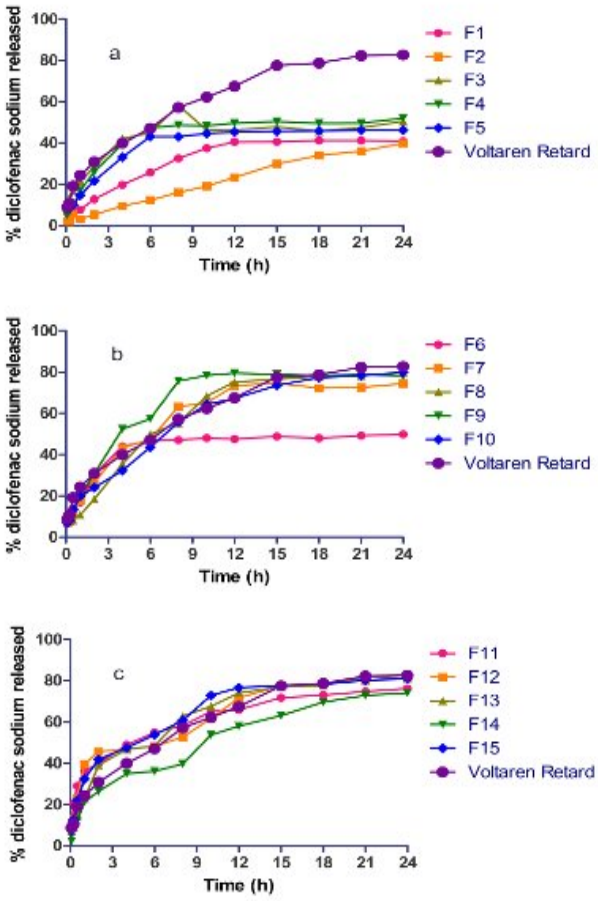

Figure 2: Drug release profiles of diclofenac sodium matrix tablet formulations in phosphate buffer pH 7.5.

The hydrophilic polymers used in formulations F1- F6 inhibited drug release from the tablets to such an extent that only about 50 % release was attained in 24 h, whilst other formulations did not meet the requisite specifications and therefore failed the dissolution test. Thus, matrix tablets formulated using cashew gum alone (F1), xanthan gum alone (F2), HPMC alone (F3), cashew gum/HPMC (F4-F6), xanthan gum/HPMC (F7-F9), cashew gum/xanthan gum (F11) and cashew gum/xanthan gum/HPMC (F14) failed the dissolution test.

Table 5: Difference and similarity factors of different formulations of diclofenac sodium matrix tablets

	Formulation														
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**	**F14**	**F15**
Difference factor (f_1)	48	66	27	28	34	27	10	11	13	7	13	8	7	17	10
Similarity factor (f_2)	29	23	36	38	34	37	62	59	52	69	57	60	68	52	60

Table 6: The mechanism and drug release kinetics of diclofenac sodium matrix tablets

Formulation	**Zero order**		**First order**		**Higuchi**		**Hixson-Crowell**		**Korsmeyer-Peppas**	
	K_0	**R^2**	**K_1**	**R^2**	**K_H**	**R^2**	**K_{HC}**	**R^2**	**n**	**R^2**
F1	0.0278	0.8107	0.0006	0.7088	1.2050	0.9325	0.0012	0.7486	0.43	0.9224
F2	0.0273	0.9880	0.0009	0.8257	1.0842	0.9563	0.0015	0.9093	0.57	0.9218
F3	0.0237	0.5265	0.0004	0.4700	1.1279	0.7310	0.0009	0.4989	0.33	0.9210
F4	0.0298	0.6313	0.0005	0.5209	1.3794	0.8308	0.0011	0.5628	0.45	0.9445
F5	0.0268	0.6664	0.0005	0.5854	1.2228	0.8542	0.0010	0.6152	0.38	0.9407
F6	0.0257	0.5913	0.0004	0.5221	1.2023	0.7952	0.0009	0.5470	0.34	0.9187
F7	0.0493	0.7735	0.0006	0.6305	2.1720	0.9231	0.0015	0.6870	0.50	0.9669
F8	0.0568	0.8392	0.0007	0.7080	2.4360	0.9493	0.0017	0.7579	0.53	0.9309
F9	0.0507	0.6997	0.0006	0.5969	2.2861	0.8753	0.0015	0.6378	0.47	0.9547
F10	0.0535	0.8816	0.0006	0.7068	2.2722	0.9750	0.0016	0.7793	0.48	0.9836
F11	0.0391	0.7951	0.0004	0.5752	1.7170	0.9404	0.0010	0.6595	0.32	0.9554
F12	0.0465	0.8247	0.0005	0.5978	1.9622	0.9373	0.0012	0.6829	0.37	0.9492
F13	0.0513	0.8119	0.0006	0.6147	2.2378	0.9497	0.0015	0.6894	0.47	0.9773
F14	0.0479	0.9147	0.0007	0.5975	2.0062	0.9873	0.0015	0.7413	0.54	0.9544
F15	0.0475	0.7863	0.0005	0.5748	2.0901	0.9363	0.0013	0.6573	0.41	0.9676

Xanthan gum alone (F2) exerted greater inhibition on drug release than HPMC alone (F3) ($p < 0.05$), while there was little difference in the effect of xanthan gum alone and cashew gum alone on drug release ($p > 0.05$). Formulations F10, F12, F13 and F15 showed good sustained release activity with a minimum of 20 % release in 2 h, 50 % release in 8 h and about 80 % release in 24 h, and thus passed the dissolution test. The tablets which passed the dissolution test contained cashew gum/xanthan gum and cashew gum/xanthan gum/HPMC. These tablets achieved a drug release pattern similar to Voltaren Retard®. This study shows that the combination of cashew gum/xanthan gum and cashew gum/xanthan gum/HPMC in suitable ratios may show synergism in controlling diclofenac sodium release leading to the formation of optimized formulations.

In an aqueous medium, the hydrophilic polymer hydrates and swells while the water dissolves the drug within the matrix. The drug eventually diffuses through the gelatinous layer formed and is released from the tablet. Some of the drugs are also released through the continuous erosion of the gelatinous layer [38]. Drug release from the matrix tablets is therefore a complex process involving swelling, diffusion and erosion. The release of drugs from matrix tablet formulations has been linked to the nature, amount and viscosity of the polymer material employed as well as the excipients used, the method of preparation and technological parameters employed[38, 39].

Table 5 shows the difference ($f1$) and similarity ($f2$) factors determined for the various tablet formulations. Data for formulations F7-F15 (52-68) fell within the acceptable range for $f2$ (50-100) while F1-F6 (23-38) fell outside the required range. For the $f1$, formulations F7-F13 and F15 (7-13) fell within the acceptable range of 0-15 and thus showed that there was very little difference in the drug release profiles of the test and reference drugs. The $f1$for formulations F1-F6 and F14 however fell outside the required range and thus the release profiles are dissimilar

to that of the reference drug. From the f_1 and f_2 data, formulations F7-F15 produced had acceptable similarity and minor difference with Voltaren Retard® tablet and could therefore be used interchangeably.

The results of the kinetic models used in the assessment of the dissolution data are summarized in Table 6. Regression values (R^2) were used to assess the best fit and the higher the R^2 value the better the fit of the dissolution profile to that kinetic model. Higher R^2 values were obtained for the Higuchi model than the other kinetic models. This occurred especially in tablet formulations which passed the dissolution tests (F10, F12, F13 and F15). Higuchi describes drug release as a diffusion process based on the Fick's law, square root time dependent [40]. This model has been used to describe drug dissolution from several types of modified release pharmaceutical dosage forms like transdermal systems and matrix tablets with water soluble drugs [24].

The dissolution data was fitted into the Korsmeyer-Peppas equation [41-43] to determine the exact mechanism of drug release. The drug release data fitted well with the equation with R^2 values of 0.9187-0.9836 and most of the 'n' values fell between 0.45 and 0.89. From literature, $0.45 \leq n$ corresponds to a Fickian diffusion mechanism, $0.45 < n < 0.89$ to non-Fickian transport, $n = 0.89$ to Case II (relaxational) transport, and $n > 0.89$ to super case II transport [24]. Drug release from the matrix tablets may have followed anomalous or non-Fickian diffusion. This means drug release involves swelling of the matrix tablets and subsequent erosion. It has been reported that for hydrophilic matrices, swelling and erosion of the polymer occurs simultaneously, and both of them contribute to the overall drug-release rate [44].

CONCLUSIONS

Sustained release diclofenac sodium matrix tablets designed for oral administration were formulated using various blends of cashew gum, xanthan gum and HPMC. Formulations F10, F12, F13 and F15 showed the requisite *in vitro* sustained drug release, as well as difference and similarity properties, and were found to be interchangeable with Voltaren retard®. The study has demonstrated that the blending of hydrophilic polymers may improve the overall sustained release properties of the resultant polymer leading to the formation of an optimized formulation for oral administration.

REFERENCES

[1] Ghosh S, Pal S. Modified tamarind kernel polysaccharide: A novel matrix for control release of aspirin. Int J Biol Macromol 2013; 58: 296-300.

[2] Chavda HV, Patel MS, Patel CN. Preparation and *in vitro* evaluation of guar gum based triple-layer matrix tablet of diclofenac sodium. Research in Pharmaceutical Sciences 2012; 7(1): 57-64.

[3] Rao TV, Kumar GK, Ahmed MG, Joshi V. Development and evaluation of chitosan based oral controlled release matrix tablets of losartan potassium. International Journal of Pharmaceutical Investigation 2012; 2(3): 157-61.

[4] Ravi Kumar N, Narayana SVB, Senthil A, Mahalaxmi R. Development and *in vitro* evaluation of sustained release matrix tablets of losartan potassium. Indian Journal of Novel Drug Delivery 2011; 3(4): 278-88.

[5] Iqbal Z, Khan R, Nasir F, Khan JA, Rashid A, Khan A, *et al*. Preparation and *in-vitro in-vivo* evaluation of sustained release matrix diclofenac sodium tablets using PVP-K90 and natural gums. Pak J Pharm Sci 2011; 24(4): 435-43.

[6] Dhopeshwarkar V, O'Keeffe JC, Zatz JL, Deete R, Horton M. Development of an oral sustained-release antibiotic matrix tablet using *in-vivo/in-vitro* correlations. Drug Dev Ind Pharm 1994; 20 (11): 1851-67.

[7] Toti US, Aminabhavi TM. Modified guar gum matrix tablet for controlled release of diltiazem hydrochloride. J Control Release 2004; 95 (3): 567-77.

[8] Colombo P, Bettini R, Santi P, Peppas NA. Swellable matrices for controlled drug delivery: gel-layer behaviour, mechanisms and optimal performance. Pharmaceutical Science & Technology Today 2000; 3(6): 198-204.

[9] Baviskar D, Sharma R, Jain D. Modulation of drug release by utilizing pH-dependent matrix system comprising water soluble drug verapamil hydrochloride. Pak J Pharm Sci 2013; 26(1): 137-44.

[10] Ali A, Iqbal M, Akhtar N, Khan HM, Ullah A, Uddin M, *et al*. Assessment of xanthan gum based sustained release matrix tablets containing highly water-soluble propranolol HCl. Acta Pol Pharm 2013; 70(2): 283-9.

[11] Vohra DD, Pagi KS, Rajesh KS. Losartan potassium loaded sustained release matrix

tablets: influence of various hydrophilic and hydrophobic polymers on drug release behavior. Journal of Pharmacy and Bioallied Sciences 2012; 4(Suppl 1): S79-80.

[12] Maciel JS, Paula HCB, Miranda MAR, Sasaki JM, de Paula RCM. Reacetylated chitosan/cashew gum gel: Preliminary study for potential utilization as drug release matrix. J Appl Polym Sci 2006; 99(1): 326-34.

[13] Kumar R, Patil MB, Patil SR, Paschapur MS. Evaluation of *Anacardium occidentale* gum as gelling agent in aceclofenac gel. International Journal of PharmTech Research 2009; 1(3): 695-704.

[14] Ofori-Kwakye K, Asantewaa Y, Kipo SL. Physicochemical and binding properties of cashew tree gum in metronidazole tablet formulations. International Journal of Pharmacy and Pharmaceutical Sciences 2010; 2(4): 105-9

[15] Katzhendler I, Mader K, Friedman M. Structure and hydration properties of hydroxypropyl methylcellulose matrices containing naproxen and naproxen sodium. Int J Pharm 2000; 200: 161-79.

[16] Macleod GS, Collett JH, Fell JT. The potential use of mixed films of pectin, chitosan and HPMC for bimodal drug release. J Control Release 1999; 58: 303-10.

[17] Macleod GS, Fell JT, Collett JH. An *in vitro* investigation into the potential for bimodal drug release from pectin/chitosan/HPMC coated tablets. Int J Pharm 1999; 188: 11-8.

[18] Ofori-Kwakye K, Adom ENN. Mechanical properties of khaya and albizia films intended for pharmaceutical coating. Journal of Ghana Science Association 2007; 9(2): 43-53.

[19] Ofori-Kwakye K, Adom ENN, Kipo SL. Preparation and *in vitro* characteristics of tablet cores coated with albizia, albizia/khaya and albizia/HPMC films. International Journal of Applied Pharmaceutics 2009; 1(1): 22-9.

[20] Ofori-Kwakye K, Amekyeh H, El-Duah M, Kipo SL. Mechanical and tablet coating properties of cashew tree (*Anacardium occidentale* L) gum-based films. Asian Journal of Pharmaceutical and Clinical Research 2012; 5(4): 62-8.

[21] British Pharmacopoeia. Her Majesty's Stationery Office, London, UK, 2009.

[22] Bowen FE, Vadino WA. A simple method for differentiating sources of pregelatinized starch. Drug Dev Ind Pharm 1984; 10(3): 505-14.

[23] Carr R. Evaluating flow properties of solids. Chem Eng 1965; 72: 163-8.

[24] Suvakanta D, Padala NM, Lilakanta N, Prasanta C. Kinetic modelling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutica - Drug Research 2010; 67: 217-23.

[25] Gohel MC, Sarvaiya KG, Mehta NR, Soni CD, Vyas VU, Dave RK. Assessment of similarity factor using different weighting approaches. Dissolution Technologies 2005; 12 (4): 22-27.

[26] Gowthamarajan K, Kanaka Phani Kumar G, Narayan Babulal Gaikwad, Suresh B. Preliminary study of *Anacardium occidentale* gum as binder in formulation of paracetamol tablets. Carbohydrate Polymers 2011; 83(2): 506-11.

[27] Ejikeme P. Investigation of the physicochemical properties of microcrystalline cellulose from agricultural wastes I: orange mesocarp. Cellulose 2008; 15: 141-7.

[28] Andreopoulos A, Tarantili P. Xanthan gum as a carrier for controlled release of drugs. Journal of Biomaterials Applications 2001; 16: 34-46.

[29] da Silveira Nogueira Lima R, Rabelo Lima J, Ribeiro De Salis C, de Azevedo Moreira R. Cashew-tree (*Anacardium occidentale* L.) exudate gum: a novel bioligand tool. Biotechnol Appl Biochem 2002; 35: 45-53.

[30] McGovern TW. Botanical briefs: The cashew tree – *Anacardium occidentale* L. Cutis Cutaneous Medicine for the Practitioner 2001; 68: 321-2.

[31] Aulton ME. Pharmaceutics: The Science of Dosage form *Design*, 2nd ed. Edinburgh: Churchill Livingstone, 2002.

[32] Odeku OA, Itiola OA. Evaluation of the effects of khaya gum on the mechanical and release properties of paracetamol tablets. Drug Dev Ind Pharm 2003; 29: 311-20.

[33] Odeku OA. Assessment of *Albizia zygia* gum as a binding agent in tablet formulations. Acta Pharm 2005; 55: 263-76.

[34] Bakre LG, Jaiyeoba KT. Evaluation of a new tablet disintegrant from dried pods of *Abelmuscus esculentus* L (okra). Asian Journal of Pharmaceutical and Clinical Research 2009; 2 (3): 82-91.

[35] Adetunji OA, Odeniyi MA, Itiola OA. Compression, mechanical and release properties of chloroquine phosphate

tablets containing corn and trifoliate yam starches as binders. Tropical Journal of Pharmaceutical Research 2006; 5 (2): 589-96.

[36] United States Pharmacopoeia and National Formulary. United States Pharmacopoeia, XXIII. Rockville: U.S.P Convention Inc. 2002.

[37] US Food and Drugs Administration. Guidance for Industry SUPAC-MR: Modified – Release Solid Oral Dosage Forms Scale-Up and Post Approval Changes: Chemistry, 1997.

[38] Oyi R., Mahmud S, Ofuokwu A. The effect of formulation variables on the swelling capacity of *Khaya senegalensis* gum. Indian Journal of Novel Drug Delivery 2010; 2 (4): 132-7.

[39] Vazquez MJ, Perez-Marcos B, Gomez-Amoza J, iAnez-Pacheco R, Souto C, Concheiro A. Influence of technological variables on release of drugs from hydrophilic matrices. Drug Dev Ind Pharm 1992; 18 (11-12): 1355-75.

[40] Kalam MA, Humayun M, Parvez N, Yadav S, Garg A, Amin S, *et al*. Release kinetics of modified pharmaceutical dosage forms: A Review. Continental Journal of Pharmaceutical Sciences 2007; 1: 30-5.

[41] Korsmeyer RW, Gurny R, Doelker E, Buri P, Peppas NA. Mechanism of solute release from porous hydrophilic polymers. Int J Pharm 1983; 15: 25-35.

[42] Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Helv 1985; 60: 110-1.

[43] Ritger PL, Peppas NA. A simple equation for description of solute release. II. Fickian and anomalous release from swellable devices. J Control Release 1987; 5: 37-42.

[44] Gohel MC, Panchal MK, Jogani VV. Novel mathematical method for quantitative expression of deviation from the Higuchi model. AAPS PharmSciTech 2000; 1 (4): 43-8.