AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Borassus flabellifer Fruit Mucilage: Novel Matrix Forming Material for Sustained Drug Delivery

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ABSTRACT

The present study was undertaken to investigate the release retardant potential of *Borassus flabellifer* mucilage in tablet formulations. In the present study six batches of diclofenac sodium matrix tablets were prepared by wet granulation method with different concentrations of BFM (2.5, 5, 7.5,10 and 12.5%w/w) and compared with guar gum as standard release retardant polymer. The tablets had uniform physical appearance, average weight, drug content, and adequate hardness. The results *of in vitro* release revealed that as the proportion of mucilage in the matrix was increased there was a corresponding decrease in the release of drug. Among the formulations studied formulation F5 containing BFM in the concentration of 12.5% showed sustained and required dissolution profile of drug for 12hrs with cumulative percent release of 98%. Further, the matrix tablets were found to release the drug by diffusion coupled with erosion mechanism. The swelling studies revealed that, as the proportion of mucilage in tablets was increased, there was a corresponding increase in percent swelling of tablets. The SEM photomicrographs showed both pores and gelling structures were present on the surface of tablets indicates the combination of diffusion and erosion mechanism in the release of diclofenac. No chemical interaction between drug, mucilage and mixture of mucilage/drug was seen as confirmed by DSC and IR studies. Optimized formulation (F5) showed no change in physical appearance, drug content, or in dissolution pattern after storage at 40±2°C and 75±5% RH for 3 months.

Keywords: Matrix tablet, diclofenac, release retardant, matrix tablet, *Borassus flabellifer* mucilage.

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Received 19 July 2012, Accepted 30 July 2012

Please cite this article in press as: Ravi Kumar *et al.*, *Borassus flabellifer* Fruit Mucilage: Novel Matrix Forming Material for Sustained Drug Delivery. American Journal of PharmTech Research 2012.

INTRODUCTION

Drug products designed to reduce the frequency of dosing by modifying the rate of drug absorption have been available for many years[1]. Regular research is going on in field of use of natural occurring biocompatible polymeric material in designing of dosage form for oral controlled release administration[2-4]. Natural gums are biodegradable and nontoxic, which hydrate and swell on contact with aqueous media, and these have been used for the preparation of dosage form[5].Guar gum a polysaccharide derivative with glycoside linkage has been used as matrix former for controlled release of isoniazide[6] and diltiazem[7]. Pectins, including high and low ester and amidated, are used in food all over the world. It is an edible plant polysaccharide, has been shown to be useful for the construction of drug delivery systems for specific drug delivery[8]. Xanthan gum is a high molecular weight extra cellular polysaccharide, produced on commercial scale by the viscous fermentation of gram negative bacterium *Xanthomonas campesteris*. The molecule consists of a backbone identical to that of cellulose, with side chains attached to alternate glucose residues. It is a hydrophilic polymer, which until recently had been limited for use in thickening, suspending and emulsifying water based systems[9].

Oral route is the most preferred route for administration of drugs. Tablets are the most popular oral formulations available in the market and preferred by the patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses, and therefore have several disadvantages[10]. Controlled release (CR) tablet formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase safety margin for high potency drugs[11].

Sustained release dosage form is mainly designed for maintaining therapeutic blood or tissue levels of the drug for extended period of time with minimized local or systemic adverse effects. Economy and greater patient compliance are other advantages. Sustained release dosage forms would be most applicable for drugs having low therapeutic indices and short elimination half lives[12]. Sustained release can be achieved by formulating drugs as matrix devices using HPMC, Sodium CMC and other swellable polymer[13-15]. Combination of nonionic polymer HPMC and anionic polymer Sodium CMC as the polymer matrix resulted in near zero-order release[16]. Matrix tablets are easy to prepare and they are cost effective and exhibit predictable release behavior[17].

The *Borassus flabellifer* is a tall and erect palm, with large, fan-shaped leaves which are quite

unlike the pinnate leaves of other palms. *Borassus* is from a Greek word describing the leathery covering of the fruit and *flabellifer* means "fan-bearer". Synonyms of the plant include jaggery palm, Palmyra palm, toddy palm, wine palm. This species is globally distributed from Africa to Australia. Within India, it is found throughout tropical regions, especially along the peninsular coast and in West Bengal and Bihar. It is often cultivated. The Palmyra palm has long been one of the most important trees of Cambodia and India. The different parts of the plant is used for the various ailments like secondary syphilis, antiperiodic, heart burns, liver and spleen enlargement etc. Other than these pharmacological uses the juice of the plant is used in preparation of health drinks, jellies etc. The leaves are use to make baskets, hats and many other useful items. *Borassus flabellifer* contains albuminoids, fats and the fresh pulp is reportedly rich in vitamins A and C. The fresh sap is reportedly a good source of vitamin B-complex. Male inflorescence constitutes spirostane-type steroid saponins like borassosides and dioscin. It also contains 20 known steroidal glycosides and carbohydrates like sucrose. It also contains bitter compound called flabelliferrins, these are steroidal saponins[18-21]. The endosperm contains a high proportion of mucilage. The two major polysaccharides present in this endosperm are galactomannan and mannan.

During earlier study in our laboratory, the disintegrating, binding, gelling and suspending properties of *Borassus flabellifer* mucilage (BFM) were evaluated. Literature survey reveals that comprehensive physicochemical characterization and pharmaceutical application of the BFM as release retardant in pharmaceutical formulation has not been reported yet. Hence the present work was attempted to evaluate release retardant potential of BFM extracted from endosperm of *Borassus flabellifer* fruit. Diclofenac sodium was used as a model drug.

MATERIALS AND METHODS

Materials

Diclofenac sodium was obtained from BPRL, Bangalore, India as gift sample. *Borassus flabellifer* endosperm was procured from the local market. All the other solvents, reagents and chemicals used were of either Pharmacopoeial or analytical grade.

Methods

Isolation and purification of mucilage from *Borassus flabellifer* endosperm[22]

The endosperm of *Borassus flabellifer* fruit contains mucilage. To increase the yield of the mucilage the endosperm of *Borassus flabellifer* fruit were extracted by different solvents. The endosperm of *Borassus flabellifer* were collected, cut into small pieces and dried using tray dryer

at 37°C for 24 h at room temperature, made fine powder by crushing in a mixer. The fine powder was soaked in different solvents such as water, hot-water, phosphate buffer solution (PBS) of pH 4.0, 6.8, 9.2, separately for 2-3h and heated up to 80-90°C for 30-45 min for complete release of the water soluble mucilage into the solvents. The mucilage was then extracted by using a multi layer muslin/cheese cloth bag to remove the marc and concentrated viscous solution under reduced pressure at 60-70°C. Acidified ethanol (5% HCl in 75% ethanol) was added to the concentrated viscous solution with constant stirring. The gel like precipitate was formed and separated by filtration. The precipitate was washed 2-3 times with 75% and 95% ethanol. After complete washing of the precipitate with ethanol 95%, brownish white powder was obtained. The powder was dried in an oven at 37°C, collected, grounded, passed through a # 80 sieve and stored in a desiccator till use. The brownish white powder was considered as mucilage for pharmaceutical use

Physicochemical characterization, phytochemical screening and toxicity studies of the isolated mucilage were carried out as per the reported procedure[23-26].

Drug-Excipient Compatibility study

This study has been done to check whether there is any compatibility related problems are associated with drug and excipients used for the formulation of tablet.

Fourier Transform Infrared (FTIR) Spectral analysis

FTIR spectra of pure drug and physical mixture of drug and excipients were recorded on samples prepared in potassium bromide (KBr) disks using a FTIR Spectrophotometer, (FTIR-8300, Shimadzu, Japan). Samples were prepared in KBr disks by means of a hydrostatic press at 6-8 tons pressure. The scanning range was 400 to 4000 cm^{-1}.

Differential Scanning Calorimetry (DSC) analysis

DSC analysis was performed using Shimadzu DSC-60, Shimadzu Limited Japan. A 1:1 ratio of drug and excipient was weighed into aluminum crucible. And sample was analyzed by heating at a scanning rate of 20^0C over a temperature range 50-330^0C under nitrogen environment.

Formulation of diclofenac sodium matrix tablets

In the present study six batches of diclofenac sodium matrix tablets were prepared with different concentrations of BFM (2.5, 5, 7.5,10 and 12.5%w/w) as standard release retardant polymer. Wet granulation method was used to prepare granules of drug using IPA: water (3:1) as binder solvent, lactose as diluent, and mixture of talc and magnesium stearate as glidant and lubricant respectively. BFM was included in the formulations containing 100 mg of diclofenac sodium. BFM were passed though mesh no. 85 and mixed with diclofenac sodium and lactose which was

previously passed through mesh no. 85. The powders were mixed, granulated with IPA: water (3:1) and the wet mass was passed through mesh no.12. The wet granules obtained were dried at 40°C. The dried granules were subjected to dry screening by passing through mesh no. 16, blended with a mixture of talc and magnesium stearate and compressed into tablets using rotary tablet press (Cemach, Ahmadabad, India). Similar procedure was employed for preparation of diclofenac tablets using 12.5%w/w guar gum as a known matrix polymer. The compositions of each formulation were shown in table 1.

Table 1: Composition of different batches of diclofenac sodium matrix tablets

Ingredients (mg/tablet)	Formulations					
	F1	F2	F3	F4	F5	F6
Diclofenac Sodium	100	100	100	100	100	100
BFM*	6.25	12.5	18.75	25	31.25	--
Guar gum	--	--	--	--	--	31.25
Lactose	136.25	130	123.75	117.5	111.25	111.25
Magnesium stearate	5	5	5	5	5	5
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Total weight of tablet	250	250	250	250	250	250

*BFM: *Borassus flabellifer* mucilage*;* # All quantities are in milligrams;

All the batches contained 1% w/w talc and 2% w/w magnesium stearate

Evaluation of Diclofenac sodium granules

Angle of repose

The angle of repose of granules was determined by the funnel method. The accurately weight granules were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The granules were allowed to flow through the funnel freely on to the surface. The diameter of the granules cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = h / r, \theta = \tan^{-1} (h / r)$$

Where, h = height of the powder cone.

r = radius of the powder cone.

Bulk density

Both loose bulk density (D_b) and tapped bulk density (D_t) was determined. A quantity of 2 gm of granules from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at 2 second intervals. Tapping was continued until no further change in volume was noted. D_b and D_t were calculated using as the following equations.

D_b = Weight of the granules /Untapped Volume of the packing

D_t =Weight of the granules /Tapped Volume of the packing

Compressibility index

The Compressibility Index of the granules was determined by Carr's (compressibility) index. It is a simple test to evaluate the D_t and D_b of a granules and the rate at which it packed down. The formula for Carr's Index is as below:

$$\mathbf{I = \frac{D_t - D_b}{D_t} X\ 100}$$

Where, D_t is the tapped density of the powder, D_b is the bulk density of the powder

Hausner's ratio

Hausner's ratio is an index of ease of powder flow; it is calculated by following formula.

$$\mathbf{Hausner\ ratio = D_t / D_b}$$

Total porosity

Total porosity was determined by measuring the volume occupied by a selected weight of a granule (V_{bulk}) and the true volume of the granule (The space occupied by the powder exclusive of spaces greater than the intermolecular spaces,V).

$$\mathbf{Porosity\ (\%) = \frac{V_{bulk} - V}{V_{bulk}} x100}$$

Evaluation of diclofenac sodium matrix tablets

The prepared tablets were evaluated for general appearance, content uniformity, hardness, friability, weight variation, thickness, diameter, disintegration time and *in vitro* dissolution profile using methods specified in Indian Pharmacopoeia. The following evaluation tests were carried out on formulated tablets which includes;

General appearance

Two tablets from each formulation were randomly selected and organoleptic properties such as colour, odour, taste, and shape were evaluated.

Weight variation test

Randomly twenty tablets were selected after compression, weighed individually and average weight was determined.

Hardness Test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The crushing strength of the tablets was measured using a Monsanto hardness tester. It is expressed in

kg/cm^2.Five tablets from each formulation batch were tested randomly and the average reading noted.

Friability Test

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W_0) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W). The % friability was then calculated by,

$$\%F = 100\ (1-W_0/W)$$

Drug content

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in Phosphate buffer pH 6.8, the drug content was determined measuring the absorbance at 276 nm after suitable dilution using a Shimadzu UV-Vis double beam spectrophotometer 1601.

Thickness and diameter

The thickness and diameter of the tablets was determined by using vernier calipers. Five tablets were used and average values were calculated.

Swelling index

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of all formulation was studied. One tablet from each formulation was kept in a Petri dish containing pH 6.8 phosphate buffers. At the end of 2, 4, 6, 8, 10 and 12 hrs tablets were withdrawn, soaked on tissue paper and weighed and then percentage weight gain by the tablet was calculated by formula;

Disintegration test

The test was performed using Disintegration test apparatus by placing each tablet in each basket with the disc. The process was carried out using pH 6.8 phosphate buffer maintained at 37°C.

***In vitro* drug release study**

Drug release study was carried out by using USP dissolution rate test apparatus-II (Electro lab, Mumbai, India). The study was conducted at 37°C and 50 rpm for 2 h in 900 ml buffer of pH 1.2 and then the dissolution medium was replaced with 900 ml of pH 6.8-phosphate buffer and studied for drug release up to 12 h. Five ml of sample was withdrawn at different time intervals, filtered and the drug content was estimated at 276 nm after suitable dilution.

Kinetics of drug release

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to

models representing zero order (Q v/s t), first order [Log(Q_0-Q) v/s t], Higuchi's square root of time (Q v/s $t_{1/2}$) and Peppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q_0-Q) is the cumulative percentage of drug remaining after time t.

Scanning Electron Microscopy

The optimized formulation (F5) was selected for Scanning Electron Microscopy (SEM) analysis. The tablet surface morphology was studied at zero time and 12th hour of dissolution. The morphological characters of these 2 scans were compared to hypothesize the mechanism of drug release and swelling.

Stability studies

To determine any change in *in vitro* drug release profile and physicochemical properties of tablets on storage, short term stability study was performed at 40±2°C and 75±5% RH over a period of 90 days on the optimized matrix tablet formulation (F5). At the end of 90 days period, tablets were evaluated for physical appearance, drug content and *in vitro* release pattern.

RESULTS AND DISCUSSION

Additives play an important role in pharmaceutical preparations like tablet, lotions, suspensions, syrups and ointments. Recent trends towards the use of the vegetable and nontoxic products demand the replacement of synthetic excipients with natural ones. Vegetable gums provide appropriate solution to the current problem. Hydrophilic matrices are an interesting option when developing an oral sustained release formulation. The drug release from such matrices can be controlled through their physical properties. Polysaccharides are the choice of materials among the hydrophilic polymers used, because they are nontoxic and acceptable by the regulating authorities. In view of the easy availability of the *Borassus flabellifer* fruit, the mucilage from the *Borassus flabellifer* fruit was investigated for its application as a release retardant in diclofenac sodium matrix tablet.

The mucilage was extracted using solvents such as distilled/demineralised water, hot water, PBS pH 4.0, pH 6.8 and pH 9.2 and the yield of the dry water soluble mucilage was varied depends upon the solvents used. Percent yield of the dry water soluble mucilage was 45%, 60%, 22%, 30% and 35% in distilled/demineralised water, hot water, PBS pH 4.0, PBS pH 6.8, and PBS pH 9.2 respectively. The solvents like distilled/demineralised water, hot water and phosphate buffer pH 9.2 could be used for extraction for better yield.

Drug-Excipients Compatibility Studies

Fourier transform infrared (FTIR) analysis

FTIR spectra were recorded to assess the compatibility of the drugs and excipients. FTIR spectra of diclofenac sodium showed principal peaks at 1284 and 1306 cm^{-1} resulted from C-N stretching and the peak at 1604 and 1575 cm^{-1} resulted from C=C stretching and C=O stretching of carboxylate group, respectively. The observed FTIR spectrum of drug was matched with reference spectra. Confirming the purity of the drug as per established standards. All characteristic peaks of drug(s) were observed in the FTIR spectra of physical mixture of drug and different excipients. The results showed there was no appearance or disappearance of peaks in the polymer–drug mixture this confirmed the absence of any chemical interaction between the drug and the polymers. The FTIR spectra of pure drug and physical mixture of drug and different excipients are shown in figure 1 and 2 respectively.

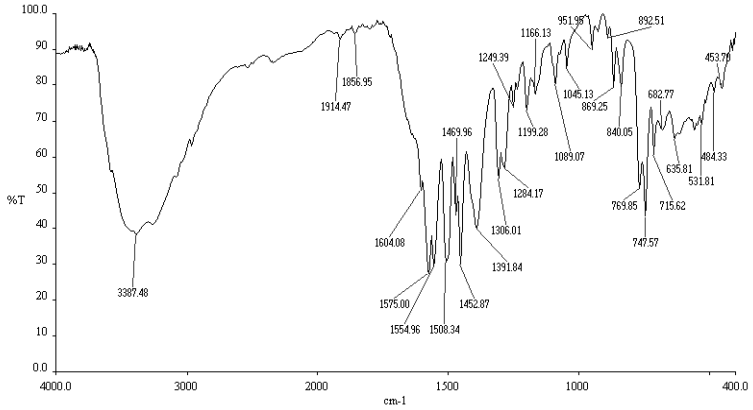


Figure 1: IR spectrum of diclofenac sodium

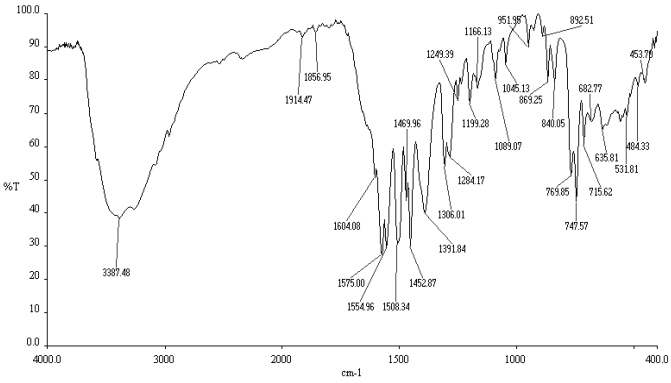


Figure 2: IR spectrum of diclofenac sodium and different excipients

Differential Scanning Calorimetry (DSC)

The DSC thermograms for drug and physical mixture of drug and excipients are represented in figure 3 and 4 respectively. DSC analysis of Diclofenac sodium shows the exothermic peak at its melting point i.e. at 283.62^0C, which is in agreement of earlier observation and corresponds to

the reported melting point of diclofenac. The DSC analysis of physical mixture of drug and excipients revealed negligible change in the melting point of diclofenac sodium in the presence excipients. This also indicated that there are no changes in its crystallinity of the drug and it may not affect the stability of formulation and it is confirmed that drug is compatible with excipients.

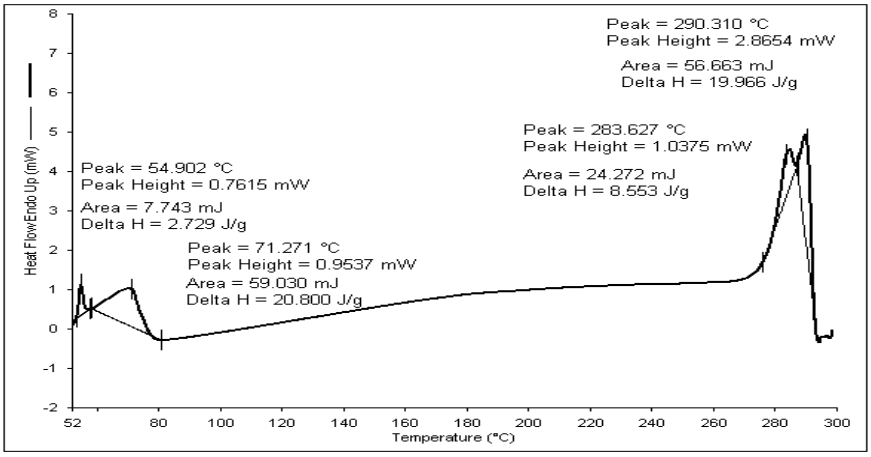


Figure 3: DSC thermogram of diclofenac sodium

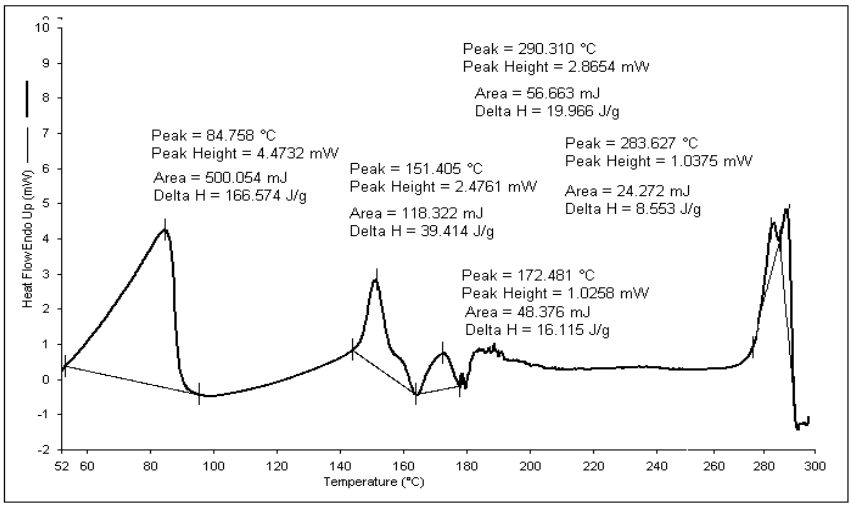


Figure 4: DSC thermogram of Diclofenac sodium and different excipients

Evaluation of Diclofenac sodium granules

The granules of different formulations were evaluated for angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio, total porosity and drug content. The results of angle of repose and compressibility index (%) ranged from 21.84 ± 0.03 to 24.68 ± 0.02, and 11.01 ± 0.03 to 21.20 ± 0.03, respectively. The results of LBD and TBD ranged from 0.267 ± 0.02 to 0.421 ± 0.03 and 0.30 ± 0.03 to 0.485 ± 0.05, respectively. The results of percentage porosity of the granules ranged from 26.92 ± 0.06 to 34.25 ± 0.03. The drug content in a weighed amount of granules of all formulations ranged from 95.53 ± 0.02 to 98.14 ± 0.05%. Hausner's ratio ranges from 1.124±0.03 to 1.192±0.01. The percentage porosity values of the granules ranged from

26.92% to 34.25%, indicating that the packing of the granules may range from close to lose packing and also further confirming that the particles are not of greatly different in sizes. All these results indicate that the granules prepared from different batches possessed good flow properties, compressibility and drug content (table 2).

Table 2: Results of Pre-compression characteristics of diclofenac sodium granules

Formulations	Angle of repose (θ)*	Bulk density(gm/cm^3)*	Tapped density (gm/cm^3)*	Carr's index (%)*	Hausner's ratio (H_R)*	Bulkiness (cc/g)*	flowability	Total porosity	Drug Content (%)
F1	24.68 ±0.02	0.39 ±0.03	0.44 ±0.06	11.01 ±0.03	1.128 ±0.05	2.564	Good	34.25 ±0.03	97.86 ±0.06
F2	23.97 ±0.08	0.267 ±0.02	0.30 ±0.03	11.29 ±0.02	1.124 ±0.03	3.745	Good	33.09 ±0.07	96.4 ±0.01
F3	22.73 ±0.04	0.407 ±0.05	0.485 ±0.05	16.08 ±0.02	1.192 ±0.01	2.457	Good	27.2 ±0.02	95.62 ±0.03
F4	21.84 ±0.03	0.312 ±0.02	0.364 ±0.01	14.28 ±0.01	1.167 ±0.01	3.205	Good	31.42 ±0.01	95.64 ±0.04
F5	23.91 ±0.01	0.338 ±0.07	0.385 ±0.02	21.20 ±0.03	1.139 ±0.04	2.958	Good	28.43 ±0.03	98.14 ±0.05
F6	24.11 ±0.07	0.421 ±0.03	0.481 ±0.07	12.47 ±0.02	1.143 ±0.05	2.375	Good	26.92 ±0.06	95.53 ±0.02

*All values are expressed as mean ± SD, n=3.

Evaluation of diclofenac sodium matrix tablets

The tablets of different formulations were subjected to various evaluation tests. The shape of the tablets of all formulations remained off white, smooth, flat faced circular with no visible cracks. The thickness and diameter of formulated matrix tablets was ranged from 3.60±0.04 to 3.67±0.04 mm and 8.01±0.01 to 8.03±0.02 respectively. The values are almost uniform in all formulations. In a weight variation test, the Pharmacopoeial limit for the percentage deviation for the tablets of more than 250mg is ± 5%. The average percentage deviation of all tablet formulations was found to be within the above limit, it was found to be form 249±0.05 mg to 252±0.04 mg. and hence all formulations passed the test for uniformity of weight as per official requirements. The content uniformity test was performed for all the six formulations and drug content in the formulated tablets was ranged from 98.0±0.01 to 99.5±0.05. The results indicated that drug content was found to be uniform among different batches of the tablets. The hardness of the tablets of all batches ranged from 4.5±0.21 to 6.5±0.09 kg/cm^2. It can be observed from results that the increase in the concentration of mucilage in the tablet resulted in a corresponding increase in the hardness of tablets, which may be attributed to the plastic nature of mucilage and also due to presence of higher concentration of mucilage, which is generally responsible for

more hardness of the tablet. In the present study, the percentage friability for all the formulations was below 1% indicating that the friability is within the prescribed limits. The formulated tablets were found to have good hardness and minimal weight loss on friability indicates that the tablets can with stand the mechanical shocks during their handling and transport. Formulations F1-F2 were found disintegrated within 45 minutes of dissolution testing in pH1.2 buffers where as formulation F3-F6 were found to retain their shape for up to 12 hours of dissolution testing table 3.

Table 3: Results of evaluation of diclofenac sodium matrix tablets

Formulation code	Thickness (mm)*	Diameter (mm)*	Hardness (kg/cm^2)*	Friability (%)**	Drug content (%)*	Weight variation (mg)***	Appearance
F1	3.61±0.04	8.02±0.02	4.5±0.21	0.25±0.01	98.5±0.02	251±0.04	+
F2	3.67±0.04	8.01±0.02	5.0±0.11	0.30±0.06	98.0±0.01	249±0.05	++
F3	3.62±0.03	8.03±0.02	5.5±0.12	0.45±0.04	99.0±0.01	252±0.04	+++
F4	3.60±0.04	8.01±0.01	6.0±0.16	0.55±0.02	99.5±0.05	250±0.01	++
F5	3.62±0.02	8.01±0.03	6.5±0.09	0.21±0.03	98.0±0.01	250±0.03	+++
F6	3.67±0.03	8.01±0.04	5.6±0.08	0.35±0.03	99.0±0.01	251±0.02	+++

*All values are expressed as mean ± SE, n=5; **All values are expressed as mean ± SE, n=10; ***All values are expressed as mean ± SE, n=20; += Average; ++= good, +++= excellent

Swelling Behavior of diclofenac matrix tablets

Since the rate of swelling is related and may affect the mechanism and kinetics of drug release, the penetration of the dissolution medium and swelling of tablets were determined. The extent of swelling was measured in terms of percentage weight gain by the tablets. The swelling behavior of all the formulations was studied. The swelling index was calculated with respect to time. As time increases, the swelling index was increased, because weight gain by tablet was increased proportionally with rate of hydration up to 6 h. Later on, it decreases gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The results of swelling studies show that, as the proportion of mucilage in the tablets was increased, the percent swelling increased, and the percent erosion decreased. Similar results were earlier reported for mucilage of *Hibiscus rosasinensis* matrix tablets formulated using pure mucilage showed greater swelling as compared with the matrix tablets containing mucilage and drug. The release of drug from hydrophilic matrices occurs as a result of complex interaction between diffusion, dissolution, and erosion mechanisms. On coming in contact with water, hydrophilic matrices undergo gel formation, and progressive phase transition from glassy to rubbery state takes place. This results in solvation of individual polymer chains. As the swelling continues, the swollen matrix retains more water until the shear forces in the dissolution medium disentangle the individual polymer chains from the

matrix. It has been observed that the cumulative percent drug release decreases with increasing concentration of mucilage and swelling index (figure 5).

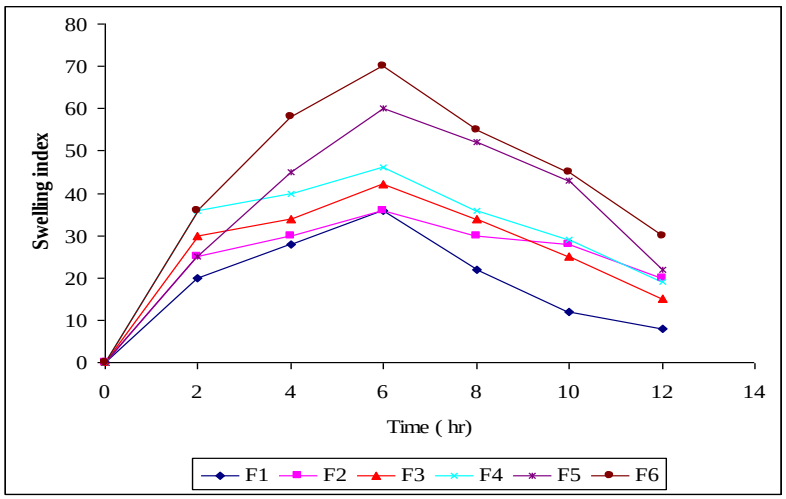


Figure 5: Swelling behavior of different batches of diclofenac matrix tablet

***In vitro* Drug Release Study**

The *in vitro* drug release characteristics were studied in simulated gastric and intestinal fluids for a period of 12 hours using USP XXIII dissolution apparatus 2 (paddle type at 50 rpm). The results show that less amount of the drug dissolved during the first 2 h in 0.1 N HCl. Sustained, but complete drug release was displayed by all formulations in phosphate buffer (pH 6.8). Thus it can be concluded, that drug dissolution was a function of drug solubility, at various pH ranges. Indeed, pH dependent solubility of diclofenac is well known. It can be observed from the results that, as the proportion of mucilage in tablets was increased there was a decrease in the release rate. The results of dissolution studies indicated that F1, F2, and F3 released 34%, 24%, and 20% of diclofenac at the end of 2 hours; and 96%, 93%, and 92 % of drug at the end of 8 hours, 9 hours, and 10 hours, respectively. The high dissolution rate observed with F1 could be due to its low swellability, indicated by lower viscosity values and lower concentration of mucilage. The Formulation F5 showed a slow and complete drug release of 98% over a period of 12 hr. The results of *in vitro* studies indicated that the rate and extent of drug release were decreased significantly with an increase in BFM concentration, which may be attributed to increase in the polymer matrix, gel strength and to the formation of gel layer with longer path of diffusion, resulting in reduction of diffusion coefficient of the drug. When the BFM matrix tablets of diclofenac come into contact with the dissolution medium, they take up water and swell, forming a gel layer around the matrix. Then the dissolved drug diffuses out of the swollen BFM matrix at a rate determined by the amount and viscosity of BFM in the tablet formulation. Formulation

containing 12.5%w/w concentration of the BFM showed slow and sustained release of the diclofenac over a period of 12 h. From the results it suggests that the nature of excipient used appeared to play a minor role in regulating the release, while the mucilage content was a major factor. F6 give 70% drug release in 12 hours and which indicate that % of guar gum used in the formulation it sustained the drug release but the results were not satisfactory. From the findings, obtained so far it can be concluded that BFM in the concentration of 12.5%w/w (F5) was promising concentration for oral controlled release tablet of diclofenac which showed slow and sustained release of the diclofenac over a period of 12 h. Hence F5 is considered as the optimized batch. *In vitro* drug release profile of optimized batch F5 and the commercial sustained-release tablet of diclofenac sodium (Voveran SR®) were compared; the results indicated that formulation F5 gave the release profile close to the marketed product(figure 6 and 7 respectively).

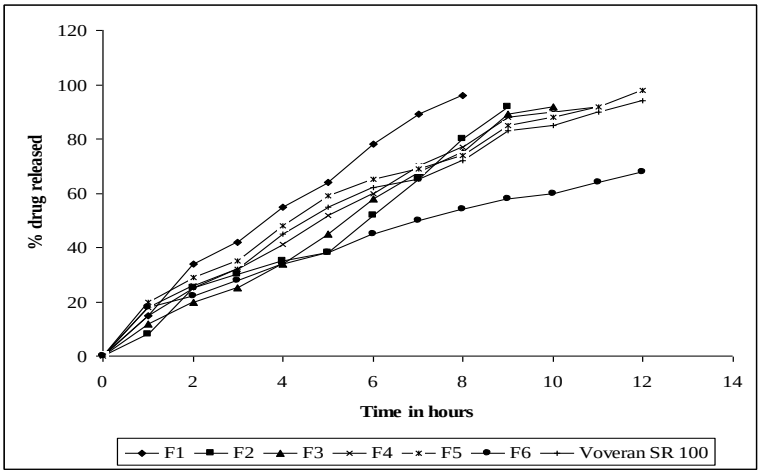


Figure 6: Comparison of *in vitro* release profile from different batches of diclofenac sodium matrix tablet and commercial tablet

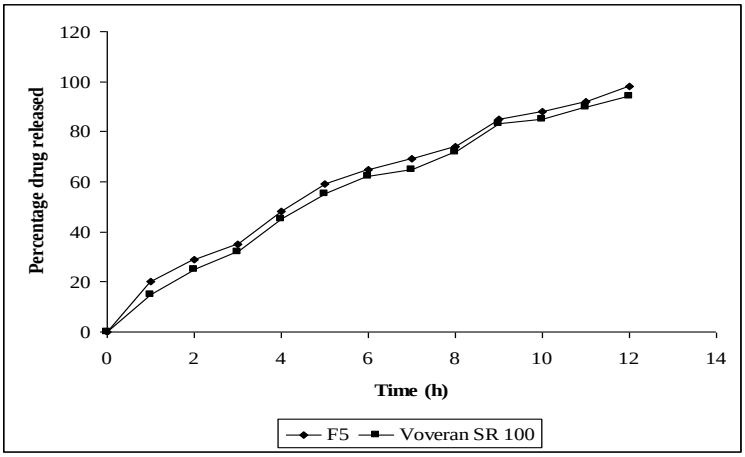
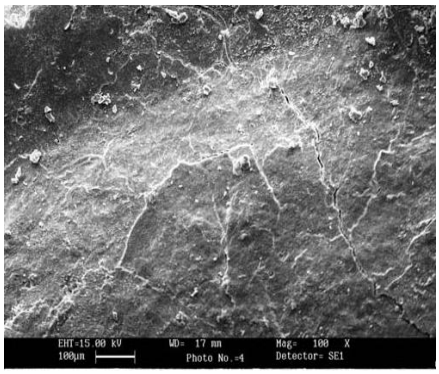


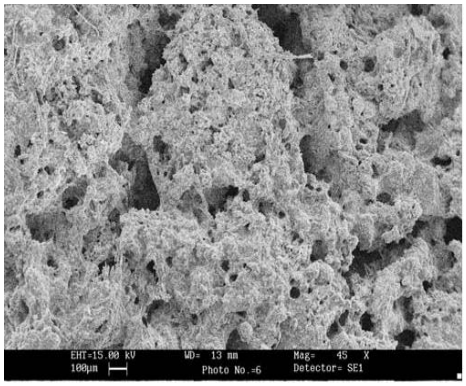
Figure 7: Comparison of *in vitro* release profile from optimized batch of Diclofenac sodium matrix tablet and commercial tablet

Scanning electron microscopy

The surface morphology of optimized formulation (F5) at zero time and at 12th hour of dissolution study was observed. SEM photographs before dissolution it showed intact surface without any perforations, channels, or troughs. After dissolution, the solvent front enters the matrix and moves slowly toward the center of the tablet. The drug diffuses out of the matrix after it comes in contact with dissolution medium. The images of the tablet showed the presence of both gelling structures and pores on the surface. Thus, the presence of both pores and gelling structure indicates the combination of diffusion and erosion mechanism in the release of diclofenac from the matrix tablet of batch F5. The SEM photographs of diclofenac matrix tablet (F5) were shown in figure 8.



At zero time of dissolution study



At 12th hour of dissolution study

Figure 8: SEM photomicrographs of optimized batch of diclofenac matrix tablet (F5)

Mechanism of drug release

To determine the mechanism of drug release kinetics from optimized formulation F5, the dissolution data were treated according to Higuchi, Korsmeyer-Peppas model and Hixson-Crowell model along with zero order pattern. It can be observed from the results that the release rate data of optimized formulation of diclofenac sodium matrix tablets F5 formulated using mucilage as the matrix did not follow a zero-order release pattern. By using Higuchi's kinetics or square-root kinetics this would explain why drug diffuses at a comparatively slower rate as the distance of diffusion increases. In our experiments, the *in-vitro* release profiles of drug from optimized formulation F5 could be best expressed by Higuchi's equation, as the plots showed high linearity (R^2= 0.9908). To confirm the diffusion mechanism, the data were fit into Korsmeyer-Peppas model. The optimized formulation F5 showed high linearity (R^2= 0.9907, with slope (n) values 0.6661, this (n) value indicating that coupling of diffusion and erosion mechanism so called anomalous non-Fickian diffusion and may indicate that the drug release is

controlled by more than one mechanism, which indicate that formulation F5 release the drug by diffusion coupled with erosion mechanism. Hixson-Crowell plots showed linearity (R^2= 0.9867) indicated a change in surface area and diameter of the tablet with the progressive dissolution of the matrix as a function of time. The result of modeling and drug release kinetics of optimized diclofenac sodium matrix tablet Batch F5 were shown in table 4 and in figure 9-12.

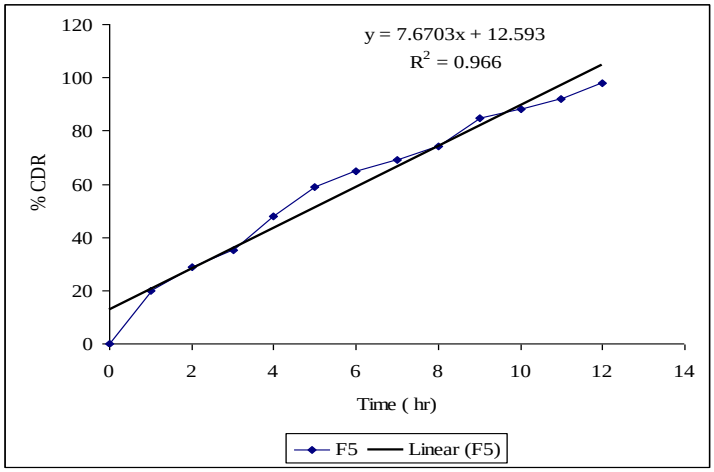


Figure9: Zero order release plot of optimized diclofenac matrix tablet batch F5

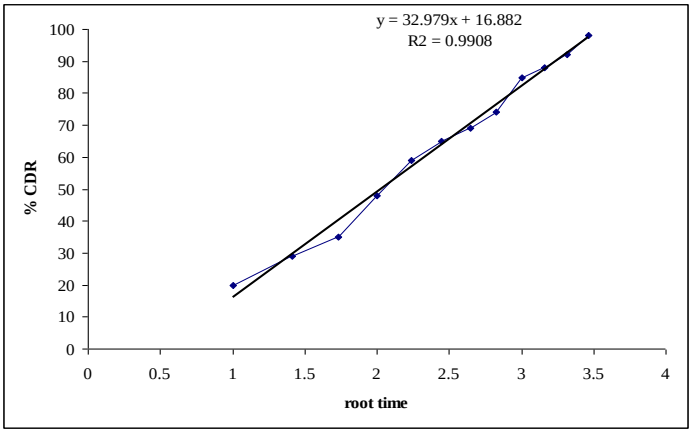


Figure 10: Higuchi plot of optimized diclofenac matrix tablet batch F5

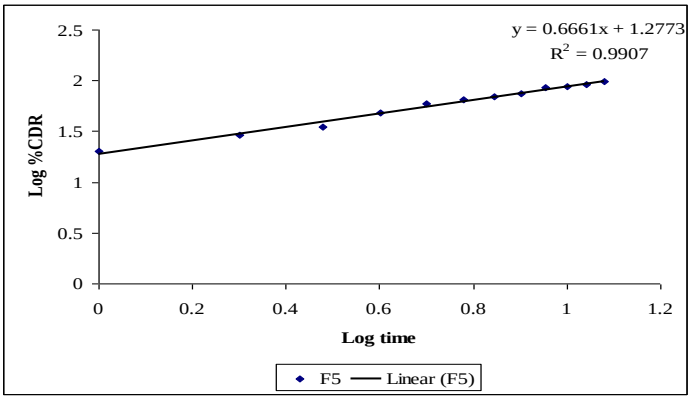


Figure 11: Korsmeyer-Peppas plot of optimized diclofenac matrix tablet batch F5

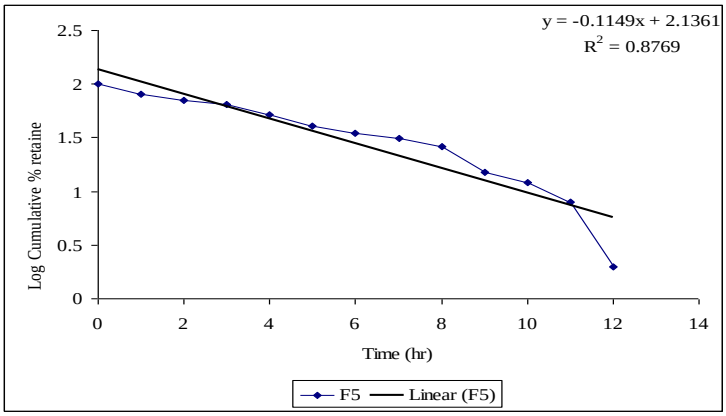


Figure 12: First order release plot of optimized diclofenac matrix tablet batch F5

Table 4: Release Kinetics of optimized diclofenac sodium matrix tablet

Formulation	First order		Zero order		Higuchi's		Peppa's		HixonCrowell's	
F5	r^2	K	r^2	K	N	r^2	n	r^2	N	r^2
	0.8769	0.2646	0.966	7.670	32.973	0.9908	0.6661	0.9907	0.1855	0.9867

Stability studies

Stability studies were conducted on optimized matrix tablet formulation (F5) to assess their stability with respect to their physical appearance, drug content, and drug release characteristics after storing it at 40°C/75%RH for 3 months. At the end of the testing period, the matrix tablets were observed for changes in physical appearance, analyzed for drug content, and subjected to *in vitro* drug release studies. No visible changes in the appearance of the matrix tablets were observed at the end of the storage period. The drug content was found to be 97.6% ± 0.01%. There was no significant difference in the mean amount of diclofenac sodium released from F5 matrix tablets after storing for 3 months at 40°C / 75% RH, indicating that the formulation could provide a minimum shelf–life of 2 years. However, a detailed investigation is necessary to determine the exact shelf- life(figure 13).

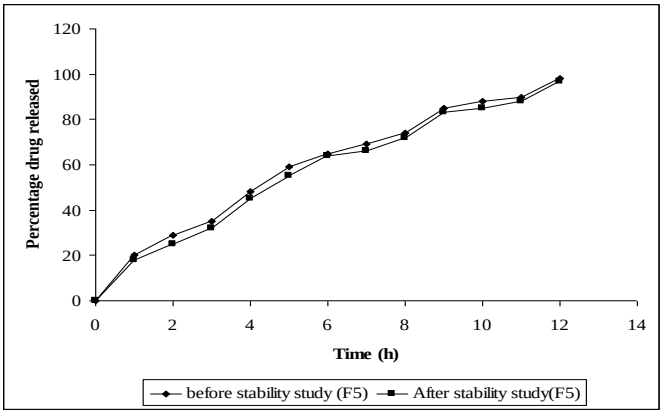


Figure 13: Comparison of *in vitro* release profile of optimized formulation of diclofenac matrix tablet (F5) after stability study

CONCLUSION

The study deals with the investigation of release retardant potential of BFM when formulated as a matrix tablet. The mucilage exhibited an appreciable physicochemical properties, good swelling, good flow and suited best for the development of sustained release tablets as indicated by the drug release studies. The matrix tablets of diclofenac (F5) employing 12.5% BFM were considered suitable for sustained release over 12 h. These matrix tablets (F5) provided slow and complete release of Diclofenac over 12 h and were suitable for once a day (12 h) administration. Thus BFM can be used as a potential natural source over the synthetic release retardant for sustaining the drug release from the formulation.

ACKNOWLEDGEMENTS

The authors are thankful to ICMR for the financial support for this research project (21/12/17/09/HSR, dated: 24/06/2010). The authors are also thankful to BPRL, Bangalore, India for generous gift samples of diclofenac.

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