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Exploitation of *Borassus flabellifer* fruit mucilage as novel natural gelling agent

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ABSTRACT

Natural gums and mucilages have been extensively explored as pharmaceutical excipients. These gums and mucilages are biocompatible, cheap and easily available. The present study was undertaken with an objective to find out the gelling potential of natural mucilage obtained from endosperm of Borassus flabellifer fruit. Mucilage extracted from endosperm of Borassus flabellifer fruit was subjected to toxicity studies for its safety and preformulation studies for its suitability as a gelling agent. Diclofenac sodium was used as model drug for the formulation of gels. In the present study eight batches of Diclofenac sodium gels were prepared with different concentrations of mucilage (viz; 3.0, 4.0, 5.0 and 6.0 %w/w) and compared with existing gum tragacanth as standard gelling agent. The gels were evaluated for drug content, viscosity, in vitro permeation (across dialysis membrane), skin irritation and stability tests. The gels prepared with 4.0%w/w of mucilage were found to be more effective in comparison to that of gel with 6%w/w of gum tragacanth. The gels prepared with 4.0%w/w of mucilage were found to be ideal and comparable with a commercial preparation(Voltaren gel®).The prepared gels did not produce any dermatological reactions and were well tolerated by the guinea pig. Stability study revealed that the gel formulations were physically stable and has no syneresis. Briefly, it could be concluded that the Borassus flabellifer mucilage can be used as a pharmaceutical excipient in gel formulations; it has the potential to also replace some synthetic gelling polymers upon further modifications.

Keywords: *Borassus flabellifer* mucilage, *in vitro* permeation, Diclofenac sodium, gum tragacanth, Carrageenan.

INTRODUCTION

Gels are transparent to opaque semisolids containing gelling agent that merges or entangles to form a three-dimensional colloidal network structure. It is responsible for gel resistance to deformation and its visco-elastic properties. Gels have better potential as a vehicle to administer drug topically in comparison to ointment, because they are non-sticky, require low energy during formulation, are stable and have aesthetic value. Skin injuries (major and minor) or local infection can best be treated by application of product that form transparent water vapour and air permeable film over the skin surface from which the drug releases continuously from the application site[1].

Excipients are the additives used to convert active pharmaceutical ingredients into pharmaceutical dosage form suitable for administration to patient[2]. New and improved excipients continue to be developed to meet the needs of conventional drug delivery systems. The high cost of synthetic polymers and environmental pollution by chemical industry has made the scientists in developing countries to enter into an era, in which plant products serve as alternative to synthetic products because of their economy, local accessibility and environmental friendly nature. Herbs are non-polluting renewable resources for sustainable supplies of cheaper pharmaceutical products. Today, we

have a number of plant-based pharmaceutical excipients. A number of researchers have explored the utility of plant-based materials as pharmaceutical excipients[3-9]. These natural materials are used as diluents, binders, disintegrants in tablet, protective colloids in suspension, thickeners in oral liquid, gelling agents in gel and bases in suppository. Plant mucilage's, which provide high concentration of complex sugars and these, when mixed with water, a protective and soothing preparation results, which can be applied externally[10-11]. Majority of investigations on natural polymers in drug delivery systems are centered on polysaccharides and proteins, due to their ability to produce a wide range of materials and properties based on their molecular structures [12].

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[13-16]. 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 physicochemical characterization of *Borassus flabellifer* mucilage (BFM), the disintegrating property, binding property, release retardant property, carrier for colonic drug delivery and suspending property of BFM were evaluated and reported by the author. Literature survey reveals that comprehensive physicochemical characterization and pharmaceutical application of the BFM as gelling agent in pharmaceutical formulation has not been reported yet. Hence the present work was attempted to evaluate gelling properties of BFM extracted from endosperm of *Borassus flabellifer* fruit. Diclofenac sodium was used as a model drug.

MATERIALS AND METHODS

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[17]

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 [18-21].

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 40-330^0C under nitrogen environment.

Preparation of Diclofenac gel[22]

BFM at different concentration is dispersed in hot water using a magnetic stirrer (Remi magnetic stirrer 2MLH, Mumbai, India) to facilitate complete dispersion. The co-solvent glycerin is added at its required amount as shown in table1 with continuous stirring. Diclofenac sodium, methyl paraben were added with stirring. Finally it was adjusted to the required amount with distilled water. Eight batches of diclofenac gels were prepared and stored in cool place until further use. The composition of each batches of diclofenac gels were presented in table 1.

TABLE 1: Formulation of different batches of diclofenac gel containing BFM

Ingredients (%)	F1	F2	F3	F4	F5	F6	F7	F8
BFM*	3	4	5	6	--	--	--	--
Gum Tragacanth	--	--	--	--	3	4	5	6
Diclofenac	1	1	1	1	1	1	1	1
Glycerin	10	10	10	10	10	10	10	10
Methyl paraben	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Purified water q.s. to (g)	10	10	10	10	10	10	10	10

BFM Borassus flabellifer mucilage*

Evaluation of Diclofenac gel[23-28]

The prepared gels were evaluated for various evaluation parameters which includes;

Viscosity determination

Viscosity of diclofenac gels were determined using Brookfield synchronic viscometer with helipath stand at room temperature with a shear rate of 5 rpm for 5 min. The spindle no. used is 07. The viscosity measurements were made in triplicate using fresh samples each time.

pH determination

Two grams of prepared gel was dissolved in the 100 ml of phosphate buffer solution and pH of the resulted solution was measured by Elico digital pH meter at 25±1^0C.

***In vitro* diffusion profile**

Release of diclofenac sodium from various gel formulations and the commercial preparation (Voltaren® gel) were studied employing the permeation apparatus as described. A glass cylinder with both ends open, 10 cm height and 3.7 cm outer diameter was used as a permeation cell. The mice were obtained from the animal house of Karavali College of Pharmacy, Mangalore. The mice were maintained on standard animal feed and had free access to water. The mice were kept under standard conditions as approved by the animal ethical committee (Approval No:KCP/IAEC/Ph.Ceutics/05/2011-2012). Fresh, full thickness and hairless skin obtained from 6-8 weeks old mice was used as permeation barrier. The hair of the mice was removed 3 days before from the date of commencement of the experiment using electrical hair clipper. The animals were housed individually for at least 7 days before an experiment to allow scratches, bites and other small skin imperfections to heal. After sacrificing the mice by cervical dislocation, abdominal and dorsal skin sections were excised with surgical scissors. Adhering subcutaneous fat on the dermal side was carefully removed from the underside of the skin. The skin section thus prepared was clamped carefully to one end of the hollow glass tube (dialysis cell) so that the stratum corneum was facing up on the receiver compartment. The excised hairless mouse skin was fixed to one end of the cylinder by adhesive tape. One gram of the prepared gel was taken in the cell (donor compartment) and the cell was immersed in a beaker containing 100 ml of phosphate buffer of pH 6.8 (receptor compartment). The cell was immersed in to a depth of 1 cm below the surface of buffer, which was agitated by a magnetic stirrer and the temperature was maintained at 37°±1°C throughout the experiment. Aliquots were withdrawn from the receptor compartment periodically (1, 2, 3, 4,5,6,7 and 8 h). After each withdrawal, the volume of liquid in the receptor compartment was replaced by phosphate buffer of pH 6.8. The drug concentration was determined spectrophotometric method at 276nm.

Skin irritation study
Guinea pigs (400-500 g) of either sex were used for testing of skin irritation. The animals were obtained from the animal house of Karavali College of Pharmacy, Mangalore. The animals were maintained on standard animal feed and had free access to water. The animals were kept under standard conditions as approved by the animal ethical committee (Approval No:KCP/IAEC/Ph.Ceutics/05/2011-2012). Hairs were depleted from the back of guinea pigs and area of 4cm^2 was marked on both the sides, one side served as control while the other side as test. Gel was applied (500 mg/guinea pig) twice a day for 7 d and the site was observed for any sensitivity and the reaction if any, was graded as

0 : No reaction
0.5 : Slight patchy erythema
1 : Slight but confluent or moderate but patchy erythema
2 : Moderate erythema
3 : Severe erythema with or without edema

Homogeneity
All developed gels were tested for homogeneity by visual inspection after the gels have been set in the container. They were tested for their appearance and presence of any aggregates.

Spreadability
It was determined by wooden block and glass slide apparatus. Weights about 20g were added to the pan and the time were noted for upper slide (movable) to separate completely from the fixed slides.

Spreadability was then calculated by using the formula:

$$S = M.L/ T$$

Where; S = Spreadability; M = Weight tide to upper slide; L = Length of glass slide; T = Time taken to separate the slide completely from each other.

Consistency
The measurement of consistency of the prepared gels was done by dropping a cone attached to a holding rod from a fix distance of 10cm in such way that it should fall on the centre of the glass cup filled with the gel. The penetration by the cone was measured from the surface of the gel to the tip of the cone inside the gel. The distance traveled by cone was noted down after 10sec.

Drug content
A specific quantity (100mg) of developed gel and marketed gel were taken and dissolved in 100ml of phosphate buffer of pH 6.8. The volumetric flask containing gel solution was shaken for 2hr on mechanical shaker in order to get complete solubility of drug. This solution was filtered and estimated spectrophotometrically (UV-1601, Shimadzu, Japan) at 276 nm using phosphate buffer (pH 6.8) as blank.

Stability testing
All the selected formulations were subjected to a stability testing for three months as per ICH norms at a temperature of 40º±2ºC in stability chambers (EIE instrument Pvt Ltd, India). All selected formulations were analyzed for the change in appearance, pH, drug content and also physical stability and syneresis (spontaneous contraction of gel exuding some of the fluid medium).

***In vitro* anti-inflammatory activity[29]**
The *in vitro* anti-inflammatory activity of the optimized gel formulation was performed using carrageenan induced rat hind paw edema model. Albino rats of Wistar strains of either sex between 140-170 grams were selected for the studies. The animals were kept on standard diet and allowed free access to water.

The animals were divided into three groups comprising six animals in each group.
Group 1:- Control, received placebo gel
Group 2:- Received 1.2 mg/kg equivalent to diclofenac in gel formulation
Group 3:- Marketed gel Received 1.2 mg/kg equivalent to diclofenac in gel formulation)

Immediately after drug administration 0.05 mL of 1% w/w solution of carrageenan was injected into the planter surface of the hind paw. The hind paw volume was measured at different time intervals for 4 h after carrageenan

treatment using a Plethysmograph. The percent inhibition in hind paw edema volume was calculated using the following formula and compared with those recorded for control group.

Anti-inflammatory activity (%) = (1-A/B) × 100

Where **A** is the change in paw volume in the treated group and **B** is the change in paw volume in the control group.

RESULTS AND DISCUSSION

The fact for increase in importance of natural plant based material is that plant resources are renewable and if cultivated or harvested in a sustainable manner, they can provide a constant supply of raw materials. However, substances from plant origin also pose several potential challenges such as being synthesized in small quantities and in mixtures that are structurally complex, which may differ according to the location of the plants as well as other variables such as the season. This may result in a slow and expensive isolation and purification process. Another issue that has become increasingly important is that of intellectual property right.

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 drug–excipients mixture this confirmed the absence of any chemical interaction between the drug and the excipients. The FTIR spectra of pure drug and physical mixture of drug and different excipients are shown in figure 1 and 2 respectively.

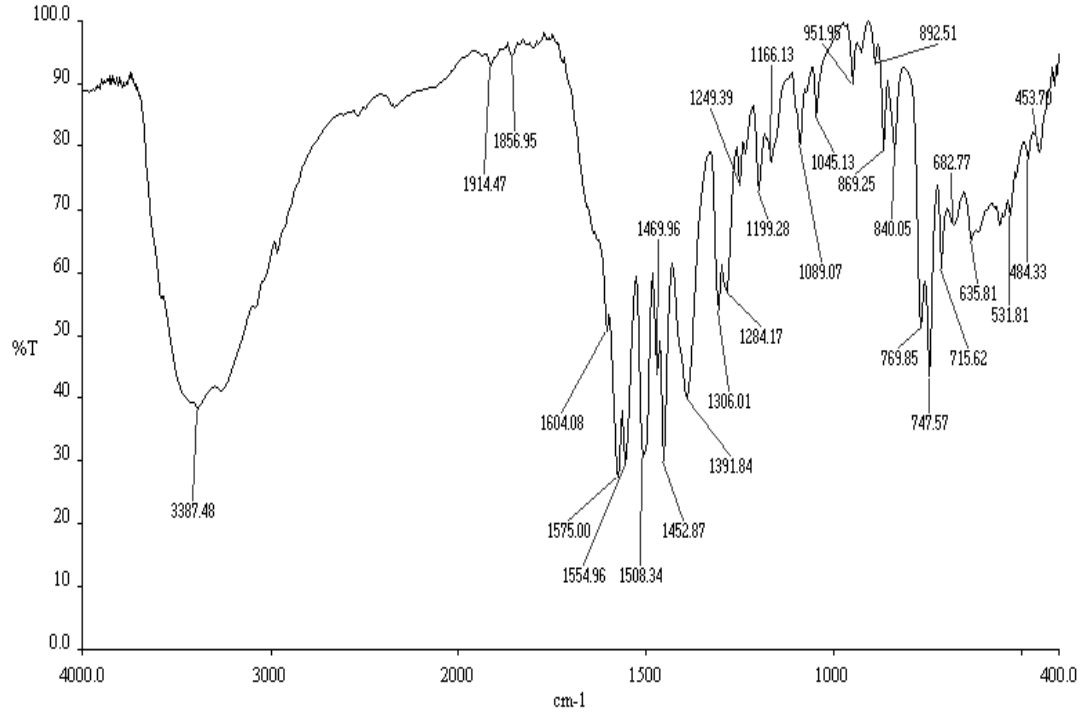

Figure 1: FTIR spectrum of Diclofenac sodium

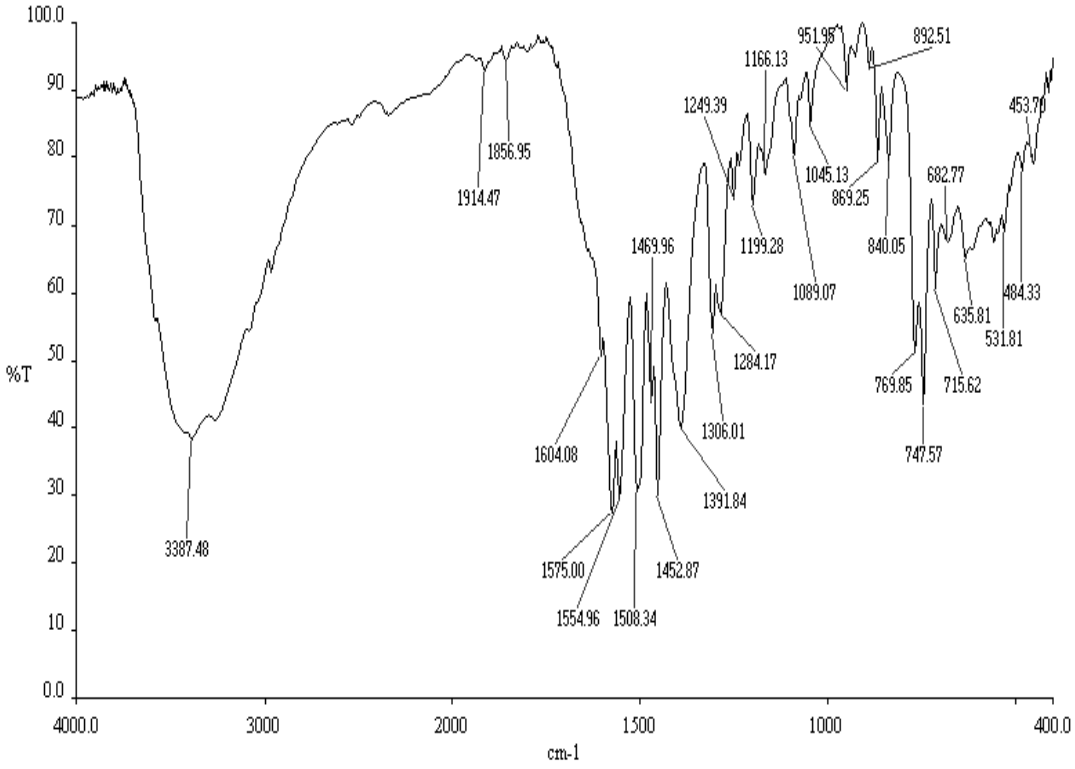

Figure 2: FTIR spectrum of diclofenac sodium and different excipients

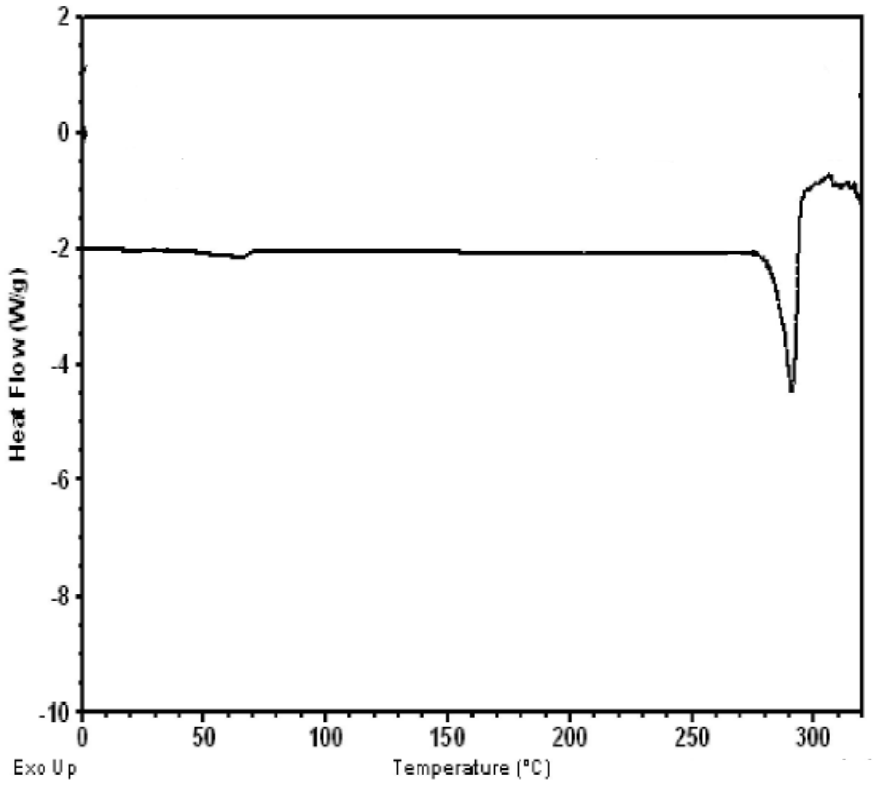

Figure 3: DSC thermogram of diclofenac sodium

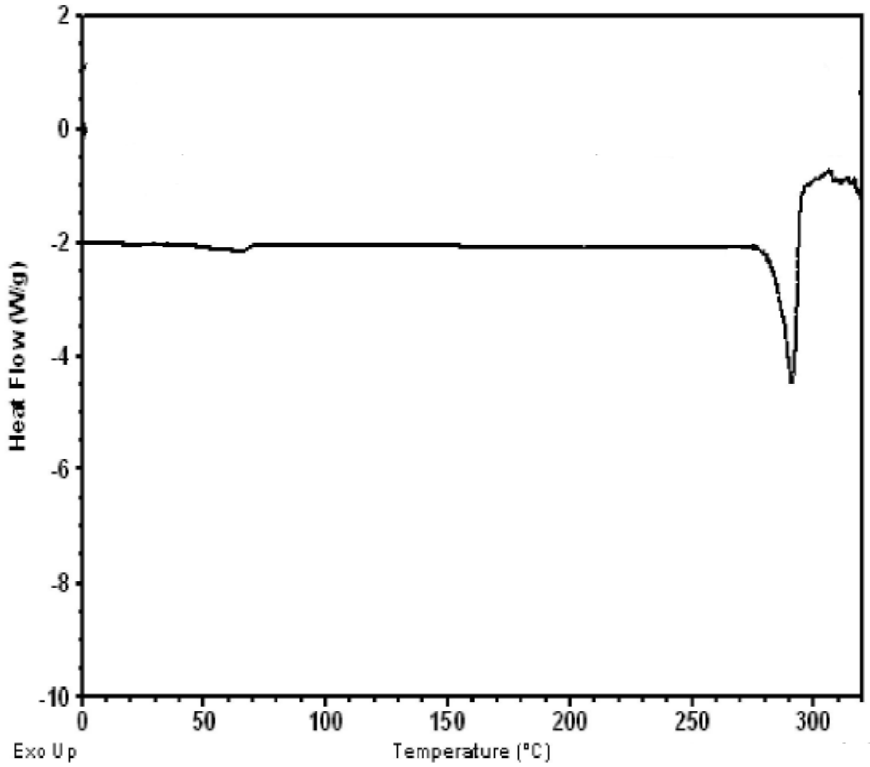

Figure 4: DSC thermogram of Diclofenac sodium and different excipients

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 289^{0}C(range 289-292˚C), 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.

F7 **F2** **F1**

Figure 5: Photographs of selected batches of diclofenac sodium Gel

Physical characteristics of diclofenac gel

The prepared gels were evaluated for drug content, pH, viscosity, *in vitro* diffusion profile and skin irritation test using Guinea pigs. The gelling concentration of the mucilage was found to lie between 3.0 and 4.0% w/w but better gel characteristics were observed at the concentration of 4.0%. The pH of the mucilage was below 6.5, which is ideal for topical application. Eight batches of gel were prepared using different concentrations viz; 3.0, 4, 5 and 6 % w/w of BFM and standard gelling agent like gum tragacanth, 1% w/w of Diclofenac, 0.2% w/w methyl paraben as preservative and 10% w/w glycerin as plasticizer. The pH values of all the batches were determined. There was no significant difference in pH between pure mucilage solution and the different batches of gels formulated. Hence the

gels were ideal for topical application. Among the prepared gels the batch containing 4 % BFM had white color without any characteristic odor and pH of 6.48. Therefore this was considered as ideal batch. The viscosity of the 0.5% aqueous dispersion of BFM was found to be 325cP indicates that the BFM is colloidal in nature following non- Newtonian bodies which do not settle down quickly. The viscosity of the different formulated batches were determined and it was found that gel exhibited pseudoplastic flow (shear thinning) the viscosity was found to be ideal for topical application. The photographs of selected batches of diclofenac sodium gel are presented in figure 5.

The values of spreadability indicate that the gel is easily spreadable by small amount of shear. Spreadability of marketed gel was 6.5g.cm/sec while F2 was 8.0g.cm/sec, indicating spreadability of mucilage at a concentration of 4% containing diclofenac gel was good as compared to the marketed gel. The consistency reflects the capacity of the gel, to get ejected in uniform and desired quantity when the tube is squeezed. Consistency in terms of distance travel by cone was 7.0 mm for F2 batch as compared to 6.5 mm of marketed gel. Consistency is inversely proportional to the distance traveled by falling cone. Hence, the consistencies of mucilage at a concentration of 4% containing diclofenac gel were better as compared with marketed gel. All developed and marketed gel showed good homogeneity with absence of lumps. The developed preparations were much clear and opaque as compared to marketed gel. The skin irritation studies of developed gel were carried out on guinea pig and that confirmed the absence of any irritation on the applied surface. The drug content of all developed gel formulations and marketed formulation shown uniformity in drug content. The physical characteristics of diclofenac gel are presented in table 2.

Table 2: Physical Characteristics of diclofenac gel

Batch No	pH	Spreadability (g.cm/sec)	Consistency (60 sec)	Homogeneity	Skin irritation test	Drug content (%)	Physical Appearance	Viscosity (cP)
F1	6.32±0.01	5.5	6.0	H*	Nil	98.50	Opaque	320
F2	6.48±0.02	8.0	7.0	H	Nil	99.65	White	327
F3	6.45±0.01	6.5	6.2	H	Nil	97.21	White	335
F4	6.47±0.04	5.5	6.5	H	Nil	98.50	Opaque	340
F5	5.81±0.02	5.6	5.5	H	Nil	98.50	Opaque	360
F6	5.77±0.03	5.8	6.0	H	Nil	99.65	White	375
F7	5.79±0.01	6.5	6.5	H	Nil	97.21	White	380
F8	5.81±0.01	7.0	6.0	H	Nil	98.10	Opaque	390
M* gel	6.12±0.03	6.5	6.5	H	Nil	98.87	White	420

**H=Homogeneous; *M= Marketed (Voltaren® gel)*

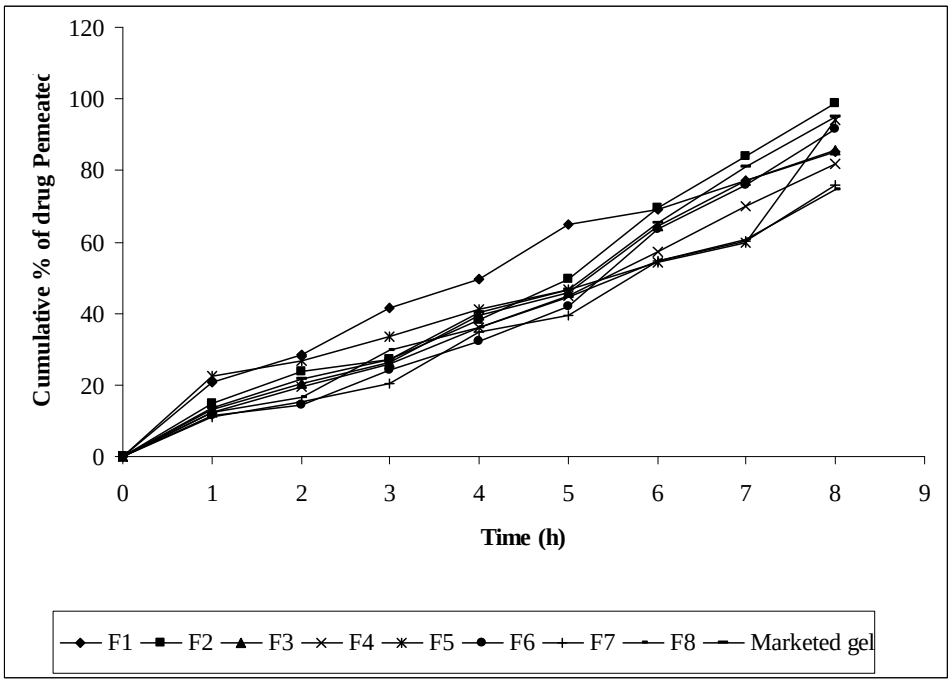

Figure 6: *In vitro* diffusion profile of different batches of Diclofenac gel

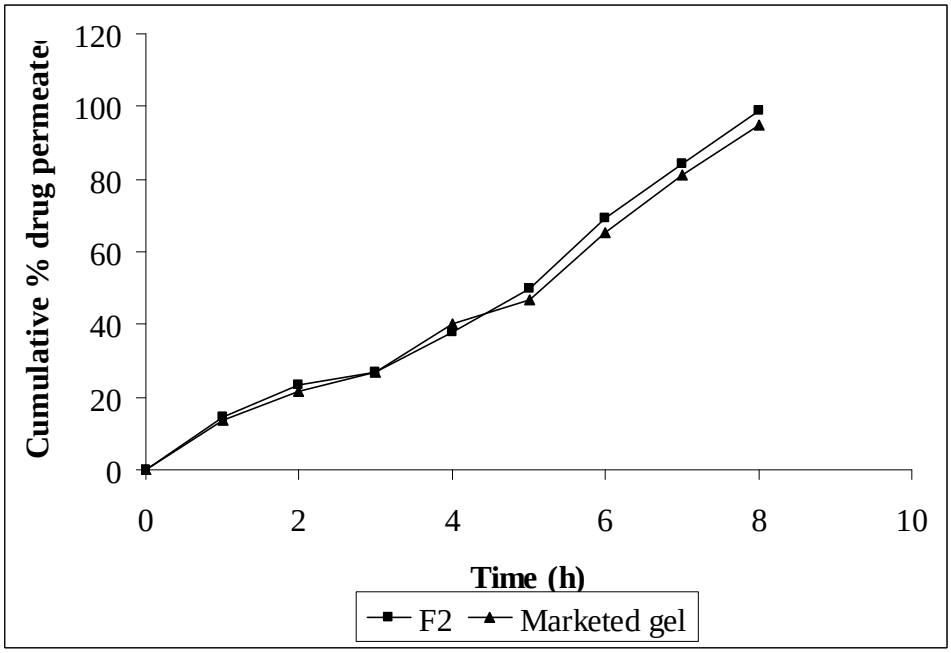

Figure 7: Comparative i*n vitro* diffusion profile of optimized diclofenac gel and marketed gel

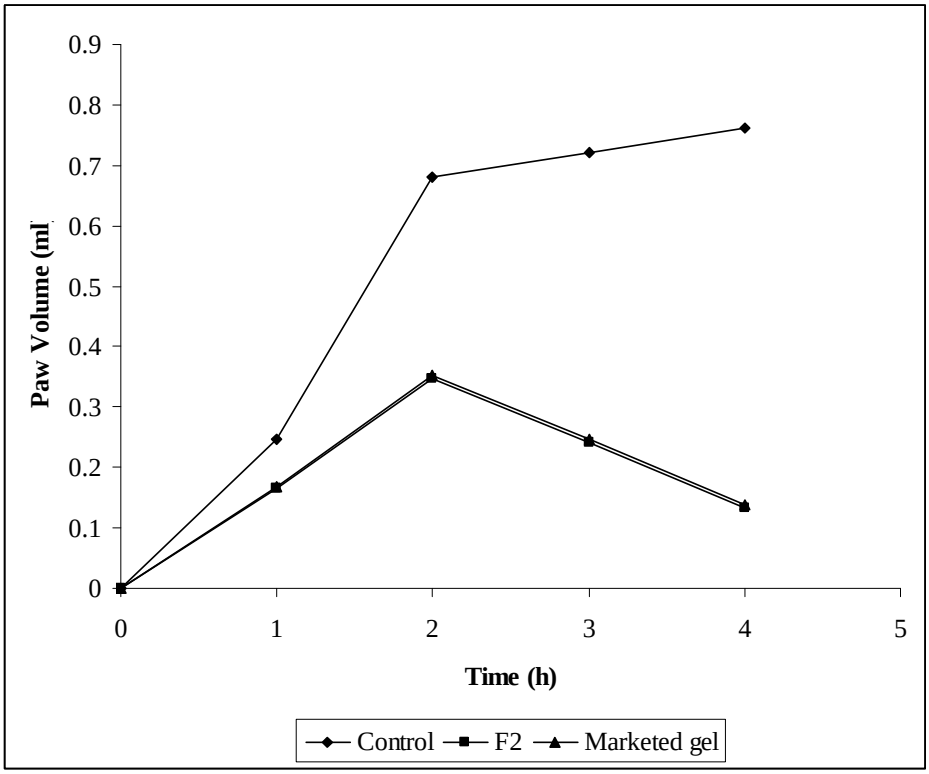

Figure 8: Comparison of rat paws edema volume of optimized diclofenac gel, control and marketed formulation

***In vitro* diffusion study**

The *in vitro* diffusion profiles of diclofenac sodium from the gels containing different concentrations of BFM and gum tragacanth are shown in figure 6. All the gels showed only slight difference in release profile, the gel prepared with 4% BFM showed a maximum release of 98% over a period of 8 h. Hence this was considered as ideal batch for comparison with marketed preparation. The gel prepared with 4% BFM showed a maximum release of 98 % over a period of 8 hr, when compared with the marketed gel showed a maximum release of 94%. The release profile of ideal batch and the marketed formulation were nearly identical over a period of 8 h diffusion study. The comparison of the release profile of ideal batch and marketed gels was shown in figure 7.

Anti-inflammatory activity

Anti-inflammatory activity of the optimized diclofenac gel and the marketed gel was evaluated using carrageenan induced rat hind paw edema method. The result of Anti-inflammatory activity indicated the maximum 82.6 % inhibition of edema was observed with the optimized diclofenac gel formulation at 4h after carrageenan treatment and maximum 81.8% inhibitions of edema was observed with marketed gel formulation at 4 h after carrageenan treatment. It may be due to the initial slower release of drug from the gel formulation. The better anti-inflammatory activity found with the developed gel formulation. The results of anti-inflammatory activity are shown in figure 8 and 9.

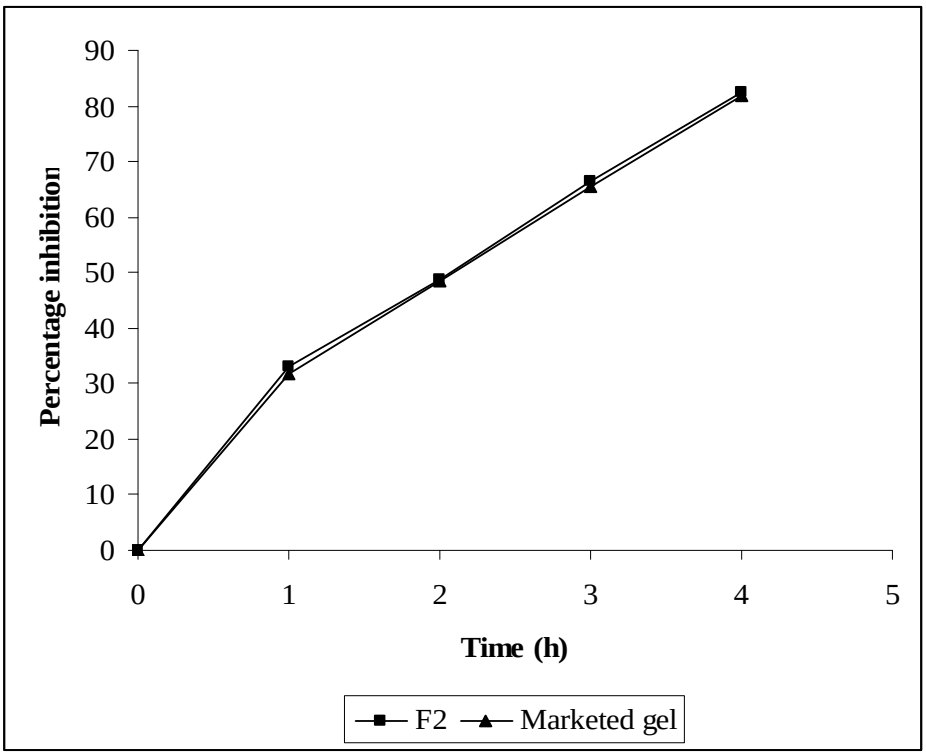

Figure 9: Comparison of Percentage inhibition of paw volume of optimized diclofenac gel and marketed diclofenac gel

Stability study

Optimized diclofenac gel formulation (F2) and marketed formulation were subjected to a stability testing for three months as per ICH norms at a temperature of 40º±2ºC in stability chambers. All selected formulations were analyzed for the change in appearance, pH or drug content and also physical stability and syneresis. During the stability studies the appearance was clear and no significant variation in pH and it is also found that they were physically stable and syneresis was not observed. The results of stability studies of optimized diclofenac gel formulation and marketed formulation were shown in table 3 and in figure 10.

Table3: Stability study of optimized diclofenac gel and marketed gel

Batches	Months	pH	Appearance	Drug content	Consistency	Spreadability
F2	0	6.48±0.02	white	99.65	NC*	NC*
	1	6.51±0.01	white	99.60	NC	NC
	2	6.52±0.01	white	98.52	NSC	NSC
	3	6.54±0.02	white	97.00	NSC	NSC
Marketed gel	0	6.12±0.03	white	98.87	NC	NC
	1	6.15±0.02	white	98.60	NC	NC
	2	6.25±0.03	white	98.50	NSC	NSC
	3	6.30±0.03	white	97.40	NSC	NSC

NC = No change; NSC**= No significant change*

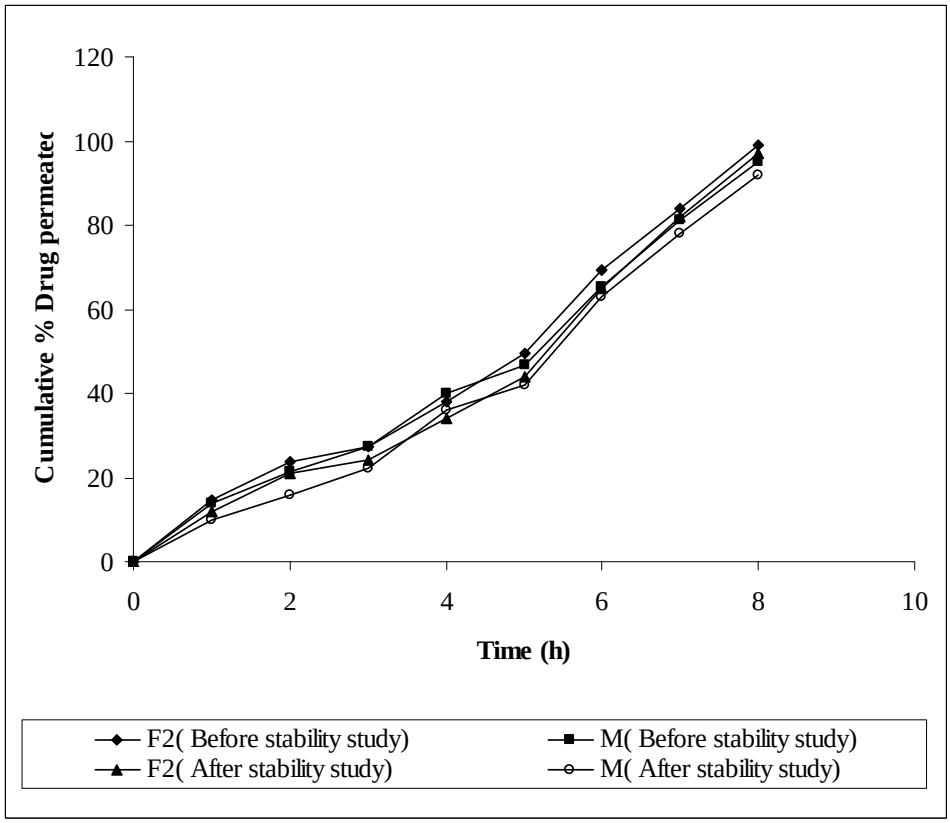

Figure 10: Comparison of *in vitro* dissolution profile of optimized diclofenac gel and marketed gel after stability study

CONCLUSION

The result of the present study demonstrated that the BFM obtained from the endosperm of *Borassus flabellifer* is having a potential gelling property and it can be used for the development of gel formulations, because of its good release profile, water-soluble nature, physical stability and good spreadability. It is effective in a very low concentration as compared to that of the standard gelling agent (tragacanth) used. The formulation F2 consisting of 4% w/w BFM was found to be suitable for topical application based upon its physicochemical properties. While comparing the gelling characteristics of gels prepared by BFM and that of tragacanth it had been found that the gel prepared with 4%w/w of BFM is more effective in comparison to that of the gel prepared by using 6%w/v of gel using tragacanth. The anti-inflammatory activity of this gel formulation in rat hind paw edema model reveals that diclofenac was delivered to the inflammation site at a controlled level over a period of 4 h. Moreover as this plant is widely distributed in nature, *Borassus flabellifer* endosperm are eaten by the local tribes and used as food supplement, available chiefly in India and many other countries and easily available option without destroying the natural sources as compared to that of the other available natural option will be one of the suitable options to utilize as pharmaceutical excipient. Since the primary ingredients are in expensive, devoid of toxicity, biocompatible, biodegradable and easy to manufacture, and they can also be modified to have tailor-made products for drug delivery systems and thus can compete with the synthetic pharmaceutical excipients available in the market. They can be used as gelling agents in place of currently marketed synthetic gelling agents. Further studies will be worthy to establish the BFM as potent gelling agent.

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