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INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

FORMULATION AND EVALUATION OF GEL BASED ON *BORASSUR FALBELLIFER* AS A GELLING AGENT

Rajesh Venkataraman*, M Ashok Prabhu
JSS college of Pharmacy, Ooty, The Tamilnadu Dr. MGR Medical University, Chennai, INDIA.

ARTICLE INFO

Article history
Received 01/07/2012
Available online
30/11/2012

Keywords
Natural gums,
Mucilages,
Diclofenac sodium,
Borassus flabellifer.

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; 2.6, 2.7, 2.8, 2.9 and 3.0 % 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 2.9 % 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.

Corresponding author
Dr. Rajesh Venkataraman
rajeshvenky_research@hotmail.com
Phone :+91-8722620779,

*Please cite this article in press as **Rajesh Venkataraman** et. al. Formulation and evaluation of gel based on Borassur falbellifer as a gelling agent. Indo American Journal of Pharm Research.2012:2(10).*

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INTRODUCTION

Plant products serve as an alternative to synthetic products because of local accessibility, eco friendly nature and lower price compared to imported synthetic products. Natural gums and mucilage have been widely explored as pharmaceutical excipients. Tablet disintegration has received considerable attention as an essential step in obtaining fast drug release. The present study was undertaken to isolate mucilage from *Borassus flabellifer* fruits and explored its use as disintegrant by formulating tablets of Diclofenac diethylammonium. Extracted Mucilage was subjected to toxicity studies for its safety and preformulation studies for its suitability as a disintegrating agent. The extracted mucilage is devoid of toxicity. No chemical interaction between drug and excipients was confirmed by FTIR, TLC and DSC studies. Mouth dissolving tablets of Diclofenac diethylammonium were prepared and compared with different concentrations viz; 0.5,1, 1.5, 2.0 and 2.5%(w/w) of *Borassus flabellifer* mucilage powder. The prepared tablets were characterized by FTIR, TLC and DSC studies. Ten formulations were prepared and evaluated for physical parameters such as thickness, hardness, friability, weight variation, drug content, disintegration time and drug dissolution. The formulated tablets had good appearance and better drug release properties. The study revealed that *Borassus flabellifer* mucilage powder was effective as disintegrant in low concentrations (1%). The mucilage was found to be a superior disintegrating agent than Ac-Di-Sol ®. Studies indicate that the extracted mucilage may be a good source of pharmaceutical adjuvant, specifically a disintegrating agent.

MATERIALS AND METHODS

Materials

Palm fruits, Acetone, Ethanol, Methanol, Glycerol, methyl paraben, Diclofanac diethylammonium,

Extraction of mucilage

The fresh *Borassus flabellifer* fruits were collected and separately washed with purified water to remove dirt and debris. Incisions were made on them, left over night. The fruits were crushed and soaked in water for 5–6 h, boiled for 30 min and left to stand for 1 h to allow complete release of the mucilage into the water. The mucilage was filtered using a multi-layer muslin cloth bag to remove the marc from the solution. Acetone (in the quantities of three times the volume of filtrate) was added to precipitate the mucilage (yield: 40%). The mucilage was separated, dried in an oven at 40°C, collected, grounded, passed through a # 80 sieve and stored in desiccators at 30 °C & 45% relative humidity till use. Physical characteristics of mucilage such as solubility, swelling index, loss on drying, pH and viscosity were studied.

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.

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}. 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.

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 200C over a temperature range 40-3300C under nitrogen environment. DSC analysis of Diclofenac sodium shows the exothermic peak at its melting point i.e. at 2890C(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.

Preparation of Diclofenac diethylammonium gel

Mucilage of *Borassus flabellifer* 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 tablet 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

Evaluation of Diclofenac gel

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 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±10C.

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.

In vitro diffusion profile

Release of diclofenac sodium from various gel formulations and the commercial preparation (Voltaren® gel) were studied employing the permeation apparatus. A glass cylinder with both ends open, 10 cm height and 3.7 cm outer diameter was used as a permeation cell. In vitro release profile of diclofenac diethylammnium were prepared using different gelling concentrations such as 2.5, 2.6, 2.7, 2.8, 2.9 and 3.0 % w/w of *Borassus flabellifer* showed a maximum release of 84.04 %. The in vitro diffusion profiles of diclofenac sodium from the gels containing different concentrations of BFM were carried out. All the gels showed only slight difference in release profile, the gel prepared with 2.9% 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.

Stability testing

All 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). 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.

RESULTS AND DISCUSSION

Among the prepared gels the batch containing 2.9 % 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 values of spreadability indicate that the gel is easily spreadable by small amount of shear, indicating spreadability of mucilage at a concentration of 2.9% containing diclofenac gel was good as compared to the marketed gel.

Table 1: Physical and microbial parameters of the isolated mucilage

Parameter	Value
Sweeling index	-
Loss on drying	-
p^H	-
No of cfu/g of mucilage on bacterium medium	+
No of cfu/g of mucilage on bacterium medium	-

Table 2: Gelling concentration of *Borassus flabellifer* mucilage.

Concentration (% w/w)	Observation of gel	Spread ability
2.2	-	-
2.3	-	-
2.4	-	-
2.5	+	+
2.6	+	+
2.7	+	+
2.8	++	++
2.9	+++	+++
3.0	++	++
3.1	+	+
3.2	-	-

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.

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 consisting of 2.9 % w/w BFM was found to be best formulation in comparing with the different concentration of gelling characteristics of gels prepared by BFM and that of tragacanth.

Table 3: In vitro drug profile of gel prepared with *Borassus flabellifer* (2.9 %w/w)

Time in mins	Absorbance	Concentration (µg/ml)	Amount release (mg)	% release	Cumulative % release
20	0.384	19.260	1.926	19.260	19.206
40	0.692	36.041	3.604	36.041	36.425
60	1.119	59.305	5.930	59.305	60.026
80	1.261	67.042	6.704	67.042	68.228
100	1.409	75.105	7.510	75.105	76.446
120	1.573	84.041	8.404	84.041	85.543

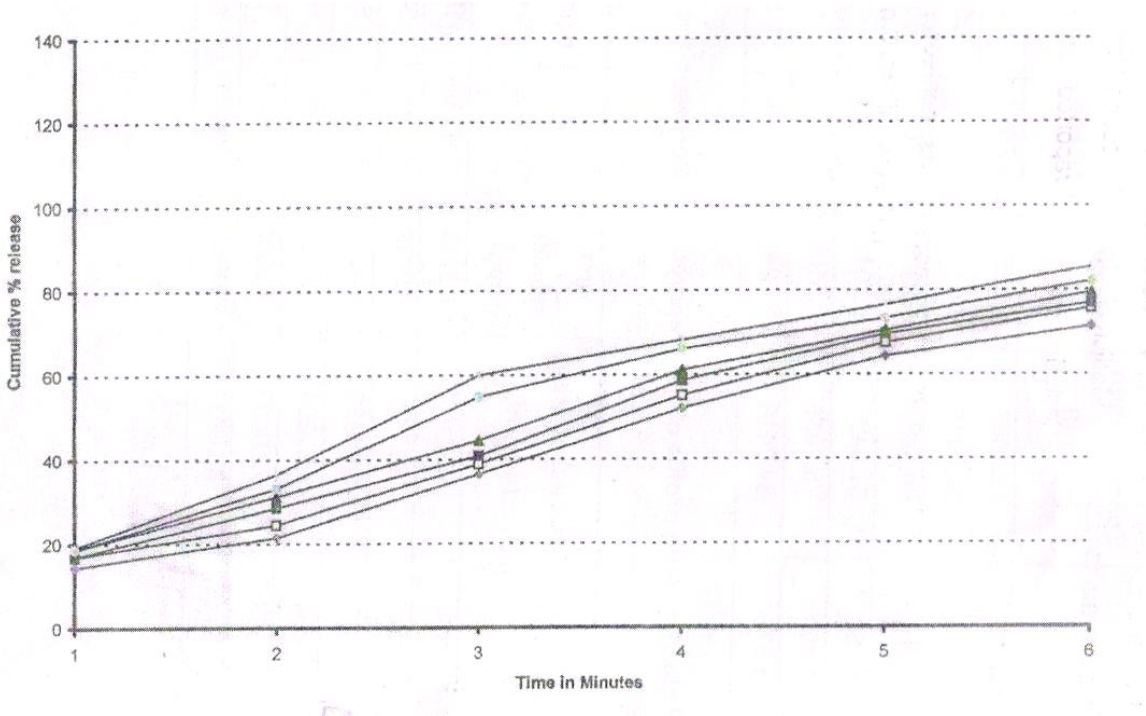

Figure 1: Comparison of batch release with different gelling agent.

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