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Original Article

FORMULATION AND CHARACTERIZATION OF MATRIX TABLETS USING MUCILAGE OF *TINOSPORA CORDIFOLIA* AS NATURAL BINDER

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ABSTRACT

Objective: The present research work was to formulate matrix tablets of diclofenac sodium using mucilage extracted from *Tinospora cordifolia* as a novel binding agent. Also, a comparative study on binding properties of mucilage and carbopol were performed.

Methods: Fresh stems of *Tinospora cordifolia* were collected and mucilage was extracted out using standard method. The isolated mucilage was characterised for physicochemical parameters. Formulation of diclofenac sodium tablets (f1-f6) was done by dry granulation method using 2%, 4%, 6%, 8% and 10% concentration of mucilage of *Tinospora cardifolia* as natural binder. Carbopol 2% was used as synthetic matrix forming agent. Microcrystalline cellulose was used as diluents, magnesium stearate and talc as lubricant. The formulated tablets were evaluated for parameters such as tablet thickness, hardness, weight variation, disintegration time, percent friability and *in vitro* drug release characteristics. The drug release mechanism was determined by fitting the release data into different kinetics models.

Results: The results revealed that all the pre and post compression parameters of the formulated tablets (f1-f6) were in compliance with pharmacopoeial limits. *In vitro* drug release studies showed that formulation f6 containing maximum concentration of mucilage release the drug in a most controlled and sustained manner with maximum drug release of 63.6% in 15 h in comparison with f1(2% carbopol) giving 80% release and was found to be stable for 3 mo as indicated by stability studies. The mechanism of drug releases from formulation f1-f6 was found to be polymer disentanglement and erosion. Preformulation studies using FTIR study reveals that there is no incompatibility between the pure drug and mucilage of *tinospora cardifolia* used.

Conclusion: Based on the experimental findings it can be concluded that *Tinospora cordifolia* mucilage can be used as a release retardant agent in the formulation of sustained release dosage forms.

Keywords: *Tinospora cordifolia*, Natural polymer, Matrix tablets

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INTRODUCTION

In pharmaceutical dosage form various excipients and additives are mixed together to form a suitable dosage form for patient administration [1]. Each and every excipient has its own role to determine the quality and bioavailability of drug and binder is also one of the important excipient in tablet formulation [2]. Binders are the agents which hold various powders together to form a tablet. They impart cohesiveness to the granules to improve compression and flow properties which derived the hardness of tablet [3]. Different binders have different mechanical strengths and drug release properties to achieve different pharmaceutical purposes. While formulating the tablet, extensive knowledge of binder properties for enhancing the strength and also the interaction between various materials constituent should also be considered. This is the reason that development of new excipients as tablet binder is of continuous interest. Different types of polymers both natural and synthetic are used as binders in tablet formulation. Natural binders like starch, gums and mucilage are used widely due to their low cost, less toxicity, biocompatibility and environmental friendly processing[4, 5]. In the present work, an attempt has been made to formulate matrix tablets of diclofenac sodium an effective anti-inflammatory, analgesic and antipyretic drug. It has short biological half-life of 1.2-2h due which it is rapidly eliminated from the system so it would be a great advantage to formulate it as controlled released dosage form using mucilage extracted from fresh stems of *Tinospora cordifolia* (Menispermaceae). The objective of the work was to explore a novel natural binding agent and to formulate sustained released tablets of diclofenac sodium so as to reduce its frequent administration and to enhance patient compliance. Hence the novelty of the proposed work is the use of *tinospora cardifolia* mucilage as matrix forming agent to retard the release of drug.

MATERIALS AND METHODS

Materials

Fresh stems of *Tinospora cordifolia* were collected locally from Rajpura, Punjab. Authentication of the sample was confirmed from Punjabi University Patiala, India and voucher specimen no is 03/2017/CCP (chitkara university, Punjab). Diclofenac sodium was obtained from Yarrow Chem Mumbai, India, carbopol from Ozone international Mumbai India, Magnesium stearate and talc used were of Loba Chem.

Isolation of mucilage

Fresh stems of *Tinospora cordifolia* was collected and thoroughly washed with water to remove impurities. The stem was sliced into half and then cut into small pieces. It was crushed and mixed with distilled water in a beaker and placed on the heating mantle at 100°C for four hours. The mass was kept soaking overnight. After 12 h the mass was filtered with muslin cloth and liquid was kept undisturbed. Carefully, the supernatant was decanted and collected in a separate beaker. Acetone was added slowly to the filtrate till precipitation is completed. The precipitate mucilage was separated and washed thrice with acetone to remove the traces of water. The separated mucilage was spread on a glass plate and dried at 45±0.5 °C. Dried mucilage was grinded and passed through sieve no. #60 and was stored in air tight container [6, 7].

Physicochemical evaluation of mucilage

The isolated mucilage was evaluated for various physicochemical properties [8].

Drug excipient compatibility studies

Drug excipient compatibility studies were performed using Fourier transforms infra-red (FTIR) spectroscopy. FTIR spectra of the diclofenac sodium, *Tinospora cordifolia* mucilage and combined mixture (1:1) of both were taken (Bruker Alpha T) within the range of 3500-500 cm^{-1}

Standard calibration curve of Diclofenac sodium

To plot standard calibration curve of diclofenac sodium 100 mg of drug was weighed and transferred to 100 ml of volumetric flask and 10 ml of methanol was added to dissolve the drug and the volume was adjusted to 100 ml using 0.1 N HCL (stock I). 10 ml of solution was withdrawn from stock I to 100 ml volumetric flask and volume was made up to 100 ml using 0.1 N HCL (stock II). Stock II was then used to prepare working standards by pipetting out 0.2, 0.4, 0.6, 0.8, 1and1.2 ml of solution in 10 ml volumetric flask and finally the volume was adjusted to 10 ml. The absorbance of the resulting solution was measured at 276 nm using UV-VS spectrophotometer [9].

Formulation of diclofenac sodium tablets

Formulation of diclofenac tablets was done by dry granulation method. Microcrystalline cellulose was used as diluents, magnesium stearate and talc as lubricant respectively. 2%, 4%, 6%, 8% and 10% concentration of mucilage of *Tinospora cardifolia* was used as binder. All ingredients were weighed as per the composition given in the table 1 and passed through the sieve no.40 and mixed uniformly in geometrical order. The formulated blend was then subjected to compression to form slugs of hardness 4-4.5 kg/cm^2. The slugs are then milled to granulate and screened through 22/44 mesh. Granules retained on sieve no. 44 were lubricated and evaluated for various pre compression parameters. For comparison carbopol 2% was used as synthetic matrix forming agent.

Pre compression parameters

The formulation blends was characterized for pre compression parameters such as bulk density, tapped density, angle of repose and % compressibility to assess their flow behaviour and were compressed in to tablets using double punch tablet compression machine of weight equivalent to 200 mg [10].

Table 1: Composition of diclofenac sodium matrix tablets formulation (mg)

Ingredients	f1	f2	f3	f4	f5	f6
Diclofenac	50	50	50	50	50	50
Talc	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5
Micro crystalline cellulose	132	132	128	124	120	116
Carbopol	2%	-	-	-	-	-
Mucilage total weight (mg)	-	2%	4%	6%	8%	10%
	200	200	200	200	200	200

(Quantities in mg/tablet)

Characterization of tablets

The prepared sustained released matrix tablets were evaluated for various post compression parameters like physical appearance, weight variation, hardness, friability, and disintegration time as per the official procedure. The hardness of the tablets was evaluated by Monsanto hardness tester. For hardness at random three tablets were taken from each formulation batch and average of three measurements was taken. For friability numbers of tablets equivalent to 6.5 gm were taken and placed in a friability chamber rotated at 25±1 rpm for 4 min and the percentage of weight loss was determined as an indicator of friability. The disintegration test was performed in phosphate buffer pH 6.8 at 37±0.5 °C. The disintegration time reported is an average of three determinations [11].

***In vitro* dissolution study**

The *in vitro* dissolution study of the various tablet formulations was performed using the USP dissolution test apparatus II paddle type (Electrolab, India). The dissolution study was done by placing one tablet in 900 ml of 0.1 N HCL (pH1.2) as dissolution medium maintained at 37±0.5 °C with a speed of 75 rpm.

The amount of drug released was estimated by removing the 5 ml of dissolution medium at different time intervals, filtered (though 0.45 μm), and absorbance was measured at 276 nm using Systronic double beam UV spectrophotometer [12].

Drug release kinetics

To determine the order and mechanism of drug release from the formulated matrix tablets, the *in vitro* release data was fitted to kinetic models viz; zero order, first-order, Higuchi square root equation and Korsmeyer Peppas model.

Q ¼ $Q_0 + k_0 t$ (Zero order)

In Q ¼= In $Q_0 + k_1 t$ (First order)

$Q = K_H t^n$ (Higuchi)

$Q_0^{1/3} - Q_R^{1/3} = K_s t$ (Hixson-Crowell)

$Q/Q_T = K_{kp} I^n$ (Korsmeyer-peppas)

Where Q is amount of drug release at time t, Q_0 is the initial amount of drug, Q_R is the amount of drug remaining at time t, and Q_T is the total amount of drug release. k_0, k_1, k_H, ks and K_{kp} are the kinetic constants for zero order, first order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models, respectively, and n is the release exponent [13-15].

Stability study

The stability studies of selected tablet batches were carried out in stability chamber (Remi Instruments, India) kept at 40±0.5°C and 75% RH conditions for three months. The effects of temperature and time on the physical characteristics and release profile of the tablet were evaluated to study the stability of the prepared formulations [16].

RESULTS AND DISCUSSION

Physicochemical evaluation of mucilage

The standard procedure was used to isolate mucilage from stems of *Tinospora cordifolia.* The total yield of mucilage by acetone precipitation method was found to be 15%. The isolated mucilage was of greyish white colour, odourless, mucilaginous taste and amorphous in nature. The isolated mucilage was evaluated for various physicochemical properties and results are listed in table 2.

Standard calibration curve of Diclofenac sodium

The standard calibration curve of diclofenac sodium was obtained by plotting absorbance versus concentration as shown in fig.1. The standard calibration curve shows the correlation coefficient of 0.990.

Drug-excipients compatibility studies

FTIR spectra of diclofenac sodium, *Tinospora cordifolia* mucilage and mixture of drug and mucilage are given in fig. 2, 3 and 4. Spectral analysis indicated all the important peaks of drug in the FTIR of drug and mucilage which means that diclofenac sodium is functionally compatible with the mucilage.

Table 2: Characterisation of *Tinospora cordifolia* mucilage

S. No.	Properties evaluated	Observations
1.	Colour	Greyish white
2.	Odour	Odourless
3.	Taste	Mucilaginous
4.	Solubility	Forms colloidal solution in water and insoluble in ethanol and acetone
5.	% yield	15%
6.	Average particle size(µm)	161.18±0.23*
7.	Loss on drying	10%
8.	Swelling ratio(in distilled water)	8*
9.	pH (By digital pH meter)	6.2*
10.	Ash Value (%)	2.1±0.02*
11.	Viscosity (1% solution)	353 cps*
12.	Surface tension (0.1% w/v)	79.11±0.32 dynes/cm
13.	Test for Carbohydrates (Molisch's test)	+ve
14.	Test for reducing sugar (Fehling's solution)	+ve
15.	Test for Tannins (Ferric chloride test)	-ve
16.	Test for Glycosides	-ve
17.	Test for Starch	-ve
18.	Test for Terpenoids	-ve
19.	Test for Flavonoids (shinoda test)	+ve
20.	Test for saponins (foam test)	-ve
21.	Test for alkaloids (Mayer's test)	-ve
22.	Test for Mucilage(Ruthenium red test)	+ve
23.	Mucilage+Methylene blue	Deep blue (+)
24.	Mucilage+Aqueous KOH	Swell (+)
25.	Test for chlorides (silver nitrate test)	-ve
26.	Test for Sulphates (barium chloride test)	-ve
27.	Test for uronic acid	+ve

*Data are represented as mean±standard deviation (n=3), +ve = Positive,-ve = Negative

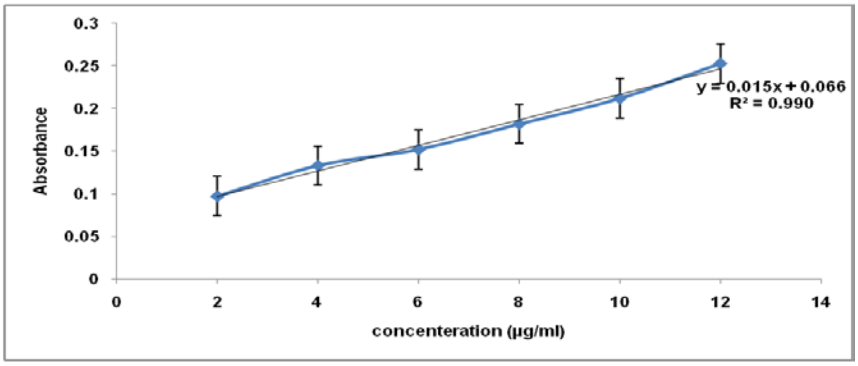

Fig. 1: standard calibration curve of diclofenac sodium

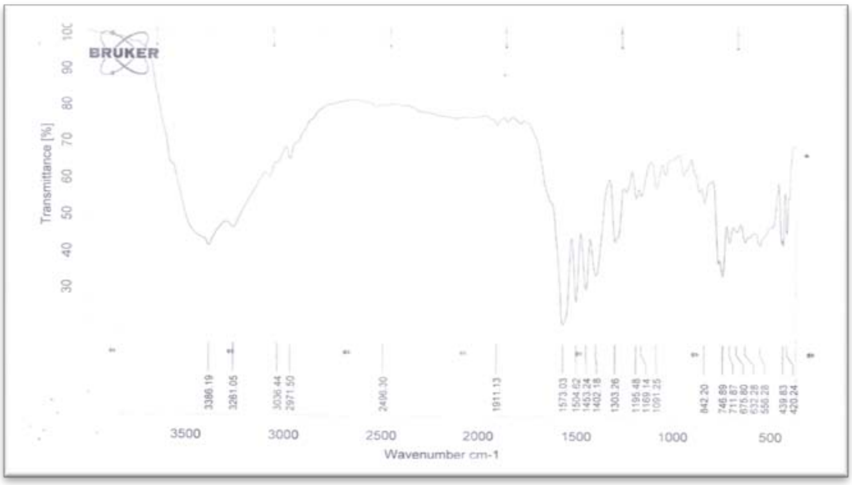

Fig. 2: FTIR of diclofenac

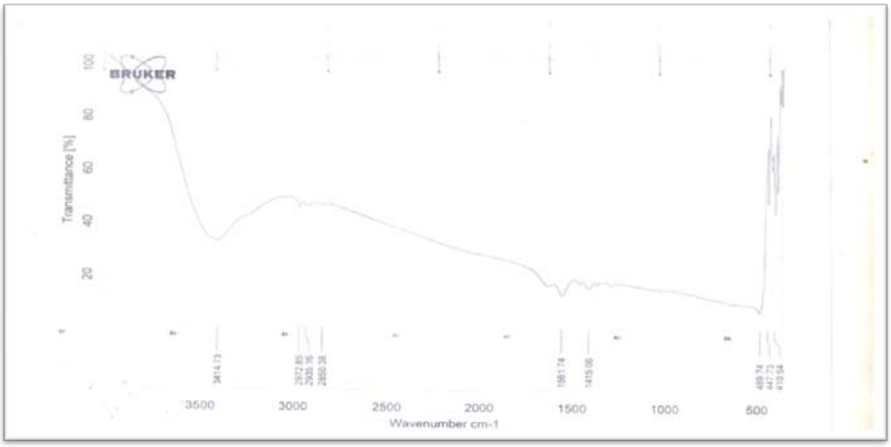

Fig. 3: FTIR of *Tinospora cordifolia* mucilage

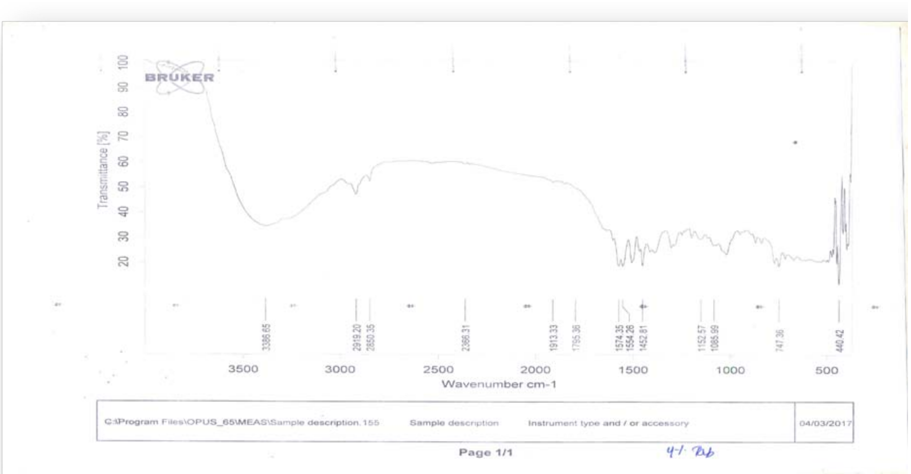

Fig. 4: FTIR of *Tinospora cordifolia* mucilage and diclofenac sodium

Pre compression parameter

Six different formulation batches of diclofenac sodium matrix tablets were prepared using different concentration of mucilage as a matrix forming agent to retard the drug release rate. The flowability of different formulation powder blend was assessed by using hausner ratio, Carr's index and angle of repose. Hausner ratio values ranging between 1.25-1.42 appeared to indicate good flow characteristic. Carr's index<16% of all formulations is indicative of good flow. In terms of angle of repose the value<25° ranging between 25.4-27.2 indicated average to good flowability. The results of pre compression characterisation of formulation blends (bulk density, tapped density, Carr's index) are shown in table 3.

Table 3: Characterisation of formulation blends of diclofenac matrix tablets

Formulation code	Bulk density (g/cc)[a]	Tapped density (g/cc)[a]	Angle of repose[a]	Carr' s Index	Hausnor ratio
f1	0.572±0.01	0.789±0.02	25.6±0.21	12.4	1.25
f2	0.514±0.11	0.763±0.03	27.2±0.11	12.8	1.38
f3	0.557±0.02	0.767±0.11	26.8±0.05	13.2	1.42
f4	0.571±0.10	0.754±0.01	27.5±0.23	12.7	1.26
f5	0.563±0.01	0.761±0.02	25.4±0.01	13.8	1.30
f6	0.523±0.02	0.80±0.11	26.2±0.02	13.4	1.28

[a]mean±SD, *n* = 3.

Post compression parameter

Microcrystalline cellulose was used in the formulation of sustained released matrix tablets of diclofenac sodium because of its versatility as direct compression excipient to improve the tablet ability of physical blend of the formulation. The average weight of all the formulations ranges between 199-206 mg which means all the formulations passed uniformity in weight test as per the pharmacopeia (±7.5% mean weight). All tablet formulations exhibit good mechanical strength with hardness ranging 4.3-6.0 kg/cm^2. Formulation f6 containing 10% of mucilage exhibit maximum hardness of 6 kg/cm^2. The friability test was carried out to measure the ability of tablets to withstand abrasion, chipping during handling, packaging and transportation and as per IP it should not exceed 1%, all formulation showed percent friability in the range between 0.12-0.5% which means they passed the friability test as per the official specifications and has good mechanical resistance. Disintegration time increases as the concentration of mucilage increases, which may be due to strong binding potential of the increasing mucilage concentration and varies between 20-31 min, the results for characterisation are given in table 4 [17]. *In vitro* drug release decreases with increase in mucilage concentration. This may be due to the fact that at higher concentration of mucilage there is formation of dense matrix which reduces the mobility of drug particles and slow down the dissolution rate [18]. With f6 formulation giving 63.6% release after 15 h and formulation f1 containing 2% carbopol showed 80% release after 15 h. *In vitro* drug release profile of all the formulation batches is shown in fig. 5.

Table 4: Characterisation diclofenac sodium matrix tablet formulations

Formulation Code	Weight variation (mg)	Hardness (Kg/cm²)[a]	Thickness (mm)[a]	% friability	Disintegration time(min)[a]	Drug content (%)[a]
f1	201	4.3±0.27	3.7±0.15	0.5	20±0.01	98.2±0.05
f2	200	4.5±0.11	3.2±0.02	0.21	22±0.33	99.4±0.12
f3	205	4.6±0.23	4.3±0.21	0.3	24±0.24	97.5±0.11
f4	199	5.0±0.15	4.7±0.02	0.2	25±0.06	99.3±0.25
f5	200	5.3±0.22	4.0±0.05	0.3	30±0.32	99.2±0.01
f6	206	6.0±0.23	3.7±0.21	0.12	31±0.24	98.7±0.21

[a]mean±SD, $n = 3$.

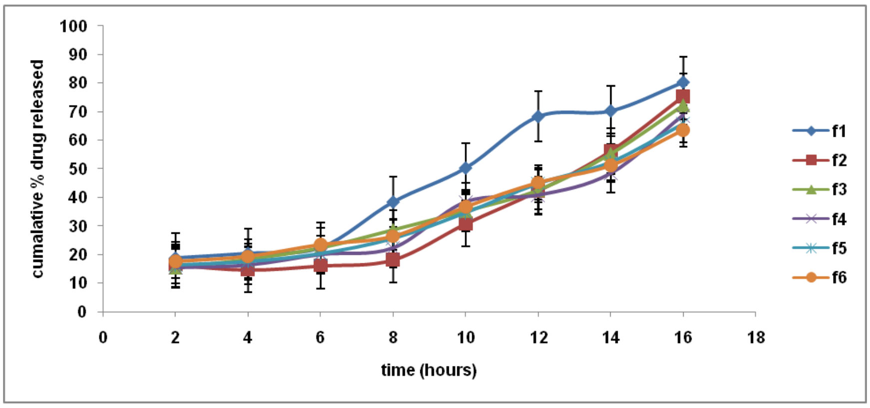

Fig. 5: *In vitro* drug release of dicofenace matrix tablet

The release data as given in table 5 was fitted to various mathematical models to evaluate the kinetics and mechanism of drug release. The kinetic data of all formulations f-1 to f-6 could be best expressed by zero order equation as the plots showed highest linearity (R^2: 0.902 to 0.954). The n values obtained from Korsmeyer Peppas plots range from (0.804 to 1.122) indicate that mechanism of release from formulations f-1tof-6 was polymer disentanglement and erosion.

Table 5: Release kinetic study diclofenac matrix tablets in 0.1N HCl at 37°C

Formulations	Zero order	First order	Higuchi	Korsmeyer-Peppas	
	(R^2)	(R^2)	(R^2)	(R^2)	Slope n
f1	0.954	0.915	0.961	0.942	1.122
f2	0.952	0.829	0.858	0.860	0.860
f3	0.928	0.937	0.894	0.963	0.861
f4	0.902	0.936	0.883	0.920	0.923
f5	0.939	0.936	0.928	0.946	0.944
f6	0.950	0.951	0.933	0.944	0.804

Stability studies

On the basis of *in vitro* drug released characteristics f-6 formulations was selected for stability studies. The test parameters were disintegration time, hardness, *in vitro* drug release and drug content. The results of stability study are shown in table 6, which indicates no remarkable change in the physical characteristics and release profile of the prepared formulation and was found to be stable for three months.

Table 6: Stability studies of f6 formulation at 40 °C±2 °C/75% RH±5%

Parameter	Days			
	0	15	30	60
In vitro drug release (%)	63.6	63.4	63	62.6
Hardness (kg/cm²)[a]	6.0±0.01	6.2±0.01	6.0±0.01	6.3±0.01
Disintegration time (min)[a]	31±0.01	32.3±0.11	31±0.25	30±0.06
Drug content[a]	98.7±0.21	97.2±0.03	98.2±0.11	98.3±0.22

[a]mean±SD, $n = 3$.

CONCLUSION

The experimental data of the present research work carried out indicated the potential of *Tinospora cardifolia* mucilage as release retardant agent in the formulation of sustained release tablets of diclofenace. *In vitro* released studies of formulation f1-f6 showed, formulation f6 containing maximum amount of mucilage release the drug in a controlled and sustained manner with maximum amount of 63.6% drug in 15 h. Hence it is concluded that *Tinospora cardifolia* can be utilized as natural matrix forming agent in the formulation of sustained released tablets.

AUTHORS CONTRIBUTIONS

Ritima Sharma and Shivali Garg helped in the isolation and physico chemical characterisation of mucilage from the plant. Tejeswini Vasisht, Rajni Bala and Reecha Madaan were the main investigators of this project.

CONFLICTS OF INTERESTS

All authors have none to declare

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