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Original Article

EXPLORING PROPERTIES OF SWEET BASIL SEED MUCILAGE IN DEVELOPMENT OF PHARMACEUTICAL SUSPENSIONS AND SURFACTANT-FREE STABLE EMULSIONS

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ABSTRACT

Objective: The objective of the investigation was to isolate mucilage from sweet basil seeds and explore its physicochemical properties for the development of pharmaceutical suspensions and surfactant-free stable emulsions.

Methods: Possible applications of sweet basil seed mucilage in the pharmaceutical field for dosage form development are being explored. The physicochemical and functional properties of the mucilage from the seeds of the *Ocimum basilicum* L. (Sweet basil) have been investigated for stabilization of suspensions and emulsions. The following analyses were performed: FTIR spectroscopy, phytochemical tests, XRD, swelling and rheological studies.

Results: The analyses showed that the mucilage is rich in glucose, mannose, and xylose. High swelling index values varying from 100±10 to 200±13%, high water-holding capacity of 97.5±2.4 g/g mucilage and reasonable oil holding capacity of the mucilage (13.2±1.3 g/g mucilage) makes it an ideal candidate for utilization as viscosifier and stabilizer of suspensions and surfactant-free emulsions. Adult and paediatric paracetamol suspension formulations with 1%w/v mucilage have exhibited flocculated nature and good stability owing to its high sedimentation volume(F= 0.85-0.98) and good redispersibility. Sunflower oil emulsions prepared with 0.25%w/v mucilage demonstrated emulsion stability index of 105.714 on 5th day and extremely low creaming rate of 0.0004 cm/h thus confirming maximum stability compared to emulsions developed with 0.3-0.5% w/v mucilage.

Conclusion: The mucilage isolated from *Ocimum basilicum* L. seeds may be regarded as a functional biomaterial for pharmaceutical use to ensure quality and stability of liquid dosage forms.

Keywords: Basil seed mucilage, Oil-holding capacity, Surfactant-free emulsion, Suspension, Water-holding capacity

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INTRODUCTION

Typically, excipients of synthetic origin are being widely used in the formulation of stable and effective pharmaceutical suspensions and emulsions as drug delivery vehicles. However, there is a need to explore easily available, comparatively cheaper, non-toxic and biodegradable materials of plant and animal origin as suspending agents and emulsifiers. Gums and mucilages are being currently investigated as natural excipients for conventional and novel dosage forms. Mucilage is a long chain polysaccharide substance extracted as a viscous or gelatinous dispersion from plant parts (roots, seeds, leaves, fruits etc.) and containing monosaccharides such as L-arabinose, D-galactose, L-rhamnose, D-xylose, and galacturonic acid in various proportions [1, 2]. Differences in branching, molecular weight ranges, ionic charge of these non-starch polysaccharides have a profound influence on their water absorption capacity, water holding capacity, rheological and swelling behavior of their dispersions in aqueous medium and ultimately their applications in pharmaceutical field in design and formulation of sustained-release tablets, suspensions, emulsions, gels etc. [3].

Natural gums from *Irvingia gabonnsis, Albizia zygia, Grewia mollis,* and *Khaya grandifolia* have been successful in improving the quality attributes of suspensions due to their ability to impart high viscosity to the dispersion medium on exposure to the aqueous medium by virtue of their swellability [4].

Surfactant-free emulsions or quasi-emulsions have been successfully developed for topical application by employing polymeric emulsifiers of high molecular weight such as hydroxypropyl methylcellulose (HPMC) which increase the viscosity and add yield value to the external phase [5]. Other approaches for surfactant-free emulsions or pickering emulsions or atypical emulsions have also been reported [6-8]. Emulsion stabilisation may occur via different mechanisms [9]. Natural or synthetic polymers of high molecular weight such as xanthan gum, hydroxyethyl cellulose, alginates, carragenans produce high viscosities at low stresses or shear rates. Such high values prevent creaming or sedimentation. However, the concentration of natural gum or mucilage as emulsion stabilizer is crucial in the formation of stable surfactant-free emulsions [10].

The widespread availability of *Ocimum basilicum* L. (Fam. Lamiaceae) chiefly in India and many other countries, high yield, reported medicinal uses of its seeds, simplicity of extraction and its use as food supplement serve as an impetus for its commercial exploitation [11]. The secondary wall of the epidermis cells of the sweet basil seed is mucilaginous and produces a thick layer of mucilage around the testa within first 20 min after hydration [12, 13].

Optimization of extraction conditions for mucilage from sweet basil seed and production of mucilage aerogels have been reported in the literature [14]. Basil seed mucilage has been investigated as a substitute of fat source in the preparation of spongy cake and as rate controlling matrix in the development of sustained release tablets [15]. However, no study could be found indicating the use of sweet basil seed mucilage as a suspending agent or emulsion stabilizer in the formulation of pharmaceutical suspensions and surfactant-free emulsions. To satisfy the ever-increasing demand for highly specific and functional biomaterial as a pharmaceutical excipient, *Ocimum basilicum* L. has been selected in the present investigation for the purpose of isolation of mucilage from its seeds and evaluation of the physicochemical and functional properties of the mucilage, to employ it as suspending agent and as an emulsion stabiliser.

MATERIALS AND METHODS

Materials

Sweet basil seed i.e. *Ocimum basilicum* L. seeds used for mucilage extraction was purchased from the local market, Kolkata, West Bengal, India. The seeds were cleaned and stored in airtight containers until further use. Identification and authentication of the *Ocimum basilicum* L. plant specimen D-C1 was done at Central National Herbarium, Botanical Survey of India, Shibpur, Howrah. Sunflower oil used in the

preparation of emulsions was also procured from the local market. All reagents used in the investigation were of analytical grade and were purchased from Merck Specialities Pvt. Ltd. or prepared from the raw materials in the laboratory according to standard procedures (as for phytochemical reagents). For rheological measurements and for suspensions, sodium carboxymethylcellulose (Na-CMC) was selected as the control. Guar gum was the control of choice during the manufacture of emulsions. For the swelling study, psyllium was employed as the control.

Macroscopy of seed

The three principal dimensions of the seed, length (L), width (W) and thickness (T) were measured. The geometric diameter (Dg), sphericity (Φ) and surface area (S) of the seed were determined as follows [3]:

$$Dg = (LWT)^{1/3} \quad \text{.... (1)}$$

$$\Phi = \frac{(LWT)^{2/3}}{L} \quad \text{.... (2)}$$

$$S = \pi(Dg)^2 \quad \text{.... (3)}$$

Water Absorption Capacity (WA*b*C)

The water absorption capacity was determined according to AACC method 88-04 [16]. Approximate water absorption capacity was first determined by weighing 0.1 g (dry basis) of a sample and adding water until saturation (approximately 5 ml). It was then centrifuged in a centrifuge (REMI Test Master) at 2000×g for 10 min. Excess water was discarded and the residue was weighed. Approximate water absorption capacity was calculated by dividing the increase in sample weight (g) by the quantity of water needed to complete original sample weight to 15 g. Average water absorbed was calculated, and the WAbC was calculated and expressed as g water absorbed per g of the sample [11, 16, 17].

Extraction of *Ocimum basilicum* L. seed mucilage

Basil seed mucilage was obtained by the thermal-hydration process. The whole nutlets were soaked in hot distilled water, in a seed: water ratio of 1:50. The mucilage of basil seeds was extracted by continuous stirring on a mechanical stirrer at 1500 rpm for 4 h at 40 °C. Vacuum filtration was carried out to remove all likely seed residuals from the separated mucilage. Pure ethanol was added to the extracted mucilage in the 3:1 ratio and left overnight at 4 °C for removal of protein and ash content. Crude extract was concentrated at 55 °C with rotary vacuum evaporator (REMI Instruments Ltd.) to remove extra water/ethanol content and then dried on stainless steel trays in a laboratory oven at 50 °C for 6 h to produce dry basil seed mucilage (BSM) [14]. The dried mucilage was ground into powder to pass 200 µm sieves. The mucilage powder was stored in a desiccator at a temperature of 30 °C and 75%RH for further studies [3].

Chemical characterization of seed mucilage

Melting point

The temperature at which the sample decomposes was noted with the help of melting point determination apparatus (Testing Instrument Manufacturing, India) [3].

Fourier-transformed Infra-red (FTIR) spectroscopy

FTIR spectroscopy was carried out in order to assign functional groups to the isolated mucilage [18]. For sample preparation, the samples were powdered as finely as possible to minimize IR scattering on the particle surface, and the portion of the reflected light and pellets were prepared using potassium bromide. The potassium bromide-sample pellets were observed in the FTIR spectrometer (Bruker, Alpha-T) in the range 400–4000 cm^{-1}.

Phytochemical test

Dried and powdered BSM were analyzed for the presence of various phytoconstituents such as carbohydrates, alkaloids, phenols, flavonoids, saponins, tannins, steroids, glycosides based on the standard protocols [19].

Physical characterization of seed mucilage

X-ray Diffraction (XRD) study

Pure samples of BSM were analysed for X-ray diffractogram [RIGAKU–(Japan), ULTIMA–III]. The Cu Kα radiation (λ=1.541 Å) wasNi-filtered. A system of diverging and receiving slits of 10 mm respectively was used. The pattern was collected with 40 kV of tube voltage and 30 mA of tube current and scanned over the 2θ range of 10-90 ° [20].

Water-holding (WHC) and oil-holding capacity (OHC)

For estimation of WHC and OHC, 0.1 g (d. b.) of the sample was weighed and then stirred into 20 ml of medium (distilled water or sunflower oil) for 1 min. Sunflower oil density was 0.93 g/ml [21]. The corresponding mucilage dispersions were then centrifuged at 2200 X g for 30 min, and the supernatant volume was measured. Water-holding capacity was expressed as g of water held per g of sample, and oil-holding capacity was expressed as g of oil held per g of mucilage [17].

Swelling study

Powdered samples were added to a definite volume of water in varying concentrations (0.1-0.5% w/v). It was then left undisturbed for 6 h at controlled room temperature (25 °C). The volume occupied by mucilage was measured every hour and at 6th hour, the supernatant was decanted and the volume of the final swollen gel was recorded. The swelling index was calculated as follows [3]:

$$Swelling\ Index\ (\%) = \frac{Final\ volume\ of\ swollen\ sample - Initial\ volume\ of\ sample}{Initial\ volume\ of\ sample} X\ 100 \quad (4)$$

Rheological study

BSM dispersions (0.1–0.5% w/v) were prepared in distilled water using a mechanical stirrer at 40 °C. After cooling, the dispersions were left overnight at 4 °C to ensure complete hydration prior to the rheological measurements. The viscosity of BSM dispersions were determined using Ostwald viscometer at 25 °C by employing the following equation:

$$Relative\ Viscosity = \eta_{rel-mucilage,conc} = \frac{\rho_{mucilage}\, t_{mucilage}}{\rho_{water}\, t_{water}} \quad \text{.... (5)}$$

Relative viscosity of BSM dispersion (0.25%w/v) was also determined in the presence of 1%v/v Tween 80 and 9%v/v propylene glycol as they are common additives in preparation of conventional liquid preparations [22].

Functional characterisation of seed mucilage

As suspending agent

Paediatric and adult paracetamol (PCM) suspensions were prepared according to the composition given in table 1. The prepared suspensions were evaluated for pH, sedimentation volume (F), re-dispersibility and flowability for a period of 5 d at 25 °C [23, 24].

Table 1: Composition of paediatric and adult suspensions

Ingredients	Composition (% w/v)	
	Paediatric	Adult
BSM	1	1
Paracetamol	2.4	10
Methyl paraben	0.2	0.2
Propyl paraben	0.2	0.2
Tween 80	2-4 drops	2-4 drops
Glycerin	5	5
Distilled water	qs to 30 ml	qs to 30 ml

As emulsion stabiliser

Mucilage dispersions (0.25, 0.3-0.5% w/v) were prepared as done for rheological characterisation. Four batches of oil-in-water emulsions (O: W=20:80) (E1-E4) were prepared with sunflower oil by homogenizing at 11,000 rpm for 2 min and dispensed in amber coloured glass bottles with metal caps and stored at 25 °C. An aliquot of the sample was taken from the bottom of the emulsion at various time intervals of 0, 24, 48, 72, 96 and 120 h, diluted 1000 times with distilled water and vortexed for 1 min. The absorbance of the diluted emulsion was recorded spectrophotometrically at 500 nm.

The turbidity of the emulsion (T, expressed in m^{-1}) was calculated using

$$T = 2.303 \times \frac{A}{L} \times D \quad \text{.... (6)}$$

Where A is the absorbance at 500 nm, D is the dilution factor, and L is the path length of the cell (m).

The emulsion activity index (EAI, expressed in g. m^{-1} ml^{-1}) was calculated using

$$EAI = \frac{2 \times T_0}{\emptyset \times C \times 1000} \quad \text{.... (7)}$$

Where T_0 is the turbidity of fresh emulsion (at t=0 h), $\emptyset$ is the volume fraction of oil (dimensionless) and C is the concentration of the mucilage present in the emulsion ($mgml^{-1}$).

The emulsion stability index (ESI, expressed in terms of time) was calculated as follows

$$ESI = \frac{A_0 \times A_t}{A_0} \times t \quad \text{.... (8)}$$

Where t is the time interval (h) and A_0 and A_t are the absorbances at t=0 and after 24 h respectively [18].

Creaming, coalescence and flocculation studies

Emulsion (10 ml) was poured into a measuring cylinder, covered and allowed to stand undisturbed for 5 d at 25 °C. Cream height was measured at an interval of 24 h. The emulsions were carefully observed daily for signs of coalescence and flocculation throughout the period of the experiment [25].

Globule size determination

On the 5th day of observations on sunflower oil emulsion, a drop was placed on a glass slide, mixed with a drop of methylene blue and viewed under an optical microscope (Magnus Microscope, Olympus Opto System India Pvt. Ltd.). The colourless oil droplets were measured and analyzed for average globule size from 100 observations [25].

Statistical analysis

Data have been obtained from each experiment in triplicate (n=3) and were subjected to statistical analysis using one-way analysis of variance (ANOVA). Results are quoted as significant where $p<0.05$.

RESULTS AND DISCUSSION

Macroscopy of seed

The geometric diameter, sphericity and surface area of the seed were 1.24±0.31 mm, 0.62±0.01 and 4.83±0.5 mm^2 respectively. Standard deviations are listed, and data represent the averages and of 3 experiments. The water absorption capacity (WAbC) of the seed was found to be 45.5 g of water per g of seeds.

Extraction and characterisation of seed mucilage

The yield of the mucilage from the basil seeds was approximately 20-25% of dry seed mass. In the literature, yields of 7.86-25 %have been reported [13, 15]. The mucilage started to char or decompose at 250 °C. Decomposition or oxidative degradation of the chia seed gum was noted with an endothermic peak being observed at 244 °C [18].

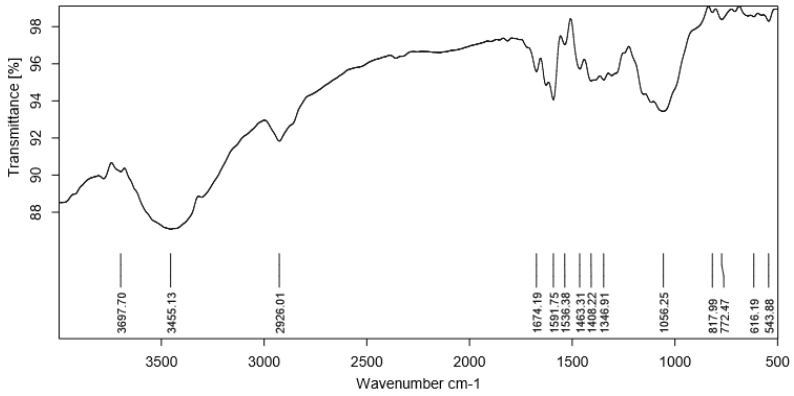

Fig. 1: FTIR spectrum of BSM

Chemical characterization of seed mucilage

FTIR spectroscopic features

FTIR spectrum (fig. 1) of BSM shows characteristic bands at approximately 3455.13, 2926.01 and 1674.19 cm^{-1}, which are commonly observed in polysaccharides and represent hydroxyl (-OH) stretching, C-H stretching of the CH_2 groups, and–COO^- (asymmetric vibrations) groups, respectively, in carbohydrate and uronic acid molecules. Similar functional group assessment has been reported with xanthan gum and guar gum [26]. In a previous study, the peak at 1589 cm^{-1} observed for basil seed mucilage was attributed to N-H primary amide. It was suggested that the basil seed mucilage is neither starch nor cellulosic polysaccharide, but possesses peptide cross-links and amino sugars [14]. The absorption band at 1674.19 cm^{-1}may be attributed to ring stretching of mannose as has been reported for locust bean gum and guar gum [27].

Phytochemical test

Preliminary phytochemical screening of *Ocimum basilicum* L. seed mucilage isolated in the present study revealed the presence of non-reducing sugars, proteins, gums, and mucilage and confirmed the absence of alkaloid, tannins and saponins.

Physical characterization of seed mucilage

XRD

X-ray diffraction pattern is represented in fig. 2. BSM presented amorphous structure with very low overall crystallinity. The crystalline regions were seen at an angle (2θ) of 23-25 ° [20].

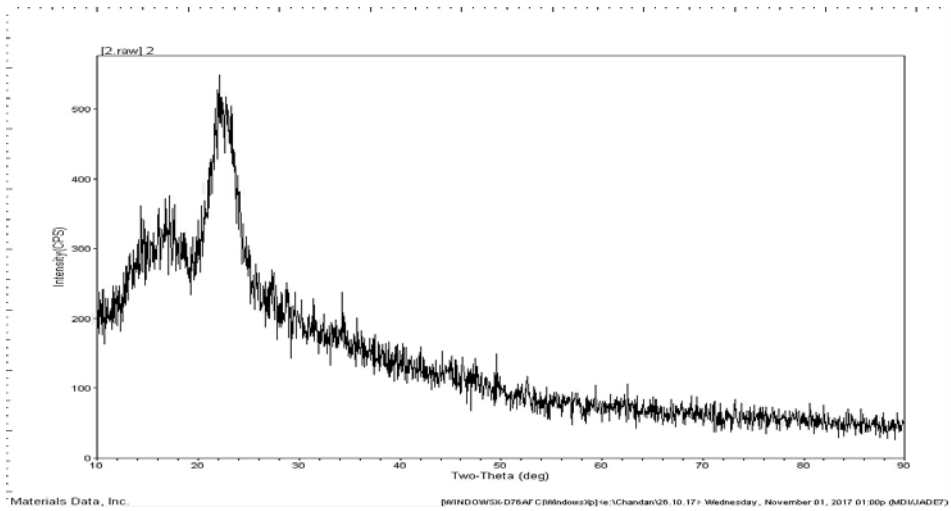

Fig. 2: X-ray diffractogram of *Ocimum basilicum* L. seed mucilage

Water-holding (WHC) and oil-holding capacity (OHC)

The water-holding capacity and oil-holding capacity of mucilage from sweet basil seeds have been found to be 97.5±2.4 g/g mucilage and13.2±1.3 g/g mucilage respectively. The reported parameter values for fatted chia gum are 25.7 g oil/g fiber and 103.2 g water/g fiber respectively. From the study, it can be deduced that the mucilage will demonstrate good swelling index and may function as a suspending agent. The study also indicates that BSM can be used as an emulsion stabiliser since it can entrap oil molecules which is attributed to its protein content as evidenced from FTIR study and phytochemical profiling of the mucilage. An absence of hemicellulose also accounts for the high OHC value of BSM [17].

Swelling studies

An abundance of hydroxyl and carboxylic groups, as well as mannose and glucose sugars in BSM (fig. 1) and water holding capacity value of the mucilage, indicate its hydrophilic nature and its propensity to imbibe large amounts of water or biological fluids and swell. The swelling ability of the mucilage may endow it to act as a hydrogel which may replace synthetic hydrogels used frequently in different liquid dosage forms as suspending agents or emulsion stabilisers. Experimentally, BSM has been found to absorb 84 times its own weight of water. Swelling of hydrogel has a profound influence on the rheological property of the continuous phase of heterogeneous biphasic dispersions such as suspensions and emulsions. Viscosity enhancement can induce better protection against sedimentation of suspended particles or coalescence of the dispersed oil globules [28].

Swelling index values of BSM in water at concentrations varying from 0.1-0.5% w/v were in the range of 100±10 to 200±13 at 25 °C. Concentration-dependent changes in the values are graphically represented in fig. 3. Rapid swelling was observed in the first 3 min followed by the decline in the rate of swelling till equilibrium condition was achieved at 4 h.

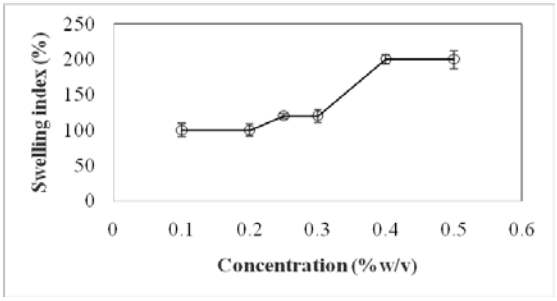

Fig. 3: Swelling index of BSM in water. Error bars represent standard deviations for 3 experiments

Rheological study

Morris proposed gel formation in mucilage by overlapped and entangled flexible random coil chains. The mechanism of gelation is considerably more complicated for a food polymer than a synthetic polymer, because of the involvement of factors such as coil–helix transitions, disulfide bonds, and hydrogen bonds [29, 30].

With an increase in the concentration of BSM from 0.1% to 0.5% (w/v) (fig. 4), the viscosity of the dispersions increased probably due to the formation of aggregates with larger sizes. In dispersions of lower concentrations, the randomly positioned chains of polymer molecules might have become aligned with one chain adjacent to another in the direction of the flow, generating dispersions with lower viscosity. Similar behavior was observed for dispersions of flaxseed, *Opuntia ficusindica*, *Lepidium sativum*, tragacanth, and *Lepidium perfoliatum* gums [31]. Owing to its viscosity-enhancing property, high values of WHC and OHC, good hydration and swelling ability, BSM dispersion can be used to control flow properties of suspensions and also to stabilize emulsions by virtue of rendering protection against coalescence and creaming of dispersed oil globules.

Propylene glycol and Tween 80 produced 55±6 and 80±4 % reduction in relative viscosity of BSM in comparison to that of BSM dispersion in the absence of additives and thus should be used with care in liquid preparations. Propylene glycol is reported to increase the swelling time of tragacanth mucilage [32].

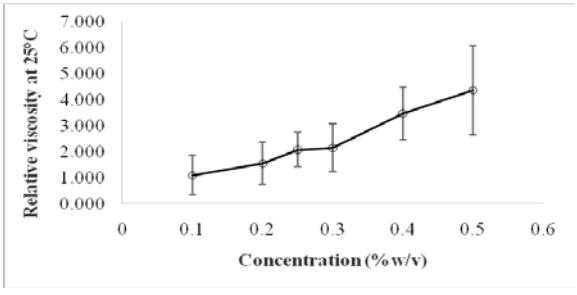

Fig. 4: Effect of mucilage concentration on relative viscosity. Error bars represent standard deviations for 3 experiments; mucilage concentration had significant influence ($p<0.05$) on the relative viscosity of the aqueous dispersion

Functional characterization of seed mucilage

As suspending agent

Since BSM has demonstrated reasonable water holding capacity, hydration capacity and swelling index, its ability to act as

suspending agent for pediatric and adult suspensions have been investigated. No change in pH, aggregation of particles, caking or crystal growth formation was observed for paediatric (2.4%w/v) and adult (10%w/v) paracetamol suspensions containing 1%w/v BSM as the suspending agent, when stored at 25 °C for 5 d. High sedimentation volume (F= 0.85-0.98) as observed with both the suspensions indicates that the suspended paracetamol particles might possess low terminal settling velocity. The results are in conformation with the flow rate study. Re-dispersibility of the suspensions remained unaffected. This happens because of the presence of flocculated particles in suspensions with mucilage as suspending agents [23]. The mucilage might have stabilized the suspensions by forming a protective sheath around the suspended drug particles and improving the viscosity of the dispersion medium. Thus, it can be concluded that BSM (1 %w/v) can effectively act as a suspending agent in the development of stable paediatric and adult PCM suspensions with visual elegance and good flowability. Okra mucilage alone or in combination with sodium sesquicarbonate exhibited potential as a suspending agent for metronidazole suspensions. Similarly, mucilages obtained from leaves of *Adansonia digitata*, *Spinacia oleracea* leaves demonstrated their ability to act as suspending agent in paracetamol suspensions [33, 34]. Another potential application of mucilages isolated from Aloe vera, Flax seeds, Fenugreek seeds, Purslane and Malabar spinach has been in the field of jaggery clarification by suspending the impurities and colloidal particles in the form of a scum [35].

As emulsion stabilizer

Both EAI and ESI were observed to decrease with BSM concentration, i.e., with an increase in the gum-to-oil ratio in the sunflower oil emulsions. EAI ranged from 2±0.5 to 6±0.2 g. m^{-1} ml^{-1}, the highest being observed with the lowest concentration of mucilage (0.25%w/v). ESI value at 120 h was maximum for E1 (table 2, fig. 5). The formed emulsion was stable during a 5d long storage period showing no detectable flocculation, creaming or coalescence. The average globule size for E1 at the end of 120 h was found to be 9.70±154.65 µm. The proposed mechanism of emulsifying activity of BSM is via the formation of multimolecular films around the droplets of the dispersed phase. Its excellent gelation behavior, ability to reduce the kinetic mobility and retard coalescence of the dispersed oil droplets have further improved the emulsion stability [9, 10, 36, 37]. However, other formulations showed visible flocculation due to insufficient film formation and incomplete surface coverage of the oil droplets by the gum molecules as at higher concentrations, chains overlap or molecular crowding occurs which restricts diffusional transport of the molecules to and adsorption at the air-water interface [36]. Coalescence was observed only in E4 formulation where the creaming rate was maximum. The ranking of globule size for other 3 emulsions is as follows E4>E3>E2.

From the above observations on sunflower oil emulsions prepared with BSM, it appears that higher the continuous phase viscosity, lower is the efficiency of the mucilage in the stabilisation of dispersed oil globules. At low concentrations, the polysaccharide molecules are well separated, and they have more freedom to move so that they migrate more easily to the oil-water interface. This adsorption of polysaccharide chains at the interface retards the free movement of the oil globules thereby reducing their propensity to coalesce. At an optimum mucilage concentration, oil droplets have been physically captured by the polymer network of BSM leading to surfactant-free stable emulsions. Emulsifier concentration outside the effective window may thus have a negative impact on emulsion stability.

Table 2: ESI and EAI of BSM based PCM emulsions

Batch	ESI at					EAI	Creaming rate (cm/h)	Globule size (µm)*	Remarks
	24 h	48 h	72 h	96 h	120 h				
E1	15.714	44.571	52.286	92.571	105.714	6.190	0.0004	9.70±154.65	No flocculation and no coalescence
E2	14.177	39.753	66.600	87.600	103.500	4.913	0.0022	17.95±350.83	Slightly flocculated and no coalescence
E3	22.588	39.529	47.647	76.235	95.238	3.132	0.0098	56.31±144.03	Flocculated and no coalescence
E4	3.048	34.286	36.571	76.190	84.706	2.321	0.0115	70.29±102.71	Flocculated and signs of coalescence

*Values indicate significant influence ($p<0.05$) of BSM concentration on the size of the dispersed oil globules of the emulsions under investigation.

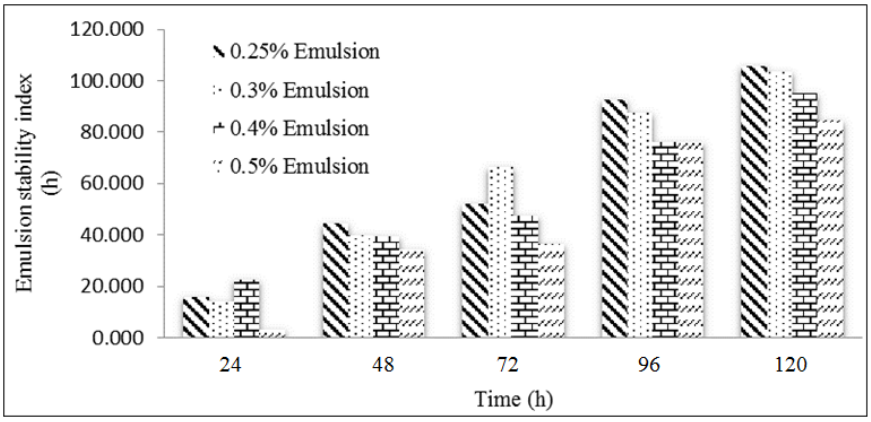

Fig. 5: ESI vs time plot of E1, E2, E3 and E4

CONCLUSION

The growing interest in the use of natural hydrocolloids such as plant-derived gums and mucilages, as an alternative to synthetic pharmaceutical excipients, in the formulation of stable suspensions and surfactant-free emulsions, forms the basis of the present study. The results of the study indicated that the sweet basil seed mucilage possesses desired physicochemical characteristics such as water holding capacity, oil holding capacity, swelling index, and rheological property for being explored as suspending agent and emulsion stabiliser.

Investigations on adult and paediatric paracetamol suspensions and surfactant-free emulsions reveal that mucilage from sweet basil seed at an optimum concentration is a potential additive for stabilization of liquid dosage forms and thus may be regarded as a functional

biomaterial for pharmaceutical use. Further investigations and animal studies are necessary to create a niche market for the mucilage from *Ocimum basilicum* L. seeds in the highly demanding field of pharmaceutical excipients.

AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICTS OF INTERESTS

All authors have none to declare

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