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HIBISCUS LEAF MUCILAGE AS STABILISER FOR PHARMACEUTICAL DISPERSE SYSTEMS

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ABSTRACT

Objective: Stable pharmaceutical disperse systems are defined as heterogeneous, biphasic systems as suspensions and emulsions, stabilized by third agent or stabilizer. The aim of the present investigation was to extract mucilage from the leaves of *Hibiscus rosa-sinesnsis* L. and explore its ability to function as stabiliser for adult (10%w/v) and paediatric (2.4%w/v) paracetamol (PCM) suspensions and 2% v/v sunflower oil emulsions.

Methods: Isolated mucilage powder was subjected to phytochemical tests to identify the major phytochemical constituents, FTIR spectroscopy to establish compatibility with formulation ingredients, X-ray diffractometry to determine the crystalline nature and viscosity study by Ostwald viscometer and swelling behaviour in water to determine the swelling index.

Results: Qualitative phytochemical screening of the mucilage (HM) revealed the presence of non-reducing sugars, gums and mucilage. HM possesses a highly amorphous structure with extremely low overall crystallinity. The mucilage belongs to the class of carbohydrate as it contains–OH groups with intermolecular hydrogen bonding, with 1→4 glycosidic bonds which accounts for its high hydration capacity. Swelling index and relative viscosity of 0.5% w/v mucilage in water was found to be 1050 and 4.84 respectively at 25 °C. Although adult PCM suspensions containing 4% w/v mucilage exhibited poor redispersibility, paediatric suspension containing 1 and 2% w/v mucilage showed gradual settling of particles with good re-dispersibility and flowability. Emulsion activity index (EAI) values of the three emulsions (0.5, 0.75 and 1%w/v HM) were found to be close to 2 g. m^{-1} ml^{-1}suggesting concentration independent activity of HM as an emulsifier. Emulsion stability index (ESI) values at 72 h showed comparatively less stability with increasing concentration of mucilage probably due to polysaccharide chain overlapping at high concentration leading to less effective surface coverage per unit gum concentration.

Conclusion: Therefore, hibiscus leaf mucilage has the capacity to stabilize a suspension or emulsion based on its capacity to adsorb onto solid or liquid interfaces.

Keywords: Emulsion activity index, Emulsion stability index, Hibiscus leaf mucilage, Suspension, Swelling index

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INTRODUCTION

Pharmaceutical disperse systems are defined as heterogeneous systems where the dispersed phase consisting of solid or liquid component is dispersed within an external dispersion medium. Suspensions and emulsions are such kind of disperse systems which are inherently thermodynamically unstable although stabilised by the addition of dispersants and emulsifiers. Stabilisers commonly employed include solid particles, polymers, proteins or surfactants. Physical stability of pharmaceutical formulations is critical to their *in vitro* and *in vivo* performance. Stability issues in pharmaceutical suspensions arise due to interactions among different physical and electrochemical forces and natural propensity of the suspended particles to aggregate and settle down. It is to be noted that well-stabilized but settled suspensions will quickly re-disperse on shaking [1]. Pharmaceutical emulsions are said to be stable as long as the thin film formed around each of the dispersed globule by the primary and/or secondary emulsifying agent resists rupture under pressure of approaching or coalescing droplets. Stability of particle-stabilized emulsions is attributed either due to the formation of mechanically strong coherent monolayer which exerts barrier properties (steric or mechanical) against coalescence of dispersed oil droplets in an o/w emulsion or due to flocculation by particle bridges between adjacent oil globules whose surfaces are insufficiently covered by the film [2-4].

Introduction of a gelling polysaccharide such as mucilage or gum to the aqueous dispersion medium in disperses systems will create a favorable environment for the solvated polymer chains to extend to the maximum possible length and be firmly adsorbed on to the dispersed particles or globules with numerous points of contact [1]. Presence of a membrane of solid particles is known to improve the lifespan of the oil droplets through manipulation of the tendency to coalesce [2]. Gum isolated from the bark of *Moringa oleifera* has been investigated as a suspending agent and tablet binder [5]. Similar studies have also been reported with shea tree gum [6].

The purpose of the present investigation was to explore the ability of the mucilage isolated from the leaves of *Hibiscus rosa-sinesnsis* L. to function as stabiliser for adult and paediatric paracetamol suspensions and sunflower oil emulsions.

MATERIALS AND METHODS

Materials

The leaves of *Hibiscus rosa-sinensis* L. were collected from the garden of Department of Pharmacy, NSHM Knowledge Campus, Kolkata. The leaves were washed with water to remove dirt and debris, dried at 50 °C and stored in airtight containers until further use. Identification and authentication of the *Hibiscus rosa-sinensis* L. plant specimen, P-H1 was done at Central National Herbarium, Botanical Survey of India, Shibpur, Howrah. Sunflower oil used in the preparation of emulsions was procured from 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 carboxymethyl cellulose (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.

Extraction of *Hibiscus rosa-sinensis* L. leaf mucilage

The dried leaves were powdered and sieved through sieve no. #10. The powdered leaves were soaked in hot distilled water (60 °C) for 1 h with powder: water in the ratio of 1:8, stirred for 30 min and left to stand for 1 h to allow the complete release of the mucilage into the water. The mucilage was extracted using a multi-layer muslin cloth bag to remove the marc from the dispersion. Acetone (in the volumes of three times to the volume of filtrate) was added to precipitate the mucilage. Precipitated mucilage was dried on stainless steel trays in a laboratory oven at 40 °C for 6 h to produce

dry mucilage (HM). The obtained dried mucilage was ground and finally stored in airtight container for evaluation [7].

Chemical characterization of leaf mucilage

Melting point

The temperature at which the sample decomposed was noted with the help of melting point determination apparatus (Testing Instrument Manufacturing, India) [8].

Fourier-transformed Infra-red (FTIR) spectroscopy

FTIR spectroscopy of mucilage was carried out in order to assign functional groups to the isolated sample [9]. For sample preparation, the samples were powdered as finely as possible to minimise IR scattering on the particle surface and pellets were prepared using potassium bromide. The potassium bromide-sample pellets were observed in the FTIR spectrometer (Bruker, Alpha-T) in the range 4000–400 cm^{-1}.

Phytochemical test

Dried and powdered HM was analyzed for the presence of various phytoconstituents such as carbohydrates, alkaloids, phenols, flavonoids, saponins, tannins, steroids, glycosides based on the standard protocols [7].

Physical characterization of leaf mucilage

X-ray diffraction (XRD) study

Pure samples of HM were analysed for X-ray diffractogram [RIGAKU–(Japan), ULTIMA–III]. The Cu Kα radiation (λ=1.541Å) was Ni-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 ° [10].

Mucilage hydration study

The hydration capacity of the powdered mucilage was determined by taking 10 mg of the sample in a pre-weighed filter paper sachet and immersed simultaneously in a minimum volume of water (pH 7.0) taken in petri dishes to wet the sachet under-surface. During the initial 15 min the net weight of each sachet was recorded in every 3 min and then weighed every 15 min to a constant value [8]. Effect of time on mucilage hydration was graphically represented.

Swelling study

Aqueous mucilage dispersion (0.5%w/v) was prepared and left undisturbed for 6 h at 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 [8]:

$$Swelling\ Index\ (\%) = \frac{Final\ volume\ of\ swollen\ sample - Initial\ volume\ of\ sample}{Initial\ volume\ of\ sample} X\ 100 \quad (1)$$

Rheological study

HM dispersions (0.0625–1% w/v) were prepared by hydrating dried mucilage powder in deionized water for 30 min using a mechanical stirrer. The dispersions were then left overnight to ensure complete hydration prior to the rheological measurement. The viscosity of HM dispersions was determined using Ostwald viscometer at 25 °C by employing the following equation:

$$Relative\ Viscosity = \eta_{rel-mucilage,conc} = \frac{\rho_{mucilage}\, t_{mucilage}}{\rho_{water}\, t_{water}} \quad (2)$$

Relative viscosity of HM dispersion (0.5%w/v) was also determined in the presence of common additives employed in preparation of conventional liquid preparations, namely 0.9%w/v NaCl, 5%v/v sorbitol, 9%v/v propylene glycol, 4%w/v sucrose, 6.8 mmol $CaCl_2$, 4%w/v mannitol, 4%w/v dextrose, 1%v/v Tween 80 and 1M urea [11].

Functional characterization of leaf 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 [12, 13].

Table 1: Composition of paediatric and adult paracetamol suspensions

Ingredients	Composition (% w/v)		
	Paediatric		Adult
	P1	P2	A1
HM	1	2	4
Paracetamol	2.4	2.4	10
Methyl paraben	0.2	0.2	0.2
Propyl paraben	0.2	0.2	0.2
Tween 80	2-4 drops	2-4 drops	2-4 drops
Glycerine	5	5	5
Distilled water	qs to 30 ml	qs to 30 ml	qs to 30 ml

As emulsion stabiliser

Mucilage dispersions (0.5, 0.75 and 1.0% w/v) were prepared as for rheological characterisation. Three batches of oil-in-water emulsions (O: W=20:80) (E1-E3) were prepared with sunflower oil by homogenizing (REMI Instruments Ltd.) 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 emulsion was withdrawn from the bottle at time intervals of 24, 72 and 120 h, diluted 1000 times with distilled water and vortexed for 1 min. The absorbance of the diluted emulsion was recorded spectrophotometrically (UV 1800 UV-vis spectrophotometer, Shimadzu Corporation) at 500 nm.

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

$$T = 2.303 \times \frac{A}{L} \times D \quad (3)$$

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 the following equation

$$EAI = \frac{2 \times T_0}{\emptyset \times C \times 1000} \quad (4)$$

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 (mg. ml^{-1}).

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

$$ESI = \frac{A_0 \times A_t}{A_0} \times t \quad (5)$$

Where, t is the time interval (h) and A_0 and A_t are the absorbances at t=0 and after 24 h respectively [9].

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 and creaming rate was calculated. The emulsions were carefully observed daily for signs of coalescence and flocculation throughout the period of the experiment [14].

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 [14].

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

Extraction and characterization of leaf mucilage

The yield of the mucilage from the Hibiscus leaves was approximately 10-15% of dry leaf mass. In the literature, yields of 5.5 and 17 % have been reported [15, 16]. The mucilage started to char or decompose at 240 °C. Decomposition or oxidative degradation of the chia seed gum was noted with an endothermic peak being observed at 244 °C [9].

Chemical characterization of leaf mucilage

FTIR spectroscopic features

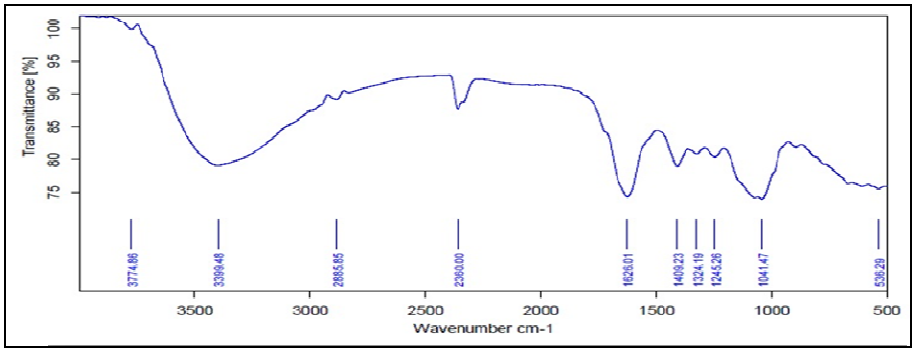

Fig. 1: FTIR spectrum of *Hibiscus rosa-sinensis* L. leaf mucilage

FTIR spectrum (fig. 1) of HM shows characteristic bands at approximately 3399.48 and 1409.23 cm^{-1}, which are commonly observed in polysaccharides and represent hydroxyl (-OH) stretching 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 [17]. In a previous study, the peak at 1626.01 cm^{-1} observed for hibiscus leaf mucilage was attributed mainly due to the C=O stretching of the peptide groups, revealing the presence of a protein [8]. The absorption band at 1041.47 cm^{-1} may be attributed to C-O-C stretching of 1-4 glycoside bonds as has been reported for locust bean gum and guar gum [8, 18].

Phytochemical test

Preliminary phytochemical screening of *Hibiscus rosa-sinensis* L. leaf mucilage revealed the presence of non-reducing sugars, proteins, gums and mucilage and confirmed the absence of alkaloid, tannins and saponins.

Physical characterization of leaf mucilage

XRD

X-ray diffraction pattern is represented in fig. 2. HM presented an amorphous structure with very low overall crystallinity.

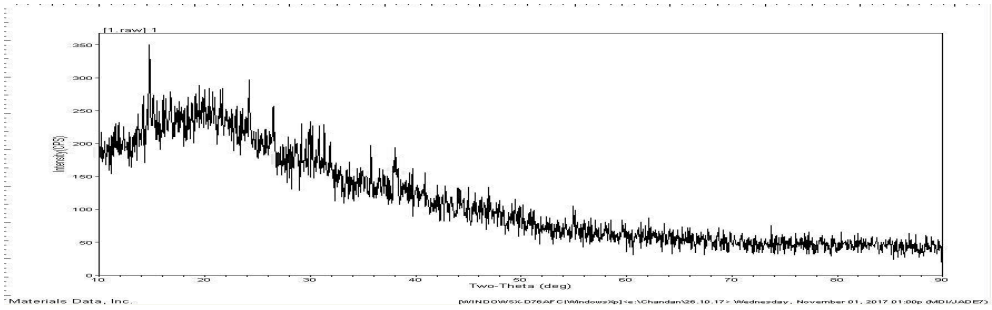

Fig. 2: X-ray diffractogram of *Hibiscus rosa-sinensis* L. leaf mucilage

Mucilage hydration study

Graphical representation of mucilage hydration values revealed a slow and steady increase in weight of HM on hydration till 3h with the most rapid increase in the first 6 min (fig. 3).

Swelling studies

Phytochemical screening and FTIR spectrum of the mucilage revealed the occurrence of non-reducing sugars and presence of hydroxyl and carboxylic groups (fig. 1), indicating its affinity for

water and propensity to imbibe large amounts of water or biological fluids and swell. Swelling index value of 0.5% w/v HM in water was found to be 1050±20 at 25 °C. Synthetic polymers used as stabilisers for pharmaceutical disperse systems may be replaced by the mucilage owing to its high swelling index values. Swelling is assumed to induce structuring of the vehicle of liquid dosage forms by promoting an increase in viscosity. Viscosity enhancement renders effective protection against sedimentation of suspended particles in suspensions or coalescence of the dispersed oil globules in emulsions [19].

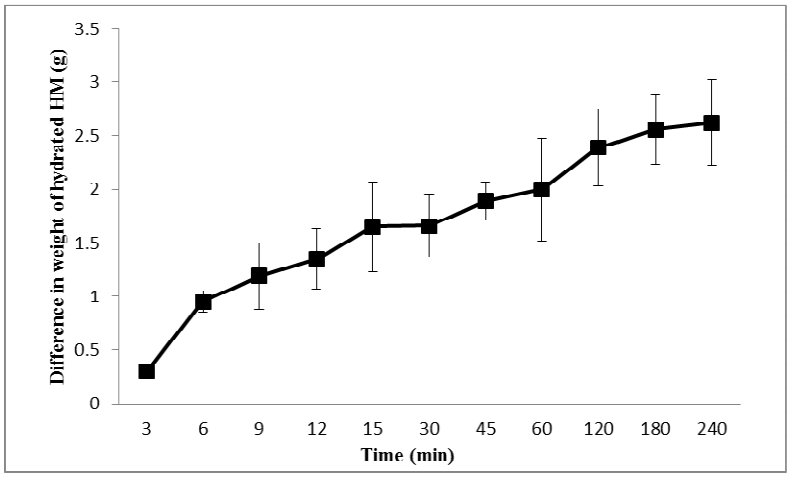

Fig. 3: Effect of time on hydration of *Hibiscus rosa-sinensis* leaf mucilage. Error bars represent mean±standard deviations for 3 experiments (n=3)

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 [20, 21].

With an increase in HM concentration from 0.0625% to 1.0% 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. A similar behavior was observed for dispersions of flaxseed, *Opuntia ficusindica*, *Lepidium sativum*, tragacanth and *Lepidium perfoliatum* gums [22]. Owing to its viscosity-enhancing property, good hydration and swelling ability, HM dispersion can be used to formulate flocculated suspensions and also to stabilise emulsions by virtue of rendering protection against coalescence and creaming of dispersed oil globules.

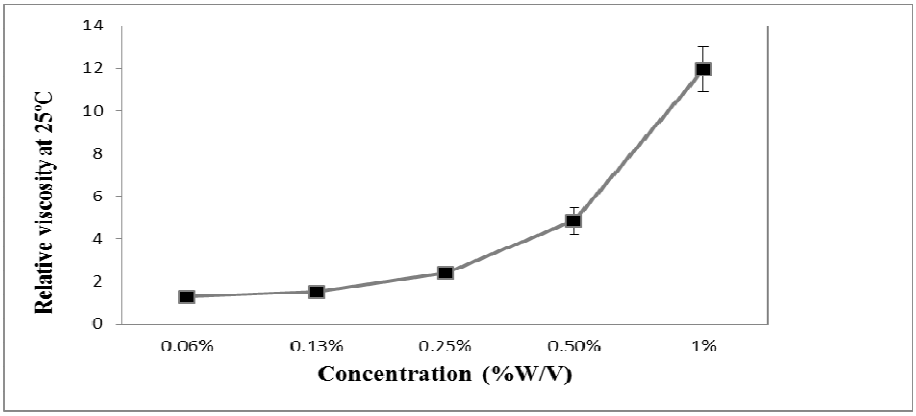

Fig. 4: Effect of mucilage concentration on relative viscosity of hibiscus leaf mucilage (HM). Error bars represent mean±standard deviations for 3 experiments (n =3)

Effect of additives on relative viscosity of mucilage dispersion has been graphically presented in fig. 5. There was a decrease in the relative viscosity of HM in the presence of dextrose, propylene glycol and urea in the order mentioned. Hence, these commonly employed additives should be carefully used in the formulation of ophthalmic preparations, parenterals, suspensions and urea gels respectively [23]. Inorganic salts, NaCl and $CaCl_2$ did not produce significant changes in the viscosity. Sorbitol and Tween 80 were found to lower the viscosity of HM aqueous dispersion and thus should be used with caution in preparation of suspensions of relatively poorly water-soluble drugs. Since sucrose increased the viscosity significant, its concentration in syrup based formulations should be carefully selected without adversely affecting the pourability and microbiological stability of the preparation. Opposite effects of sugars like dextrose and sucrose on HM viscosity are to be noted. Moreover, HM should be used with consideration in preparations to be lyophilised as mannitol also enhanced the mucilage viscosity.

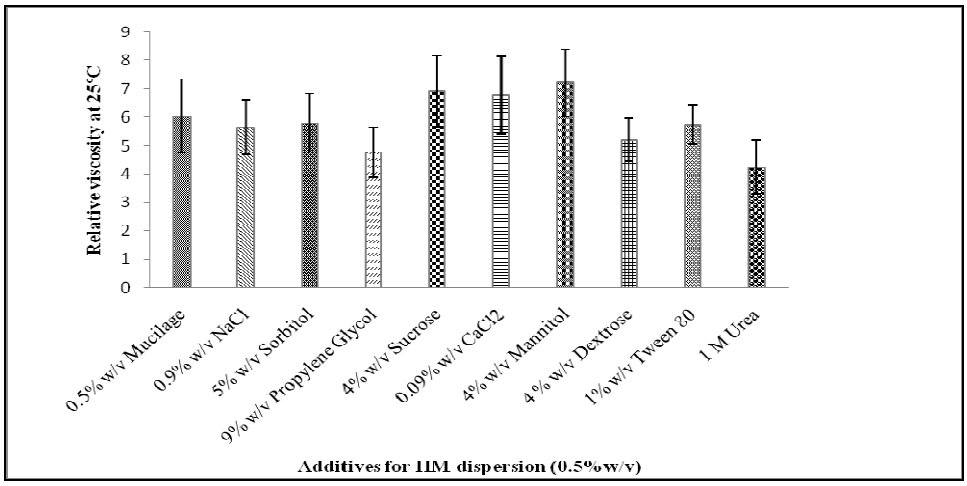

Fig. 5: Effect of different additives on relative viscosity of mucilage. Error bars represent mean±standard deviations for 3 experiments (n=3)

Functional characterisation of leaf mucilage

As suspending agent

Okra mucilage alone or in combination with sodium sesqui-carbonate 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 a suspending agent in paracetamol suspensions [24, 25]. 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 [26]. High swelling index of HM might enable it to function as suspending agent for pediatric and adult suspensions. The pH of the paracetamol suspensions was found to be 7.0 during the study period. Quick settling of drug particles was observed in adult paracetamol suspensions containing 4% w/v HM. Suspensions demonstrated poor flowability and redispersibility. Deflocculation could be detected with the formation of a clear supernatant. However, paediatric suspensions containing 1 and 2% w/v HM showed gradual and slow settling of particles. The results are in conformation with the flowability study. Sediment formed could be redispersed easily. Moreover, no appreciable change in sedimentation volume (F=0.87-0.93) has been observed in paediatric suspensions till day 5 of the study. This happens because of the presence of flocculated particles in suspensions with mucilage as suspending agents [12]. The mucilage might have stabilized the suspensions by forming protective sheath around the suspended drug particles and improving the viscosity of the dispersion medium. Thus, it can be concluded that HM (1 and 2%w/v) can effectively act as a suspending agent in the development of stable paediatric PCM suspensions with visual elegance and good flowability.

As emulsion stabiliser

EAI values of the three emulsions were found to be close to 2 g. m^1 ml^{-1}suggesting concentration independent activity of HM as an emulsifier. The formulation, E1 remained stable during storage period showing no detectable flocculation, creaming or coalescence. The average globule size for E1 was found to be the least at 159.26±24.35µm (table 2). However, ESI values at 72h showed comparatively less stability with increasing concentration of mucilage (fig. 6). At low HM concentration (0.5% w/v), the polysaccharide molecules are well separated, can move freely, can migrate more easily to the oil-water interface and get adsorbed as a mono or multilayer film at the interface promoting decrease in interfacial tension [27-30]. Moreover, adsorption of polysaccharide chains at the interface retards the free movement of the oil globules thereby reducing their propensity to coalesce. Low stability of emulsions at higher concentrations of HM might be due to steric hindrance exhibited by the overlapping and crowding of the polymeric chains of the mucilage and therefore, insufficient film formation and incomplete surface coverage of the oil droplets by the mucilage molecules [29].

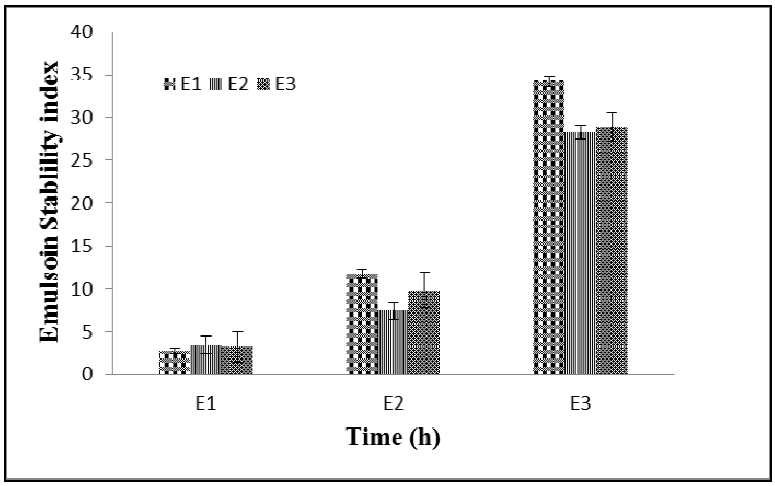

Fig. 6: Emulsion stability index (ESI) of sunflower oil emulsions E1, E2 and E3 stabilised by *Hibiscus rosa-sinensis* leaf mucilage at various time (h) intervals, error bars represent mean±standard deviations for 3 experiments (n=3)

Table 2: Emulsion stability index (ESI) and Emulsion Activity Index (EAI) of HM based paracetamol emulsions

Batch	ESI at			EAI	Creaming	Globule size (mean±SD)	Remarks
	24 h	72 h	120 h	(g. m^1 ml^{-1})	rate (cm/h)	(µm)(n=100)	
E1	2.75	11.80	34.23	2.248	0.0024	159.26±24.35	No flocculation and no coalescence
E2	3.43	7.43	28.29	2.063	0.0059	177.75±30.49	Slightly flocculated and no coalescence
E3	3.21	9.86	28.93	2.063	0.0107	316.11±54.83	Flocculated and no coalescence

CONCLUSION

Recent surge in the use of natural polymers such as plant-derived gums and mucilages, as pharmaceutical excipients, has prompted an investigation into the suspending and emulsifying ability of *Hibiscus rosa-sinensis* L. leaf mucilage. From the above studies it can be concluded that the leaf mucilage possesses desired physicochemical characteristics such as hydration capacity, high swelling index in aqueous medium and viscosity. Stable and visually elegant paediatric paracetamol suspensions possessing good flowability and high sedimentation volume have been successfully developed with the mucilage as a suspending agent. Decreased stability of sunflower oil emulsions at higher mucilage concentration might be due to restriction in polymer chain extension and thus the formation of incomplete structure-mechanical barrier around the dispersed oil globules. Therefore, hibiscus leaf mucilage has been proven to stabilize a suspension or emulsion based on its capacity to adsorb onto solid or liquid interfaces.

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICTS OF INTERESTS

All authors have none to declare

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