Evaluation of mucilages isolated from seeds of *Hyptis suaveolens*, *Salvia hispanica* and *Linum usitatissimum* as pharmaceutical excipients in solid dose and liquid formulations.

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ABSTRACT

In this work, the performance of mucilages obtained from the seeds of *Hyptis suaveolens, Linum usitatissimum* and *Salvia hispanica* were evaluated for their potential use as stabilizers in liquid formulations and as binders and disintegrants in solid pharmaceutical forms. The behavior of both liquid and solid formulations prepared with the extracted mucilages was examined and compared with reference excipients showing, in most cases, very similar performance. In addition, parallel investigation of these mucilages in both liquid and solid pharmaceutical forms showed some relationships between their physico-chemical properties and the performance of the final formulation.

KEYWORDS: Mucilages, excipients, formulations, suspensions, solid dose, tablets

INTRODUCTION

Polymers have been used as pharmaceutical excipients in solid, liquid and semi-solid dosage forms for various reasons such as to modulate physicochemical properties, to control the release and to improve stability and bioavailability of the active ingredient (1-3). Although both synthetic and natural polymers, have been useful as additives in pharmaceutical formulations, the desirable properties of natural polymers including low toxicity, biodegradability, biocompatibility, low cost and susceptibility for chemical or enzymatic modifications, have attracted considerable attention from the scientific community in recent years. In fact, plant-derived polymers have been investigated due to their potential diverse applications, including for use as diluents, binders, disintegrants in tablets, thickeners in oral liquids or stabilizers in suspensions, gelling agents among others (4-6).

The edible seeds of the plant species *Hyptis suaveolens*, *Linum usitatissimum* and *Salvia hispanica* are known to contain mucilage and there have been reports describing their application in pharmaceutical formulation as binders and disintegrants in solid forms, as stabilizers and thickening agents in liquid forms and in microcapsule preparations (7-10). The structure of the polysaccharides of these plants have been described previously (11-13).

The work presented here focused on using these plants' mucilages in solid and liquid formulations. Their physico-chemical properties and their performance as excipients are discussed and compared with reference materials. As far as can be ascertained, this is the first

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study examining a head-to-head comparison of the performance of these mucilages in both solid and liquid pharmaceutical formulations.

MATERIALS AND METHODS

General experimental procedures

A stereoscope, Premiere SY (Georgia, USA) was utilized using a 4x enhancing lens for morphology analysis for the examination of the seeds and a micrometer SPI 31-415 Dial Typ 6921 (Japan) for accurate size measurements. Specific gravity was determined with a pycnometer (Gradco, UK). pH measurements were carried out using a pH meter 420A (ORION, USA). Rheological parameters were determined using a rheometer Brookfield DV-III Ultra. A centrifuge (Universal 320 R Hettich Zentrifugen, Switzerland) was employed during mucilage purification. For moisture content determination, an infrared moisture determination balance (A&D, Japan) was utilized. Emulsions were prepared using a homogenizer (IKA Ultraturrax T25, Germany). Wet granulates were prepared with a planetary mixer (Kitchen Aid, Heavy Duty, USA) and were calibrated using an oscillating granulator (Erweka AR400 motor drive with FGS wet granulator, Germany). Wet granulates were dried with a fluid bed dryer (Sherwood Scientific, UK). Tablets were made using a rotary tablet press (Junior Express Talleres Sánchez SRL, Argentina). The tablets' friability were measured with a friability/abrasion tester (TAR series, Erweka, Germany). Tablet disintegration was measured using a Erweka disintegration tester (model ZT2, Germany). Mineral oil (light mineral oil NF), Span® 60 (sorbitan monostearate NF) and Tween® 80 (polysorbate 80 NF) were purchased from Spectrum, USA. Acetaminophen, methylparaben, propylparaben USP were acquired from Sigma Aldrich, USA, propylene glycol and glycerin from Fisher Scientific, USA, sorbitol 70% from SPI Pharma, USA, avicel RC-591, microcristalline cellulose, and crosscarmellose sodium from FMC Corp., USA, xanthan gum from Jungbunzlauer, Austria, PVP K-25 from BASF, Germany, anhydrous lactose from Sheffield Pharma Ingredients, USA, corn starch from Cargill Corp., USA, talc from Riedel-de Haën, Germany, magnesium stearate from Biesterfeld Spezialchemie GmbH, Germany, sodium starch glycolate from J. Rettenmaier & Söhne, Germany and crospovidone from ISP Technologies, Inc., USA.

Plant material and the extraction of the mucilages

Seeds of *Hyptis suaveolens* (HS), *Salvia hispanica* (SH) and *Linum usitatissimum* (LU) were purchased from a local market ("Mercado Central") in San Jose, Costa Rica. According to the seller, the seeds of HU and LU were cultivated in Guanacaste, Costa Rica. The seeds of SH were imported from Nicaragua.

In general, mucilage was extracted from the seeds as has been reported previously by several authors with few modifications (8, 14-17). Briefly, the LU seeds were soaked in water (1:25 seeds to water ratio) at 80°C at a pH between 6.5 and 7.0 (adjusted with NaOH 2 M) during 30 minutes whilst stirring. The seeds were then removed by filtering through a 40-mesh sieve and the resulting viscous solution was concentrated under vacuum (approximately 20% original volume) and the mucilage precipitated with 80% ethanol (6:1 mucilage to ethanol ratio).

For extraction of the HS mucilage the seeds were initially wetted with distilled water (1:25 seeds to water ratio) for 30 minutes at 37°C, then extracted for two hours whilst stirring. The seeds were removed by filtering through a 40-mesh sieve and the resulting viscous solution was concentrated under vacuum (approximately 20% of original volume). The mucilage was recovered by precipitation using ethanol 80% (6:1 mucilage to ethanol ratio) and separated from the supernatant liquid using centrifugation (1920 G for 30 minutes).

Finally, the seeds of the SH were extracted using distilled water (1:40 seeds to water ratio) at 80°C, during two hours whilst stirring. The viscous solution including the seeds was dried overnight in a convection oven at 50°C and the mucilage was then separated from the seeds filtering through a 40-mesh sieve. The

Table 1 The composition of the emulsions formulated to investigate the use of *H. suaveolens, L. usitatissimum* and *S. hispanica* mucilages as stabilizers

FORMULATION CODE*	EREF	EL0.25	EL0.50	EL0.75	EL1.0	ECa0.25	ECa0.50	ECa0.75	ECa1.0	ECi0.25	ECi0.50	ECi0.75	ECi1.0
OIL PHASE													
MINERAL OIL	10,00 %	10,00 %	10,00 %	10,00 %	10,00 %	10,00 %	10,00 %	10,00 %	10,00 %	10,00 %	10,00 %	10,00 %	10,00 %
SPAN® 60	1,55 %	-	-	-	-	-	-	-	-	-	-	-	-
AQUEOUS PHASE													
GLYCERINE	10,00 %	10,00 %	10,00 %	10,00 %	10,00 %	10,00 %	10,00 %	10,00 %	10,00 %	10,00 %	10,00 %	10,00 %	10,00 %
METHYLPARABEN	0,15 %	0,15 %	0,15 %	0,15 %	0,15 %	0,15 %	0,15 %w	0,15 %	0,15 %	0,15 %	0,15 %	0,15 %	0,15 %
PROPYLPARABEN	0,05 %	0,05 %	0,05 %	0,05 %	0,05 %	0,05 %	0,05 %	0,05 %	0,05 %	0,05 %	0,05 %	0,05 %	0,05 %
TWEEN® 80	2,45 %	-	-	-	-	-	-	-	-	-	-	-	-
LU MUCILAGE	-	0.25%	0.50%	0.75%	1.00%	-	-	-	-	-	-	-	-
HS MUCILAGE	-	-	-	-	-	0.25%	0.50%	0.75%	1.00%	-	-	-	-
SH MUCILAGE	-	-	-	-	-	-	-	-	-	0.25%	0.50%	0.75%	1.00%
WATER CSP	100.00g	100.00g	100.00g	100.00g	100.00g	100.00g	100.00g	100.00g	100.00g	100.00g	100.00g	100.00g	100.00g

Data shown in percentage (%) w/w

HS = *H. suaveolens,* LU = *L. usitatissimum* and SH = *S. hispanica*

dried mucilages were stored in a desiccator until used.

Physico-chemical characterization of the mucilages

Mucilages obtained from HU, LU, and SH were subject to several physical and chemical analyses including appearance (color and odor), pH determination, rheological parameters, specific gravity using a 1% w/w reconstituted solution of each mucilage, swelling index, ash content, and moisture content according to previously reported procedures (18-21).

Preparation and evaluation of the emulsions

To investigate the isolated mucilages as stabilizer agents of emulsions with mineral oil as the internal phase, several formulations were prepared using different concentrations of mucilages (Table 1). The minimum mucilage concentration to stabilize the emulsion and maximum concentration to ensure viscosities lower than 25 000 cP whilst stirring gently have been determined previously. A reference emulsion using Span® 60 (1.55%) and Tween® 80 (2.45%) as stabilizers was also prepared for comparison purposes. The Span® 60 and Tween® 80 ratio was calculated to ensure a HBL value of 11, as recommended in the literature for a stable oil-water emulsion using mineral oil (22).

The emulsions were prepared adding the oil phase to the aqueous phase under agitation (4000 RPM), both phases were heated up to 85°C prior to mixing. After room temperature was reached, the dispersion was homogenized at 11000 RPM for two minutes and placed in 50 mL flasks and observed for a week (every hour for 12 hours, then every 12 hours). The height of the remaining emulsified layer was measured, and the stability calculated using Equation 1:

$$ES(\%) = \frac{HEL}{HE} x\,100 \qquad \text{Eq. 1}$$

Where, ES is emulsion stability, HEL is the height of the emulsified layer and HWL is the height of emulsion at time zero.

The preparation and evaluation of the suspensions

The capacity of mucilages to stabilize suspensions was determined using a formulation of acetaminophen in water. Suspensions were prepared by dissolving methylparaben and propylbaraben in a mixture of propilenglycol and glycerine, and the isolated mucilage was dissolved in sorbitol 70% and water (using about 75% of total water). Both solutions were then mixed, and the rest of the ingredients added slowly before completing the final volume with water (Table 2). Maximum and minimum mucilage concentrations were previously determined as described in the previous section. Reference suspensions using Avicel® RC 591 (1.55% w/v) and xanthan gum (0.14% w/v) as stabilizers were also prepared. Finally, the suspensions were placed in 100 mL flasks and observed for a week (every hour for 12 hours, then every 12 hours). The stability of the suspension was calculated using Equation 2:

$$SS(\%) = \frac{V_s}{V_0} x\,100 \qquad \text{Eq. 2}$$

Where, SS is suspension stability, Vs is the volume of sediment and Vo is original volume of suspension.

The preparation and evaluation of tablets made by wet granulation

Placebo tablets were prepared by wet granulation to evaluate isolated mucilages as binders as previously reported. Three different concentrations of mucilages were tested and their performance compared with the standard binder polyvinylpirrolidone (PVP K-25) (Table 3). Microcrystalline cellulose, anhydrous lactose and corn starch were measured and sieved through a 20-mesh sieve, and then mixed in a planetary mixer for 5 minutes. The granulating fluid was prepared by dispersing the mucilage or PVP in 100 mL of distilled water with a propeller stirrer until a clear liquid was obtained. Granulation was performed in the planetary mixer by adding the binder solution and mixing at low

Table 2 The composition of suspensions formulated to examine *H. suaveolens, L. usitatissimum* and *S. hispanica* mucilages as stabilizers

FORMULATION CODE*	SREF	SL0.25	SL0.50	SL0.75	SL1.0	SCA0.25	SCA0.50	SCA0.75	SCA1.0	SCI0.25	SCI0.50	SCI0.75	SCI1.0
Acetaminophen	10,00%	10,00%	10,00%	10,00%	10,00%	10,00%	10,00%	10,00%	10,00%	10,00%	10,00%	10,00%	10,00%
Sorbitol 70%	62,00%	62,00%	62,00%	62,00%	62,00%	62,00%	62,00%	62,00%	62,00%	62,00%	62,00%	62,00%	62,00%
Avicel® RC 591	0,70%	-	-	-	-	-	-	-	-	-	-	-	-
Xhantan Gum	0,14%	-	-	-	-	-	-	-	-	-	-	-	-
Glycerine	10,00%	10,00%	10,00%	10,00%	10,00%	10,00%	10,00%	10,00%	10,00%	10,00%	10,00%	10,00%	10,00%
Propilenglycol	2,50%	2,50%	2,50%	2,50%	2,50%	2,50%	2,50%	2,50%	2,50%	2,50%	2,50%	2,50%	2,50%
Methylparaben	0,15%	0,15%	0,15%	0,15%	0,15%	0,15%	0,15%	0,15%	0,15%	0,15%	0,15%	0,15%	0,15%
Propylparaben	0,05%	0,05%	0,05%	0,05%	0,05%	0,05%	0,05%	0,05%	0,05%	0,05%	0,05%	0,05%	0,05%
Citric acid (anhydrous)	0,002%	0,002%	0,002%	0,002%	0,002%	0,002%	0,002%	0,002%	0,002%	0,002%	0,002%	0,002%	0,002%
Acesulfame potassium	0,50%	0,50%	0,50%	0,50%	0,50%	0,50%	0,50%	0,50%	0,50%	0,50%	0,50%	0,50%	0,50%
LU mucilage	-	0.25%	0.50%	0.75%	1.00%	-	-	-	-	-	-	-	-
HS mucilage	-	-	-	-	-	0.25%	0.50%	0.75%	1.00%	-	-	-	-
SH mucilage	-	-	-	-	-	-	-	-	-	0.25%	0.50%	0.75%	1.00%
Water csp	100.0 mL	100.0 mL	100.0 mL	100.0 mL	100.0 mL	100.0 mL	100.0 mL	100.0 mL	100.0 mL	100.0 mL	100.0 mL	100.0 mL	100.0 mL

Data is shown in percentage (%) w/v

*HS = *H. suaveolens*, LU = *L. usitatissimum* and SH = *S. hispanica*

Table 3 The composition of tablets formulated to examine L. *sativum, H. suaveolens* and *S. hispanica* mucilages as disintegrants

FORMULATION CODE*	DBL	DRC	DRG	DRP	DL	DS	DH
Microcrystalline cellulose type 101	49,00	47,00	47,00	47,00	47,00	47,00	47,00
Microcrystalline cellulose type 302	50,00	50,00	50,00	50,00	50,00	50,00	50,00
Magnesium Stearate	0,50	0,50	0,50	0,50	0,50	0,50	0,50
Colloidal Silicon Dioxide	0,50	0,50	0,50	0,50	0,50	0,50	0,50
Croscarmellose sodium	-	2,00	-	-	-	-	-
Sodium starch glycolate	-	-	2,00	-	-	-	-
Crospovidone NF	-	-	-	2,00	-	-	-
Dried mucilage from *Linum usitatissimum*	-	-	-	-	2,00	-	-
Dried mucilage from *Salvia hispanica*	-	-	-	-	-	2,00	-
Dried mucilage from *Hyptis suaveolens*	-	-	-	-	-	-	2,00

Data shown in percentage (%) w/w

*Formulation Code: DBL = Blank, DRC = Croscarmellose reference, DRG = Sodium starch glycolate reference, DRP = Crospovidone reference, DL = *Linum sativum*, DS = *Salvia hispanica*, DH = *Hyptis suaveolens*.

speed for 7 minutes, then adding 50 mL of distillated water and mixing between 10 to 20 minutes until granulation final point was achieved. The wet granules were calibrated using an oscillating granulator with an 18-mesh sieve, and they were dried in a fluid bed dryer at 70°C for 20 to 30 minutes in order to obtain granules with a moisture content between 2,0-2,5%. The dry granules were calibrated using the oscillating granulator with a 35-mesh sieve and mixed on the planetary mixer at low speed with talc and magnesium stearate for 5 minutes. The tablets were prepared using a 10-station rotative tablet machine equipped with 6,5 mm diameter shallow concave punches adjusted to a weight of 150 mg ± 7,5 mg and tablet's hardness of 50 and 70 N.

The dry granulates were evaluated by measuring Carr's index, bulk density, tapped density, and particle size distribution. Additionally, the prepared tablets were evaluated by determining their hardness, friability, wetting time, disintegration time, weight variation and thickness using standard analytical procedures (23-26). The disintegration time was measured according to USP procedures using an Erweka disintegration tester with water at 37°C. The friability was determined using an Erweka friability test apparatus and the angle of repose was determined using a standardized funnel with a 6.0 diameter circular base.

The preparation and evaluation of tablets made by direct compression

Placebo tablets were prepared by direct compression using the isolated mucilages in 2% (w/w) concentration as disintegrants. The performance of the mucilages was compared to croscarmellose sodium, sodium starch glycolate and crospovidone also at 2% (w/w) concentration as standard additives (Table 4). All materials, except the magnesium stearate, were measured and sieved through a 45-mesh and mixed on a planetary mixer at low speed for 15 minutes. The magnesium stearate was added and mixed for an additional 5 minutes. The tablets were prepared as described previously here, the weight adjusted to 150 ± 7.5 mg and hardness adjusted to between 50 and 65 N.

Statistical analysis

The data were evaluated for normality using the Shapiro-Wilik's W test and homogeneity of variances was evaluated using Levene's test. For normal data, one-way analysis of variance (ANOVA) and Tukey's test was used for establishing the statistical significance

Table 4 The composition of tablets prepared to examine *L. sativum, H. suaveolens* and *S. hispanica* mucilages as binders

FORMULATION CODE*	BL	AR1	AR3	AR5	AL1	AL1.6	AL1.8	AS0.25	AS0.5	AS0.75	AH0.5	AH0.75	AH1
Microcrystalline cellulose type 101	33.00	32.67	32.00	31.33	32.67	32.47	32.40	32.92	32.83	32.75	32.83	32.75	32.67
Anhydride lactose	33.00	32.67	32.00	31.33	32.67	32.47	32.40	32.92	32.83	32.75	32.83	32.75	32.67
Corn starch	33.00	32.67	32.00	31.33	32.67	32.47	32.40	32.92	32.83	32.75	32.83	32.75	32.67
Polyvinylpyrrolidone K30	-	1.00	3.00	5.00	-	-	-	-	-	-	-	-	-
Talcum powder	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Magnesium stereate	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Dried mucilage from *Linum usitatissimum*	-	-	-	-	1.00	1.60	1.80	-	-	-	-	-	-
Dried mucilage from *Salvia hispanica*	-	-	-	-	-	-	-	0.25	0.50	0.75	-	-	-
Dried mucilage from *Hyptis suaveolens*	-	-	-	-	-	-	-	-	-	-	0.50	0.75	1.00

Data shown in percentage (%) w/w
*BL = Blank, AR = Reference binder, AL = Binder *Linum usitatissimum*, AS = Binder *Salvia hispanica*, AH = Binder *Hyptis suaveolens*

($P \leq 0.05$). When the data showed non-normal distribution, the non-parametric Wilcoxon/Kruskal-Wallis test was applied to determine the statistical significance ($P \leq 0.05$). All data analysis was carried out using the SPSS Statistics 23.0 software package.

RESULTS AND DISCUSSIONS

Physico-chemical characterization of the mucilages

The mucilages were obtained from the seeds of LU, HS and SH by water extraction and solvent precipitation method in comparable yields as previously reported and their physicochemical properties (Table 5) agreed with values found in literature (7, 8, 11, 15, 17). The rheological properties of the 1% (w/w) mucilage solutions were also measured as shown in Figure 1. Solutions containing mucilages isolated from LU and SH followed the power-law and the Ostwald-de Waele relationship (Equation 3):

$$\log F = n \log V + \log K \qquad \text{Eq. 3}$$

Where, F is shear stress (N m^{-2}), n is the flow index, V is the shear speed (s^{-1}) and K is the flow consistency index. Both solutions were considered pseudo plastic fluids as their flow indexes (n) had values lower than one (0.7688±0.0022 for LU and 0.495±0.011 for SH). However, the SH mucilage solution was more viscous than the LU mucilage solution as their flow consistency index (K) was significantly higher (59.8±3.5 and 1.554±0.082 respectively). On the other hand, the HS mucilage solution did not follow the power-law and it presented a rather complex behavior. At higher shear speed the solution behave closer to a pseudo plastic fluid. However, at lower shear speed values a hysteresis loop resembling a thixotropic fluid was observed. This rheological behavior is desirable when selecting an appropriate viscosity enhancer for a pharmaceutical suspension (27). A more detailed investigation about the physicochemical behavior of HS mucilage solution was out of the scope of this present work.

Stabilizers in emulsions

Liquid formulations may require several excipients to provide stability, homogeneity and viscosity among

Table 5 Physico-chemical characterization of mucilages

	L. usitatissimum	*H. suaveolens*	*S. hispanica*
Yield (%)	5.0±0.7	3.4±0.4	2.8±0.5
Color	White	Gray	White
Odor	Odorless	Odorless	Creamy
pH	5.060±0.072	8.157±0.037	5.817±0.012
Specific gravity	1.0037±0.0006	1.0029±0.0037	0.9900±0.0070
Swelling index (mL)	1.93±0.06	3.60±0.52	3.13±0.13
Ash content (% w/w)	8.47±0.07	9.44±0.07	9.15±0.40
Moisture content (% w/w)	11.6±1.0	9.1±0.9	8.9±1.1

Data is show as mean ± SD (n=3)

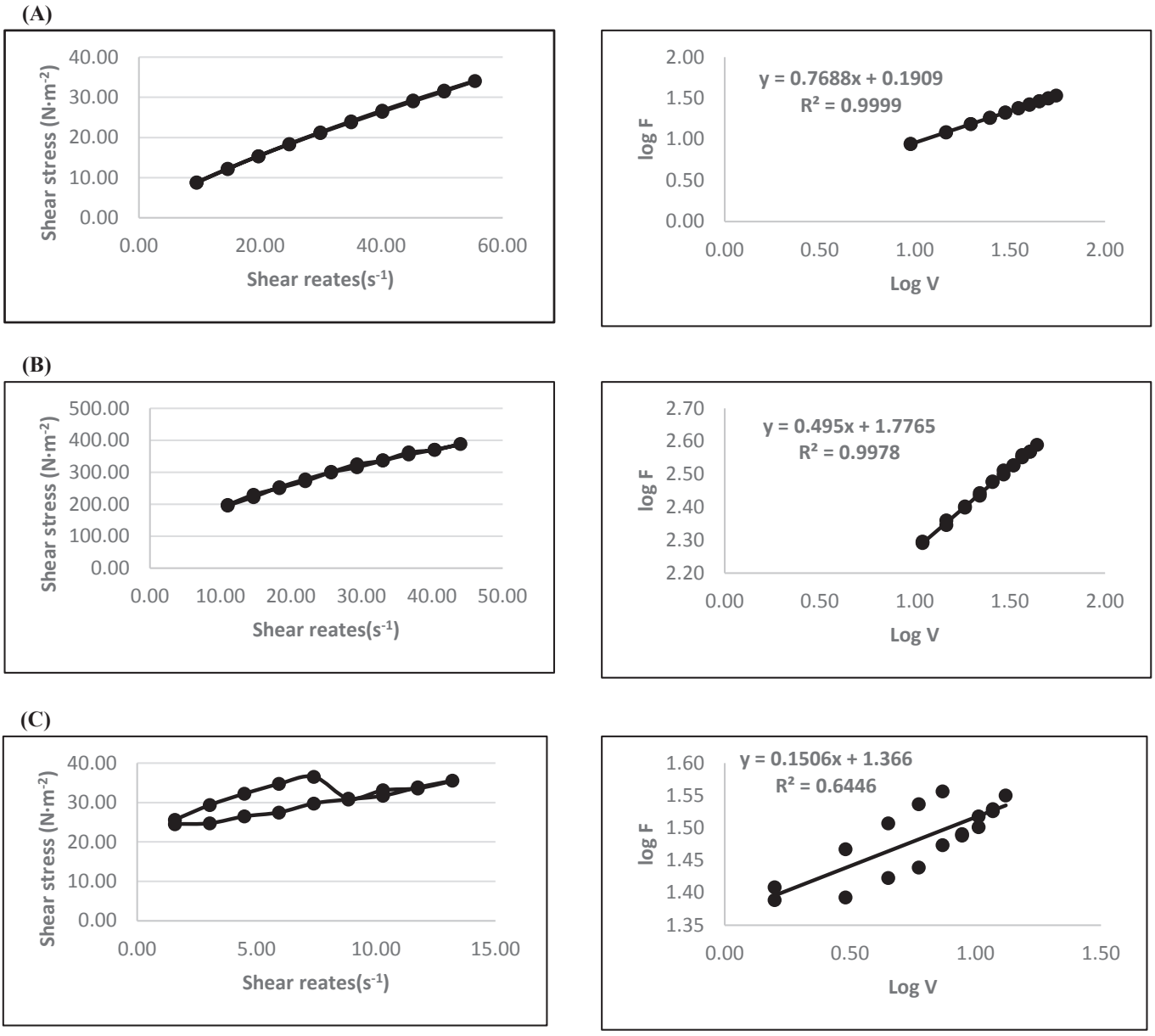

Figure 1 Rheological behavior (right) and logartimic rheogram (left) of 1% (w/w) mucilage solution prepared with (A) *H. suweolens*, (B) *L. usitatissimum* and (C) *S. hispanica.*

other properties (28, 29). The isolated mucilages were tested as stabilizers of emulsions prepared with mineral oil and water (see Experimental Section). A range of mucilage concentrations were evaluated from 0.15 to 1.0% (w/v) depending upon mucilage source and the emulsion stability, measured as the layer separation, was followed for 180 hours (see Figure 2). Differences in the emulsion stability were noticeable between mucilages and between concentrations, except for SH as its mucilage-containing emulsions showed complete stability at all concentrations tested (0.25-0.75% w/w) with no layer separation during the observation period. Additionally, emulsions containing the LU and HS mucilages as stabilizer showed clear concentration-dependent and time-dependent stability profiles, where higher concentrations displayed better stability. As expected, a direct correlation between the mucilages' viscosity and the stability of the emulsion

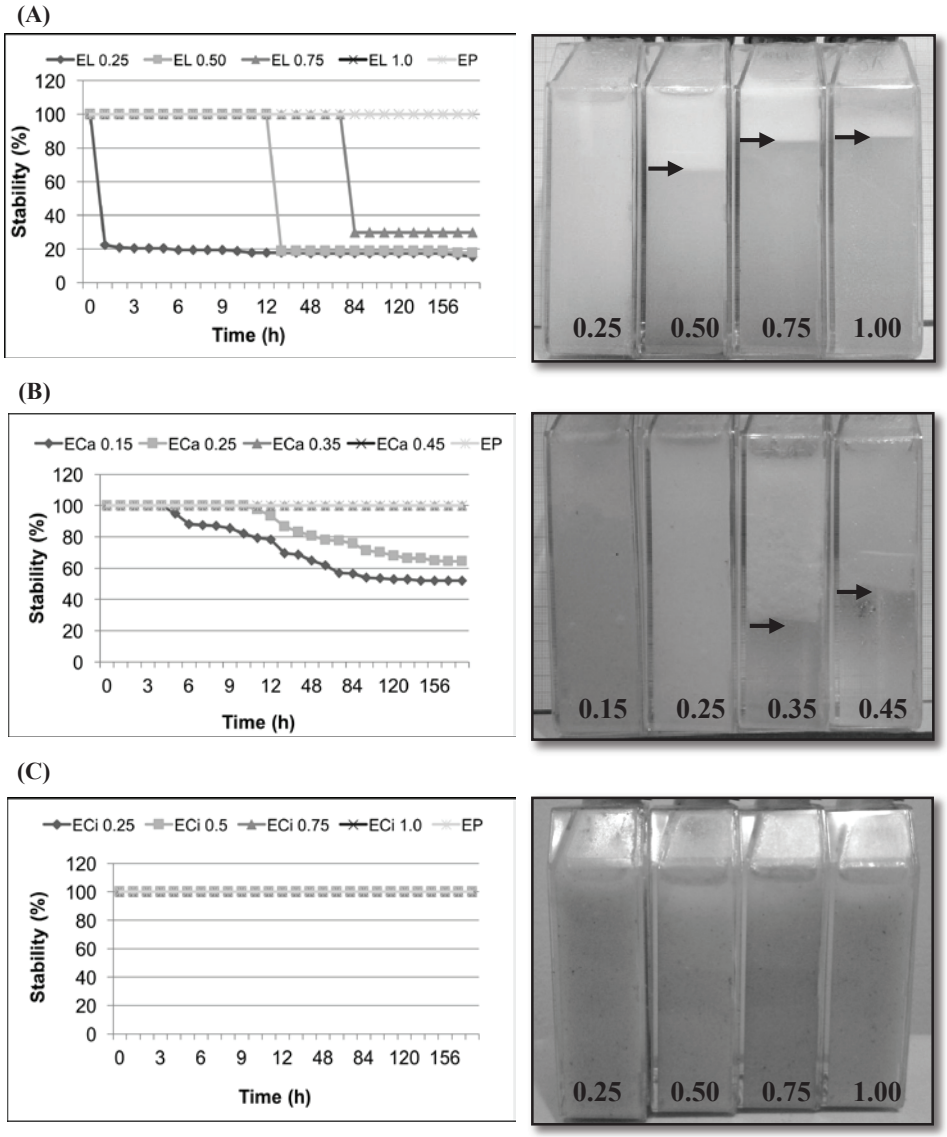

Figure 2 Stability curves (left) of emulsions prepared with *L. usitatissimum* (A) *H. Suweolens* (B) *S. hipanica* (C) and emulsion's pictures (right) after 180 hours with different mucilageconcentrations (% w/w). EL = Emulsion containing *L. usitatissimum* mucilage, ECa = Emulsion containing *H. suweolens* mucilage, ECi = Emulsion containing *S. hipanica* mucilage, EP = Reference emulsion.

was observed. The reference emulsions (containing Span® 60 and Tween® 80 as stabilizers) exhibited complete stability with no layer separation during the observation period and was comparable to the higher concentration of LU and HS as well all concentrations of SH mucilages.

Stabilizers in suspensions

Suspensions were formulated using aqueous acetaminophen (10% w/v) at four different concentrations of the isolated mucilages (see Experimental Section). The stability of the formulated suspensions was similar or better than the reference suspensions prepared with Avicel® and Xanthan gum, measured as volume of the sediment formation (shown in Figure 3). Only suspensions prepared with lower concentrations of the LU and SH mucilages presented sedimentation faster than the reference suspension. Interestingly, the best performance was observed with HS mucilage as all concentrations tested showed no sediment formation during the observation period of 180 hours. For the stability of suspensions, a direct correlation between viscosity and stability was not observed, and the best performance was achieved with the HS mucilage that displayed a thixotropic behavior in the rheological curves.

Binders in solid tablets

Granulating fluids were prepared using the prepared mucilages as binders and compared with polivynilpirrolidone PVP K-25 (see Experimental Section). The tablets were made by direct compression of dried granulates. Physicochemical properties of granulating fluids including apparent density, tapped density, and angle of repose were measured (Table 6) and the values were comparable with reference binders and within the expected values (30). Based on the measured repose angles, all formulas showed excellent flow properties according to USP guidelines (26). Also, the particle size distribution (see Figure 4) was comparable among the reference- and mucilage-containing formulations except for the HS mucilage where most particles had smaller sizes (less than 177 mm) regardless of concentration of mucilage added.

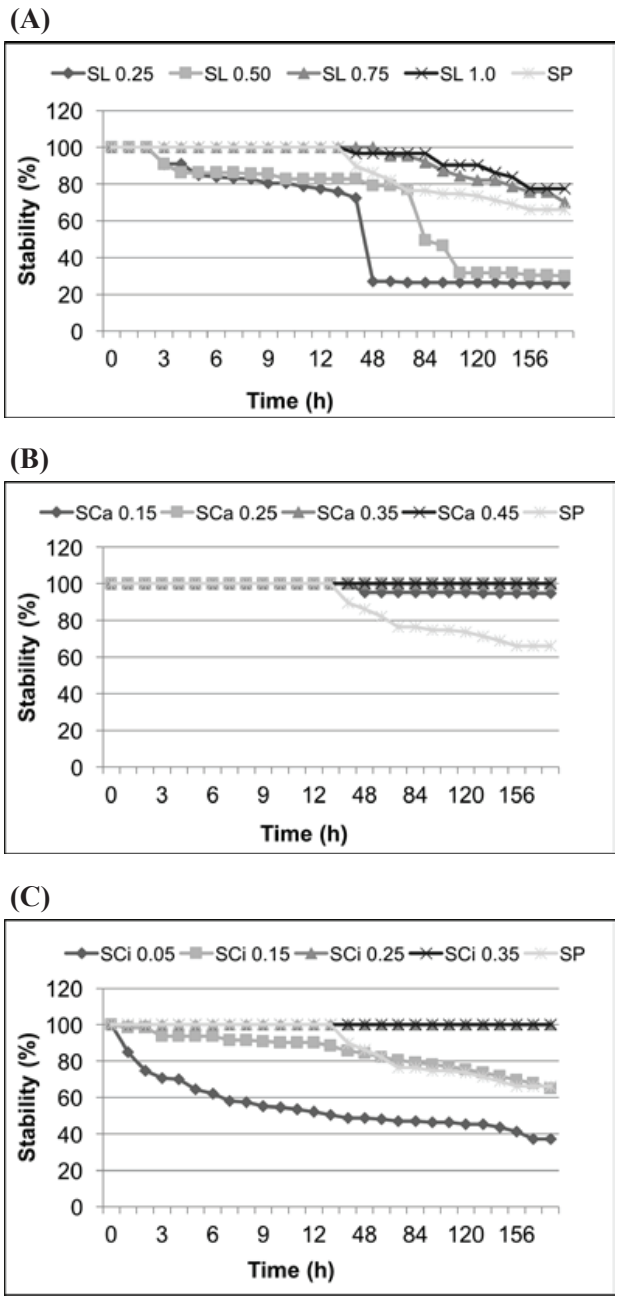

Figure 3 Stability curves of suspensions prepared with (A) *L. usitatissimum*, (B) *H. suweolens* and (C) *S. hipanica* as stabilizers. SL = Suspension with *L. usitatissimum* mucilage, SCa = Suspension with *H. suweolens* mucilage, Sci = Suspension with *S. hipanica* mucilage, SP = Reference suspension

In addition, a number of parameters for the tablets prepared withthis method were determined including thickness, weight variation, moisture content, Carr's index, friability and wetting and disintegration times

Table 6 The performance parameters for wet granulations prepared with mucilages from *L. usitatissimum*, *H. suweolens* and *S. hispanica* as binders

FORMULATION CODE*	BULK DENSITY (g/cm³)	TAPPED DENSITY (g/cm³)	ANGLE OF REPOSE
BL	0.510±0.015	0.650±0.035	13.9±2.2
AR1	0.530±0.006	0.657±0.015	20.6±1.5
AR3	0.535±0.006	0.647±0.006	19.5±1.3
AR5	0.500±0.042	0.623±0.023	18.4±2.8
AL1	0.520±0.006	0.630±0.017	18.71±0.68
AL1.6	0.575±0.010	0.723±0.006[a,b,c,d]	19.81±0.38
AL1.8	0.570±0.020	0.710±0.010[a]	19.5±1.34
AS0.25	0.545±0.026	0.677±0.025	21.6±3.2
AS0.50	0.530±0.006	0.663±0.006	23.2±1.9
AS0.75	0.535±0.015	0.720±0.020	23.7±3.6[b,c]
AH0.5	0.535±0.026	0.647±0.021	16.7±1.6[a]
AH0.75	0.520±0.010	0.657±0.032	16.2±1.4[a]
AH1.0	0.525±0.006	0.667±0.006[a,b,c,d]	11.54±0.83[a]

Data is show as mean ± SD (n=3)

*BL = Blank formulation without binder added, AR = Reference formulation with polyvinylpyrrolidinone K30, AL = Formulation with *L. usitatissimum*, AH = Formulation with *H. suweolens*, AS = Formulation with *S. hispanica*

[a]Indicates significant variation from blank (BL) formulation ($P \leq 0.05$)
[b]Indicates significant variation from reference (AR1) formulation ($P \leq 0.05$)
[c]Indicates significant variation from reference (AR2) formulation ($P \leq 0.05$)
[d]Indicates significant variation from reference (AR5) formulation ($P \leq 0.05$)

(see Table 7). As expected, significant differences were found in wetting and disintegration times, specially between the formulation without a binder showing low stability and the tablets formulated with LU mucilage showing very long disintegration times. On the other hand, SH and HS mucilages containing tablets showed comparable results to those prepared with PVP K-25.

Disintegrating agent in solid tablets

Placebo tablets made by direct compression were prepared to evaluate the disintegration capacity of the isolated mucilages at 2% w/w (see Experimental Section). For comparison purposes, formulations without a disintegrant (blank) and standard disintegrants (crosscaramelose sodium, sodium starch glycolate and crospovidone) were also prepared. The measured tablets' parameters of weight, thickness, friability and hardness showed no significant differences. On the other hand, as shown in Table 8, wetting and disintegration times for the tablets prepared with mucilages were comparable to those prepared with sodium starch glycolate and crospovidone, but significantly higher for the croscarmellose's containing tablets. Nevertheless, the disintegration capacity of mucilages was significantly higher when compared to the blank formulation. In addition, the observed disintegration times were within acceptable values for pharmaceutical solid dosage forms (1).

CONCLUSION

The present work is in agreement with previous studies showing that natural polysaccharides have valuable properties for pharmaceutical applications in both solid and liquid dosage forms. In addition, by running a parallel analysis and comparing the investigated mucilages it was possible to show the relationships between the physico-chemical properties of the mucilages and their performance in different formulations. The observed differences in behavior among the isolated mucilages in the prepared solid and liquid formulations suggest that polysaccharides from natural sources could have useful properties for oral and liquid pharmaceutical dosage forms and it should encourage the scientific community to continue the investigations in this growing field.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1 Prajapati VD, Jani GK, Moradiya NG, Randeria NP. Pharmaceutical applications of various natural gums,

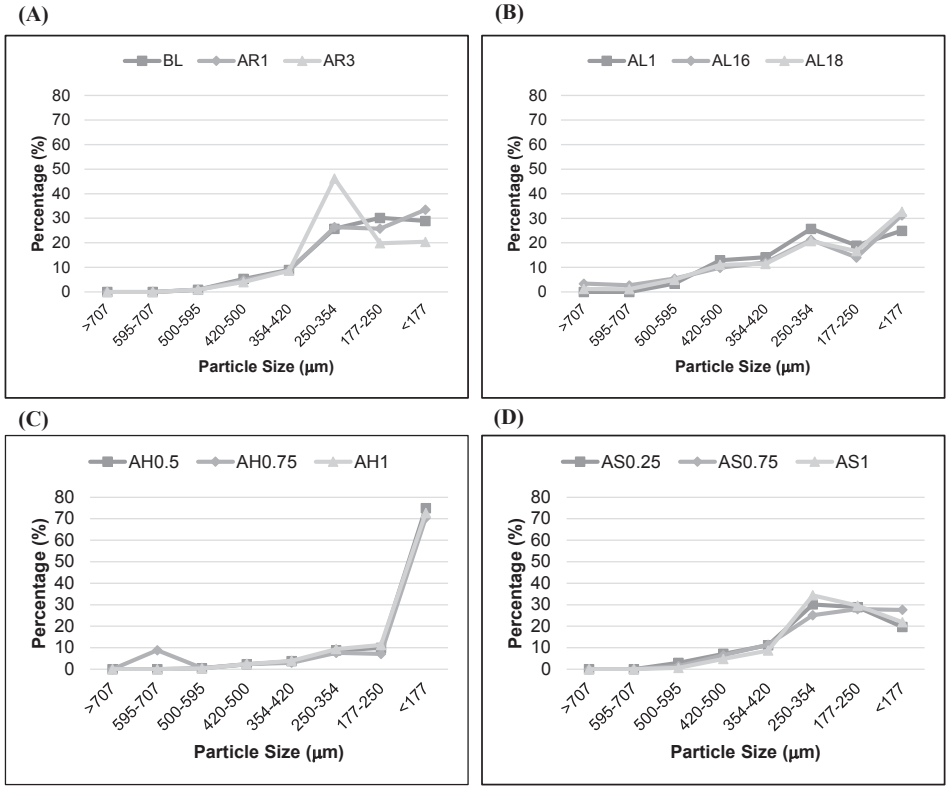

Figure 4 Particle size distribution in granulates using (A) Reference Standards, (B) *L. usitatissimum*, (C) *H. suweolens* and (D) *S. hispanica* mucilages as binders in the formulation. BL = Blank formula without binder added, AR = Formulation with polyvinylpyrrolidinone K30, AL = Formulation with *L. usitatissimum,* AH = Formulation with *H. suweolens,* AS = Formulation with *S. hispanica*

mucilages and their modified forms. Carbohy Polym, 92: 1685–99, 2013

2 Jani GK, Shah DP, Prajapati VD, Jain VC. Gums and mucilages: versatile excipients for pharmaceutical formulations. Asian J Pharm Sci, 4: 309–23, 2009

3 Beneke C, Viljoen A, Hamman J. Polymeric Plant-derived Excipients in Drug Delivery. Molecules, 14: 2602–2620, 2009

4 Archana G, Sabina K, Babuskin S, Radhakrishnan K, Fayidh MA, Babu PAS, Sivarajan M, Sukumar M. Preparation and characterization of mucilage polysaccharide for biomedical applications. Carbohy Polym, 98: 89–94, 2013

5 Prajapati ST, Prajapati VD, Acharya SR. Characterization of disintegration properties of Plantago ovata mucilage in the formulation of dispersible tablets. Indian J Pharm Ed, 40: 208–11, 2006

6 Avachat AM, Dash RR, Shrotriya SN. Recent investigations of plant based natural gums, mucilages and resins in novel drug delivery systems. Indian J Pharm Ed Res, 44: 86–99, 2011

7 Panda PB, Gregory J. Extraction and Performance Evaluation of *Salvia hispanica* Mucilage as Natural Disintegrants for Optimization of Pyrilamine Maleate Fast Dissolving Tablets. Nat Prod J, 5: 288–98, 2015

8 Capitani MI, Corzo-Rios LJ, Chel-Guerrero LA, Betancur-Ancona DA, Nolasco SM, Tomás MC. Rheological properties of aqueous dispersions of chia (*Salvia hispanica* L.) mucilage. J Food Eng, 149: 70–77, 2015

9 Yadav IK, Jain DA. Formulation and evaluation of diclofenac sodium SR tablets using *Linum usitatissimum* seed mucilage Matrixing. Indian J Res Pharm Biotech Vijaywada, 3: 367–72, 2015

10 Basu S, Bandyopadhyay AK. Characterization of mucoadhesive nasal gels containing midazolam hydrochloride prepared from *Linum usitatissimum* L. mucilage. Braz J Pharm Sci, 47: 817–23, 2011

11 Praznik W, Čavarkapa A, Unger FM, Loeppert R, Holzer W, Viernstein H, Muller M. Molecular dimensions and structural features of neutral polysaccharides from the seed mucilage of *Hyptis suaveolens* L. Food Chem, 221: 1997–2004, 2017

Table 7 The performance parameters for tablets made by wet granulation using mucilages from *L. usitatissimum*, *H. suveolens* and *S. hispanica* as binders

FORMULATION CODE*	THICKNESS (mm)	WEIGHT VARIATION (mg)	WETTING TIME (s)	DISINTEGRATION TIME (min)	CARR'S INDEX (%)	FRIABILITY (%)
BL	4.64±0.15	154.8±1.8	32.6±4.6[c,d]	22.9±3.1[c,d]	20.2±2.3	0.36±0.39
AR1	4.57±0.074	155.5±1.7	43.4±4.0[a,d]	34.5±4.9[d]	18.8±2.5	0.05±0.09
AR3	4.61±0.10	153.6±1.3	58.9±6.5[a]	103.0±13.2[a,b]	18.2±0.8	0.05±0.09
AR5	4.61±0.14	150.0±2.5	63.8±7.5[a,b]	129.0±17.3[a,b,d]	16.4±3.8	0.00
AL1	4.55±0.049	153.1±2.2	73.8±5.7[a,b,d]	302.0±47.4[a,b,c,d]	17.3±1.2	0.00
AL1.6	4.75±0.11	155.6±1.9	101.2±6.0[a,b,c,d]	757.9±32.9[a,b,c,d]	20.7±0.9	0.15±0.15
AL1.8	4.77±0.16	154.9±1.5	99.6±8.5[a,b,c,d]	928.3±35.1[a,b,c,d]	19.9±2.2	0.00
AS0.25	4.76±0.14	153.5±1.1	60.5±8.5[c,d]	57.6±5.4[d]	18.6±5.2	0.05±0.09
AS0.50	4.65±0.11	155.3±1.0	60.8±14.1[c,d]	53.4±5.2[a]	21.2±0.9	0.00
AS0.75	4.64±0.084	153.8±2.0	76.8±16.7[a]	71.8±7.0[a,b]	26.2±0.6	0.00
AH0.5	4.60±0.091	154.0±1.2	39.8±7.9[a]	46.3±5.8[d]	17.6±1.8	0.00
AH0.75	4.50±0.12	151.8±2.7	35.0±5.2[a]	89.7±13.4[a,c,d]	21.1±2.8	0.00
AH1.0	4.58±0.13	152.7±1.9	57.2±8.5[a,b,c]	97.1±5.2[a,d]	21.6±1.7[b,c,d]	0.00

Data is shown as mean ± SD (n=3)

*BL = Blank formulation without binder added, AR = Reference formulation with polyvinylpyrrolidinone K30, AL = Formulation with *L. usitatissimum*, AH = Formulation with *H. suveolens*, AS = Formulation with *S. hispanica*

[a] Indicates significant variation from blank (BL) formulation (P ≤0.05)
[b] Indicates significant variation from reference (AR1) formulation (P ≤ 0.05)
[c] Indicates significant variation from reference (AR2) formulation (P ≤ 0.05)
[d] Indicates significant variation from reference (AR5) formulation (P ≤ 0.05)

Table 8 Wetting and disintegration time for tablets formulated using mucilages from *L. usitatissimum*, *H. suveolens* and *S. hispanica* as disintegrating agents

FORMULATION CODE*	WETTING TIME (s)	DISINTEGRATION TIME (min)
DBL	21.1±2.1	94±15
DRC	13.7±2.4[a]	4.2±0.5[a]
DRG	13.8±1.5[a]	6.1±0.5[a,d]
DRP	17.9±1.9[a,b]	26±10[a,b,c]
DL	17.4±2.1[a,b]	43±11[a,b,c]
DH	17.4±2.2[a,b]	20±2[a]
DS	16.7±1.5[a,b]	14±3[a]

Data show as mean ± SD (n=3)

*DBL = Blank, DRC = Croscarmellose reference, DRG = Sodium starch glycolate reference, DRP = Crospovidone reference, DL = *Linum sativum*, DS = *Salvia hispanica*, DH = *Hyptis suaveolens*.

[a]Indicates significant variation from blank (DBL) formulation (P ≤ 0.05)
[b]Indicates significant variation from reference (DRC) formulation (P ≤ 0.05)
[c]Indicates significant variation from reference (DRG) formulation (P ≤ 0.05)
[d]Indicates significant variation from reference (DRP) formulation (P ≤ 0.05)

12 Lin K-Y, Daniel JR, Whistler RL. Structure of chia seed polysaccharide exudate. Carbohy Polym, 23: 13–8, 1994

13 Warrand J, Michaud P, Picton L, Muller G, Courtois B, Ralainirina R, Courtois, J. Structural investigations of the neutral polysaccharide of *Linum usitatissimum* L. seeds mucilage. Int J Biol Macromol, 35: 121–125, 2005

14 Fabre J-F, Lacroux E, Valentin R, Mouloungui, Z. Ultrasonication as a highly efficient method of flaxseed mucilage extraction. Ind Crop Prod, 65: 354–360, 2015

15 Ziolkovska A. Laws of flaxseed mucilage extraction. Food Hydrocolloid, 26: 197–204, 2012

16 Muñoz LA, Cobos A, Diaz O, Aguilera JM. Chia seeds: Microstructure, mucilage extraction and hydration. J Food Eng, 108: 216–224, 2012

17 Gowda DC. Polysaccharide components of the seed-coat mucilage from *Hyptis suaveolens*. Phytochem. 23: 337–338, 1984

18 Mistry S, Biswal PK, Mishra B, Sahoo S. Isolation, characterization and pharmaceutical evaluation of the mucilage from *Polyalthia suberosa* leaves. Int J PharmTech Res, 2: 1455–9, 2010

19 Kumar VJ, Sati OP, Singh R. A potential natural tablet binder from *Grewia optiva*. Der Pharmacia Lettre, 3: 120–7, 2011

20 Gangurde AB, Perumal P, Malpure PS. Characterization of *Ziziphus mauritiana* LAM. seed (Jujube) mucilage for physicochemical and mucoadhesive properties. Int J PharmTech Res, 4: 150–5, 2012

21 Mishra SK, Kumar A, Talukdar A. Evaluation of binding property of mucilage from *Litsea glutinosa* wall. Pharmacog Res, 2: 289–92, 2010

22 Atlas Chemical Industries Inc. The Atlas HLB System. Wilmington, Delawere, USA. pp., 1963

23 Ramu G, Mohan GK, Jayaveera KN. Preliminary investigation of patchaippasali mucilage (*Basella alba*) as tablet binder. Int J Green Pharm, 5: 24-8, 2011

24 Morton JF. Mucilaginous plants and their uses in medicine. J Ethnopharm, 29: 245–66, 1990

25 Sachin BN, Vidyasagar G, Anil GJ, Atul RB, Kalpen NP. Isolation and evaluation of mucilage of *Artocarpus heterophyllus* as a tablet binder. Journal of Chemical and Pharmaceutical Research. J Chem Pharm Res, 2: 161–6, 2010

26 USP United States Pharmacopeia, Rockville, MD, USA, 2007

27 Nash NA. Suspensions. In: Swarbrick J, Boylan JC, editors. Encyclopedia of Pharmaceutical Technology. 2nd ed. New York, NY, USA, pp. 2045–3032, 2002

28 Ogaji IJ, Nep EI, Audu-Peter JD. Advances in Natural Polymers as Pharmaceutical Excipients. Pharm Anal Acta, 3: 1-16, 2012

29 Isimi CY, Kunle OO, Bangudu AB. Some emulsifying and suspending properties of the mucilage extracted from kernels of *Irvingia gabonensis*. Boll Chim Farm, 139: 199–204, 2000

30 Jani GK, Shah DP, Jain VC, Patel MJ, Vithalani DA. Evaluating mucilage from *Aloe barbadensis* Miller as a pharmaceutical excipient for sustained-release matrix tablets. Pharm Tech, 31: 90–98, 2007