



The extraction and investigation of polysaccharide mucilages for use as excipients in drug delivery systems and their application for developing floating tablets of silymarin.

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ABSTRACT

In the present investigation, polysaccharide mucilages were extracted from the fruits of *Coccinia grandis* (CG), the leaves from *Rumex vesicarius*, the seeds from *Trigonella foenum-graecum* (Fenugreek (FG)) and rhizomes from *Colocasia esculenta* (CE) using a solvent precipitation method and their physicochemical properties were evaluated for their *in-vitro* buoyancy and *in-vitro* drug release study by developing silymarin loaded floating tablets. The percentage yield of the extracted mucilages for CG, RV, CE and FG were 7.7 ± 0.5 , 6.5 ± 0.50 , 13.0 ± 0.50 and 16 ± 1.50 respectively. The results from Carr's Index (CI) were 18.91 ± 1.40 , 13.71 ± 2.00 , 14.41 ± 1.5 , 13.15 ± 1.80 , 35.55 ± 1.23 and 10 ± 0.91 for CG, RV, CE, FG, Guar Gum and HPMC K4M respectively. The FTIR spectra showed the presence of strong band stretching between the ranges of 3324 cm^{-1} and 576 cm^{-1} . The diffractograms of extracted mucilages indicated that RV, CE and FG are crystalline polysaccharide mucilages, whereas CG exhibited a straight line. The LD_{50} value for orally administered CG, RV CE and FG was $\geq 2000 \text{ mg/kg}$. The Floating lag time (sec) for formulations F1-F5 was 120 ± 13 , 160 ± 10 , 180 ± 16 , 60 ± 4 and 60 ± 4 respectively. Further, *In-vitro* drug results were in the range of 86-100% for the floating tablets of silymarin (F1-F5). Based on the results it can be concluded that the CG, RV CE and FG could be suitable macromolecules for developing floating tablets and could be considered novel hydrocolloids for use in the pharmaceutical industrial.

KEY WORDS: Adhesiveness, excipients, DSC, floating tablets, polysaccharide mucilages, swelling index, XRD

INTRODUCTION

There is an increasing need for low cost, non-toxic, biodegradable, environmentally-friendly and freely available natural excipients for design of pharmaceutical dosage forms. Naturally arrived mucilages are widely accepted and may be strong competitors to previously explored additives (1). Scientists have explored naturally available plant mucilages and novel additives

such as suspending agents, diluents, binders (2), superdisintegrants (3), thickeners, protective colloids in suspensions (4), gelling agents (5), suppository bases, film formers (6), viscosity enhancers, stabilizers, solubilizers and emulsifiers in pharmaceutical dosage forms such as sustained-release tablets (7-10). Mucilages have also been investigated widely for the development of various dosage forms, tablet coating materials, bioadhesiveness polymers in mucosal drug delivery systems, liquid formulations, ocular drug delivery systems and nanoparticles preparations (11-13). As there has been an increased attention towards

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the acceptance of natural excipients there is an urgent need to investigate possible the natural materials for use in the pharmaceutical industry (14,15).

Pharmaceutical excipients are non-drug substances used in the manufacturing of specific types of dosage forms to provide easy administration to the patient (16). Innovative and chemically modified additives continue to emerge due to improved drug delivery performance fostering a need to increase research into plant based pharmaceutical excipients (17). A literature search shows that mucilages extracted from the leaves from *Hibiscus rosasinensis* L. (18), *Pereskia aculeate* (19), fruits from *Roxburghii* Tratt (20), *Musa sapientum* (21), and seeds from *Plantago ovata* seeds (22) have been investigated for the use as additives in pharmaceutical dosage forms (23).

Coccinia grandis L. belongs to the *Cucurbitaceae* family and it is a climbing perennial herb found all around the globe (24), *Rumex vesicarius* L., also known as Bladder dock, belongs to the family *Polygonaceae* and can be found globally (25), *Trigonella foenum-graecum*, commonly called Fenugreek belongs to the *Leguminaceae* family and is widely distributed in Asia and Europe. It has been extensively explored as controlled release matrix forming agent (26), *Colocasia esculenta* (L.) Schott belongs to the *Araceae* family and has been used as a disintegrant and binder in solid dosage forms for oral administration. Moreover, *Colocasia esculenta* mucilage was explored as a directly compressible ingredient in tramadol tablets (27-28).

In this study polysaccharide mucilages were extracted from the fruits from *Coccinia grandis* (CG), leaves from *Rumex vesicarius* (RV), seeds from fenugreek (FG) and rhizomes from *Colocasia esculenta* (CE) to investigate their drug delivery applications and pharmaceutical industrial utilization (29-31). The extracted solution of polysaccharide mucilages were subjected to the analysis of their physicochemical properties, phytochemical investigations, micromeritics properties, adhesiveness, gel strength, swelling index, viscosity studies, FTIR, DSC, XRD and acute oral toxicity study for their

toxicity profile. Additionally, polysaccharide mucilages were compared with the synthetic polymers HPMC E15 and HPMCK4M and other well-known natural powders such as Acacia, Guar gum (GG), Xanthan gum (XG) and Tragacanth (TG). Additionally, Silymarin loaded floating tablets were prepared using direct compression which were then analyzed for their physical characteristics, buoyancy and *in-vitro* drug release.

MATERIALS AND METHODS

Materials

The fruits from *Coccinia grandis* (CG), leaves from *Rumex vesicarius* (RV), rhizomes from *Colocasia esculenta* (CE) and, seeds from fenugreek (FG) were collected in Narsampet, Telangana, India. Acetone, HPMC K4M, HPMC E15, acacia, GG, TG, XG, microcrystalline cellulose (MCC), talc (purified), citric acid, sodium bicarbonate, magnesium stearate were purchased from Qualikems Fine Chem Pvt. Ltd, Vadodara, Gujarat India. All reagents and chemicals employed in this study were of analytical grade.

Methods

Extraction of natural powders

The polysaccharide mucilages were extracted using a solvent precipitation technique reported previously (19). The fruits from CG, leaves from RV, rhizomes from CE and seeds from FG were cleaned and washed with water. The seeds, leaves and rhizomes were soaked in distilled water for 15 hours, then heated at 60°C for 1 hour and allowed to cool to room temperature. The obtained viscous solution was filtered using a muslin cloth and precipitated by the addition of a double quantity of acetone during constant stirring. Finally, the mucilages were separated by filtration using Whatmann filter paper (No.1) and dried in an oven at 60°C to a constant weight. Thereafter, the dried powder was ground into fine powder and passed through a No. 60 sieve.

Physicochemical characterization

Organoleptic evaluation

The polysaccharide mucilages (CG, RV, CE and FG) were subjected to color, odor, taste and texture analysis to investigate their possible use as novel hydrocolloids in the pharmaceutical industry.

Percentage yield

The percentage yield from the CG, RV, CE and FG polysaccharide mucilages were calculated as the dry weight of the fine powder compared to the initial weight of CG, RV, CE and FG (32-33). The percentage yield study was carried out in triplicate and the results were reported as mean $\pm$ standard deviation (SD).

Loss on drying(LOD)

The LOD was performed according to the previously reported method (34). 1.0 grams of the polysaccharide mucilages was weighed and transferred into a petri dish, followed by drying in an oven at 105°C to a constant weight. The LOD was calculated as the percentage of the weight of mucilage lost after drying compared to the initial weight of the powder. This study was carried out in triplicate and the results are presented as mean $\pm$ SD.

Phytochemical investigations

The polysaccharide mucilages were investigated using various qualitative tests such as the Molisch's test, iodine test, ruthenium red, ferric chloride test, silver nitrate test, barium chloride test for the identification of carbohydrates, starch, mucilage, tannins, chlorides and sulphates respectively (35).

Solubility test

The solubility of the polysaccharide mucilages were characterized using the Mirhosseini and Amid method (36). A concentration of 0.5% (w/v) solution of the powder sample was prepared by agitating the mixture in a magnetic stirrer at 30-40°C for a period of 30 minutes. Then, insoluble materials were removed by

centrifuging the solutions at 6000 x g for 30 minutes. The supernatant was collected and dried in a hot air oven at 105°C for 24 hours and, the final concentrations were determined as total solids after drying in the oven using the following Equation 1. The solubility of polysaccharide mucilages was determined in water, acetone, chloroform, methanol and ethanol.

$$\text{Solubility (\%)} = \frac{C1}{C2} * 100 \quad \text{Eq. 1}$$

Where, C1 is the concentration of supernatant and C2 is the initial concentration of the polysaccharide mucilages initial.

Moisture content

The moisture content (MC) of the polysaccharide mucilages was using Equation 2:

$$\text{Moisture Content (\%)} = \frac{WDS}{ISW} * 100 \quad \text{Eq. 2}$$

Where, WDS is the weight of the dried sample and ISW is the initial weight of the sample.

Measurement of pH

The pH of the mucilages was analysed by shaking a 1% (w/v) dispersion of polysaccharide mucilages in deionized water. The pH was measured using a digital pH meter (Labindia Analytical Instruments Pvt. Ltd., Mumbai, India).This study was performed in triplicate and the results are presented as mean $\pm$ SD (18).

Particle size determination

Polysaccharide mucilages were dispersed in water (suspension) and particle size was measured using light microscopy. A drop of mucilage suspension was poured on a glass slide, and thin film was formed after spreading. The stage micrometer was calibrated with an eyepiece micrometer. The particle size was then observed and average particle size $\pm$ SD was reported (38).

Swelling index

1.0 gram each of the CG, RV, CE, FG, GG and HPMC K4M samples were kept separately in 15 mL plastic centrifuge tubes and the volume was noted. Then, a 10 mL buffer solution (buffers pH1.2 and 7.2) was added to the 15 mL test tube and vortexed on a vortex mixer (Remi, India) for 2 minutes. The mixture was then immediately subjected to centrifugation at 1000 RPM for 10 minutes at 4°C. The supernatant was carefully removed, and the volume of the sediment was noted. The swelling index (SI) was computed using Equation 3 (39). The SI study was carried out in triplicate and the results are reported as mean $\pm$ SD.

$$SI = \frac{S1}{S2} \quad \text{Eq. 3}$$

Where, S1 is the volume of mucilage prior to hydration and S2 is the volume of mucilage after hydration.

Viscosity

The viscosity of a 1% (w/v) solution of polysaccharide mucilages from CG, RV, CE and FG was determined using a Brookfield DV-II+Pro Viscometer, Spindle LV-1 (Brookfield Engineering Laboratories, Inc, USA), for their rheological behavior at 25°C. The measurements were at speeds from 10 to 100 RPM with 30 seconds between 2 successive speeds and then in a reverse order (2, 40). The viscosity study was carried out in triplicate and the results were reported as mean $\pm$ SD.

Adhesive strength

A 2.5% (w/v) gel from CG, RV, CE, FG, HPMC E15, HPMC K4M, Acacia, GG, TG and XG was prepared and the adhesive strength (adhesiveness (kg/mM) and adhesive force (kg) was characterized using an EZ-X500N Texture Analyzer (Shimadzu Texture Analyzer, Singapore). The prepared gel was poured into a glass beaker and a penetration test was performed using the Texture Analyzer jig with 100N load cell. Double successive penetrations were performed at a pre-determined distance (10 mm) in the gel using a flat-

bottomed cylindrical plunger at speed of 15 mm/min and results of detachment force was recorded in kg/mM (2, 41). The test was carried out in triplicate and the results are presented as mean $\pm$ SD.

Powder micromeritics characteristics

Various powder micromeritics parameters, that is, the angle of repose, bulk density, tapped density, Carr's Index (CI) and Hausner ratio were carried out (42).

Angle of repose

The angle of repose for CG, RV, CE, FG, Guar gum and HPMC K4M were carried out using a fixed funnel method. The known quantity of the above samples were put into the funnel (43). The height of the funnel was maintained in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was permitted to flow through the funnel without any conflict on the surface. The height and diameter of the powder cone were then measured. Then, angle of repose was calculated using Equation 4. This study was carried out in triplicate and the results are reported as mean $\pm$ SD.

$$\theta = \tan^{-1} h/r \quad \text{Eq. 4}$$

Where, r and h are the radius and height of the powder cone respectively.

Bulk density and tapped density

10 grams of each powder from CG, RV, FG, CE, GG and HPMC K4M were transferred into a 100 mL measuring cylinder and the volume V_a occupied by each powder sample was noted without tapping. The cylinder was lightly shaken initially to breakdown any clumps of the powders and initial volume. The cylinder was then permitted to fall under its own weight onto a hard surface from the height of 2.5 cm for 2 seconds. The tapping was continued until a constant volume was obtained and the V_b volume was noted. The bulk and tapped densities were calculated as the ratio of weight to volume (V_a and V_b respectively). This test was

carried out in triplicate and the results were presented as mean $\pm$ SD.

Carr's index and Hausner ratio

Equation 5 was used to establish Carr's index of the powder samples:

$$\text{Carr's index} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100 \quad \text{Eq. 5}$$

The Hausner ratio was calculated using Equation 6 as the ratio of tapped density to the bulk density of the powder. This study was carried out in triplicate and results are presented as mean $\pm$ SD.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}} \quad \text{Eq. 6}$$

FTIR spectroscopy

FTIR spectroscopy of the polysaccharide mucilages were mixed with fine KBr powder and crushed very fine then placed in a pellet-forming die. A force of around 8 tons was applied under a vacuum for five minutes which yielded transparent pellets. For spectra observation, the pellet was loaded on the FTIR holder (Bruker, Alpha FTIR). The spectrum was recorded over the wave number ranging from 4000 to 400 cm^{-1} and used to identify the structural characteristic as well as functional groups of the powdered mucilages (44-45).

Differential scanning calorimetry

Differential scanning calorimetry (DSC) (Hitachi High-Tech Sciences-Model DSC7020, USA) was used to study the thermal properties of the polysaccharide mucilages. 5 mg of polysaccharide mucilage was sealed in an empty pre-weighed aluminium pan and scanned over a temperature range of 25-300°C under an atmosphere of nitrogen at a rate of 10°C.min⁻¹, followed by a cooling cycle back to 25°C at a rate of 20°C.min⁻¹ (44).

X-Ray powder diffraction

X-ray powder diffraction (XRD) patterns of CG, RV, FG and CE were analyzed using an X-ray-diffractometer (PANalytical, The Netherlands). The polysaccharide mucilage samples were packed in rectangular aluminium cells, illuminated using Cu-K α radiation ($\lambda = 1.54056\text{\AA}$) at 45 kV and 30mA. The extracted powder was scanned between diffraction angles 6° to 80° . A scan step of 0.008 was used and the dwell time was 10 seconds. A nickel filter was used to reduce the K β contribution to the X-ray signal. The 'd' spacing was computed according to Bragg's law of diffraction (45).

Acute oral toxicity study

An acute oral toxicity study was carried out in accordance with guidelines No. 423 provided by the Organization for Economic Co-operative and Development (OECD) (46). Eight-week-old Swiss albino mice (male and female, weighing 20-25 g) were purchased from Mahavir Enterprises, Hyderabad, India. The animals were housed in standard (28 $\times$ 21 $\times$ 14 cm, six per cage) opaque polypropylene cages and provided with dust free paddy husk as bedding material. They were maintained on a photoperiod 12-hour light/dark cycle in the registered animal house (1694/PO/Re/S/13/CPCSEA) of Balaji Institute of Pharmaceutical Sciences. Food and water were provided *ad libitum*. The room temperature was maintained at approximately 22 $\pm$ 5°C with relative humidity at 50-70%. All experimental test paradigms were approved by the "Institutional Animal Ethics Committee" (IAEC), Balaji Institute of Pharmaceutical Sciences according to protocol no: BIPS/IAEC/01/07 and were carried out in accordance with the guidelines stipulated by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Fisheries, Animal Husbandry and Dairying, Department of Animal Husbandry and Dairying, Government of India.

After a seven-day adaptation to laboratory conditions, mice were randomly assigned into 5 groups consisting of 6 animals in each group. The control group received normal saline (10 mL/kg) and the remaining groups

of mice received 2000 mg/kg of CG, RV, CE and FG dispersion in distilled water. The animals were observed individually after dosing at least once during the first 30 minutes for first 4 hours and then every 4 hours thereafter for the next 24 hours. After 24 hours the animals were observed once a day for 14 days. Observation were made with regard to clinical signs, gross behavioral changes and mortality.

Development of the gastroretentive floating tablets of silymarin

Silymarin loaded floating tablets were prepared using polysaccharide mucilages from CG (F1), RV (F2), CE (F3), FG (F4) and HPMC K4M (F5). These polymers form a gel-like matrix after contact with the gastro intestinal fluid. Sodium bicarbonate and citric acid were used as effervescent agents to produce carbon dioxide, talc (purified) and MCC were used as glidant and diluent respectively. All the excipients except magnesium stearate were passed through a No 60 sieve. The ingredients used for the preparation of the gastroretentive floating tablets were mixed in a cubic mixer for 15 minutes. Magnesium stearate was added into the formulation blend and mixed for the next 5 minutes. The blend was then tableted using direct compression (47). The weight of sodium bicarbonate, citric acid, talc (purified), MCC and magnesium stearate was 70 mg, 30 mg, 30 mg, 5 mg and 5 mg respectively in each tablet. The developed 350 mg weight tablet contained 70 mg of silymarin.

Characterization of the gastroretentive floating tablets of silymarin

The floating tablets of silymarin were characterized for thickness, weight variation, hardness, friability, and drug content uniformity according to USP specifications.

In vitro buoyancy study

An *in vitro* buoyancy test was used to determine the floating lag time and buoyancy of the tablets, using a previously reported method (48). One tablet was added to a 900 mL glass beaker with 0.1 N HCl (pH 1.2) media. The time required for the tablet to reach to

the surface of the media from the bottom (floating lag time, FLT) and the time at which the tablet persistently floated on the surface of the medium (duration of floating or buoyancy) were determined (47). For this study six tablets from each formulation were evaluated and reported as mean $\pm$ SD.

In vitro drug release studies

The *in vitro* drug release of silymarin from the floating tablets was studied using US Pharmacopeia dissolution paddle apparatus (Labindia, Mumbai, India) at $37 \pm 0.5^\circ\text{C}$ at 50 RPM (49). The tablets were transferred into 900 mL of 0.1 N HCl (pH 1.2). Aliquots of 5 mL were withdrawn at predetermined time intervals (0.5, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours) and replenished with fresh medium. The samples were filtered through a $0.45 \mu\text{m}$ membrane filter and the absorbance of these solutions was measured at wavelength 277 nm using a UV spectrophotometer to determine the drug release. Various release kinetic models (First-order, Zero-order and Higuchi) were applied to the data to understand the drug release from the matrices, and the model with the highest correlation coefficient (R^2) value was considered to be the best fit. The drug release mechanism of developed formulations was determined by n value (release exponent) using the Korsmeyer-Peppas kinetics model.

RESULTS AND DISCUSSION

Polysaccharide mucilages were successfully extracted from CG, RV, CE and FG using a solvent precipitation method (28). The percentage yield of extracted polysaccharide mucilages was 7.7 ± 0.5 , 6.5 ± 0.5 , 13.0 ± 0.5 and 16 ± 1.5 respectively for CG, RV, CE and FG. The result of the color, odor, taste, nature, foreign organic matter (FOM) (%), and fracture are presented in Table 1. The results of physicochemical properties of polysaccharide mucilages revealed that they were pharmaceutically acceptable by organoleptic properties. It is indicated that there was a minimal loss of substances during the drying of solution of polysaccharide mucilages(50) and the LOD of developed polysaccharide mucilages was very low. The physicochemical properties data

Table 1 Physicochemical properties of the polysaccharide mucilages (n=3)

PARAMETER	CG	CE	RV	FG
Color	Green Creamy or almost white Green			
Odor	Odorless			
Taste	Mucilaginous			
Nature	Free flowing powder			
FOM (%)	NMT 0.50			
Moisture content (%)	1.0±0.24	1.50±0.25	1.0±0.50	1.0±0.60
Fracture	Rough	Smooth	Rough	Smooth
LOD (%)	1.5±0.20	2.9 ± 0.40	1.6±0.60	3 ±0.6
pH	6.8±0.50	6.5±0.50	7.1±0.50	7.0±0.50

indicated that the extracted natural powders could be used for pharmaceutical applications. The results of phytochemicals investigation test are shown in Table 2. It was confirmed that the polysaccharide mucilages of CG, RV, FG and CV contain carbohydrates, starch, mucilage and polysaccharides (35). Phytochemical tests, showed that polysaccharide mucilages obtained from CG, RV, CE and FG do not contain tannins, chlorides, and sulphates indicating that the polysaccharide mucilages obtained from CG, RV, CE and FG were pure (35). The solubility of CG, RV, CE and FG polysaccharide mucilages was $94.12 \pm 4.36\%$, $91.00 \pm 2.31\%$, $95.30 \pm 1.60\%$ and $89.41 \pm 46.87\%$ respectively in hot water. A solubility study of polysaccharide mucilages is considered an important

criteria when used in industrial applications. From a functional point of view, the complete solubility of polysaccharide mucilages is encouraging. The excipients i.e., GG, XG and CMC are soluble in cold water, however, carrageenan gum, locust bean, and alginates are soluble in hot water (50). Interestingly, CG, RV, CE and FG exhibited significantly greater solubility than the locust bean gum (30%) and *Lepidium perfoliatum* seed gum (18–25%) (51-52). CG, RV, CE and FG polysaccharide mucilages were fairly soluble in cold water and absolutely insoluble in acetone, ethyl alcohol, chloroform and methyl alcohol solvents. A natural gum may not be completely soluble in water due to the presence of insoluble particles (53). Hence, further purification is required to reduce the insoluble matters and thereby increase the solubility of the crude gum (54).

Moisture content plays an essential role in final drug formulations. When the moisture content is above a critical limit, it may affect the stability of the final formulation and could increase the possibility of microbial contamination. Moisture content affects the preparation of oral solid dose formulations (55). High moisture content in the powder is contraindicated. It can result in poor powder flow, which could in turn, cause irregular tablet parameter performance. It could also result in sticking problems on the surface of the tablet punches (56). When moisture is present below a critical level, it helps the API and excipient in binding. For direct compression, different types of excipients are used for example starch, microcrystalline cellulose (MCC), polyethylene glycol (PEG) and HPMC (57).

Table 2 Phytochemical investigations of polysaccharide mucilages (n=3)

MUCILAGE	MOLISCH TEST	RUTHENIUM RED TEST	IODINE TEST	FECL ₃ TEST	SILVER NITRATE TEST	BARIUM CHLORIDE TEST
CG	+	+	+	-	-	-
CE	+	+	+	-	-	-
RV	+	+	+	-	-	-
FG	+	+	+	-	-	-

+ = Present

- = Absent

MCC is a common excipient used for the preparation of tablets by direct compression or wet granulation (55-57). The moisture content of MCC is about 4%-5 % which is good for direct compression formulation. Numerous studies have reported that higher and extra low moisture content of MCC influences the hardness of direct compressible tablets (57). The moisture content of CG, RV, CE and FG were within acceptable limits (as presented in Table1) and could be suitable for the preparation of tablets by direct compression or wet granulation technique (55, 58).

The pH of all polysaccharide mucilages results is also presented in Table 1 showing that they were neutral. The pH results indicated the formulations developed with these polysaccharide mucilages or hydrocolloids could be biocompatible and is likely not to cause any irritation to the mucous membrane in the gastrointestinal tract (GIT) and therefore should be safe (59). The particle sizes of polysaccharide mucilages were $239 \pm 5.36 \mu\text{M}$, $191 \pm 8.52 \mu\text{M}$, $243 \pm 5.89 \mu\text{M}$ and $115 \pm 9.12 \mu\text{M}$ respectively for CG, RV, CE and FG. The polysaccharide mucilages were fine powders and were able to easily pass through a No. 60 sieve. Therefore, the powders of polysaccharide mucilages are unlikely to cause any problems in powder flow properties (60).

The results of the swelling index is shown in Table 3. The extracted CG, RV, FG, CE, GG and HPMC K4M powders exhibited greater swelling at pH 7.2 compared to pH 1.2. It may be ascribed to the formation of strong hydrogen bond between the hydroxyl groups of the mucilages and the water molecules (61). Furthermore,

the SI of the polysaccharide mucilages was similar to GG and HPMC K4M. Thus, the polysaccharide mucilages can be used in the development of various drug delivery systems like gastroretentive, colonic, rectal and buccal.

The results of the viscosity studies of 1%(w/v) for the CG, RV, CE and FG powder samples were in the range from 240 to 69 cps, 190 to 10 Cps, 230 to 97 Cps and 240 to 90 Cps respectively. The results of the gel strength (sec) was 33 ± 0.50 , 36 ± 0.82 , 45 ± 0.45 and 55 ± 0.56 respectively for CG, RV, CE and FG. The viscosity of polysaccharide mucilage solutions was moderately high which may depend on the composition and chemical structure (19). Figure 1 shows the rheogram of viscosity versus shear rate. It was observed that the viscosity decreases with an increase in the shear rate and the mucilages exhibited pseudoplastic flow or shear thinning flow, and good gel strength. Hence, based on the results of the viscosity, rheological properties and gel strength, it could be used as an excipient in developing sustained release delivery systems. The industrial use of any polysaccharide mucilages mainly depend on the viscosity and rheological characteristics (51). For example, any material used for sustained release should retain specific properties such as quick hydration, high gel strength and be stable throughout the shelf life of product (62). Thus, naturally sourced materials could be substitutes to for semisynthetic and synthetic polymers (29-31, 62).

The texture properties of gel formulations such as adhesiveness (kg/mM) and adhesive force (kg) are

Table 3 Swelling index and micromeritics results of polysaccharide mucilages (n=3)

	PARAMETER	CG	RV	CE	FG	GG	HPMC K4M
Swelling Index (%)	pH(1.2)	26.89 $\pm$ 1.76	73.5 $\pm$ 5.00	26.54 $\pm$ 4.70	78.90 $\pm$ 3.00	45.30 $\pm$ 4.65	65.78 $\pm$ 5.00
	pH(7.2)	51.54 $\pm$ 2.40	99.03 $\pm$ 4.20	59.30 $\pm$ 3.80	109.31 $\pm$ 4.50	68.74 $\pm$ 6.34	101.90 $\pm$ 2.00
	Angle of repose(θ)	25.00 $\pm$ 1.00	20.00 $\pm$ 1.00	19.00 $\pm$ 0.50	22.00 $\pm$ 0.75	26.00 $\pm$ 1.02	22 $\pm$ 0.87
Micromeritics Properties	BD (g/mL)	00.90 $\pm$ 0.10	01.07 $\pm$ 0.28	00.95 $\pm$ 0.09	00.66 $\pm$ 0.05	0.58 $\pm$ 0.030	0.45 $\pm$ 0.012
	TD(g/mL)	01.11 $\pm$ 0.20	01.25 $\pm$ 0.32	01.11 $\pm$ 0.45	00.76 $\pm$ 0.02	0.9 $\pm$ 0.031	0.5 $\pm$ 0.045
	CI (%)	18.91 $\pm$ 1.40	13.71 $\pm$ 2.00	14.41 $\pm$ 1.50	13.15 $\pm$ 1.80	35.55 $\pm$ 1.23	10 $\pm$ 0.91
	Hausner ratio	01.23 $\pm$ 0.30	01.15 $\pm$ 0.30	01.16 $\pm$ 0.20	01.15 $\pm$ 0.40	1.55 $\pm$ 0.30	1.11 $\pm$ 0.32

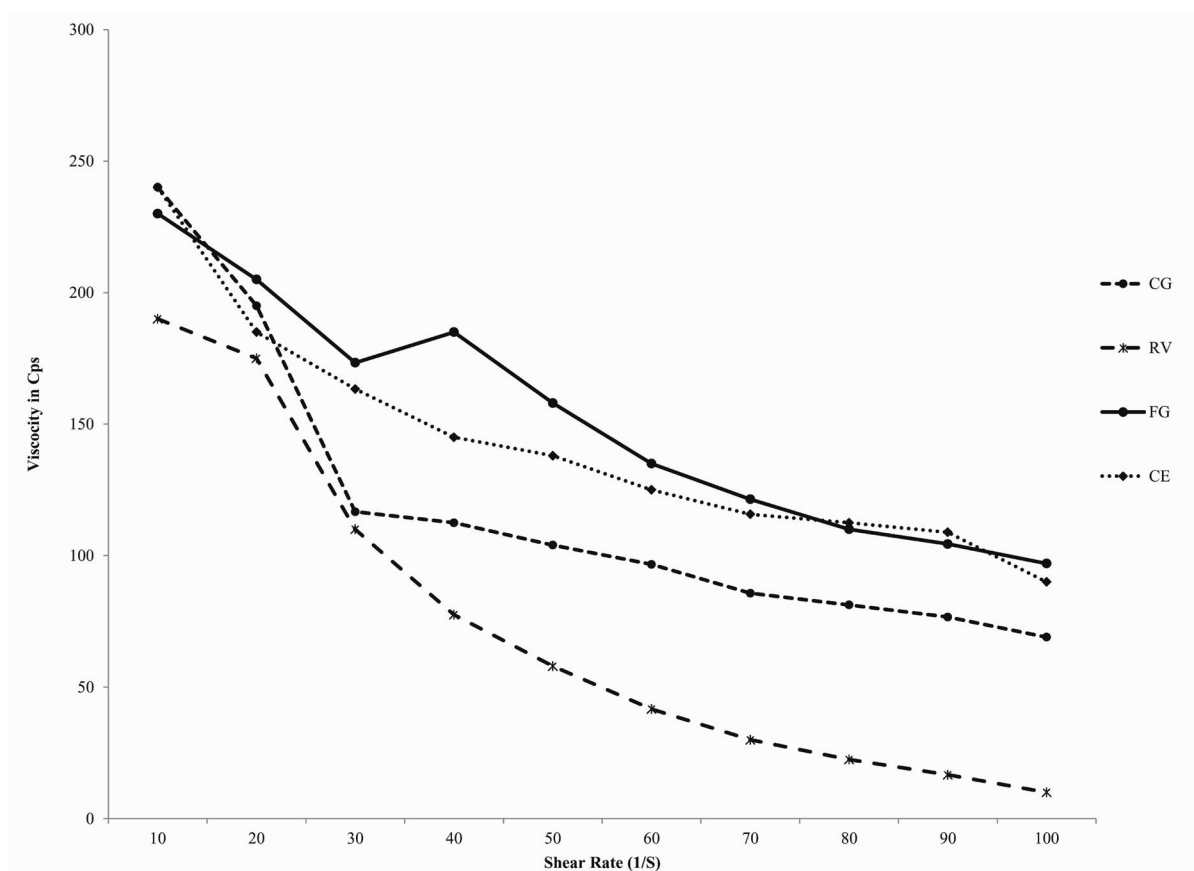


Figure 1 Rheogram of viscosity *versus* shear rate

important parameters for the optimization of topical or hydrogel formulations. Adhesiveness is the upwards movement of a jig; it specifically measures the ability of the formulation to adhere on the disc. Adhesive force is defined as the force required to deform the hydrogel by downward movement of the jig. The adhesive strength properties of hydrogels may affect the release of drug from dosage forms (32). The results of the adhesiveness strength are shown in Table 4. The results show that CG, RV, FG and CE powder samples could be replacements for synthetic and other excipients in pharmaceutical use (39-40). The CG, RV, FG and CE polysaccharide mucilages exhibited superior adhesive strength as compared to synthetic polymers (HPMC E15 and HPMC K4M) and well characterized natural powders (Acacia, GG, TG and XG). The adhesiveness (kg/M) of CG, RV, and CE results were negative which could be attributed to the sticky nature of mucilages. However, the adhesive force of CG, RV and CE powders were negative which indicates that less force

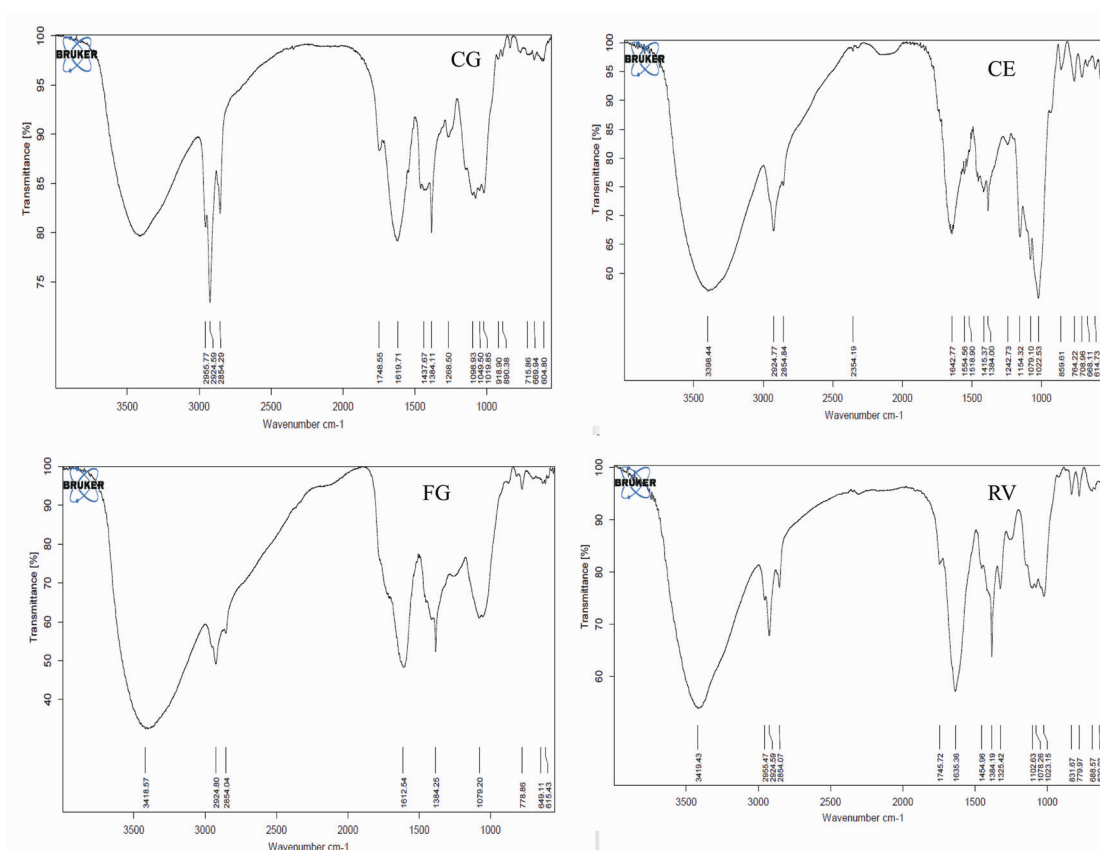
may be required for the deformation of hydrogels (60). The powder micromeritics characteristics were employed to find out the flow behavior of powders and results are shown in Table 3. The results of the angle of repose was excellent for CG, RV, CE, FG and HPMC K4M (reference material) and better than GG. The bulk density and tapped density results of polysaccharide mucilages were nearly equal to the HPMC and based on these results Carr's index and the Hausner ratio were calculated. Furthermore, low bulk density and tapped density of CG, RV, FG and CE indicated that they can be packed and transported easily in bulk quantity (44-45). The results of the ratios of the Carr's index and Hausner ratio indicated that all the polysaccharide mucilages exhibited good to excellent flow properties, whereas, GG showed poor flow characteristics. Therefore, the CG, RV, CE and FG hydrocolloids could be used for the manufacturing of tablets using the direct compression (63).

Table 4 Adhesiveness strength studies of polysaccharide mucilages (n=3)

MUCILAGE	ADHESIVENESS (Kg/mm)	ADHESIVE FORCE (Kg)
FG	$1 \times 10^{-4} \pm 5.78 \times 10^{-8}$	$8 \times 10^{-3} \pm 1 \times 10^{-3}$
CG	$3.69 \times 10^{-3} \pm 2.45 \times 10^{-5}$	$-5.5 \times 10^{-4} \pm 5 \times 10^{-4}$
RV	$-1.74 \times 10^{-1} \pm 3.03 \times 10^{-3}$	$-5.7 \times 10^{-3} \pm 3.6 \times 10^{-4}$
CE	$1.35 \times 10^{-3} \pm 2.08 \times 10^{-6}$	$6.13 \times 10^{-4} \pm 1.5 \times 10^{-6}$
ACACIA	$8.57 \times 10^{-2} \pm 5 \times 10^{-5}$	$-4.1 \times 10^{-4} \pm 1 \times 10^{-4}$
GG	$7.54 \times 10^{-2} \pm 2.51 \times 10^{-6}$	$6.7 \times 10^{-4} \pm 6.08 \times 10^{-6}$
HPMC E15	$-4.87 \times 10^{-3} \pm 2.51 \times 10^{-4}$	$-1.4 \times 10^{-3} \pm 1 \times 10^{-3}$
HPMC K4M	$876 \times 10^{-3} \pm 4.04 \times 10^{-6}$	$3.66 \times 10^{-4} \pm 5.7 \times 10^{-6}$
TG	$5.14 \times 10^{-2} \pm 3.17 \times 10^{-4}$	$-4.33 \times 10^{-4} \pm 1.52 \times 10^{-4}$
XG	$-2.03 \times 10^{-2} \pm 5.29 \times 10^{-4}$	$-3.23 \times 10^{-3} \pm 1.52 \times 10^{-4}$

FTIR analysis has been used for preliminary identification of functional groups in polysaccharide mucilages (38). Figure 2 shows the FTIR spectra of CG, RV, CE and FG. They all exhibited strong band stretching between 3324 cm^{-1} and 576 cm^{-1} . The

various functional groups like OH ($3300\text{--}3400 \text{ cm}^{-1}$) (32), C-H (2914 cm^{-1}), C-O (1024 cm^{-1}) were observed in mucilages. The results of the FTIR confirmed the presence of the carbohydrates in polysaccharide mucilages (38). Conglomerate stretch in the region of 2914 cm^{-1} and $1000\text{--}1200 \text{ cm}^{-1}$ showed the presence of C-O-C functional groups, characteristic of carbohydrate polymers (32, 59). Furthermore, the presence of a peak at 1420 cm^{-1} indicated deprotonated carboxylic acid groups ($-\text{COO}-$) which is attributed to the uronic acid. The absorption band at 893 cm^{-1} corresponds to β -dglucose. It is suggested that, due to the presence of hydrogen bond forming carboxyl and hydroxyl groups, they may have bio adhesive properties. This data suggest that polysaccharide mucilages could be employed as novel hydrocolloids for developing novel drug delivery systems (64). The extracted hydrocolloids could be suitable for application in pharmaceutical industry and could be used for developing drug delivery systems. Moreover, holding the moisture or bound water for long time indicates that the polysaccharide mucilages

**Figure 2** FTIR spectra of the polysaccharides

can be stable at high temperature (44-45, 65).

DSC characterization was performed to study the thermal behavior of polymers to determine the optimal final application in development of various dosage forms. The DSC thermograms indicate that the loss or gain of heat resulting from the physicochemical property changes in the samples were based on temperature (50). The samples exhibiting sharp melting points (endothermic peaks) indicate that they were relatively pure and crystalline. On the other hand, samples with broad asymmetric peaks suggest impurities and a less regular packing of the powders (42, 51). DSC thermograms of the CG, RV, CE and FG powders are shown in Figures 3A-D. CG, CE and FG show a single endothermic peak at 80.3°C, 85.2°C and 77.1°C, respectively for loss of bound water. Though, CG exhibited broad endothermic peak it may

be indication of slow release of bound water. DSC thermograms of RV exhibited three endothermic peaks at 63.5°C, 175.6°C and 213.2°C. The initial peak suggested moisture loss and the second and third peak confirms its ability to hold moisture for a prolonged period with higher stability at high temperature conditions(43).

XRD studies can determine the crystallinity of polysaccharide mucilages. Figure 4 shows the diffractograms of CG, RV, CE and FG. The XRD results of RV, CE and FG showed numerous small and sharp peaks, indicating that they are crystalline polysaccharide mucilages, whereas CG exhibited a straight line. This could indicate that the extracted CG powder was amorphous in nature and it decomposes or degrades very slowly at higher temperatures (65-66).

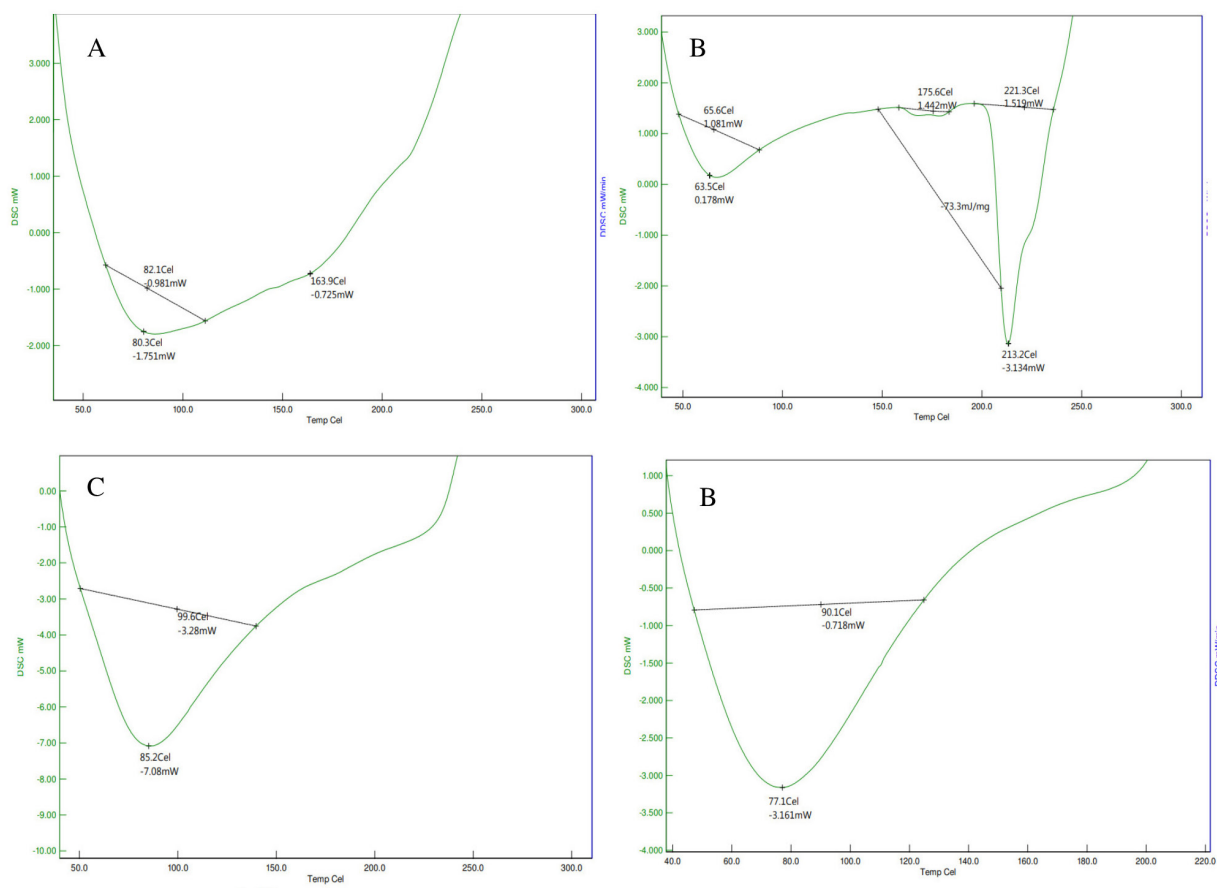


Figure 3 DSC thermograms of (A) CG:Fruits from *Coccinia grandis*, (B) RV:Leaves from *Rumex vesicarius*, (C) CE: Rhizomes from *Colocasia esculenta* and (D) FG: Seeds from Fenugreek

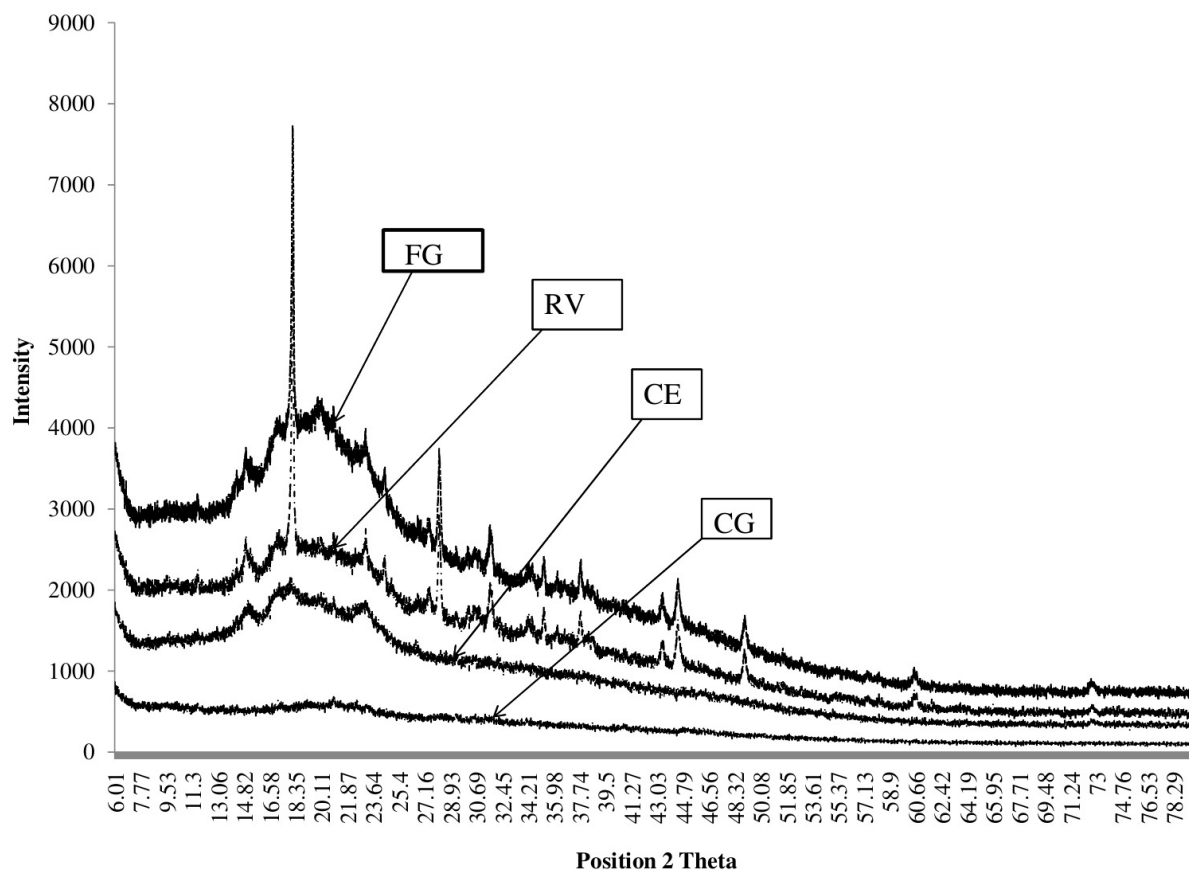


Figure 4 XRD diffractograms of polysaccharide mucilages. CG:Fruits from *Coccinia grandis*, RV:Leaves from *Rumex vasicarions*, CE: Rhizomes from *Colocasia esculenta* and FG: Seeds from Fenugreek

The acute effect of CG, RV, CE and FG at single oral dose at 2000 mg/kg did not show any mortality or alter the behavioral changes of the animals during the period of study. Also, the animals showed no significant differences in body weight between the control and treatment groups. However, the body weight of the males and females of all groups gradually increased throughout the study period in (data not shown). All the major organs was found to be normal in size and appearance in gross necropsy and no significant difference in relative organ weights between the treated and control rats. The oral acute toxicity study observations suggest that CG, RV, CE and FG are non-toxic. Therefore, the LD₅₀ value for orally administered CG, RV CE and FG was ≥ 2000 mg/kg as per the OECD 423 guidelines (67).

The development of gastroretentive floating tablets of silymarin

The main objective of this investigation was to study the buoyancy properties of silymarin-loaded floating tablets prepared using CG, RV, FG and CE with the aim of exploring upolysaccharide mucilages as potential matrix forming agents and buoyancy enhancers (68). Silymarin loaded floating tablets (formulations F1-F5) were successfully prepared by direct compression. The results show that the formulations prepared with polysaccharide mucilages of CG, RV, CE and FG are comparable to using HPMC K4M. The results for the final optimized formulations F1-F5 are shown in Table 5. Thickness and weight variations ranged from 4.50 to 4.70 mm and 348-351 mg respectively. The developed floating tablets conformed with limits given in the USP. The hardness of the tablets ranged from 5.46 to

Table 5 Physical characteristics of silymarin loaded floating tablet formulations (F1-F5).

FORMULATION No	THICKNESS (mm)±SD (n=6)	WEIGHT VARIATION (mg)±SD (n=20)	HARDNESS (kg/cm ²) (n=6)	FRIABILITY (%) (n=20)	DRUG CONTENT UNIFORMITY (mean±SD) (n=3)	FLOATING LAG TIME (mean ± SD) (sec) (n=3)	TOTAL FLOATING TIME (hr)
F1	4.59±0.09	349.7±0.674	5.46±0.046	0.392±0.05	99.43±1.2	120±13	>8
F2	4.6±0.06	349.4±0.699	5.6±0.19	0.35±0.03	101.41±0.98	160±10	
F3	4.58±0.078	349.5±0.707	5.5±0.099	0.38±0.04	98.93±1.41	180±16	
F4	4.62±0.07	349.4±0.843	5.58±0.145	0.29±0.03	99.68±1.52	60±4.0	
F5	4.61±0.087	349.6±0.516	5.51±0.097	0.293±0.02	101.91±1.00	60±4.0	

5.70 kg/cm². The prepared floating tablets are stronger and may be able to withstand stress throughout packaging and transportation. The friability values of the 5 tablet formulations were less than 0.4% and within the specified limits of 1% by weight. The drug content uniformity of the floating tablet formulations was between 97-102% and within Pharmacopoeia limits. The results of the floating lag time (sec) of the formulations were 120±13, 160±10, 180±16, 60±4 and 60±4 respectively for formulations F1-F5. The floating duration time was more than 8 hours.

All the floating tablets of silymarin were optimized focusing on the floating property of the tablets such as increased gastric retention by lowering the floating lag time and prolonging floating duration with a controllable sustained drug release profile. Due to their prolonged floating duration, the tablets may prevent gastric emptying and sustain drug release for a longer period of time. Hence, the polysaccharide mucilages are potential buoyancy enhancers and equal compared to HPMC K4M(68-69). Though, the drug release mostly depends on the concentration of the hydrophilic polymer, the entrapped gas within the hydrogel also influences the release of the drug from the matrix. The extracted macromolecules such as CG, RV FG and RV may be suitable as matrix forming agents in floating tablets of silymarin in combination with citric acid together with using NaHCO₃ as an effervescent agent (70). The results from the *in vitro* drug release of silymarin floating tablets are shown in Figure 5.

The results show that the floating tablets were floating throughout the study for a period of 8 hours.

Moreover, the results showed that the floating tablets of silymarin prepared with CG, RV, CE and FG macromolecules showed sustained drug release, similar to floating tablets prepared with HPMC K4M. The release mechanisms from CG, RV, FG, CE and HPMC could be a result of quick hydration of the polymers on the surface of the tablets resulting in a gel or a highly viscous solution adjacent to the matrix that controls water penetration into the core. The overall result is a decrease in the rate of drug release as a function of time (8). Thus, this study suggests that the floating tablets of silymarin developed with CG, RV, CE and FG were similar to the floating tablets developed with HPMC K4M. CG, RV, FG and CE could thus be good buoyancy-enhancing agents for tablets. Furthermore, the floating tablets were subjected to drug release kinetic modeling and the results are summarized in Table 6. The correlation coefficient (R²) results showed that the floating tablet formulations F1-F2 and F4-F5 revealed first order kinetics, whereas F3 exhibited Higuchi kinetics. The value of the Korsmeyer-Peppas release exponent (n) explains the release mechanism. The floating tablets F1 and F5 followed a quasi-Fickian diffusion and diffusion drug release mechanism, whereas F2-F4 followed anomalous diffusion or non-Fickian diffusion, and diffusion and swelling drug release.

CONCLUSIONS

The results from this study confirmed that the powders prepared from CG, RV CE and FG showed the presence of carbohydrates, starch, mucilage and polysaccharides with good adhesiveness properties. The presence of polysaccharide mucilage functional

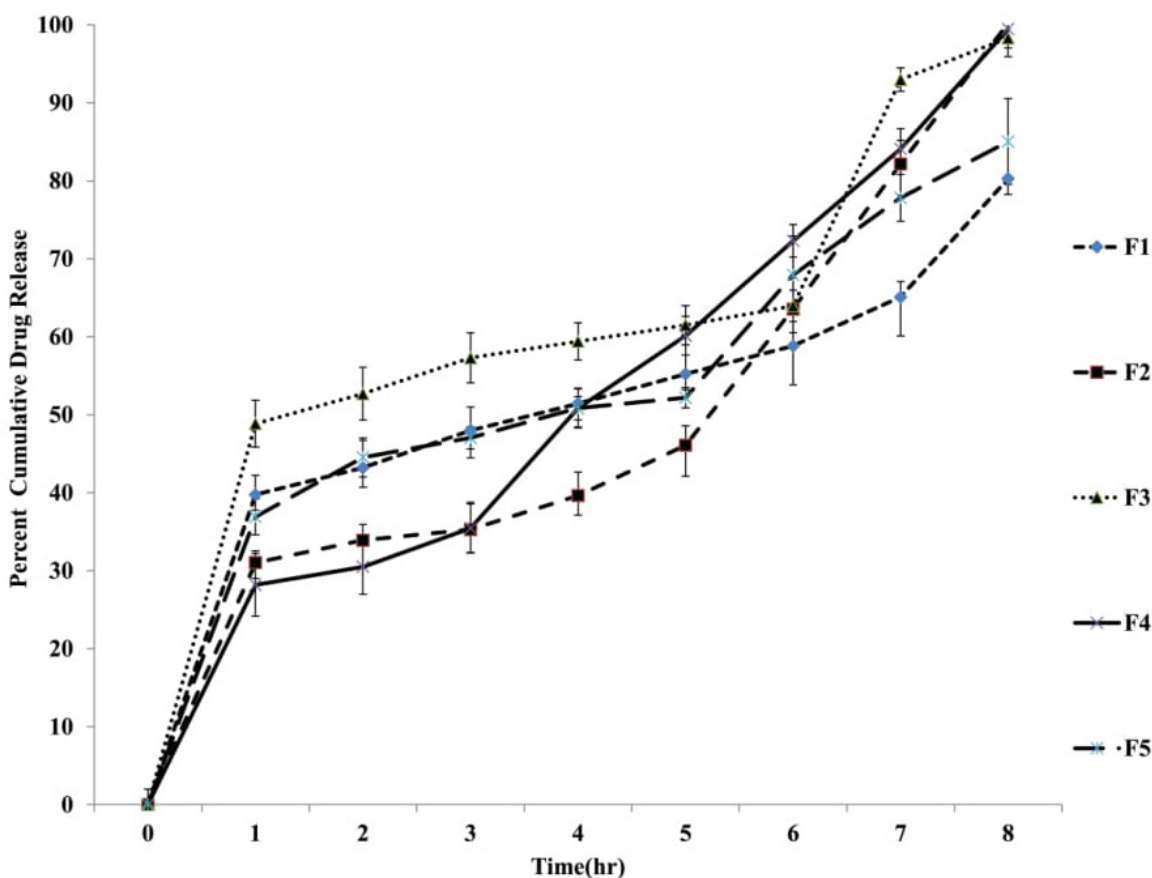


Figure 5 Cumulative percentage drug release profile of silymarin loaded floating tablet formulations F1-F5 (n=3)

Table 6 Drug release kinetic analysis data of Silymarin loaded floating tablet formulations (F1-F5)

FORMULATION	R ²					DRUG RELEASE MODEL No	MECHANISM AND INDICATION OF DRUG RELEASE
	FIRST ORDER	ZERO ORDER	HIGUCHI EQUATION	KORSMEYER PEPPAS	n VALUE (RELEASE COMPONENT)		
F1	0.9391	0.8699	0.7986	0.8082	0.3137	2	Quasi Fickian diffusion and Diffusion drug release
F2	0.9352	0.8689	0.7704	0.7448	0.5383	2	Anomalous diffusion or non Fickian diffusion and diffusion and swelling drug release
F3	0.8633	0.8116	1	0.3018	0.6974	4	Anomalous diffusion or non Fickian diffusion and diffusion and swelling drug release
F4	0.9842	0.9725	0.854	0.8935	0.6402	2	Anomalous diffusion or non Fickian diffusion and diffusion and swelling drug release
F5	0.9601	0.9331	0.9015	0.852	0.3813	2	Quasi Fickian diffusion and Diffusion drug release

groups was confirmed using FTIR. The polysaccharide mucilage samples were stable at high temperatures, confirmed using DSC and XRD. Furthermore, the polysaccharide mucilages exhibited the absence of toxicity via oral route in animals. The floating tables

of silymarin developed using CG, RV, CE and FG showed prolonged gastric retention, sustained drug release over a period of several hours. These results were comparable to floating tablets developed using HPMC K4M as the matrix forming agent and buoyancy enhancer. These polysaccharide mucilages

may be suitable for use in formulating other drugs. Therefore, the polysaccharide mucilages could be good biomaterials for the development of controlled release drug delivery systems and could be used as novel hydrocolloids in pharmaceutical applications.

CONFLICTS OF INTEREST

The authors of this manuscript declare that there is no conflict of interest.

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