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Research Article

Evaluation of Modified Date Palm (*Phoenix dactylifera* L.) Mucilage as a Potential Pharmaceutical Excipient

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Investigation on natural sources from plants, animals, and microorganisms that produce gums and mucilages goes on increasing day by day to check their pharmaceutical applications. Different mucilages have been studied for their pharmaceutical effects but the use of date palm (*Phoenix dactylifera* L.) mucilage as a pharmaceutical excipient is still under the cover. The aim of this study was therefore to evaluate and compare the flow property and binding ability of crude, purified, modified (hydrolyzed and grafted), green synthesized nanoparticles (Zinc oxide (ZnO), cuperic oxide (CuO), silver (Ag), and gold (Au)) of date palm mucilage with hydroxy propyl methyl cellulose (HPMC) and commercially available paracetamol tablets. Previously purified mucilage (with 58.4% yield) was subjected to modification (i.e., acidic, basic, and enzymatic), grafting (polyacrylamide), and green synthesis of nanoparticles. Flow properties of powdered (granular) crude, purified, modified, and nanoparticles were studied and compared with flow properties of HPMC and paracetamol tablet granules. Tablets were made using granules of all types of date palm mucilage (discussed above), HPMC, and granules of paracetamol tablets to study and compare weight uniformity, hardness, friability, dissolution rate, and disintegration time. When 100 mg/kg of mucilage sample was given to mice no oral toxicity was found. The results obtained during this study were within the acceptable ranges given in pharmacopeias. The pseudoplastic flow behavior, hygroscopic nature, increased solubility, and swelling index across the increase in temperature, hardness of the tablets, friability, and drug release behavior were found better than HPMC and the binders used in commercially available paracetamol, hence making the date palm mucilage (crude, purified, and modified) an excellent excipient to be used in pharmaceutical dosage forms.

1. Introduction

In the current period of time, the natural sources (plants, animals, and microorganisms) especially the gums and mucilages have been explored due to their pharmaceutical properties [1]. The inertness, cost-effectiveness, availability, and biodegradability are some reasons of great interest in gums and mucilages when they are compared to synthetic pharmaceutical ingredients [2]. Plants, algae, and microorganisms are good sources of gums and mucilages [3] but those from plant origins have become the center of interest for many researchers due to their diverse pharmaceutical applications in different dosage forms [4].

Natural gums and mucilages have been modified to overcome certain drawbacks such as uncontrolled rate of hydration, thickening, drop in viscosity on storage, and microbial contamination [5]. The presence of anti-oxidative enzymes in natural resources (plants) reduces the fungal attack to some extent [6] as secondary metabolites are produced from fungal filaments [7]. As gums and mucilages are polymeric materials [8] so they are numerously used in pharmaceutical technology [9] but many attempts have been

made to modify the physical and chemical properties of gums and mucilages to make them potentially applicable in different areas of drug formulation. Derived and modified gums and mucilages have some safety concerns when used in pharmaceutical dosage forms as excipients. Therefore, screening must be done for safety purposes before their usage as pharmaceutical excipients. The binding ability, thickening nature, and stabilizing and humidifying properties of mucilages from different sources make them able to use in dosage forms of drugs and medicines [10]. Different gums and mucilages including guar gum [11–14], gum acacia [15], ghatti gum [16, 17], and khaya gum [18] have been used as binding agents in pharmaceutical formulations. Mucilages have good binding properties compared to many synthetic compounds [19].

Phoenix dactylifera L. has been studied for its antioxidant and anti-mutagenic activities [20]. Pharmaceutical potential as a binder of date palm fruit has also been studied by Ngwuluka et al. [21] by characterizing granules and tablets for their *in vitro* release studies. The reason for the present study was to remove the cover from the hidden pharmaceutical properties of date palm mucilage. The pharmaceutical properties of crude date palm mucilage were also compared with the properties of modified mucilage as only the least research has been done on this mucilage to explore its pharmaceutical ability as an excipient.

2. Material and Methods

2.1. Materials. Date palm (*Phoenix dactylifera* L.) mucilage was purchased from the herbal medicine seller (Bara Dawa Khana) located in Karkhana Bazar, Faisalabad, and identified from the Department of Botany, Government College University, Faisalabad and kept in the air-tight jar before further analysis. Faisalabad itself is a rich source of ethnomedicinal plants containing almost 61 plants of 53 genera and 29 families [22] and these plants along with some others have been used to treat different ailments across the whole of Pakistan [23]. Trifluoroacetic acid (TFA), sulfuric acid, ammonium chloride and potassium persulfate, gold muriate, zinc acetate dihydrate, and copper (II) chloride dihydrate were purchased from E. Merk (Germany). Silver nitrate, barium hydroxide, citric acid, sodium hydroxide, and acrylamide were of Sigma-Aldrich (USA). Lactose and cellulose were purchased from JRS Pharma, Germany. Hydroxypropyl methylcellulose (HPMC) and paracetamol were obtained from Saffron Pharmaceuticals, Pakistan. High-quality analytical grade chemicals were purchased from Sigma-Aldrich (USA), Fluka (USA), BB1 (UK), Oxoid (UK), Merck (Germany), Pharmacia, and ICN.

2.2. Methods

2.2.1. Purification and Extraction of Mucilage. The 500 g of date palm mucilage was chopped up and soaked in four liters of distilled water for 36 h for dissolution. Superfluous materials were filtered using a muslin cloth and the filtrate was treated with 90% v/v ethanol to precipitate purified mucilage. For preservation, the purified mucilage was washed with diethyl ether and dried in a hot air oven at 40°C for 18 h [24]. Dried and purified date palm mucilage was minced mechanically to make it fine powder which was also kept in an air-tight jar for further use. The percentage yield was calculated by the following formula [25]:

$$\text{Percentage yield} = \frac{\text{weight of purified mucilage}}{\text{weight of soaked mucilage}} \times 100. \quad (1)$$

2.3. Hydrolysis of Mucilage Samples

2.3.1. Acidic Hydrolysis. Purified date palm mucilage was hydrolyzed using certain modifications in standard protocols. Acidic hydrolysis was carried out as described by Größl et al. [26]. 2 M trifluoroacetic acid was taken at 100 μL/0.2 mg of mucilage sample in a capped glass vial and placed the vial for heating for 2 h at 110°C. Using the ethanol precipitation method acidic hydrolyzed mucilage was precipitated and dried in the oven.

2.3.2. Basic Hydrolysis. Basic hydrolysis was carried out using the protocol of Beltrán et al. [27]. Five grams of purified mucilage were put in 200 mL of a saturated solution of barium hydroxide and incubated the mixture at 100°C for 8 h. Then H_2SO_4 solution of 1 M was used to neutralize and precipitate the basic hydrolyzed mucilage which was dried in the oven at the end.

2.3.3. Enzymatic Hydrolysis. Cellulase and amylase enzymes were used for the enzymatic hydrolysis of date palm mucilage. This enzymatic hydrolysis was carried out using the protocol described by Tester and Sommerville [28] with some modifications. Briefly, 10 mg of each mucilage sample were taken separately in 10 mL capped tubes. To each tube, 0.5 mL of distilled water was added and mixed the mucilage samples thoroughly with a spatula. After mixing, the tubes were placed in a water bath at 40–80°C for almost 30 min so the mucilage became swollen. After this, loosely dispersed the swollen mucilage and added 1.5 mL of acetate buffer of pH 4.7. The contents were mixed thoroughly and 5 mg of cellulase and amylase were added and the final volume was made to 2.5 mL with distilled water. The mixture was incubated for 15 min at 30°C. The hydrolyzed mucilage was precipitated using ethanol and the precipitate was filtered and dried in the oven.

2.4. Grafting of Mucilage Samples. Among other reported methods and techniques for modification of mucilage, in this study, polyacrylamide grafting was carried out using the protocol, as discussed by Singh et al. [29] with some modifications. Briefly, 0.1 g of purified mucilage was added to 25 mL of distilled water and allowed to dissolve. Then, 0.16 M acrylamide, 8×10^{-3} M silver nitrate, and 0.022 M ascorbic acid solutions were added to the above mixture. The mixture was placed in a thermostatic water bath at 35°C for 30 min and then $K_2S_2O_8$ (8×10^{-3} M) was added and allowed the mixture to stand in the water bath for 1 h.

Polyacrylamide-modified mucilage was precipitated using ethanol and dried in the oven.

2.5. Green Synthesis of Nanoparticles Using Date Palm Mucilage. Green synthesis has become one of the most preferred applications in various fields including chemistry because of its eco-friendly approach. With the applications of green synthesis to nanochemistry, another area of study (i.e., green nano-synthesis) had emerged and gained increasing value. Green nano-synthesis allows a nanomaterial to be synthesized in a way that is friendly to both humans and the environment. The size is confirmed by Zetasizer.

2.6. Preparation of ZnO Nanoparticles (ZnONPs). ZnONPs were synthesized by the precipitation method as described by Sharma and Ghose [30] with some modifications. Briefly, 100 mL of 1% w/v purified mucilage solution (Solution A) was prepared and kept it stirring on a thermally controlled magnetic stirrer at 85°C for 2 h. Zinc acetate dihydrate (10.975 g) was dissolved in 50 mL of distilled water to make a 0.5 M solution (Solution B). One molar NaOH solution was prepared in distilled water (Solution C). When the temperature of solution A was maintained solutions B and C were added dropwise with continuous stirring. Milky white precipitate was produced during the above-prescribed reaction which was separated by filtration and washed off to remove impurities. Finally, the precipitate was kept in the oven at 70°C for 6 h for drying. White-colored ZnONPs were ready for further use.

2.7. Preparation of Copper Oxide Nanoparticles (CuO NPs). CuONPs were prepared by making some adjustments to the protocol described by GültekİN et al. [31]. To 2.9 mL of 10 mM copper (II) chloride solution, 300 μg/mL of purified peroxidase solution of date palm mucilage was added and incubated in the mixture for 4 h. Blue-colored solution become cloudy indicating the formation of CuO NPs. The solution was centrifuged at 15,000 rpm for 30 min and the obtained precipitate was washed and dried at 70°C for 24 h.

2.8. Preparation of Sliver Nanoparticles (Ag NPs). Silver nanoparticles were prepared by making some modifications to the methods described by Kora et al. [32] and Selvan et al. [33]. Briefly, a 100 mL solution of date palm mucilage (1% w/v) was prepared and kept for stirring on a magnetic stirrer for 6 hrs. Then, 100 mL of 1 mM silver nitrate solution was added dropwise along with a few drops of 1 M sodium hydroxide solution. The reacting mixture was autoclaved twice at 121°C and 15 psi pressure for 15 min. The color change was observed which indicated the reduction of silver ions to silver nanoparticles. The solution was centrifuged at 9,000 rpm to obtain the pellets of AgNPs. AgNPs were washed twice and let to dry for 8 h. AgNPs were stored in a sterile container wrapped with aluminum foil for further usage.

2.9. Preparation of Gold Nanoparticles (Au NPs). AuNPs were prepared by making certain modifications in Turkevish's method [34]. Briefly, mucilage solution (1% w/v) was allowed to stir on a thermally controlled magnetic stirrer and added 10 mL of mercuric chloride solution and maintained the temperature of the mixture at 90°C. Then 5 mL of sodium citrate (11 mg/mL) solution was added in fine drops. After 20 min the color of the reacting mixture changed from yellow to greenish black and then finally to deep red. The reacting mixture was cooled at room temperature and the pellets were separated by centrifuging at 17,000 rpm. The pellets were dried in an oven and stored in a sterile container.

2.10. Pharmaceutical Potential. The pharmaceutical potential of crude, purified, hydrolyzed, and modified mucilages and green synthesized nanoparticles of mucilage was determined by comparing them with HPMC and commercially available paracetamol. Properties of the powder (granules) including bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose, solubility and swelling power, loss on drying, moisture sorption properties, ash values, solubility test, viscosity, and acute oral toxicity were evaluated. Uniformity of weight, hardness of tablets, friability, disintegration time, and dissolution time was checked for the evaluation of tablets made using the above said crude, pure, and modified mucilages.

2.11. Evaluation of Granules. Dry granulation of samples was carried out following Ye et al. [35] with certain modifications and granules were passed twice through the mesh size 30. To eliminate produced aggregates, the sample was passed through a mesh No. 30. Each sample was blended for 20 minutes at 25 rpm in a V-shell blender (Maxiblend™, GCUF pharmacy). Magnesium stearate (0.2%) was added and allowed to mix for 4 minutes. The sample was extruded dry using an 11 mm co-rotating twin-screw extruder (ThermoFisher Scientific). The barrel was kept at 70–110°C (below the glass transition temperature) and 50–100 rpm speed. After the extruder reached a steady state, the material was collected. The samples were placed in plastic bags for processing and analysis.

2.11.1. Bulk Density. Ten grams of each mucilage sample were taken in a 100 mL graduated measuring cylinder separately and the volume occupied by every sample was noted down. The bulk density was calculated using the following formula [36]:

$$\text{Bulk density } (\rho B) = \frac{\text{Average weight of sample } (g)}{\text{Volume occupied by sample } (mL)}. \quad (2)$$

2.11.2. Tapped Density. The samples were tapped on the table until the volume of granules become constant. The following formula was used to calculate the tapped density [36]:

$$\text{Tapped density}\,(\rho T) = \frac{\text{Average weight of sample}\,(g)}{\text{Volume occupied by tapped sample}\,(mL)}. \tag{3}$$

2.11.3. Carr's Index and Hausner's Ratio. The following formulas and values of bulk density and tapped densities were used to calculate Carr's index and Hausner's ratio [37]:

$$\text{Carr's index} = \frac{\rho T - \rho B}{\rho T} \times 100, \tag{4}$$

$$\text{Hausner's ratio} = \frac{\rho T}{\rho B}. \tag{5}$$

2.11.4. Angle of Repose. ERWEKA granulate flow tester machine (GTB, Germany) was used for the determination of the angle of repose. The 30 g of the sample was placed in the hopper of the machine and allowed the sample to fall freely under the action of gravity on a flat surface from the nozzle of the hopper. The reading of the inclined angle of the powdered cone was recorded.

2.11.5. Solubility and Swelling Power. The solubility index and swelling power of samples were determined following the method of Takizawa et al. [38]. In a centrifuge tube, 10 mL of distilled water was taken and 0.125 g of the sample was added. The sample was dispersed by mild shaking keeping the samples in the water bath at 25°C, 35°C, 50°C, 65°C, and 80°C. After 10 min, the tube was removed from the water bath and placed in cold water for 5 min, and centrifuged for 15 min at 3,000 rpm. The supernatant was dried in an oven at 105°C until the weight become constant. Solubility index and swelling power were calculated from the masses of precipitated and dried supernatant samples using the following formulas:

$$\begin{aligned} \text{Solubility Index} &= \frac{ms}{mo - md}, \\ \%\text{age swelling} &= \frac{md}{m0} \times 100, \end{aligned} \tag{6}$$

where m_s is swollen mass, m_o is initial mass of sample, and m_d is the dried mass of the supernatant.

2.11.6. Moisture Contents. The moisture present in the samples was determined by the protocol described by Kumar et al. [39]. The sample (1 g) was placed in a hot air oven at 105°C until the constant weight was obtained and the moisture contents were calculated using the following formula:

$$\text{Loss on drying} = \frac{\text{Initial weight of sample} - \text{Weight after drying}}{\text{Initial weight of sample}} \times 100. \tag{7}$$

2.11.7. Moisture Sorption Properties. Moisture sorption properties were studied by following the protocol of Odeku and Picker-Freyer [40] where they produced 20%, 40%, 60%, 75%, and 100% humidity environments in desiccators with the help of different concentrations of distilled water, NaCl, and NaOH solutions. Briefly, 1 g of pre-dried (dried in the oven at 120°C for 4 h) sample (s) was taken in a Petri dish and placed in respective humidity chambers for one week. After 1 week, weights were recorded and moisture taken by the samples was recorded by taking the difference in weights before and after placing in desiccators.

2.11.8. Total Ash Values. One gram of the sample was taken in a pre-weighed crucible and heated at 450°C for 8 h in a furnace. Total ash contents were calculated using the following formula [41]:

$$\%\text{age ash contents} = \frac{\text{Weight of ash produced}}{\text{Initial weight of sample}} \times 100. \tag{8}$$

2.11.9. Acute Oral Toxicity. Organization for Economic Cooperation and Development (OECD) [42] gave the guidelines to study the acute oral toxicity by which female mice of 6–8 weeks of age with an average mass of 25 g were used. Female mice were retained in cages at room temperature and provided free access to standard food and water. Two groups with 5 mice each selected randomly were made and kept without food for 3 h before the administration of the oral dose. The first group received a dose of sample orally *via* gavage at 100 mg/kg while the other received distilled water only at 10 mL/kg. Behavioral changes for 4 h were observed continuously while for 48 h animals were checked at random. Two weeks follow-up was continued to check the mortality.

2.11.10. Preparation of Tablets. Tablets were prepared in the rotary machine (F3-Manestty, UK) by compressing the granules in spherical-shaped puncher [36]. Tablets were approximately 6 mm in size and 250 mg in weight. A total of 13 batches (each containing 60 tablets) were prepared using crude, purified, modified, and nanosynthesized mucilage samples, HPMC, and slandered paracetamol samples.

2.11.11. Weight Uniformity. From each batch, twenty tablets were selected at random. They were weighed separately and collectively to check the weight variations in the batch. The whole study was carried out as reported by Ahuja et al. [43].

2.11.12. Hardness Test. A tablet hardness tester (TBH-2000; Bosch, Germany) was used to check the hardness of 10 tablets randomly selected from each batch following the method of Ahuja et al. [43].

2.11.13. Friability. Ahuja et al. [43] reported the method for calculating the friability using a friability tester. CS-2 (Chinese) friability tester was used to check the friability of 20 tablets. After measuring their initial weight, they were put into the drum of the tester and allowed the drum to move at 25 rpm for 4 min. The final weight of the tablets was measured after dusting the tablets and found out the friability by the following formula:

$$\text{Friability} = \frac{\text{Initial weight of tablets} - \text{Final weight of tablets}}{\text{Initial weight of tablets}} \times 100. \quad (9)$$

2.11.14. Determination of Disintegration Time. British Pharmacopoeia, 2010 gave the guidelines for determining of disintegration time of tablets. Following the protocol, six tablets from each batch were randomly selected and placed in the disintegration test apparatus (VEEGO, VTD-4AV, India). Disintegration time was calculated using 0.1 M NH_4Cl solution maintained at a temperature of $37 \pm 5^{\circ}C$. The NH_4Cl solution provides pH near to 5.1 which is nearer to the environment of stomach where the disintegration of tablets starts) [43].

2.11.15. Determination of Dissolution Rate. The rate of drug release was determined using dissolution apparatus (USP-II, 708-DS, Agilent, Philippines) and following the British Pharmacopoeia, 2010 protocol. The HCl solution (0.1 N) at $37 \pm 5^{\circ}C$ was used as a dissolution medium. One tablet from each batch was subjected to the medium at 100 rpm for 30 min. At every 5 min interval, 1 mL of the sample was collected from the medium and analyzed by spectrophotometer at 243 nm and calculated the rate of drug release in the solution.

2.12. Statistical Analysis. Microsoft Excel and Graph Pad Prism 8 software were used to analyze the data statistically. Results were represented in the mean and standard deviation of triplicate values of each test, taking the confidence level of 95% and values were considered significant when the p-value was found less or equal to 0.05.

3. Results and Discussion

Date palm is important medicinally and pharmacologically. Different physiological and pathological products of date palms have proved their importance in scientific research. Besides fruit and mucilage, the oil is also a good source of biologically active constituents with different therapeutic effects [44]. Modification techniques such as green synthesis of nanoparticles also enhance the antibacterial activity against different strains [45]. The commercially available date palm mucilage was purified and stored in dried form. The current study is the continuation of our previous study where the percentage yield was found 58.4% [46].

3.1. Zeta Potential of Green Nanosynthesized Particles. Green synthesized nanoparticles were analyzed through a Zeta sizer to determine their particle size commercially available at National Textile University, Sheikhupura Road, Faisalabad. The results have been summarized in Figure 1.

The average particle size of ZnO NPs, CuO NPs, Ag NPs, and Au NPs was found to be 39 nm, 24 nm, 24 nm, and 33 nm, respectively. Nanoparticles have different medicinal effects on various diseases [47]. Aqueous extracts of *Bistonia affinis and Malcolmia cabulica* were used for the synthesis of medicinally effective AgNPs with a size range of 10 to 30 nm [48]. ZnO-NPs [49], CuO-NPs [50], and AuNPs [51] have been reported for pharmaceutical [52], pharmacological [53], and biological effects [54].

3.2. Evaluation of Granules

3.2.1. Flow Properties. Considering the flow properties of the powder, its densities (bulk and tapped), Carr's index, Hausner's ratio, angle of repose, moisture contents, and ash values are the most important parameters. The results of above-mentioned properties have been summarized in Table 1. Evaluation of flow properties for each type of prepared granules helps to specify the formulation with desired features and characteristics.

Bulk and tapped density (in g/mL) for crude mucilage were found to be 0.709 ± 0.13 and 0.847 ± 0.009, respectively. Change in bulk and tapped densities was found when date palm mucilage was purified and modified. Bulk and tapped density of the cellulase hydrolyzed date palm mucilage (0.694 ± 0.08 and 0.877 ± 0.59, respectively) were found to be the closest to the bulk and tapped densities of paracetamol tablet granules (0.662 ± 0.17 and 0.855 ± 0.03, respectively) and HPMC granules (0.699 ± 0.28 and 0.775 ± 0.15, respectively) taken as standard. Carr's index and Hausner's ratio were calculated (equation (4) and (5)) using bulk and tapped densities. The Carr's index (%) and Hausner's ratio for paracetamol tablet granules (29.06 ± 0.981 and 1.291 ± 0.08, respectively) and HPMC (10.85 ± 0.03 and 1.109 ± 0.14, respectively) showed that paracetamol tablet granules have poor flow properties while HPMC showed good flow properties. Granules of date palm mucilage showed fair to excellent flow properties when crude mucilage was purified and modified (Table 1).

The angle of repose is also an important factor to determine the flow properties of granules. Paracetamol tablet granules ($52^{\circ} \pm 1.9^{\circ}$) were found to have the largest angle of repose. HPMC with an angle of repose of ($30.8^{\circ} \pm 0.7^{\circ}$) showed good flow properties. Modification and purification changed the angle of repose for crude date palm mucilage granules (i.e., $37.4^{\circ} \pm 0.2^{\circ}$). Moisture contents and ash values present in the granules are also the determinant factor for the flow of granules which have been recorded and summarized in Table 1. Characterization of flow properties of

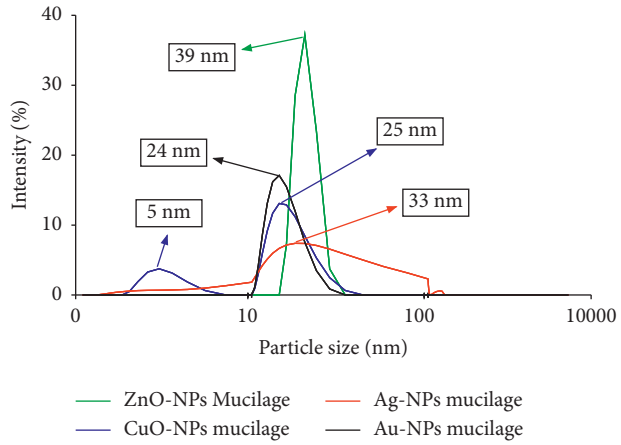

Figure 1: Size distribution of green synthesized nanoparticles of date palm mucilage.

Table 1: Flow properties of granules of date palm mucilage.

Sr.	Type of granules	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Hauser's ratio	Angle of repose (°)	Moisture contents (%)	Ash values (%)	Flow property
1	Crude mucilage	0.709 ± 0.13	0.847 ± 0.09	19.5 ± 0.02	1.195 ± 0.13	37.4 ± 0.2	13.3 ± 0.035	7.33 ± 0.015	Fair
2	Purified mucilage	0.740 ± 0.55	0.847 ± 0.05	14.4 ± 0.01	1.144 ± 0.11	32.1 ± 0.1	8.3 ± 0.080	2.66 ± 0.037	Good
3	Acidic hydrolyzed mucilage	0.719 ± 0.17	0.862 ± 0.11	19.66 ± 0.01	1.198 ± 0.19	37.7 ± 0.4	7.5 ± 0.053	2.59 ± 0.011	Fair
4	Basic hydrolyzed mucilage	0.704 ± 0.31	0.826 ± 0.07	17.36 ± 0.05	1.174 ± 0.08	37 ± 0.1	6.5 ± 0.075	2.54 ± 0.044	Fair
5	Amylase hydrolyzed mucilage	0.704 ± 0.19	0.855 ± 0.01	21.36 ± 0.11	1.213 ± 0.15	39.5 ± 0.3	6.9 ± 0.028	2.35 ± 0.025	Fair
6	Cellulase hydrolyzed mucilage	0.694 ± 0.08	0.877 ± 0.59	26.32 ± 0.09	1.263 ± 0.19	43 ± 0.1	6.3 ± 0.063	2.38 ± 0.039	Passable
7	Poly acrylamide grafted mucilage	0.724 ± 0.14	0.806 ± 0.01	11.3 ± 0.02	1.113 ± 0.16	31.6 ± 0.4	6.5 ± 0.079	2.16 ± 0.011	Good
8	ZnONPs mucilage	0.741 ± 0.52	0.819 ± 0.09	10.66 ± 0.33	1.106 ± 0.11	27.3 ± 0.3	3.4 ± 0.047	1.95 ± 0.029	Excellent
9	CuONPs mucilage	0.752 ± 0.39	0.847 ± 0.12	12.71 ± 0.06	1.127 ± 0.15	32 ± 0.4	4.6 ± 0.053	2.29 ± 0.018	Good
10	AgNPs mucilage	0.775 ± 0.4	0.847 ± 0.45	9.32 ± 0.06	1.093 ± 0.07	25.2 ± 0.6	3.8 ± 0.071	1.95 ± 0.027	Excellent
11	AuNPs mucilage	0.769 ± 0.33	0.877 ± 0.03	10.17 ± 0.02	1.102 ± 0.03	25.2 ± 0.3	3.8 ± 0.082	1.83 ± 0.015	Excellent
12	HPMC	0.699 ± 0.28	0.775 ± 0.15	10.85 ± 0.03	1.109 ± 0.14	30.8 ± 0.7	4.8 ± 0.057	2.9 ± 0.031	Good
13	Paracetamol	0.662 ± 0.17	0.855 ± 0.03	29.06 ± 0.98	1.291 ± 0.08	52 ± 1.9	3.5 ± 0.041	1.7 ± 0.019	Poor

pharmaceutical ingredients is amongst the most important steps to determine the nature of granules. Therefore, the densities (bulk and tapped) and densities related properties (Carr's index and Hausner's ratio), moisture and ash contents in the granules and angle of repose are some of the properties that collectively determine the quality of granules for their flow. Shah et al. [55] and Jeong et al. [56] reported that 5–15% of Carr's index and Hausner's ratio ≤1.25 indicate good flow properties of powdered granules.

Guiling et al. [57] described the index of the angle of repose. Powders having ≤30° angle of repose exhibit good flow properties and those having ≥40° are the materials with poor flow properties. The powdered paracetamol (from Table 1) showing poor flow property [58] and HPMC (Table 1) showing good flow property [56] were taken as standard pharmaceutical ingredients. Carr's index, Hausner's ratio, and angle of repose for crude, and modified and green synthesized nanoparticles were found in acceptable ranges showing fair to excellent flow properties except for the granules of cellulase hydrolyzed mucilage which showed passable flow. Excellent and good flow properties of granules of mucilage make their promising application as a pharmaceutical excipient. Moisture contents up to 15% in natural gums (xanthan and tragacanth) used as excipients have been specified by pharmacopeial specifications [41]. Results indicated that the crude date palm mucilage has a high moisture content (13.3 ± 0.035) which can be reduced by modifying and purifying the mucilage. This low

Table 2: Effect of temperature on solubility and swelling index of HPMC, paracetamol, and date palm mucilage granules.

Sr. No.	Property	T (°C)	Crude mucilage	Purified mucilage	Acidic hydrolyzed mucilage	Basic hydrolyzed mucilage	Amylase hydrolyzed mucilage	Cellulase hydrolyzed mucilage	Poly acrylamide grafted mucilage	ZnO-NPs mucilage	CuO-NPs mucilage	Ag-NPs mucilage	Au-NPs mucilage	HPMC	Paracetamol
1	Solubility (%)	25	5.2 ± 0.019	5.92 ± 0.024	4.7 ± 0.03	5.5 ± 0.01	6.1 ± 0.01	6.5 ± 0.02	4.3 ± 0.1	0.07 ± 0.003	0.5 ± 0.001	0.045 ± 0.001	0.03 ± 0.0019	9.6 ± 0.09	12.5 ± 0.13
		35	5.8 ± 0.02	6.8 ± 0.031	5.1 ± 0.01	5.9 ± 0.13	6.3 ± 0.08	6.9 ± 0.02	4.4 ± 0.08	0.1 ± 0.005	0.55 ± 0.003	0.051 ± 0.001	0.033 ± 0.001	11.5 ± 0.1	13.1 ± 0.11
		50	7.4 ± 0.015	8.2 ± 0.11	5.7 ± 0.01	6.1 ± 0.014	7.1 ± 0.02	7.4 ± 0.1	4.9 ± 0.12	0.12 ± 0.001	0..59 ± 0.001	0.071 ± 0.003	0.041 ± 0.002	15.3 ± 0.13	13.9 ± 0.1
		65	7.9 ± 0.05	9.1 ± 0.01	6.4 ± 0.013	6.5 ± 0.011	7.5 ± 0.14	7.7 ± 0.09	5.6 ± 0.016	0.18 ± 0.001	0.65 ± 0.002	0.085 ± 0.001	0.055 ± 0.001	15.8 ± 0.11	14.4 ± 0.1
		80	8.8 ± 0.05	11.3 ± 0.05	7.6 ± 0.06	9.5 ± 0.1	8.5 ± 0.11	8.2 ± 0.05	6.2 ± 0.06	0.26 ± 0.008	0.85 ± 0.001	0.15 ± 0.009	0.063 ± 0.0013	17.3 ± 0.1	16.9 ± 0.08
2	Swelling index	25	1.9 ± 0.022	1.99 ± 0.037	1.65 ± 0.04	1.85 ± 0.016	2.13 ± 0.01	2.2 ± 0.68	1.68 ± 0.13	0.58 ± 0.008	0.51 ± 0.006	0.43 ± 0.001	0.31 ± 0.003	3.9 ± 0.15	4.45 ± 0.17
		35	1.9 ± 0.017	2.3 ± 0.042	1.96 ± 0.09	2.11 ± 0.019	2.45 ± 0.05	2.7 ± 0.59	1.77 ± 0.07	0.67 ± 0.002	0.54 ± 0.001	0.49 ± 0.004	0.35 ± 0.002	4.5 ± 0.28	5.74 ± 0.14
		50	2.1 ± 0.009	2.5 ± 0.018	2.01 ± 0.18	2.15 ± 0.008	2.73 ± 0.05	2.8 ± 0.41	1.81 ± 0.18	0.7 ± 0.009	0.58 ± 0.009	0.53 ± 0.004	0.4 ± 0.002	6.6 ± 0.36	6.16 ± 0.09
		65	2.5 ± 0.011	2.7 ± 0.032	2.06 ± 0.18	2.22 ± 0.01	3.31 ± 0.08	3.2 ± 0.44	2.02 ± 0.14	0.76 ± 0.005	0.62 ± 0.001	0.58 ± 0.002	0.41 ± 0.001	11.39 ± 0.95	6.58 ± 0.17
		80	2.6 ± 0.025	3.3 ± 0.013	2.19 ± 0.02	2.32 ± 0.04	3.55 ± 0.16	3.4 ± 0.75	2.12 ± 0.19	0.82 ± 0.002	0.65 ± 0.007	0.61 ± 0.01	0.48 ± 0.0018	29.54 ± 1.29	6.75 ± 0.11

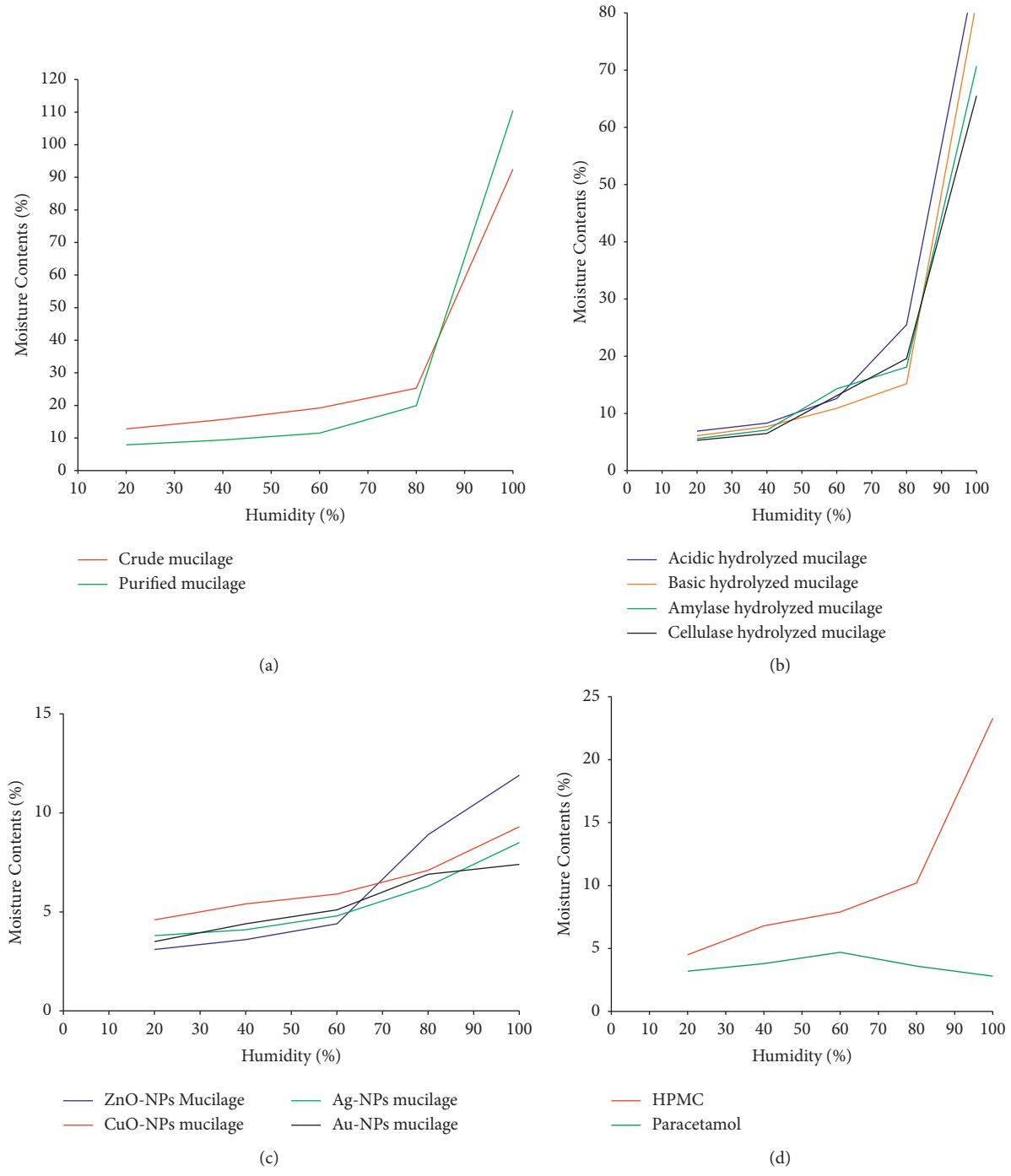

Figure 2: Moisture sorption profile of crude, purified, and modified date palm mucilage, green synthesized nanoparticles, HPMC, and paracetamol. (a) Moisture sorption profile of crude and purified date palm mucilage; (b) moisture sorption profile of modified date palm mucilage; (c) moisture sorption profile of green synthesized nanoparticles of date palm mucilage; (d) moisture sorption profile of HPMC and paracetamol.

moisture content (≤15%) in purified and modified date palm mucilage increases the quality [59] and stability (moisture contents ≤5%) of different dosage forms having moisture-sensitive active ingredients [60]. British pharmacopeia gave the limit of ash contents as 6.5–16% in xanthan gum [41]. The ash values in different date palm mucilages were found to be ≤ 8%.

3.2.2. Solubility and Swelling Power. Table 2 depicts the effect of temperature on solubility and swelling index of crude, purified, and modified date palm mucilage, HPMC, and paracetamol. Increase in temperature from 25 to 80°C causes an increase in solubility as well as the swelling index of all the granules (powder) except green synthesized nanoparticles where solubility and swelling index did not

Table 3: Analysis of tablets prepared from different samples of date palm mucilages.

Sr. No.	Pharmaceutical ingredient	Weight uniformity (mg)	Hardness (N)	Friability (%)	Disintegration time (min)	Dissolution rate (mL/min)
1	Crude mucilage	252.74 ± 1.055	98.60 ± 0.59	0.717	9.05	9.56
2	Purified mucilage	254.00 ± 1.15	99.12 ± 0.41	0.689	9.58	10.11
3	Acidic hydrolyzed mucilage	252.71 ± 0.05	93.38 ± 0.66	0.701	9.31	9.71
4	Basic hydrolyzed mucilage	253.30 ± 0.95	94.41 ± 0.22	0.680	8.93	10.37
5	Amylase hydrolyzed mucilage	253.30 ± 0.75	92.28 ± 0.19	0.702	9.00	9.82
6	Cellulase hydrolyzed mucilage	253.71 ± 1.022	92.65 ± 0.73	0.691	9.76	9.51
7	Polyacrylamide grafted mucilage	254.41 ± 1.82	85.16 ± 0.39	0.689	9.05	10.31
8	ZnONPs mucilage	252.81 ± 0.17	100.08 ± 0.51	0.686	8.94	10.34
9	CuONPs mucilage	252.52 ± 0.59	101.76 ± 0.82	0.691	8.98	10.26
10	AgNPs mucilage	253.27 ± 1.5	99.89 ± 0.13	0.693	8.33	10.05
11	AuNPs mucilage	254.24 ± 0.85	101.15 ± 0.85	0.720	8.21	10.20
12	HPMC	253.39 ± 1.27	93.10 ± 0.91	0.691	9.50	10.00
13	Paracetamol	253.32 ± 2.05	110.48 ± 1.96	0.694	8.56	10.44

vary a lot. Increase in temperature might be the source of destruction for weak cohesive intramolecular forces of mucilage molecules, allowing higher water entrapment within mucilage molecules, resulting in the increase in solubility and swelling index [61].

Adhesive forces between the mucilage molecules and water molecules depend on temperature and hydrogen bonding [62]. A high solubility index indicates high potential for water uptake by these natural materials and therefore they can be used as an excipient (i.e., suspending agent), release modifier, and mucoadhesive [59, 63]. Gradual increase in solubility and swelling index has been recorded across the temperature in *Grewia mollis* gum [64] and *Grewia ferruginea* mucilage [37]. Kumar and Ahuja [65] and Pawar and Jadhav [66] separately studied the effects of water and buffer solution and produced the result that the swelling rate in water is high.

3.2.3. Moisture Sorption Property of Granules. The moisture sorption properties of crude, purified, and modified date palm mucilages, green synthesized nanoparticles, paracetamol, and HPMC have been shown in Figure 2. Increase in moisture contents has been seen against the increase in humidity (%). The crude, purified, and modified date palm mucilages showed an abrupt increase in moisture contents (%) when the humidity of the environment increased to 80%. Green synthesized nanoparticles showed a small change in moisture contents (%) against the humidity (%). HPMC, being a standard, showed the trend of moisture sorption similar to those of crude, purified, and modified date palm mucilages. Paracetamol granules and the other standard taken showed variable moisture sorption profiles against the humid environment provided. The physical and chemical stability of pharmaceutical dosage forms depends on the moisture sorption properties of excipients used in it [67]. Moisture sorption profile of cactus mucilage as studied by Gebresamuel and Gebre-Mariam [68] had comparable and similar kinds of results.

3.2.4. Acute Oral Toxicity. No toxic signs such as respiratory distress, restlessness, convulsions, diarrhea, and coma were seen after the administration of granules of crude, purified and modified date palm mucilage in rats. During the whole observational period and continuous follow-up, no change in behavioral pattern and zero mortality were observed, indicating that up to 100 mg/kg dose of mucilage is safe to use. Oral toxicity is one of the most important factors in the selection of an excipient. Shende and Marathe [69] studied the effect of oral toxicity of hibiscus mucilage on rats and found that up to 5000 mg/kg of the dose was safe. The insignificant change was observed by the reduced dose of 500 mg/kg in body weight and hematological parameters on consecutive 30 days of follow-up. Haile et al. [37] also found *Grewia ferruginea* mucilage nontoxic during their study.

Acute oral toxicity studies of a novel natural polysaccharide gum (*Araucaria heterophylla*) were carried out in albino mice by Divvela et al. [70]. No mortality was observed in any of the groups, indicating that *A. heterophylla* is not toxic. The LD_{50} value of the gum was found to be greater than 2 g/kg body weight, indicating that the gum is not toxic to humans as well. Saikarthik et al. [71] investigated the acute oral toxicity of a methanolic extract of *Mucuna pruriens* seeds in albino mice. Symptoms such as changes in the color of fur and eyes, mucous membrane, tremors, convulsions, salivation, diarrhea, and lethargy were observed at intervals of 15, 30, 60, 180 minutes, 6 hours, 24 hours, and daily until the 14th day of the treatment to detect any signs of mortality and toxicity. According to the results, none of the animals in the group died or showed any signs of toxicity. The amount provided was 2000 mg/kg, and the animal tolerated the treatment adequately, according to the researchers. As a result, the LD_{50} will be more than 2000 mg/Kg.

3.3. Evaluation of Tablets. Using paracetamol as the active ingredient and HPMC as a standard binder, 13 batches (each batch containing 60 tablets) of crude, purified, modified, nanosynthesized mucilage samples, HPMC and paracetamol were prepared to evaluate weight variations, hardness, friability, disintegration time and dissolution rate. The results have been summarized in Table 3.

Tablets formed by different types of mucilages were found to have ≤1% friability, hardness of tablets formed was also found ≤100 N except for the tablets of ZnONPs

(100.08 ± 0.51), CuONPs (101.76 ± 0.82) and AuNPs (101.15 ± 0.85) slightly more than the limit of 40–100 N. Disintegration time (min) and dissolution rate (mL/min) were also found compromisingly close to the standard HPMC and paracetamol tablets showing that releasing rate of active ingredient from tablets, prepared from different types of date palm mucilages is less than 30 min. Bhosale et al. [72] explained in their review that natural materials like starch, gum, mucilages, and dried fruits have been used as binder, disintegrant, fillers, and sustained releasing agents. The use of okra gum as a potent binder has been reported by Hussain et al. [73] where they found that 83.54% of drug released within 1 h when 4% w/w binder was used for tablet formulation.

4. Conclusion

Crude, purified, and modified date palm mucilages and nanosynthesized green particles have shown pseudoplastic behavior, good flow properties, and swelling index. Up to 100 mg/kg of different types of date palm mucilages was found to be safer in two weeks of continuous follow-ups when given orally to the mice. Drug release, tablet hardness, weight variation, friability, and disintegration properties of all types of date palm mucilages were in acceptable pharmacopeial ranges that make it a new potent natural source as a pharmaceutical excipient.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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References

[1] M. F. Tahir, G. Mustafa, F. Anjum, M. A. Iqbal, J. Altaf, and S. A. Bukhari, "Evaluation of crude and modified *Cordia myxa* gum for its nutraceutical benefits," *Indian Journal of Pharmaceutical Sciences*, vol. 83, no. 4, pp. 671–678, 2021.

[2] M. S. Amiri, V. Mohammadzadeh, M. E. T. Yazdi, M. Barani, A. Rahdar, and G. Z. Kyzas, "Plant-based gums and mucilages applications in pharmacology and nanomedicine: a review," *Molecules*, vol. 26, no. 6, pp. 1770–1773, 2021.

[3] J. H. Chiang, D. S. M. Ong, F. S. K. Ng, X. Y. Hua, W. L. W. Tay, and C. J. Henry, "Application of chia (*Salvia hispanica*) mucilage as an ingredient replacer in foods," *Trends in Food Science & Technology*, vol. 115, pp. 105–116, 2021.

[4] S. Bahadur, U. K. Sahu, D. Sahu, G. Sahu, and A. Roy, "Review on natural gums and mucilage and their application as excipient," *Journal of applied pharmaceutical research*, vol. 5, pp. 13–21, 2017.

[5] K. Pal and D. Bera, "Natural polymers, gums and mucilages as efficacious green emissaries of essential therapeutics," in *MOL2NET, International Conference Series on Multidisciplinary Sciences*MDPI Sciforum, Basel, Switzerland, 2020.

[6] M. Qasim, H. Xiao, K. He et al., "Host-pathogen interaction between Asian citrus psyllid and entomopathogenic fungus (*Cordyceps fumosorosea*) is regulated by modulations in gene expression, enzymatic activity and HLB-bacterial population of the host," *Comparative Biochemistry and Physiology Part C: Toxicology & Pharmacology*, vol. 248, Article ID 109112, 2021.

[7] M. Qasim, S. U. Islam, W. Islam et al., "Characterization of mycotoxins from entomopathogenic fungi (*Cordyceps fumosorosea*) and their toxic effects to the development of asian citrus psyllid reared on healthy and diseased citrus plants," *Toxicon*, vol. 188, pp. 39–47, 2020.

[8] P. Srivastava, R. Malviya, and G. T. Kulkarni, "Formulation and evaluation of Paracetamol tablets to assess binding property of orange peel pectin," *International Journal of Pharmaceutical Sciences Review and Research*, vol. 3, pp. 30–34, 2010.

[9] D. Kumar, J. Pandey, P. Kumar, and V. Raj, "Psyllium mucilage and its use in pharmaceutical field: an overview," *Current Synthetic and Systems Biology*, vol. 5, pp. 1–7, 2017.

[10] P. D. Choudhary and H. A. Pawar, "Recently investigated natural gums and mucilages as pharmaceutical excipients: an overview," *Journal of Pharmaceutics*, vol. 2014, Article ID 204849, 9 pages, 2014.

[11] K. Gowthamarajan, G. Kulkarni, A. Muthukumar, N. Mahadevan, M. Samantha, and B. Suresh, "Evaluation of fenugreek mucilage as gelling agent," *Int J Pharma Excip*, vol. 3, pp. 16–19, 2002.

[12] A. Heda and U. Shivhare, "Study of some natural hydrophilic polymers as matrix forming materials for sustained release tablet formulation," *Int. J. Pharm. Expt*, vol. 8, pp. 69–74, 2004.

[13] N. Thombare, U. Jha, S. Mishra, and M. Z. Siddiqui, "Guar gum as a promising starting material for diverse applications: A review," *International Journal of Biological Macromolecules*, vol. 88, pp. 361–372, 2016.

[14] H. Pawar and P. D Mello, "Isolation of seed gum from Cassia tora and preliminary studies of its application as a binder for tablets," *Indian Drugs*, vol. 41, pp. 465–468, 2004.

[15] R. C. Rowe, P. Sheskey, and M. Quinn, *Handbook of Pharmaceutical Excipients*, Libros Digitales-Pharmaceutical Press, London, UK, 2009.

[16] J. Jain and V. Dixit, "Studies on gums and their derivatives as binding agents," *Indian Journal of Pharmaceutical Sciences*, vol. 50, pp. 1–10, 1988.

[17] P. Singh, T. Mahmood, A. Shameem, P. Bagga, and N. Ahmad, "A review on Herbal Excipients and their pharmaceutical applications," *Scholars Academic Journal of Pharmacy*, vol. 5, pp. 53–57, 2016.

[18] O. A. Odeku and O. A. Itiola, "Evaluation of the effects of khaya gum on the mechanical and release properties of paracetamol tablets," *Drug Development and Industrial Pharmacy*, vol. 29, no. 3, pp. 311–320, 2003.

[19] R. Malviya, P. Srivastava, and G. Kulkarni, "Applications of mucilages in drug delivery-a review," *Advances in Biological Research*, vol. 5, pp. 1–7, 2011.

[20] M. I. Hussain, M. Farooq, and Q. A. Syed, "Nutritional and biological characteristics of the date palm fruit (*Phoenix dactylifera* L.)–A review," *Food Bioscience*, vol. 34, Article ID 100509, 2020.

[21] N. Ngwuluka, B. Idiakhoa, E. Nep, I. Ogaji, and I. Okafor, "Formulation and evaluation of paracetamol tablets manufactured using the dried fruit of *Phoenix dactylifera* Linn as an excipient," *Research in Pharmaceutical Biotechnology*, vol. 2, pp. 025–032, 2010.

[22] M. Akram, N. Iqbal, M. Aqeel et al., "Exploration of medicinal phyto-diversity of the semi-arid area in Punjab province, Pakistan," *Journal of Animal and Plant Sciences*, vol. 30, pp. 1442–1464, 2020.

[23] A. Noman, M. Aqeel, S. Khan, S. Anwer, and Q. Ali, "Exploration of medicinal phytodiversity at Makran coast; a realm of opportunities and challenges," *Soil Biology and Biochemistry*, vol. 42, pp. 177–190, 2017.

[24] O. D. Akin-Ajani, T. O. Ajala, U. M. Okoli, and O. Okonta, "Development of directly compressible excipients from *Phoenix dactylifera* (Date) mucilage and microcrystalline cellulose using co-processing techniques," *ACTA Pharmaceutica Sciencia*, vol. 56, pp. 7–25, 2018.

[25] P. O. Ameh, "Physicochemical properties and rheological behaviour of *Ficus glumosa* gum in aqueous solution," *African Journal of Pure and Applied Chemistry*, vol. 7, pp. 35–43, 2013.

[26] M. Größl, S. Harrison, I. Kaml, and E. Kenndler, "Characterisation of natural polysaccharides (plant gums) used as binding media for artistic and historic works by capillary zone electrophoresis," *Journal of Chromatography A*, vol. 1077, no. 1, pp. 80–89, 2005.

[27] O. Beltrán, G. L. de Pinto, F. Rincon et al., "*Acacia macracantha* gum as a possible source of arabinogalactan–protein," *Carbohydrate Polymers*, vol. 72, no. 1, pp. 88–94, 2008.

[28] R. Tester and M. Sommerville, "The effects of non-starch polysaccharides on the extent of gelatinisation, swelling and α-amylase hydrolysis of maize and wheat starches," *Food Hydrocolloids*, vol. 17, no. 1, pp. 41–54, 2003.

[29] V. Singh, A. Srivastava, and A. Tiwari, "Structural elucidation, modification and characterization of seed gum from *Cassia javahikai* seeds: a non-traditional source of industrial gums," *International Journal of Biological Macromolecules*, vol. 45, no. 3, pp. 293–297, 2009.

[30] R. K. Sharma and R. Ghose, "Synthesis of zinc oxide nanoparticles by homogeneous precipitation method and its application in antifungal activity against Candida albicans," *Ceramics International*, vol. 41, no. 1, pp. 967–975, 2015.

[31] D. Demirci Gültekin, A. Alaylı Güngör, H. Önem, A. Babagil, and H. Nadaroğlu, "Synthesis of copper nanoparticles using a different method: determination of its antioxidant and antimicrobial activity," *Journal of the Turkish Chemical Society Section A: Chemistry*, vol. 3, pp. 623–636, 2016.

[32] A. J. Kora, R. Sashidhar, and J. Arunachalam, "Gum kondagogu (*Cochlospermum gossypium*): a template for the green synthesis and stabilization of silver nanoparticles with antibacterial application," *Carbohydrate Polymers*, vol. 82, no. 3, pp. 670–679, 2010.

[33] D. Arumai Selvan, D. Mahendiran, R. Senthil Kumar, and A. Kalilur Rahiman, "Garlic, green tea and turmeric extracts-mediated green synthesis of silver nanoparticles: phytochemical, antioxidant and in vitro cytotoxicity studies," *Journal of Photochemistry and Photobiology B: Biology*, vol. 180, pp. 243–252, 2018.

[34] J. Turkevich, P. C. Stevenson, and J. Hillier, "A study of the nucleation and growth processes in the synthesis of colloidal gold," *Discussions of the Faraday Society*, vol. 11, pp. 55–75, 1951.

[35] X. Ye, V. Kallakunta, D. W. Kim et al., "Effects of processing on a sustained release formulation prepared by twin-screw dry granulation," *Journal of Pharmaceutical Sciences*, vol. 108, no. 9, pp. 2895–2904, 2019.

[36] M. F. Tahir, S. A. Bukhari, F. Anjum, M. Qasim, H. Anwar, and S. A. R. Naqvi, "Purification and modification of *Cordia myxa* gum to enhance its nutraceutical attribute as binding agent," *Pakistan Journal of Pharmaceutical Sciences*, vol. 32, no. 5, pp. 2245–2250, 2019.

[37] T. G. Haile, G. G. Sibhat, and F. Molla, "Physicochemical Characterization of *Grewia ferruginea* hochst. ex A. Rich Mucilage for potential use as a pharmaceutical excipient," *BioMed Research International*, vol. 2020, Article ID 4094350, 10 pages, 2020.

[38] F. F. Takizawa, G. D. O. D. Silva, F. E. Konkel, and I. M. Demiate, "Characterization of tropical starches modified with potassium permanganate and lactic acid," *Brazilian Archives of Biology and Technology*, vol. 47, no. 6, pp. 921–931, 2004.

[39] V. J. Kumar, O. Sati, and R. Singh, "A potential natural tablet binder from *Grewia optiva*," *Der Pharmacia Lettre*, vol. 3, pp. 120–127, 2011.

[40] O. A. Odeku and K. M. Picker-Freyer, "Analysis of the material and tablet formation properties of four Dioscorea starches," *Starch Staerke*, vol. 59, no. 9, pp. 430–444, 2007.

[41] BPThe Pharmaceutical Press, London, UK, 2013.

[42] A. Rispin, D. Farrar, E. Margosches et al., "Alternative methods for the median lethal dose (LD50) test: the up-and-down procedure for acute oral toxicity," *ILAR Journal*, vol. 43, no. 4, pp. 233–243, 2002.

[43] M. Ahuja, A. Kumar, P. Yadav, and K. Singh, "*Mimosa pudica* seed mucilage: isolation; characterization and evaluation as tablet disintegrant and binder," *International Journal of Biological Macromolecules*, vol. 57, pp. 105–110, 2013.

[44] M. Choudhary and K. Grover, "Palm (*Elaeis guineensis* jacq.) oil," in *Fruit Oils: Chemistry and Functionality*Springer, Berlin, Germany, 2019.

[45] M. Rizwan, S. Amin, B. K. Malikovna et al., "Green synthesis and antimicrobial potential of silver nanoparticles with *Boerhavia procumbens* extract," *Journal of Pure and Applied Microbiology*, vol. 14, no. 2, pp. 1437–1451, 2020.

[46] A. Zar Pasha, S. Anwer Bukhari, H. Ali El Enshasy, H. El Adawi, and S. Al Obaid, "Compositional analysis and physicochemical evaluation of date palm (*Phoenix dactylifera* L.) mucilage for medicinal purposes," *Saudi Journal of Biological Sciences*, vol. 29, no. 2, pp. 774–780, 2022.

[47] R. K. Pandey and V. K. Prajapati, "Molecular and immunological toxic effects of nanoparticles," *International Journal of Biological Macromolecules*, vol. 107, pp. 1278–1293, 2018.

[48] K. Sultana, B. Ahmad, A. Rauf, L. Huang, and M. F. Ramadan, "Synthesis, characterization and pharmacological activities of silver nanoparticles using *Bistorta affinis* and *Malcolmia cabulica* extracts," *Bioinspired, Biomimetic and Nanobiomaterials*, vol. 9, no. 1, pp. 7–15, 2020.

[49] S. Hameed, A. T. Khalil, M. Ali et al., "Greener synthesis of ZnO and Ag–ZnO nanoparticles using *Silybum marianum* for diverse biomedical applications," *Nanomedicine*, vol. 14, no. 6, pp. 655–673, 2019.

[50] D. Rehana, D. Mahendiran, R. S. Kumar, and A. K. Rahiman, "Evaluation of antioxidant and anticancer activity of copper oxide nanoparticles synthesized using medicinally important plant extracts," *Biomedicine & Pharmacotherapy*, vol. 89, pp. 1067–1077, 2017.

[51] D. G. Téllez-de-Jesús, N. Flores-Lopez, J. Cervantes-Chávez, and A. Hernández-Martínez, "Antibacterial and antifungal activities of encapsulated Au and Ag nanoparticles synthesized using *Argemone mexicana* L extract, against antibiotic-resistant bacteria and Candida albicans," *Surfaces and Interfaces*, vol. 27, Article ID 101456, 2021.

[52] V. Soni, P. Raizada, P. Singh et al., "Sustainable and green trends in using plant extracts for the synthesis of biogenic metal nanoparticles toward environmental and pharmaceutical advances: a review," *Environmental Research*, vol. 202, Article ID 111622, 2021.

[53] Y. A. Haggag, A. K. Abosalha, M. M. Tambuwala et al., "Polymeric nanoencapsulation of zaleplon into PLGA nanoparticles for enhanced pharmacokinetics and pharmacological activity," *Biopharmaceutics & Drug Disposition*, vol. 42, no. 1, pp. 12–23, 2021.

[54] F. Westhauser, S. Wilkesmann, Q. Nawaz et al., "Effect of manganese, zinc, and copper on the biological and osteogenic properties of mesoporous bioactive glass nanoparticles," *Journal of Biomedical Materials Research Part A*, vol. 109, no. 8, pp. 1457–1467, 2021.

[55] R. B. Shah, M. A. Tawakkul, and M. A. Khan, "Comparative evaluation of flow for pharmaceutical powders and granules," *AAPS PharmSciTech*, vol. 9, no. 1, pp. 250–258, 2008.

[56] G. Jeong, J. Bak, and B. Yoo, "Physical and rheological properties of xanthan gum agglomerated in fluidized bed: effect of HPMC as a binder," *International Journal of Biological Macromolecules*, vol. 121, pp. 424–428, 2019.

[57] X. Guiling, C. Xiaoping, L. Cai, X. Pan, and Z. Changsui, "Experimental investigation on the flowability properties of cohesive carbonaceous powders," *Particulate Science and Technology*, vol. 35, no. 3, pp. 322–329, 2017.

[58] J.-M. Fachaux, A.-M. Guyot-Hermann, J.-C. Guyot et al., "Pure Paracetamol for direct compression Part I. Development of sintered-like crystals of Paracetamol," *Powder Technology*, vol. 82, no. 2, pp. 123–128, 1995.

[59] S. S. Rohokale, Y. D. Dhanorkar, V. Pahuja, and G. T. Kulkarni, "Characterization of selected polysaccharide hydrogels as pharmaceutical excipients," *Journal of Chronotherapy and Drug Delivery*, vol. 3, pp. 41–54, 2012.

[60] I. Tontul and A. Topuz, "Spray-drying of fruit and vegetable juices: effect of drying conditions on the product yield and physical properties," *Trends in Food Science & Technology*, vol. 63, pp. 91–102, 2017.

[61] M. A. Shende and R. P. Marathe, "Extraction of mucilages and its comparative mucoadhesive studies from hibiscus plant species," *World Journal of Pharmacy and Pharmaceutical Sciences*, vol. 4, pp. 900–924, 2015.

[62] A. Alobo and G. Arueya, "Physical, functional and chemical properties of *Grewia venusta* (ururu) mucilage extract," *International Food Research Journal*, vol. 24, pp. 2107–2115, 2017.

[63] C. R. Park and D. L. Munday, "Evaluation of selected polysaccharide excipients in buccoadhesive tablets for sustained release of nicotine," *Drug Development and Industrial Pharmacy*, vol. 30, no. 6, pp. 609–617, 2004.

[64] E. I. Nep and B. R. Conway, "Preformulation studies on grewia gum as a formulation excipient," *Journal of Thermal Analysis and Calorimetry*, vol. 108, no. 1, pp. 197–205, 2012.

[65] A. Kumar and M. Ahuja, "Carboxymethyl gum kondagogu: synthesis, characterization and evaluation as mucoadhesive polymer," *Carbohydrate Polymers*, vol. 90, no. 1, pp. 637–643, 2012.

[66] H. A. Pawar and P. Jadhav, "Isolation, characterization and investigation of *Cordia dichotoma* fruit polysaccharide as a herbal excipient," *International Journal of Biological Macromolecules*, vol. 72, pp. 1228–1236, 2015.

[67] O. Chukwu, "Moisture-sorption study of dried date fruits," *AU Journal of Technology*, vol. 13, pp. 175–180, 2010.

[68] N. Gebresamuel and T. Gebre-Mariam, "Comparative physico-chemical characterization of the mucilages of two cactus pears (*Opuntia* spp.) obtained from Mekelle, Northern Ethiopia," *Journal of Biomaterials and Nanobiotechnology*, vol. 3, pp. 79–86, 2011.

[69] M. A. Shende and R. P. Marathe, "Acute and sub-chronic oral toxicity studies of *Hibiscus esculentus* mucilage on Swiss albino mice," *Journal of Pharmaceutical Sciences and Research*, vol. 8, pp. 251–255, 2016.

[70] H. N. D. Divvela, L. Duppala, and V. R. M. Kolapalli, "Isolation and acute oral toxicity studies of *Araucaria heterophylla* novel natural polysaccharide gum in albino mice," *World Journal of Pharmacy and Pharmaceutical Sciences*, vol. 5, pp. 702–711, 2016.

[71] J. Saikarthik, J. Vijayakumar, and R. Vijayaraghavan, "Qualitative phytochemistry and acute oral toxicity testing of the methanol extract of Mucuna pruriens seeds in Albino mice," *International Journal of Pharmaceutical Sciences Review and Research*, vol. 38, pp. 198–204, 2016.

[72] R. R. Bhosale, R. A. M. Osmani, and A. Moin, "Natural gums and mucilages: a review on multifaceted excipients in pharmaceutical science and research," *International Journal of Pharmacognosy and Phytochemical Research*, vol. 15, pp. 901–912, 2014.

[73] A. Hussain, F. Qureshi, N. Abbas, M. S. Arshad, and E. Ali, "An evaluation of the binding strength of okra gum and the drug release characteristics of tablets prepared from it," *Pharmaceutics*, vol. 9, no. 4, pp. 20–28, 2017.