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Mucilage of *Coccinia grandis* as an efficient natural polymer-based pharmaceutical excipient

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Abstract: Mucilage from *Coccinia grandis* was extracted, isolated by maceration technique and precipitated, accordingly. The mucilage was evaluated for its physicochemical, binding, and disintegrant properties in tablets using paracetamol as a model drug. The crucial physicochemical properties such as flow properties, solubility, swelling index, loss on drying, viscosity, pH, microbial load, cytotoxicity was evaluated and the compatibility was analysed using sophisticated instrumental methods (TGA, DTA, DSC, and FTIR). The binding properties of the mucilage was used at three different concentrations and compared with starch and PVP as standard binders. The disintegrant properties of mucilage were used at two different concentrations and compared with standard disintegrants MCCP, SSG, and CCS. The wet granulation technique was used for the preparation of granules and were evaluated for the flow properties. The tablets were punched and evaluated for their hardness, friability, assay, disintegration time, *in vitro* dissolution profiles. *In vitro* cytotoxicity study of the mucilage was performed in human embryonic kidney (HEK) cell line using cytotoxic assay by MTT method. The outcome of the study indicated that the mucilage had good performance while comparing with starch and PVP. Further, the mucilage acts as a good disintegrant than MCCP, SSG and CCS to paracetamol tablets. Moreover, the *in vitro* cytotoxicity evaluation results demonstrated that the mucilage is non-cytotoxic to human cells and is safe.

Keywords: binding agent; disintegrating agent; natural polymer; mucilage; *Coccinia grandis*

1. Introduction

The oral route is the most preferred route of administration for various drugs as it is regarded to be the safest, most convenient, and painless route [1]. [1]. Recently, in the novel drug delivery system (NDDS), various researchers developed convenient solid dosage forms and achieved better patient compliance [2]. Various plant gums and mucilage have been used as binders and disintegrants in the formulation of tablets [3]. However, finding an optimized, novel and effective binder and disintegrant for the manufacture of tablets in the

pharmaceutical industry remains a challenging task [4]. Binders and disintegrants are the major pharmaceutical excipients that are playing an important role in the solid dosage forms [5]. Binders employed in the tablet formulations to impart cohesion on powder mix and hence improving the flow properties of the granules. It is used to hold various powders intact together to form a tablet. The wet binder is the most important ingredient in the wet granulation process, most of the binders are hydrophilic, soluble in water such as Starch, Gelatine, PVP, etc [6]. Disintegrating agents are the substances routinely included in the tablet formulations to aid in the breakup of the compacted mass when it is put into a fluid environment. They promote moisture penetration and dispersion of the tablet matrix. Notably, the commonly used disintegrating agents in the tablet formulations are MCCP, CCS, and SSG [7].

Coccinia grandis (L.) Voigt, commonly called as Ivy gourd belongs to the family Cucurbitaceae. It is commonly found in Asian countries such as India, Pakistan, and Sri Lanka and also distributed in Tropical Africa [8]. In traditional system of medicine, fruits of *Coccinia grandis* have been used to treat leprosy, fever, asthma, bronchitis, and jaundice [9–13]. Recently, it was discovered that the polysaccharide found in *Coccinia grandis* can be used as an anti-diabetic agent [14]. Considering all the above literature reports, the current study was designed to incorporate the isolation of the mucilage from the fruits, evaluation of its safety, and its useful application as a novel binding and disintegrating agent in the tablet formulations. Paracetamol**,** also known as acetaminophen or *N*-acetyl-*p*-aminophenol is widely used over-the-counter analgesic (pain reliever) and antipyretic (fever reducer) was selected in our study as a model drug [15]. Paracetamol, a drug with known capping and lamination problems that normally requires an appropriate binder for the formulation and upon the storage, the paracetamol tablet gains hardness, that normally requires a disintegrant to form ideal tablets. It was found in the literature that the mucilage of this fruit was not studied or reported for its binding and disintegrant properties. Hence, we are interested to investigate for the first time, the binding and disintegrant properties of the mucilage in the tablet formulation and comparing its efficiency with standard binding and disintegrating agents.

2. Materials and Methods

2.1. Materials

Paracetamol (Granules India), Starch (Ridhi Siddhi), Microcrystalline Cellulose Powder (Loba Chemie Pvt Ltd), Polyvinylpyrrolidone (J.B.Khokhani & co), Sodium Starch Glycollate (J.R.Pharma), Croscarmellose Sodium (Shreeji pharma), Sodium Methylparaben, Sodium Propylparaben (Nebula health care), Talc (Suprime Traders), Magnesium Stearate (Pantogan) were obtained as gift sample from Kreszent Pharma, Pondicherry, India. The fruits of *Coccinia grandis* were purchased from the local market in Coimbatore, India and the same has been properly identified and a specimen is deposited in Botanical Survey of India, Tamilnadu Agricultural University Campus, Coimbatore, India. All the other chemicals used were of analytical or reagent-grade.

2.2. Extraction and isolation of mucilage

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The fruits were thoroughly washed with water. The fruit pulp was made and initially heated with steam at 80 ^{0}C for 3 min to inhibit enzymatic browning reaction. The fruit pulp was homogenized with three times of its weight of water. The solution was soaked for 19-20 hrs for the release of mucilage into water. Then the solution was squeezed and filtered by using a muslin bag. The filtrate was collected and the mucilage was precipitated with three times its volume of ethanol. Thus, cream-coloured precipitate was obtained and was washed with acetone thrice. The obtained white-coloured solid was dried initially under vacuum for 17-18 hours followed by sunlight exposure for 30 minutes to yield 5.5 g mucilage/kg of fruits. Finally, the isolated mucilage was powdered, passed through sieve number 60, and stored in the desiccators for the future experiments or the subsequent tests.

2.3. Physicochemical and characterization of the isolated mucilage

The physicochemical properties such as identification tests, organoleptic properties, solubility, swelling index, loss on drying, viscosity, cytotoxicity, XRD, SEM, compatibility studies of TGA, DTA, DSC and FTIR, flow properties, pH and microbial load of the mucilage were determined according to the recommended protocols [16–18].

2.4. Formulations of paracetamol granules and their key compositions

The mucilage was evaluated for its binding and disintegrating properties in tablets of paracetamol (a model drug). Binding properties of granules were evaluated for each of the three different formulations containing varying concentrations (3%, 6%, and 9%) of *Coccinia grandis* mucilage as test binder, starch, and PVP, respectively [19] by wet granulation technique (Table 1). Disintegrating properties of granules were evaluated for each of the two different formulations containing varying concentrations (2%, 3%) of mucilage (test disintegrant), and MCCP, CCS, and SSG (standard disintegrants) by wet granulation technique (Table 2).

Table 1. Composition of paracetamol tablet formulation using the different binding agents of *Coccinia Grandis* mucilage, Starch and PVP.

INGREDIENTS	F1 (3%)	F2 (6%)	F3 (9%)	F4 (3%)	F5 (6%)	F6 (9%)	F7 (3%)	F8 (6%)	F9 (9%)
Paracetamol	250	250	250	250	250	250	250	250	250
Starch	125	113	101	125	113	101	125	113	101
mucilage (Binder)	**12**	**24**	**36**	-	-	-	-	-	-
Starch (Binder)	-	-	-	**12**	**24**	**36**	-	-	-
Polyvinylpyrrolidone (Binder)	-	-	-	-	-	-	**12**	**24**	**36**
Sodium methylparaben	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Sodium propylparaben	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Demineralised water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Talc	8	8	8	8	8	8	8	8	8
Magnesium stearate	4	4	4	4	4	4	4	4	4
Total weight	400	400	400	400	400	400	400	400	400

Note: All the above ingredients quantities are mg / tablet.

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Table 2. Composition of paracetamol tablet formulation using the different disintegrating agents of *Coccinia grandis* mucilage, MCCP, CCS, and SSG.

INGREDIENTS	G1 (2%)	G2 (3%)	G3 (2%)	G4 (3%)	G5 (2%)	G6 (3%)	G7 (2%)	G8 (3%)
Paracetamol	250	250	250	250	250	250	250	250
Starch (diluent)	99	95	99	95	99	95	99	95
Starch (Binder)	30	30	30	30	30	30	30	30
mucilage	**8**	**12**	-	-	-	-	-	-
Microcrystalline cellulose powder	-	-	**8**	**12**	-	-	-	-
Croscarmellose sodium	-	-	-	-	**8**	**12**	-	-
Sodium starch glycollate	-	-	-	-	-	-	**8**	**12**
Sodium methylparaben	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Sodium propylparaben	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Demineralised water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Talc	8	8	8	8	8	8	8	8
Magnesium stearate	4	4	4	4	4	4	4	4
Total weight	400	400	400	400	400	400	400	400

Note: All the above ingredients quantities are mg / tablet.

2.5. Evaluation of granules

The flow properties of the granules were determined for their bulk density, tapped density, (compressibility index), Carr's index, Hausner's ratio, and Angle of repose as per the reported protocols [20].

2.6. Production and evaluation of tablets formulations

The different batches of granules were produced and compressed into an average weight of 400 mg per tablet using a rotary punch tablet compression machine (Shakti Pharmatech Pvt Ltd.) fitted with a concave punch and die set. The prepared tablets were evaluated for their hardness and friability, weight variation, assay, disintegration time, *in vitro* dissolution profiles, and accelerated stability studies using the method specified in Indian Pharmacopoeia-2007 [21].

3. Results and discussion

3.1. Physicochemical characterization of isolated mucilage powder

The physicochemical and microbiological properties of the mucilage were determined and the results are collected in Tables 3 and 4. The identification tests of mucilage gave a positive test for carbohydrate, mucilage in molisch's and ruthenium tests, respectively and the iodine test gave negative result for the starch, thus polysaccharides are confirmed. The extracted and purified mucilage was evaluated for its viscosity, bacterial load, and pH. The microbial count of bacteria and fungi was found to be less than 300 and 100 CFU (colony forming units) per gram of mucilage, respectively. The pH of the mucilage was found to be 6.7. Since the pH value of this mucilage is near to neutral, it may be less irritating on the gastrointestinal tract (GIT) and hence, it will be suitable for the uncoated tablets formulations. The flow properties of mucilage powders were determined by Carr's index, Hausner's ratio and angle of repose and were found to be >23, >1.25, and 36°-40° respectively, all of which indicated poor and passable flow properties.

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Table 3. Identification test results of the mucilage.

Tests	Observed	Results
Molisch's test:	Violet green colour present at junction of two layers	Carbohydrate present
Ruthenium test:	Pink colour developed	Mucilage present
Iodine test:	No colour present in solution	Polysaccharides present

Table 4. Results of Physicochemical characterization of *Coccinia grandis* mucilage.

Parameters	Observed
Organoleptic properties	White colour, amorphous nature, tasteless, characteristic odour.
Solubility	Slightly soluble in hot water, in cold water forming viscous colloidal solution and practically insoluble in acetone, ethanol, chloroform and other organic solvents.
Loss on drying (%)	5.7%
Swelling index in distilled water	46.3%
Bulk density	0.083 g/cm^3
Tapped density	0.125 g/cm^3
Carr's index	33.6
Hausner's ratio	1.50
Angle of repose (º)	39.5º
pH (1%w/v)	6.7
Total Ash (%)	3.0%
Water-soluble ash (%)	6.7%
Acid insoluble ash (%)	0.5%
Viscosity (1% w/v solution)	4.9 cps
Total Microbial (Load)count	
Bacteria: (CFU/g)	107
Fungi: CFU/g)	64

3.2. Thermal methods of analysis

The drug-excipient compatibility studies were analysed by thermal analysis of TGA, DTA, and DSC. The thermal method of drug and mucilage of *C. grandis* showed that there is no change in melting point which confirmed that there is neither change in colour of the drug nor had any interaction.

3.3. Thermogravimetric analysis (TGA)

The thermogravimetric curve of the mucilage (CGM) is presented in Fig. 1. It clearly shows the weight loss corresponding to the loss of water around 25 – 190 °C. The mucilage underwent 9.26% weight loss at 65.21 °C which implied that CGM had good thermal stability. The curve also indicated that the mucilage did not decompose before 200 °C and starts decompose at 207.34 °C. Hence, water is formed by intra- and inter-molecular condensation of the mucilage hydroxyls are the main products of decomposition at a temperature below 450 °C. The TGA of CGM and drug mixture showed no major interaction of CGM and drug (Fig. 2), hence the mixtures are compatible with each other.

3.4. Differential scanning colorimetry (DSC)

The DSC curve of CGM (Fig. 1) demonstrated that it undergoes the glass transition temperature at 190.84 °C (1.132 J/G). The continuous (broad) endothermic transition that recedes the glass transition is an indicative of moisture loss in the sample and start decomposing at 313.03 °C (4.973 J/G). The sample DSC overlap curve of CGM, drug, and its mixture (Fig. 2) showed no additional peaks. Hence, it can be

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concluded that there is no physical interaction occurred in the mixture of CGM with the drug paracetamol.

3.5. Differential thermal analysis (DTA)

The DTA curve of mucilage undergoes crystallization at a temperature of 56.71°C (0.1904% / °C). The mucilage started to melt at 229.59°C (0.2773% / °C) based on the analysis conducted using DTA as shown in Figure 1. The DTA of the mixture of paracetamol drug and mucilage displayed no major interaction between CGM and drug (Figure 2). Hence, the mucilage and drug were compatible with each other. Figure 3 presents DSC, TGA, DTA of the model drug Paracetamol alone.

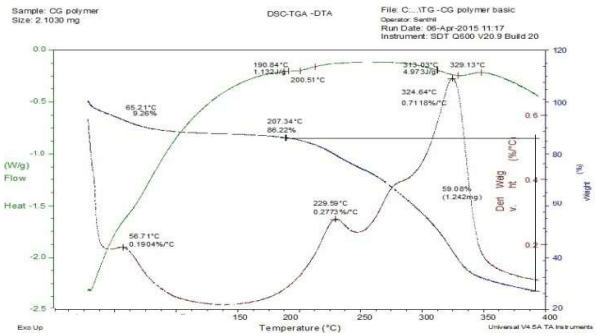

Figure 1. DSC, TGA, DTA of mucilage (CGM).

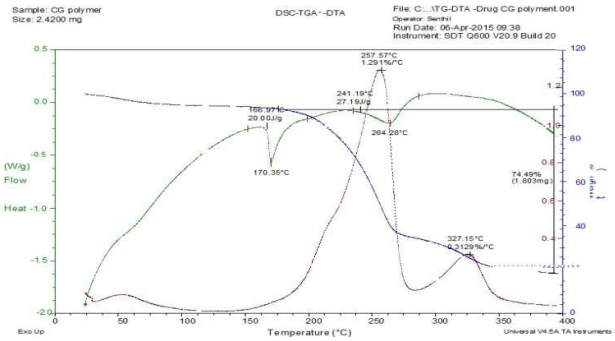

Figure 2. DSC, TGA, DTA of paracetamol + CGM.

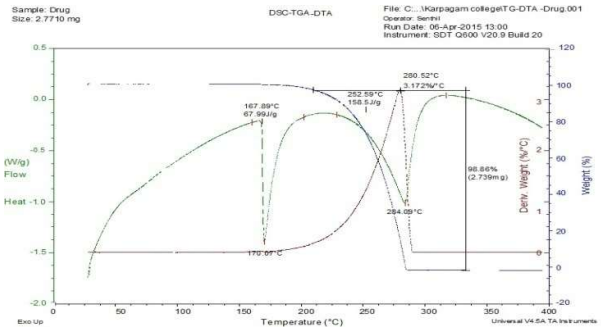

Figure 3. DSC, TGA, DTA of Paracetamol.

3.6. FTIR Analysis

The drug-excipient interaction was also checked by comparing the IR spectrum of the physical mixture of the drug with the mucilage of *C.*

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grandis with IR spectrum of the pure drug paracetamol. The main components of the mucilage (CGM) may be galactose, rhamnose, and galacturonic acid as shown in the FTIR spectrum (Figure 4). A broad peak at 3385.07 cm^{-1} found in the spectrum indicates the presence of sugar groups with O-H as the main functional group stretching which was also observed in the three main components of CGM. The O-H groups can bind with water molecules and produce bound moisture to the mucilage components. The existence of O-H groups represents the hydrophilicity of the mucilage. The carbonyl, and hydroxyl functional groups that are presented in the chemical structure of CGM are the constituents of carbohydrate molecules, which is concluded to be the main backbone of the mucilage. The FTIR spectrum of paracetamol is presented in the Figure 5. The FTIR spectrum of the mixture of mucilage and drug is shown in Figure 6 that disclosed distinctive stretching vibrational peaks at 3317.56 cm^{-1}, 3165.19 cm^{-1}, 1654.92 cm^{-1}, and 1560.41 cm^{-1} corresponding to the functional groups present in the mucilage and the drug. Further, there are no abnormal peaks and the functional groups of the drug are seen intact which in turn demonstrated that the drug is compatible with mucilage.

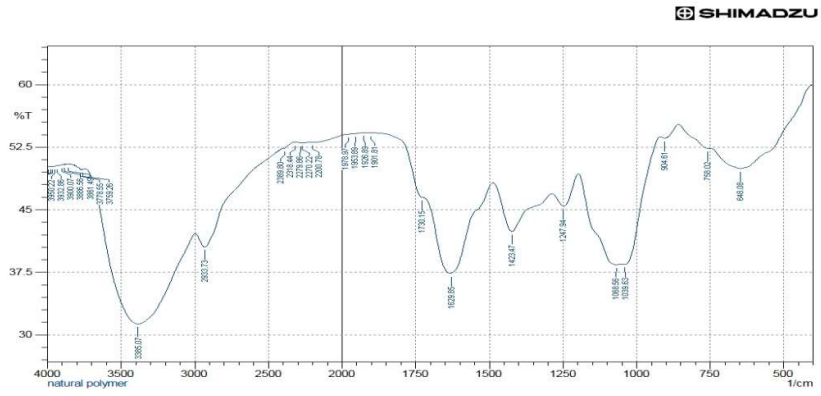

Figure 4. FTIR analysis of the mucilage.

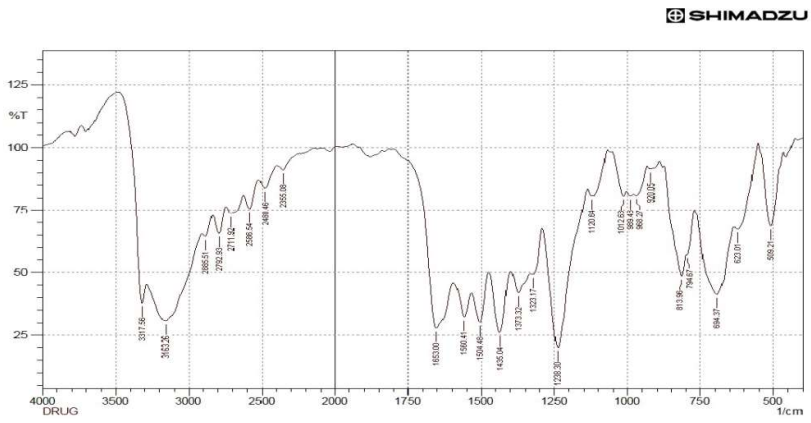

Figure 5. FTIR analysis of Paracetamol.

The vibrational frequencies of various functional groups of the pure drug remained intact in the physical mixture containing *C. grandis*

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according to the Figure 6. Thus, it was concluded that there was no major interaction occurred between the drug and *C. grandis* used in the current study. Hence, the mucilage can be used effectively as a pharmaceutical excipient in the tablet formulations.

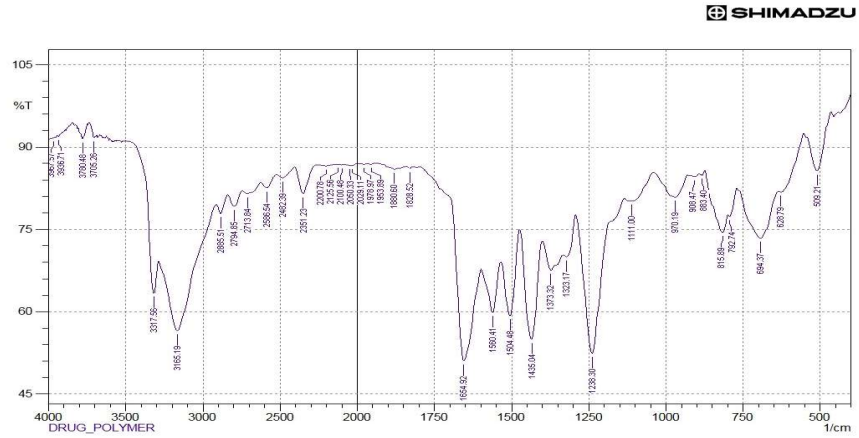

Figure 6. FTIR analysis of the mucilage (CGM) + Paracetamol.

3.7. X-ray powder diffraction study

The surface morphology of the mucilage powder was observed by XRD (X-ray diffraction method) and the results are shown in the Figure 7. From the spectra obtained through XRD, it was deduced that the mucilage powder showed the presence of numerous halos with weak peaks which in turn specified the amorphous nature of the material.

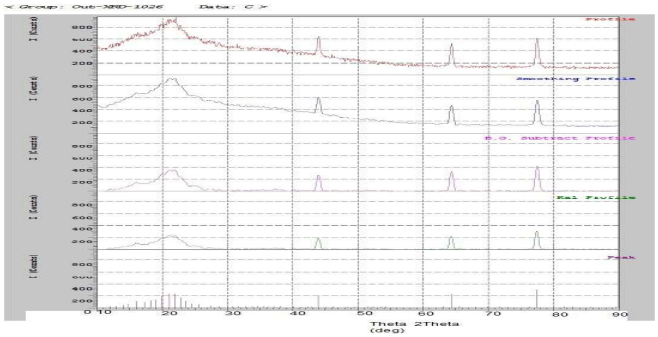

Figure 7. XRD analysis of mucilage (CGM).

3.8. Scanning electron microscopy

The surface morphology of the mucilage was also observed under scanning electron microscope (SEM) and the analysis result in X5000 is shown in Figure 8. Further, the images of SEM results under different magnification are presented in supporting information (Figures S1 to S3). The images of the mucilage revealed that the surface of particles is mostly seen as aggregates of rough, irregular in size and shapes and dimensions which were fibrous in nature, subsequently confirmed the amorphous nature of the material.

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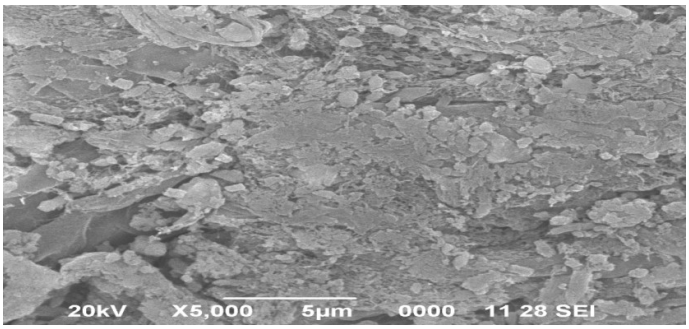

Figure 8. SEM analysis of mucilage in X5000.

3.9. In vitro cytotoxicity evaluation

The toxicity study of the mucilage was performed in the human embryonic kidney (HEK) cell line. The cells were maintained at 37 ^{0}C, 5% CO2, 95% air, and 100% relative humidity. The concentration vs absorbance and percentages of cell viability of test sample were calculated with control sample and are collected in Tables 5 and 6 and presented in supporting information (Figs S4 to S10). The HEK cell line had no morphological changes and the cell viability was nearly 100% (i.e., above 80%). The reduction of MTT by cells indicated the mitochondrial activity, which may be interpreted as a proof of cell viability. It was concluded that the CGM unable to induce cytotoxic effects to the normal cells at the used concentrations.

Table 5. Concentration vs absorbance of cell viability of test and control.

S. No	Concentration (µg/ml)	Absorbance
1	12.5	0.451
2	25	0.446
3	50	0.413
4	100	0.388
5	200	0.367

Average control absorbance = 0.451.

Table 6. Concentrations vs % cell viability.

S. No	Concentration (µg/ml)	% cell viability
1	12.5	99.92
2	25	98.81
3	50	91.65
4	100	85.96
5	200	81.38

3.10. Evaluation of the formulated granules for flow properties

The flow properties of the prepared granules of different batches were determined and the results are presented in Tables 7 and 8. It was observed that the flowability decreased when the concentration (as a binding agent) of the mucilage is increased. When compared with starch and PVP granules, the flow property of the formulated granules differs slightly. When the mucilage concentration, as a disintegrating agent, is increased, the flowability is also increased, consequently. This value slightly different from the flow properties of the granules prepared from MCCP, CCS, and SSG, respectively. The Carr's index, Hausner's ratio and Angle of repose values of the granules made from the mucilage were found to be <23, <1.25, and 25º - 30º respectively. Hence, it was discovered that all the granules exhibited excellent flow properties.

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Table 7. Flow properties of formulated granules (Binding agents).

Binders → / Formulations code → / Parameters ↓	CGM			STARCH			PVP		
	F1 (3%)	F2 (6%)	F3 (9%)	F4 (3%)	F5 (6%)	F6 (9%)	F7 (3%)	F8 (6%)	F9 (9%)
Bulk density (g/ml)	0.438 ±0.00	0.446 ±0.00	0.446 ±0.00	0.434 ±0.00	0.442 ±0.00	0.446 ±0.00	0.438 ±0.00	0.446 ±0.00	0.442 ±0.00
Tapped density (g/ml)	0.510 ±0.00	0.500 ±0.00	0.495 ±0.00	0.526 ±0.00	0.500 ±0.00	0.490 ±0.00	0.505 ±0.00	0.490 ±0.00	0.480 ±0.00
Carr's index (%)	14.1 ±0.00	10.8 ±0.00	9.9 ±0.01	17.5 ±0.01	11.6 ±0.00	9.0 ±0.03	13.3 ±0.04	9.0 ±0.03	7.9 ±0.00
Hausner's ratio	1.16 ±0.00	1.12 ±0.00	1.11 ±0.01	1.21 ±0.00	1.13 ±0.00	1.10 ±0.01	1.15 ±0.00	1.10 ±0.01	1.10 ±0.02
Angle of repose (°)	29.3°	25.1°	26.2°	29.7°	26.4°	25.9°	29.9°	28.4°	27.8°

CGM = mucilage, PVP = polyvinylpyrrolidone.

Table 8. Flow properties of formulated granules (Disintegrating agents).

Disintegrants → / Formulations code → / Parameters ↓	CGM		MCCP		CCS		SSG	
	G1 (2%)	G2 (3%)	G3 (2%)	G4 (3%)	G5 (2%)	G6 (3%)	G7 (2%)	G8 (3%)
Bulk density (g/ml)	0.446 ±0.00	0.442 ±0.00	0.446 ±0.00	0.442 ±0.00	0.442 ±0.00	0.446 ±0.00	0.442 ±0.00	0.446 ±0.00
Tapped density (g/ml)	0.495 ±0.00	0.500 ±0.00	0.500 ±0.00	0.505 ±0.00	0.500 ±0.00	0.495 ±0.00	0.505 ±0.00	0.490 ±0.00
Carr's index (%)	9.9 ±0.01	11.6 ±0.00	10.8 ±0.01	12.5 ±0.03	11.6 ±0.00	9.9 ±0.01	12.5 ±0.03	9.0 ±0.03
Hausner's ratio	1.11 ±0.01	1.13 ±0.01	1.12 ±0.01	1.14 ±0.00	1.13 ±0.01	1.11 ±0.01	1.14 ±0.00	1.10 ±0.01
Angle of repose (°)	28.3°	29.1°	28.7°	29.7°	28.4°	28.9°	29.2°	28.8°

CGM = mucilage, MCCP =microcrystalline cellulose powder, CCS =croscarmellose sodium, SSG = sodium starch glycollate.

3.11. Evaluation of tablets using isolated mucilage as a binding agent

Different batches of tablets were prepared using isolated mucilage as a binding agent at three different percentages. For the comparison, starch and PVP were used as standard binding agents. The prepared tablets were evaluated and the results of their weight variation, hardness, thickness, diameter, friability, disintegration time, and assay were presented in Table 9. All the batches of tablets exhibited a good content uniformity. The hardness of the tablets increased with an increase in the percentage of binding agents. Tablets prepared with 9% mucilage showed more hardness when compared to the tablets prepared using 3% and 6%. The friability values were found to be lower with an increase in the concentration of the binder. However, the overall friability values were within the specified limits. The disintegration time of the tablets was found to be increased with an increase in the concentration of the binder from 3% to 9%. This behaviour can be attributed to the swelling properties of the mucilage. But the overall disintegration time values were within the IP limits.

Table 9. Evaluation of tablets using different binding agents.

Binders → / Formulations code → / Parameters ↓	CGM			STARCH			PVP		
	F1 (3%)	F2 (6%)	F3 (9%)	F4 (3%)	F5 (6%)	F6 (9%)	F7 (3%)	F8 (6%)	F9 (9%)
Weight variation (mg)	400.1	400.0	401.4	400.0	401.1	400.2	401.0	401.2	400.1
Hardness (kg/cm^2)	4.0	4.5	5.5	4.0	4.5	5.0	4.5	5.0	6.5

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Thickness (mm)	4.8	4.8	5.0	4.8	5.0	4.8	4.9	5.0	4.8
Diameter (mm)	10.14	10.14	10.12	10.14	10.12	10.14	10.14	10.14	10.14
Friability (% w/w)	0.97	0.68	0.49	0.85	0.61	0.47	0.77	0.52	0.41
Disintegration time (min)	2min/5sec	4min/2sec	6min/28sec	1min/48sec	3min/52sec	5min/22sec	1min/54sec	5min/49sec	13min/36sec
Assay (%)	99.7	99.6	98.9	100.1	98.8	99.8	98.7	100.2	99.9

3.12. Evaluation of tablets using isolated mucilage as a disintegrating agent

The different batches of tablets were prepared using isolated mucilage as a suitable disintegrating agent at two different concentrations. For comparison, MCCP, CCS, and SSG were employed as standard disintegrating agents. The prepared tablets were evaluated and the results of their weight variation, hardness, thickness, diameter, friability, disintegration time, and assay are presented in Table 10. All the batches of tablets exhibited a good content uniformity and the hardness was observed between 4.0 to 4.5 kg/cm^2. The friability of the tablets was found to be within the approved range of less than 0.5 to 1% as per IP. The disintegration time of the isolated mucilage was determined to be within 15 minutes as per IP limits which indicated a slight difference or almost equal to the standard disintegrants. The disintegration time of tablets was found to be decreased with an increase in the concentration of the used mucilage. When the mucilage concentration was increased above 3%, the disintegration time also increased, accordingly. Hence, the mucilage acts as a suitable disintegrating agent, at an ideal concentration of less than 3%.

Table 10. Evaluation of tablets using different disintegrating agents.

Disintegrants →	**CGM**		**MCCP**		**CCS**		**SSG**	
Formulations code → / **Parameters** ↓	**G1 (2%)**	**G2 (3%)**	**G3 (2%)**	**G4 (3%)**	**G5 (2%)**	**G6 (3%)**	**G7 (2%)**	**G8 (3%)**
Weight variation (mg)	400.0	400.3	400.1	401.0	400.1	399.9	401.2	400.7
Hardness (kg/cm^2)	4.0	4.0	4.0	4.5	4.0	4.0	4.5	4.0
Thickness (mm)	4.8	4.8	4.8	4.9	4.8	4.8	5.0	4.9
Diameter (mm)	10.14	10.14	10.14	10.12	10.14	10.14	10.14	10.14
Friability (% w/w)	0.44	0.42	0.45	0.42	0.48	0.43	0.44	0.47
Disintegration time (min)	2min/58sec	2min/22sec	2min/51sec	2min/36sec	2min/49sec	2min/12sec	2min/51sec	2min/17sec
Assay (%)	98.9	99.9	99.7	100.1	99.8	98.9	99.6	98.7

3.13. In vitro dissolution studies of tablets using isolated mucilage as a binding agent

In vitro dissolution profile of tablets is shown in Figures 19 and 20, Tables 11 and 12. The results of this study showed that the drug release from the tablets prepared using the mucilage with 3% and 6% concentrations were found to be more than 80%, whereas using 9% concentration of the mucilage, the drug release of 80% occurred in 30 minutes. The drug release was found to be increased with a decrease in the concentration of the mucilage. From the Figure 20, the drug release of F1 and F2 batches showed a sharp increase, whereas F3 showed minimal drug release while comparing with other standard batches. The friability and disintegration time of all the formulations were identified to be within the IP standards. The drug release of F1and F2 formulations is within IP standard, except the formulation F3.

3.14. In vitro dissolution studies of tablets using isolated mucilage as a disintegrating agent

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In vitro dissolution profile of tablets is shown in Figures 9 to 11 and the parameters are presented in supporting information as Tables S1 to S3. The drug released from the tablets prepared using the mucilage with 2% and 3% concentrations were found to be more than 80% in 30 minutes (as per IP limits). The drug release was found to be increased with an increase in the concentration of mucilage (as a disintegrant). The formulation of G1 (2%) and G2 (3%) showed good disintegrant and the drug release was accomplished as above 80% (within the limit as per IP). Above 3% of the mucilage concentration, the disintegration time was slightly increased and conversely, the dissolution time decreased. Hence, the mucilage acts as an appropriate disintegrating agent within the concentration range of 1 to 3 %.

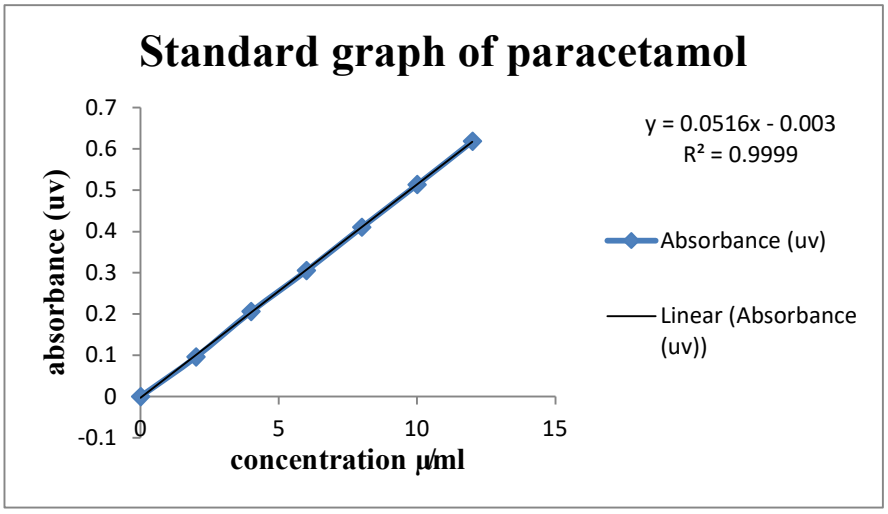

Figure 9. Standard graph of paracetamol drug.

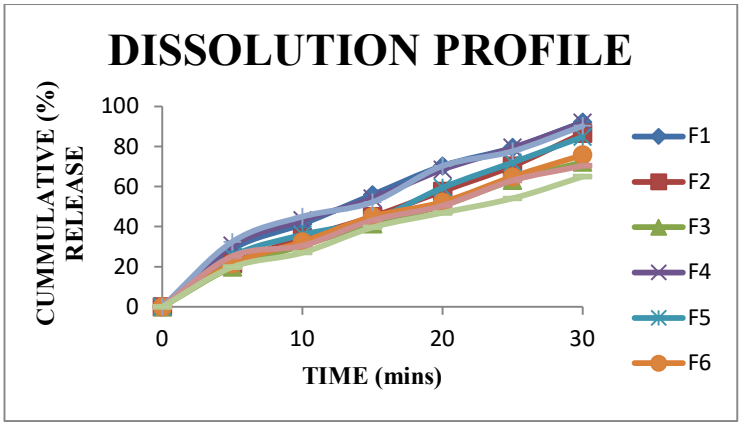

Figure 10. Comparative dissolution profiles for formulation (F1 to F9).

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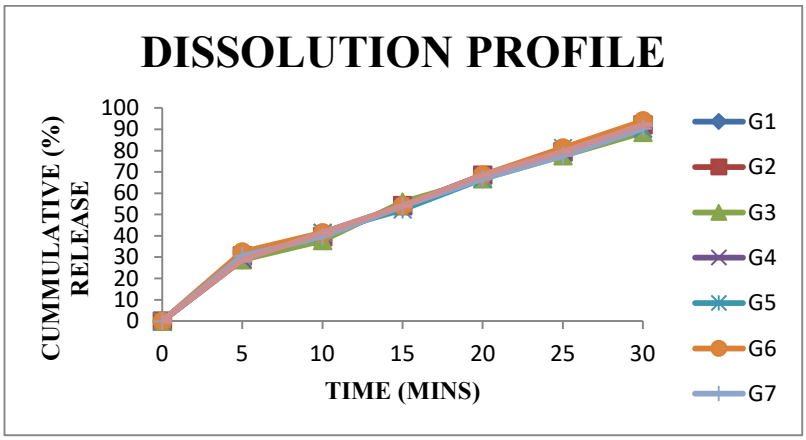

Figure 11. Comparative dissolution profiles for formulation (G1 to G8).

3.15. Statistical analysis

Statistical analysis of *in vitro* dissolution profile comparison of the mucilage (CGM) with STARCH and PVP (standard binding agents) was performed using DD SOLVER software for difference factor (f1), similarity factor (f2), and Rescigno index (ξ) values. The results It displayed that the comparison of mean (R) reference and mean (T) test values of difference factor (f1) was below 15, similarity factor (f2) was above 50 and the Rescigno index was almost 0 (Table 11). These values displayed the binding properties of the isolated mucilage are similar to that of STARCH and PVP.

Table 11. Statistical factors of CGM compared with STARCH and PVP as binding agents.

Binders →	CGM VS STARCH			CGM VS PVP		
Formulations code → / Statistical Factors ↓	F1 vs F4 (3%)	F2 vs F5 (6%)	F3 vs F6 (9%)	F1 vs F7 (3%)	F2 vs F8 (6%)	F3 vs F9 (9%)
Difference factor (f1)	2.01	3.90	4.93	3.91	13.99	9.98
Similarity factor (f2)	87.48	80.91	78.15	76.69	54.37	63.82
Rescigno index (ξ)	0.0113	0.0207	0.0252	0.0209	0.0606	0.0468

Statistical analysis of *in vitro* dissolution profile comparison of the mucilage (CGM) with MCCP, CCS, and SSG (standard disintegrating agents) was conducted using DD SOLVER software for difference factor (f1), similarity factor (f2), and Rescigno index (ξ) values. The results demonstrated that the comparison of mean (R) reference and mean (T) test values of difference factor (f1) was below 15, similarity factor (f2) was above 50, and the Rescigno index was almost 0 (Table 12). These values presented the disintegrating properties of isolated mucilage which are similar to that of standard disintegrating agents (MCCP, CCS, and SSG).

Table 12. Statistical factors of CGM compared with MCCP, CCS and SSG as disintegrating agents.

Disintegrants →	CGM vs MCCP		CGM vs CCS		CGM vs SSG	
Formulations code → / Statistical Factors ↓	G1 vs G3 (2%)	G2 vs G4 (3%)	G1 vs G5 (2%)	G2 vs G6 (3%)	G1 vs G7 (2%)	G2 vs G8 (3%)
Difference factor (f1)	2.00	1.49	1.99	1.94	1.03	0.99
Similarity factor (f2)	87.71	89.75	87.51	87.51	92.04	92.04
Rescigno index (ξ)	0.0099	0.0070	0.0114	0.0098	0.0059	0.0057

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3.16. Accelerated stability study

The stability studies at 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH, respectively were maintained for 1, 30, and 90 days as per ICH guidelines. The tablet formulation (F2) was carried out and the results are presented in Table 13. The hardness of tablets was increased slightly, but there were no significant changes in their physical appearance. The drug disintegration time and drug contents of the tablets were analyzed after 1, 30, and 90 days of the storage and there were no significant changes in the disintegration time, and drug content, correspondingly. This indicated that there were no significant changes in the physical as well as chemical characteristics of the formulations. Hence, it can be concluded that the developed formulation was stable and retained the crucial pharmaceutical properties over a period of three months.

Table 13. Accelerated stability studies of F2.

S. No	Temperature	Time in days	Physical change	Hardness Kg/cm^2	Disintegration time (min)	Drug content (%)
1.	25°C	1	No change	4.5	4 min / 22sec	99.4
		30	No change	5.0	5 min / 14sec	98.9
		90	No change	5.0	5 min / 27 sec	98.3
2.	30°C	1	No change	4.5	4 min / 15sec	99.6
		30	No change	5.0	5 min / 32sec	98.7
		90	No change	5.5	6 min / 40sec	98.1
3.	40°C	1	No change	4.5	4 min / 5sec	98.9
		30	No change	5.0	5min / 34sec	98.2
		90	No change	5.0	5min / 48sec	97.8

4. Conclusions

It can be concluded that the mucilage isolated from *Coccinia grandis* showed the presence of carbohydrates, polysaccharides and does not contain starch. It is slightly soluble in hot water, forming a viscous colloidal solution in cold water and insoluble in most of the organic solvents. It has a near neutral pH, which indicated that this mucilage does not irritate the GIT and suitable to formulating an uncoated tablet. The compatibility studies through thermal methods of analysis and FTIR showed that there were no major interactions occurred between the mucilage and the model drug (paracetamol). The *in vitro* toxicity study revealed that this mucilage can be employed safely as a pharmaceutical excipient.

The flow properties of granules prepared with mucilage had good compressibility as that of the granules formulated using starch and PVP. Post compression parameters suggested that tablets formulated with mucilage had better hardness and friability than the tablets prepared with starch and PVP. As the binding concentration of mucilage is increased, the disintegration time also increased, similar to that of the tablets prepared with starch and PVP. The formulations exhibited a better and more consistent release as compared to the standard formulations using starch and PVP (standard binders). Considering all the above parameters, our study evidenced a good potential of the mucilage as a binder for tablet formulations.

The disintegrant properties of the mucilage was studied in comparison with the standard super disintegrants (MCCP, CCS, and

SSG.) The mucilage concentration at 3% and below 3% acted as a super disintegrating agent and exhibited faster tablet disintegration and drug dissolution, thereby helping for an effective therapy and improved patient compliance. Thus, the natural super disintegrant, the mucilage can be effectively used as a suitable disintegrant in formulating solid dosage form of tablet. Further, this work can be extended to *in vivo* toxicity assessment for its safety confirmation, besides predicting its sustaining action.

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References

[1] Homayun, B.; Lin, X.; Choi, H.-J. Challenges and Recent Progress in Oral Drug Delivery Systems for Biopharmaceuticals. *Pharmaceutics*, **2019**, *11* (3), 129. https://doi.org/10.3390/pharmaceutics11030129.

[2] Tiwari, G.; Tiwari, R.; Sriwastawa, B.; Bhati, L.; Pandey, S.; Pandey, P.; Bannerjee, S. K. Drug Delivery Systems: An Updated Review. *Int. J. Pharm. Investig.*, **2012**, *2* (1), 2–11. https://doi.org/10.4103/2230-973X.96920.

[3] Choudhary, P. D.; Pawar, H. A. Recently Investigated Natural Gums and Mucilages as Pharmaceutical Excipients: An Overview. *J. Pharm.*, **2014**, *2014*, 204849. https://doi.org/10.1155/2014/204849.

[4] Al-Khattawi, A.; Mohammed, A. R. Challenges and Emerging Solutions in the Development of Compressed Orally Disintegrating Tablets. *Expert Opin. Drug Discov.*, **2014**, *9* (10), 1109–1120. https://doi.org/10.1517/17460441.2014.941802.

[5] Shanmugam, S. Granulation Techniques and Technologies: Recent Progresses. *Bioimpacts*, **2015**, *5* (1), 55–63. https://doi.org/10.15171/bi.2015.04.

[6] Pal, R. S.; Pal, Y.; Wal, A.; Wal, P. Current Review on Plant Based Pharmaceutical Excipients. *Open Med. J.*, **2019**, *6* (1), 1–5. https://doi.org/10.2174/1874220301906010001.

[7] Markl, D.; Zeitler, J. A. A Review of Disintegration Mechanisms and Measurement Techniques. *Pharm. Res.*, **2017**, *34* (5), 890–917. https://doi.org/10.1007/s11095-017-2129-z.

[8] Kuriyan, R.; Rajendran, R.; Bantwal, G.; Kurpad, A. V. Effect of Supplementation of Coccinia Cordifolia Extract on Newly Detected Diabetic Patients. *Diabetes Care*, **2008**, *31* (2), 216–220. https://doi.org/10.2337/dc07-1591.

[9] Pekamwar, S. S.; Kalyankar, T. M.; Kokate, S. S. Pharmacological Activities of Coccinia Grandis: Review. *J. Appl. Pharm. Sci.*, **2013**, *3* (5), 114–119. https://doi.org/10.7324/JAPS.2013.3522.
[10] Sakharkar, P.; Chauhan, B. Antibacterial, Antioxidant and Cell Proliferative Properties of Coccinia Grandis Fruits. *Avicenna J. phytomedicine*, **2017**, *7* (4), 295–307.
[11] Purwar, S.; Bisht, V.; Banda, N.; Neetu, S.; Purwar, V.; Bisht, N.; Kr, B. Nutritional and Therapeutic Values of Coccinea Grandis: A Review. **2020**, *8*, 1555–1561. https://doi.org/10.22271/chemi.2020.v8.i4o.9832.
[12] Tamilselvan, N.; Thirumalai, T.; Elumalai, E. K.; Balaji, R.; David, E. Pharmacognosy of Coccinia Grandis: A Review. *Asian Pac. J. Trop. Biomed.*, **2011**, *1* (2, Supplement), S299–S302. https://doi.org/https://doi.org/10.1016/S2221-1691(11)60176-7.
[13] Taur, D. J.; Patil, R. Y. Mast Cell Stabilizing, Antianaphylactic and Antihistaminic Activity of Coccinia Grandis Fruits in Asthma. *Chin. J. Nat. Med.*, **2011**, *9* (5), 359–362. https://doi.org/https://doi.org/10.3724/SP.J.1009.2011.00359.
[14] Munasinghe, M. A. A. K.; Abeysena, C.; Yaddehige, I. S.; Vidanapathirana, T.; Piyumal, K. P. B. Blood Sugar Lowering Effect of Coccinia Grandis (L.) J. Voigt: Path for a New Drug for Diabetes Mellitus. *Exp. Diabetes Res.*, **2011**, *2011*, 978762. https://doi.org/10.1155/2011/978762.
[15] McCrae, J. C.; Morrison, E. E.; MacIntyre, I. M.; Dear, J. W.; Webb, D. J. Long-Term Adverse Effects of Paracetamol – a Review. *Br. J. Clin. Pharmacol.*, **2018**, *84* (10), 2218–2230. https://doi.org/https://doi.org/10.1111/bcp.13656.
[16] Prajapati, V. D.; Jani, G. K.; Moradiya, N. G.; Randeria, N. P. Pharmaceutical Applications of Various Natural Gums, Mucilages and Their Modified Forms. *Carbohydr. Polym.*, **2013**, *92* (2), 1685–1699. https://doi.org/10.1016/j.carbpol.2012.11.021.
[17] Hamman, H.; Steenekamp, J.; Hamman, J. Use of Natural Gums and Mucilages as Pharmaceutical Excipients. *Curr. Pharm. Des.*, **2015**, *21* (33), 4775–4797. https://doi.org/10.2174/1381612821666150820100524.
[18] Wadhwa, J.; Nair, A.; Kumria, R. Potential of Plant Mucilages in Pharmaceuticals and Therapy. *Curr. Drug Deliv.*, **2013**, *10* (2), 198–207. https://doi.org/10.2174/1567201811310020006.
[19] Killedar, S. G.; Nale, A. B.; More, H. N.; Nadaf, S. J.; Pawar, A. A.; Tamboli, U. S. Isolation, Characterization, and Evaluation of Cassia Fistula Linn. Seed and Pulp Polymer for Pharmaceutical Application. *Int. J. Pharm. Investig.*, **2014**, *4* (4), 215–225. https://doi.org/10.4103/2230-973X.143128.
[20] Bharath, S.; Reddy, P.; Raja, D.; Raj B V, B.; Madhavan, V. Extraction of Polysaccharide Polymer from Dioscorea Trifida and Evaluation as a Tablet Binder. *Int. J. Pharm. Pharm. Sci.*, **2012**, *4*, 347–352.
[21] Government of India, M. of H. *Pharmacopoeia of India : (The Indian Pharmacopoeia)*; First edition. Delhi : Manager of Publications, 2007.