

Characterization of Psyllium (*Plantago ovata*) Polysaccharide and its Use as a Binder in Tablets

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ABSTRACT

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The aim of the present work was to characterize the mucilaginous components of psyllium seeds and evaluate it as a tablet binder. The seed gum was extracted and characterized in terms of physicochemical properties (swelling index, solubility studies, micromeritics properties, and test for polysaccharides, SEM and loss on drying), spectral analysis (FTIR, NMR, MS, PXRD) and bioburden analysis. Granules containing paracetamol as model drug were prepared by wet granulation using psyllium polysaccharide (PPS) and conventional binding agents (PVP K 30 and HPMC K 100M) separately and evaluated for flowability, strength and compressibility. Swelling index for PPS in phosphate buffer pH 6.8 was found to be 1572 % whereas no swelling was observed in 0.5 M NaOH. The granules were found to have good flowability and compressibility as evident from the angle of repose and Carr's compressibility index. The Heckel constant for PPS was found to be in the range of 0.21-0.65 and yield strength was found to be 1.53-4.62 psi. The tablets were also evaluated for hardness, friability, disintegration time and *in vitro* dissolution. They were found to have satisfactory tablet properties. Thus we may conclude that PPS can be used as a tablet binder and further studies may be undertaken to study its potential use as a multifunctional excipient.

Keywords: psyllium, polysaccharide, Heckel's constant, crushing strength

INTRODUCTION

Excipients are an integral part of pharmaceutical dosage forms and comprise the greatest proportion in dosage units. Knowledge of the composition, function and behavior of excipients is a prerequisite for the successful design, development and manufacture of pharmaceutical dosage forms. Interest in the physical effects and properties of the excipients used in pharmaceutical formulations has increased in recent years due to the awareness of the fundamental effect that excipients can exert on the bioavailability, bioequivalence and stability of formulations. Most of the excipients widely used are obtained from synthetic sources. Although excipients are considered to be pharmacologically inert, it is now well accepted that some have potential for untoward effects. Besides this, problems of incompatibility, stability and high cost are evident in synthetic excipients¹. Globally, there is a renewed interest in investigating drugs and excipients from natural sources, especially from plant and marine sources that include starches obtained from corn, wheat, rice and tapioca² and different types of essential and aromatic oils.

Psyllium is the common name used for the several members of the plant genus *Plantago*¹. The isapghula husk is derived from the dried ripe seeds of *Plantago ovata* Forsskaol. The

seeds of Psyllium are used commercially for the production of mucilage. The mucilage is obtained from the seed coat by mechanical milling of the outer layer of the seeds. It forms a mucilaginous gel by absorbing water. The gel nature and composition of polysaccharide extracted from the seeds of *P.ovata* has been reported in the literature^{2,3}. Psyllium has been reported as a medicinally active natural polysaccharide. It has been used for the treatment of constipation,^{4,5} diarrhoea⁶, inflammatory bowel disease,⁷ obesity in children and adolescents⁸, high cholesterol⁹ and diabetes.¹⁰

The present study focuses on the extraction, characterization and use of the mucilaginous components of the seeds as a tablet binder. Psyllium seeds generally consist of 10% w/w mucilage in the epidermis of the testa together with proteins and fixed oil. The mucilage consists of pentosan and aldobionic acid. Chemically polysaccharide is an arabinosyl (galactosyluronic acid) rhamnosylxylan.

MATERIALS

Paracetamol, psyllium polysaccharide (PPS), PVPK30, HPMC K100M, lactose, pregelatinized starch, magnesium stearate, talc. All raw materials and reagents were sourced locally and were of analytical grade.

METHODS

Extraction of seed gum

Psyllium seeds were soaked in deionized water, kept on water bath at 80°C, with occasional stirring for 2 hrs and allowed to cool to room temperature and kept overnight for soaking. 0.5 M NaOH was added while stirring (200 rpm for 15 min) to

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separate the polysaccharide from seeds and resulting slurry passed through 12# sieve. The psyllium polysaccharide (PPS) was reprecipitated by addition of 2M HCl to the filtrate. The precipitate was washed with deionized water to remove traces of acid and separated by centrifugation at 3000 rpm for 15 min. The residue was dried overnight in a tray drier at 50-60 °C.

Characterization of Polysaccharide

The PPS was characterized for physicochemical properties that included solubility studies, swelling index, micromeritic properties (bulk density, angle of repose and Carr's compressibility index), tests for polysaccharides (Molisch test, Iodine test, Benedict's test and Orcinol Bial test),

SEM and loss on drying. The PPS was also subjected to FTIR, NMR, MS and PXRD. Microbial limit test was carried out by exposing the PPS to ambient conditions for 2 months as per guidelines in IP 1996.

Physicochemical Properties:

Solubility Profile:

The solubility of PPS was evaluated at 37°C in various solvents such as acetone, alcohol, ether, chloroform, dichloromethane, dimethylamine, trimethylamine, diethyl ether, ethyl acetate, DMSO and water. A known weight of the PPS was dispersed in 25 ml of various solvents and kept in an orbital shaker at 37°C for 24 h. The dispersion was centrifuged at 3000 rpm for 45 min and residue was dried and weighed to determine the solubility.

Swelling Index:

Swelling behaviour of PPS as a function of pH was studied. It was allowed to swell for 24 h in solutions of different pH such as 0.1 N HCl, phosphate buffer pH 6.8, deionized water and 0.5 M NaOH.

Compatibility studies:

Compatibility studies of paracetamol were carried out with potential formulation excipients to determine possibility of

any drug-excipient interaction. Excipients studied include PPS, HPMC K100M, PVP K 30, lactose, pregelatinized starch, magnesium stearate, and talc. Drug was mixed with excipients in 1:1 ratio and subjected to elevated temperature and humidity conditions of 40 ± 2 °C / 75 ± 5 % RH for 30 days. IR spectra and drug content of the binary mixtures were obtained at 0 days and 30 days interval.

Preparation of calibration curve of paracetamol:

Paracetamol (50 mg) was dissolved in 10 ml 0.1 N NaOH and subsequently diluted to 100 ml using 0.1 N NaOH. This solution was further diluted with 0.1 N NaOH to produce solutions of 2-20 µg/ml. Absorbances were noted using UV/VIS spectrophotometer (JASCO) at the maximum wavelength of 257 nm using 0.1 N NaOH as blank.

PREPARATION OF GRANULES:

Granules were prepared by wet granulation using PPS and standard binding agents (PVP K30 and HPMC K 100M) separately at concentrations of 1.5, 3, 4.5 and 6 % w/w of tablet (Table1). Pregelatinised starch was added intra- and intergranularly. The required amount of the binder was dispersed in deionized water and sonicated till a homogenous dispersion was obtained. The solid ingredients were mixed in geometric proportions and the binder solution was added until a dough-like mass was formed. The mass was passed through 16# and dried in a hot air oven at a temperature of 60-70 °C for 15 min. The dried granules were again passed through 12# and evaluated for various micromeritic properties.

EVALUATION OF GRANULES

Micromeritic properties:

Angle of repose of the granules was evaluated by fixed funnel method and Carr's compressibility index was determined.¹¹ Crushing strength¹² was determined using the mercury load cell method. The cell was fabricated using modified 50 ml glass syringe. The modification included removal of the tip of the syringe barrel and the top end of the plunger. The barrel was then used as a hollow support and guide tube with

Table1: Formulae of tablets

Ingredient (mg)	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆	F ₇	F ₈	F ₉	F ₁₀	F ₁₁	F ₁₂
Paracetamol	250	250	250	250	250	250	250	250	250	250	250	250
Starch	15	15	15	15	15	15	15	15	15	15	15	15
Psyllium	4.5	9	13.5	18	-	-	-	-	-	-	-	-
PVP K30	-	-	-	-	4.5	9	13.5	18	-	-	-	-
HPMC	-	-	-	-	-	-	-	-	4.5	9	1.35	18
Lactose	20.5	16	11.5	7	20.5	16	11.5	7	20.5	16	11.5	7
Talc	4	4	4	4	4	4	4	4	4	4	4	4
Magnesium stearate	6	6	6	6	6	6	6	6	6	6	6	6

Total weight of the tablet was kept 300 mg.

closefitting tolerance to the plunger. The hollow plunger with one open end served as a load cell in which mercury could be added. A window was cut into the barrel to facilitate placement of granule on the base. The plunger acted as a movable platen and was set directly on the granule positioned on the base. Mercury was introduced from a reservoir into the hollow plunger dropwise until the granule was crushed. The total weight of plunger and mercury was crushing strength of the granule.

Heckel plots¹³:

The Heckel plot is widely used for correlating relative density of the material during compression to the applied pressure. Heckel plots were used to evaluate the compressibility of the granules. The granules (300 mg) were subjected to different compression pressures using hydraulic press (Mini Press-II MT, Make: Rimek). Pressures ranging from 300-1800 psi were used to prepare the compacts. The diameter and thickness of the compacts were determined immediately after compression and after 24h. Hardness was also determined after 24 h. The data was analyzed by PCP Disso software for determining the Heckel's constants and yield pressure.

PREPARATION OF TABLETS

Granules were blended with pregelatinised starch (intergranular disintegrant), talc and magnesium stearate and compressed using rotary tablet machine to a hardness of 4-5 kg/cm² using 8 mm flat punches.

EVALUATION OF TABLETS

Tablets were evaluated for hardness using Monsanto Hardness Tester (Nevtex) and friability using Roche Friabilator. They were also subjected to analysis of disintegration time and *in vitro* dissolution studies in 900 ml phosphate buffer (pH 7.4) using USP Dissolution Apparatus type II at 37°C and 100 rpm. Aliquots were withdrawn at time intervals of 10 min and analyzed using UV Visible spectrophotometer at λ_{max} of 257 nm. Drug content was determined by the previously reported UV spectrophotometric method.

RESULTS AND DISCUSSION

Characterization of PPS:

The dried extract obtained from psyllium seeds was found to have pale buff color and was odorless. The percent yield was found to be 70% w/w. FTIR studies revealed that PPS obtained by various modifications in the extraction procedure, such as different alkalis (NaOH / Na₂CO₃) for extraction and different reprecipitating agent (alcohol / HCl / acetic acid), were identical. Hence, extraction by NaOH and reprecipitation by HCl was kept as standard method for scale up process. PPS was found to be soluble in strong ammonia

solution and dimethyl sulfoxide after 15 min sonication at room temperature. However it was insoluble in acetone, alcohol, ether, chloroform, dichloro methane, dimethyl amine, trimethyl amine, diethyl ether and ethyl acetate. It was found to form a gel when exposed to aqueous environment such as water and buffers. Swelling profile of PPS was evaluated (Figure 1). Maximum swelling was found in phosphate buffer pH 6.8 with 1572 % swelling, whereas no swelling was observed in 0.5 M NaOH. In water nearly 1200 % swelling was observed. The swelling profile of PPS alludes to its potential for use as a hydrogel and as a release retardant in sustained release tablet formulations. Further studies may be done to evaluate these properties of PPS. The micromeritic properties of PPS were evaluated (Table 2). Micromeritic studies revealed good flow properties of PPS and were suggestive of its possible use as a directly compressible excipient. Orcinol bial test revealed the presence of pentose sugars, whereas Benedict's and Fehling's test revealed the absence of reducing sugars. Presence of arabinose and xylose were further confirmed by formation of characteristic osazone structures (Table 3). LOD was performed and was found to be 0.18% w/w, which was within official limit of 0.5%. The SEM micrographs (Figure 2) revealed needle shaped crystals which corroborated the crystalline nature of PPS. FTIR studies (Figure 3) revealed various characteristic peaks of OH, C=O, O, and CH₂. NMR spectra further confirmed the presence of OH and CH₂ groups. Mass spectra reveal the cyclic structure of the monomers. The PXRD study (Figure 4) identified the crystalline nature of the PPS with distinctive peaks evident at 2 θ angles of 30, 45, 55, 75 and 85°. Microbial limit test was performed for PPS as per IP 1996

Fig. 1: Swelling profile of PPS

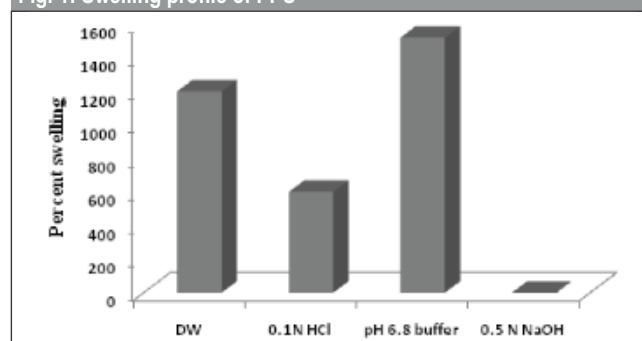


Table 2: Micromeritic properties of polysaccharide

Sr. No.	Micromeritic property	Observation
1	Bulk density	0.857 g/cc
2	Tapped density	1.142 g/cc
3	Carr's index	0.33
4	Angle of repose	29.51°

N=3

to ensure that the polysaccharide does not support microbial growth. It was found that bioburden of *Escherichia coli*, *Salmonella species*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* were within official limits of 300 cfu/g.

Compatibility studies:

Compatibility of paracetamol with potential formulation excipients was carried out to determine possibility of any drug-excipient interaction/incompatibility. UV Spectrophotometric and FTIR analysis showed no evidence of any interaction between drug and studied excipients.

EVALUATION OF GRANULES

Micromeritic properties:

The granules were studied for their flow properties. From the observations it was concluded that the granules made by using the polysaccharide had flowability comparable to that of the granules prepared by using standard binders such as HPMC and PVPK30. The angle of repose of all granules ranged between 24-27°. The study of Carr's index further supported the results for angle of repose. The results for crushing strength (Table 4) showed that there was a rise in crushing strength of granules as the concentration of polysaccharide increased from 1.5% - 4.5%. These results were comparable

with that of HPMC. However crushing strength of granules containing 6% polysaccharide was reduced which was again similar to that of HPMC. In case of PVPK30 granules a decrease in crushing strength was observed for concentrations of 1.5%, 3% and 4.5% and there was a rise for the concentration of 6%. We can conclude from these observations that the granules prepared with HPMC and PPS as binders had comparable crushing strengths which increased with increase in concentration and decreased at higher concentrations. This could be attributed to the higher viscosity of the dispersions which precluded uniform mixing of the binder with the excipients.

Heckel plots:

Process of tableting involves application of massive compressional forces which induce considerable deformation in the solid particles. With many pharmaceutical solids these forces are large enough to exceed the elastic limit of the solid. Plastic deformation and/or brittle fracture results in generation of new, clean surfaces, which when pressed against one another undergo cold welding (fusion bonding if the material melts). In 1961, Heckel postulated a linear relationship between the relative porosity of a powder and applied pressure. Slope of linear regression the Heckel constant, is a material dependent parameter inversely

Table 3: Tests for polysaccharide			
Sr.No.	Test	Observation	Inference
1	Molisch test	Positive	Carbohydrates present
2	Iodine test	Positive	Nonreducing polysaccharide present
3	Ruthenium red test	Positive	Mucilage present
4	Benedict's test	Negative	Monosaccharide absent
5	Fehling's test	Negative	Reducing sugars absent
6	Orcinolbial test	Positive	Pentoses present
7	Osazone test	Characteristic structures obtained	Xylose and Arabinose confirmed

Fig. 2: SEM micrographs A) 1000X B) 2000X

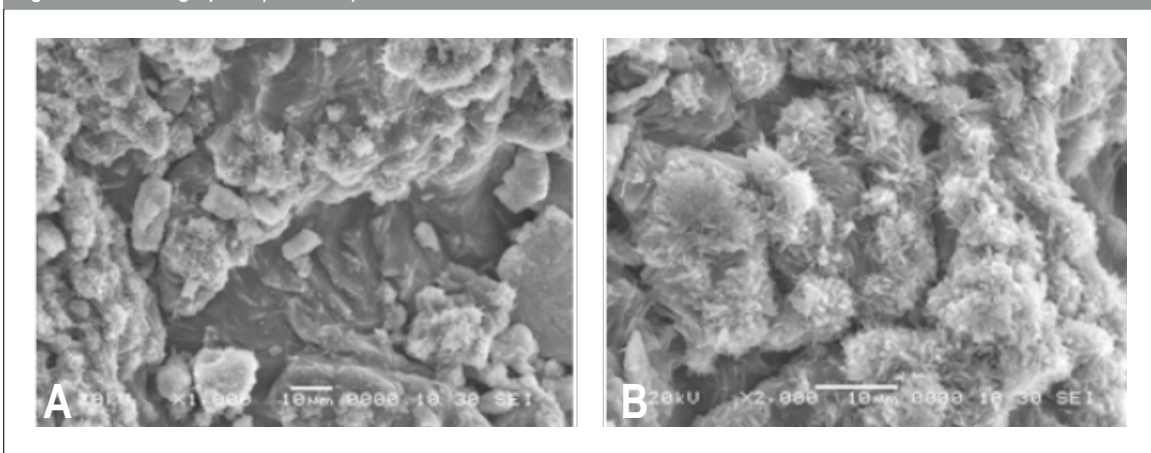


Fig. 3: FTIR Spectrum of PPS

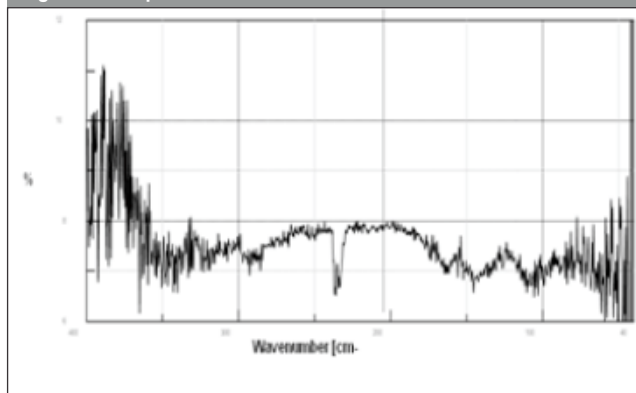
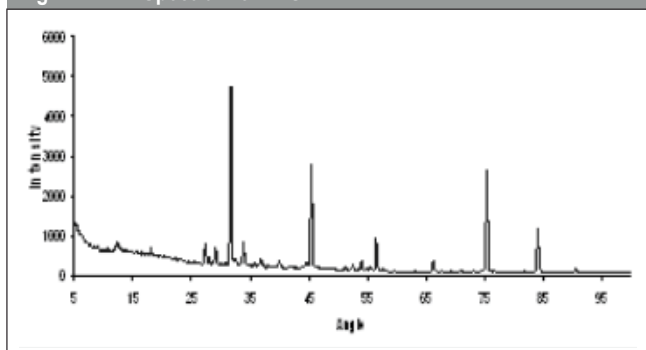


Fig. 4: PXRD Spectrum of PPS



proportional to the mean yield pressure. Higher yield pressure (Py) is indicative of soft and pliable material. In case of PPS, the Py was found to decrease with increasing concentration implying plastic deformation at the low pressure. At low PPS concentration material was soft and plastic in nature giving rise to high yield pressure. At high concentration of PPS i.e. 4.5% and 6%, Py was low indicating brittle fracture which thus leads to a denser packing of the granules (Table 5 & Fig. 5).

Evaluation of tablets

The hardness of all the formulations was found between 4-5 kg/cm². The tablets were tested for friability and from the results obtained we can conclude that the friability of tablets (Range: 0.55-0.89) obtained by using HPMC and PPS were comparable. Tablets prepared by PVPK30 as binder had higher friability. These results support the disintegration time readings. We can conclude that the tablets obtained by using PPS as binder was neither too hard nor easily dispersible or friable. The disintegration time of tablets prepared using PPS as binder ranged from 10-15 min with an obvious increase seen with increase in PPS concentration. Similar results were obtained with the tablets containing PVPK 30 and HPMC as binder. These findings are in accordance with results of crushing strength. Tablets containing HPMC had higher disintegration time and those containing PVPK30 had very low disintegration time for concentration of 1.5% and 3% and

Fig. 5: Heckel plots for PPS for A] 1.5% B] 3% C] 4.5% D] 6%

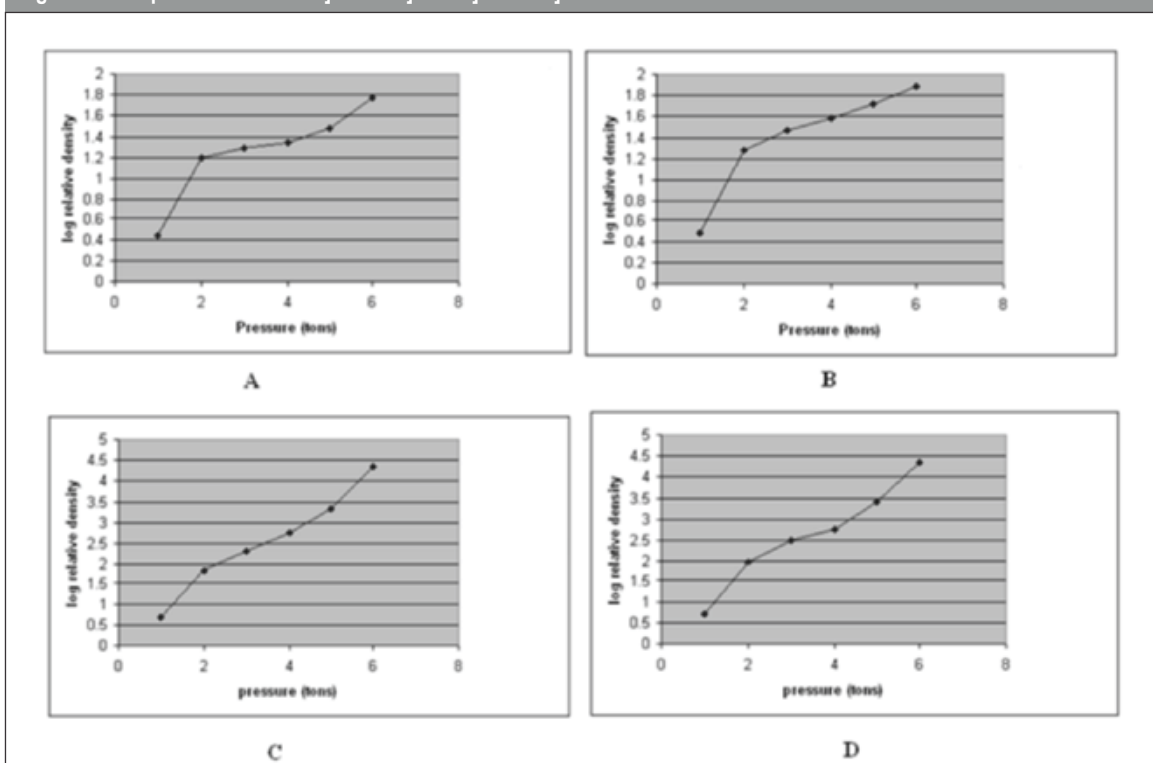


Table 4: Crushing strength of granules in grams of mercury

Binder	Concentration of binder			
	1.5 %	3 %	4.5 %	6 %
HPMCK100M	95.52 ± 26.86	95.52 ± 11.42	179.33 ± 24.81	88.5 ± 14.85
PVPK	3089.93 ± 37.99	82.75 ± 16.91	69.844 ± 3.94	73.66 ± 9.35
Psyllium	83.76 ± 14.63	87.01 ± 5.52	143.42 ± 19.18	85.43 ± 10.83

n=20

Table 5: Heckel constants of granules

Sr No	Conc.	PPS		PVP K30		HPMC	
		He*	Py#	He	Py	He	Py
1	1.5%	0.21	4.62	0.33	2.99	0.36	2.73
2	3%	0.24	4.13	0.33	2.96	0.32	3.06
3	4.5%	0.66	1.49	0.30	3.23	0.20	4.93
4	6%	0.65	1.53	0.36	2.75	0.19	5.00

* Heckel constant

Yield pressure

comparable with that of polysaccharide for 4.5% and 6% concentration. The percent drug content in all tablet formulations containing different percentages of binder were in the range of 95-105.0 % of paracetamol. The *in vitro* dissolution profile suggested that the drug release profile complied with the pharmacopoeial standards for immediate release tablets, i.e. complete drug release within 30 min. The drug release profile followed Peppas model.

CONCLUSION

Psyllium polysaccharide obtained from the seeds of *Plantago ovata* was found to have satisfactory binder properties which were comparable with that of HPMC. The Heckel's constants and yield pressure indicated varying compaction behavior at different binder strengths. The granules were also found to have sufficient mechanical strength as evident from the results of crushing strength. We can thus conclude that psyllium polysaccharide can be used as a tablet binder and future work may be directed at investigation of its use as a multifunctional excipient.

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