Formulation And Evaluation of Paracetamol Tablet Using Konjac Glucomannan as Natural Halal Binder

ABSTRACT

Introduction: Discovery and development of novel halal excipients in tablet formulation have led to continuous interest in drug delivery research. In this study, Konjac Glucomannan, a polysaccharide derived from the tuber of *Amorphophallus konjac,* was used as a halal binder in the formulation of paracetamol tablets. **Objective:** This study aims to formulate and evaluate paracetamol tablets using konjac glucomannan as a halal binder. **Methodologies:** Paracetamol tablets were formulated with different concentrations (5%, 10%, 15%, 20%) of KGM using the wet granulation method. The formulated paracetamol granules and tablets were subjected to different quality control tests. **Results:** All four formulation granules passed the pre-compression test, indicating good to passable powder flowability. The weight variation, hardness, thickness, and disintegration test results for all four formulations were within the USP limit except for the friability test. Only tablets with 20% KGM passed the test. **Conclusion:** 20% KGM shows good tablet binding properties compared to 5%, 10%, and 15% KGM. Hence, paracetamol tablets formulated with higher KGM as a binder produce paracetamol tablets with good physical and mechanical properties.

Keywords: Konjac Glucomannan; paracetamol tablet; natural binder; halal

INTRODUCTION

The discovery and development of novel halal excipients in tablet formulation have led to continuous interest in drug delivery research. This has been widely observed in pharmaceutical companies' use of novel excipients to formulate an improved version of dosage forms. Dosage formsare available in various types. The most common and widely used dosage forms are liquid and solids, such as tablets, capsules, and solutions [1].

According to “The Global Halal Pharmaceutical Market 2016”, Halal medicines refer to drugs derived from Halal sources and do not contain any prohibited ingredients deemed unlawful under Islamic guidelines. Hence, due to the unacceptability of non-halal binders in tablet formulation by specific consumers, including Muslims, Hindus, vegetarians and Jews, there is a growing interest in producing tablets derived from plant sources. The term Halal binder is used specifically to address the increasing demand for halal-certified pharmaceutical products in Muslim-majority regions. While vegan or natural binders may appeal to a broader audience, they do not necessarily meet the strict halal certification requirements. This distinction

is critical for consumers in Muslim markets, where trust in halal-certified products is a key purchasing factor. Natural polymers have proven to be a good candidate as binding agents in recent years due to their strong binding properties and inexpensive, sustainable supply [2]. Hence, this study will be based on the formulation of tablets using Konjac Glucomannan as an alternative to a non-halal binder [3].

Konjac glucomannan is a polysaccharide derived from the tuber of Amorphophallus konjac. KGM is a key hemicellulose component group in plant cell walls and can be used in pharmaceutical solid dosage form preparations. It has adhesive properties and swells to form colloids when interacting with water. The adhesive properties can be used as fillers, disintegrants, and tablet binders [4]. KGM is a heteropolysaccharide structure consisting of a D-mannose and D-glucose backbone linked by β-1, four glycosidic linkages at a molar ratio of 1:1.6 - 1:1.4, where the glucose and mannose ratios vary depending on the plant source. Additionally, acetyl groups are randomly positioned at the C-6 position of the sugar units along the molecule, roughly one every 20 sugar residues, and certain short side branches at the C-3 position of mannoses. Besides, KGM is also known to have a molecular weight ranging from 500 k to 2000 k [5].

Acetaminophen, known as paracetamol, is a popular over-the-counter painkiller and antipyretic agent [6]. Paracetamol is dispensed worldwide under various dosage forms, brand names and strengths. Furthermore, paracetamol is a white crystalline powder, a weak acid with a pKa of 9.5 and sparingly soluble in water with an estimated 23.7 mg/mL solubility at 37°C. Besides, peak plasma concentration of paracetamol is achieved within 0.17–1.2 hrs [7]. The mechanism of action of paracetamol is that it reduces fever and pain by reducing the production of prostaglandins, which are known as pro-inflammatory chemicals [6].

MATERIALS AND METHODS

Chemicals and Instruments

Konjac glucomannan powder purchased from Shoppe (250 g), distilled water, Paracetamol powder purchased from R&M Chemicals (500 g), lactose purchased from R&M Chemicals (250 g), corn starch purchased from R&M Chemicals (100 g), magnesium stearate purchased from R&M Chemicals (10 g), talc purchased from R&M Chemicals (10 g).

Tablet punching machine, oven, sieve mesh No. 12 and No. 20, mortar and pestle, weigh boat, weighing scale, hardness tester (Electro lab, EBT-2PL), friability tester (Electro lab, Dual Drum Friabilator), disintegration test apparatus (USP disintegration test apparatus, Electro lab), tapped density tester (USP tapped density apparatus, Electro lab).

Methodology

Preparation of granules and tablets

Tablets were prepared using a wet granulation technique and different concentrations of KGM as a binder. The concentration of KGM was varied from 5%, 10%, 15%, 20% (w/w). All ingredients shownin Table 1 were mixed at initial blending except for half of the disintegrant, lubricant and glidant. Distilled water was used as a granulating agent to form a wet mass. The wet mass was passedthrough 12 mesh screens, and granules were dried at 50ºC for 2 hr. The dried granules were sized through 20 mesh screens. Finally, the remaining half of the disintegrant, lubricant and glidant were added and mixed for 2-3 minutes. The granules were compressed using a single-punch tablet compression machine. The total weight of the tablet was 300 mg. However, 20% excess was added to each ingredient in Table 1 to compensate for the mechanical loss [8].

Formulations	**Ingredients (mg)**					
	API Paracetamol	**Binder** KGM	**Filler** Lactose	**Disintegrant** Corn starch	**Lubricant** Magnesium stearate	**Glidant** Talc
F1	180	18	118.8	36	3.6	3.6
F2	180	36	100.8	36	3.6	3.6
F3	180	54	82.8	36	3.6	3.6
F4	180	72	64.8	36	3.6	3.6

Table 1: Paracetamol tablet formulation with different concentrations of binder.

Evaluation of granules

Angle of repose

The angle of repose is measured by allowing 20 g of granules from each batch to flow through a funnel at a fixed height of 2 cm, and the diameter of the flowed granules are recorded. This test is repeated three times, and the mean is recorded. The formula to determine the angle of repose is below [9].

$$\theta = Tan - 1\left(\frac{h}{r}\right)$$

θ = Angle of repose
$\boldsymbol{h}$ = Height of the flowed powder
$\boldsymbol{r}$ = radius of the flowed powder

Tapped and bulk density

The bulk density of the 20g granules from each batch is measured by pouring them into a 100 mL measuring cylinder and recording their initial volume. The measuring cylinder was tapped to a constant volume using a tapped density tester (USP tap density apparatus, Electro lab)according to the USP method II [9]. The bulk and tapped densities were calculated using the formulas below.

$$\textbf{Bulk Density (g/mL)} = \left(\frac{Weight\ of\ sample}{Initial\ volume}\right)$$

$$\textbf{Tapped Density (g/mL)} = \left(\frac{Weight\ of\ sample}{Tapped\ volume}\right)$$

Hausner's ratio

Hausner's ratio, which shows the ratio of tapped density to bulk density, reveals the flow characteristics of the powder. The flow characteristic improves when Hausner's ratio decreases. Hausner's ratio is calculated using the following formula [9].

$$\textbf{Hausner's Ratio} = \left(\frac{Tapped\ Density}{Bulk\ Density}\right)$$

Carr's index

Carr's index was determined by multiplying the difference between tapped and bulk densityby 100. Carr's index is calculated using the following formula [9].

$$\textbf{Carr's Index} = \left(\frac{Tapped\ Density - Bulk\ Density}{Tapped\ Density}\right)\ x\ 100\%$$

Evaluation of tablets

Weight variation test

A weight variation test is carried out to check the uniformity of the paracetamol tablet content and to ensure that each tablet has an adequate amount of the drug. 20 tablets from each formulation were chosen randomly and weighed separately with an automated balance. The mean and standard deviation were calculated. The percentage of weight variation was calculated using the following formula [10].

$$\%\ \textbf{of weight variation} = \left(\frac{Individual\ weight - Average\ weight}{Average\ weight}\right)\ x\ 100$$

According to USP, the tablet passes the test if not more than two of the individual masses differ from the average mass by more than the percentage deviation stated in Table 2.

Table 2: USP limits for weight variation test for uncoated tablets

Average Weight (mg)	Percentage Deviation (%)
130 or less	10
130 – 324	7.5
More than 324	5

Friability test

A friability test is conducted to evaluate the ability of the tablets to withstand abrasion in packing, handling, and transporting. 20 tablets were selected randomly from each formulation, and friability was measured using an Electro lab, Dual Drum Friabilator. After 4 minutes, the tablets are weighed again, and any breaks are observed. The percentage loss in weight is calculated using the formula below [10]. According to USP, after 100 revolutions, the acceptable range for tablet weight loss is within 0.5% - 1%.

$$\%\ \textbf{Friability} = \left(\frac{Iw - Fw}{Iw\ x\ 100\%}\right)$$

% Friability = Percentage of friability
Iw = Total initial weight of tablets
Fw = Total final weight of tablets

Hardness test

A hardness test is conducted to determine tablets' ability to withstand the force applied to them. Ten tablets were selected randomly, and the crushing strength was tested using a digital hardness tester machine (Electro lab, EBT-2PL). The mean hardness of the tablet was calculated,and the standard deviation was determined [10].

Thickness test

A thickness test is conducted to ensure the quality of the tablet, as it can affect consumers' acceptance. Ten tablets were selected randomly and carefully placed between the digital hardness tester machine (Electro lab, EBT-2PL) anvils or jaws, ensuring the tablet was centred and properly aligned to avoid measurement inaccuracies. The tablet thickness is displayed on the hardness tester machine's screen. The mean thickness of the tablet was calculated [10].

Disintegration time test

A tablet disintegration time test is performed to determine that the drug ingredient is fully available for dissolution and absorption from the gastrointestinal system. Six tablets from each formulation are chosen randomly and placed in the basket-rack assembly, which is repeatedly lowered 30 times per minute into a thermostatically regulated fluid bath at 37.2°C. The average time required for all tablets to dissolve is recorded. According to USP, the permissible disintegration time for uncoatedtablets should be within 15 minutes [10].

Statistical Analysis

Experiments were conducted in triplicate, and the data are expressed as mean values ± standard deviation (SD). Analysis of variance (ANOVA) was performed using IBM SPSS Statistics 29.0 software, and significant differences in tabletting properties for each formulation were detected by Tukey's test ($p < 0.05$).

RESULTS AND DISCUSSION

Evaluation of granules

The flow property of all the batches (F1-F4) was found to be good with the angle of repose 29.39°, 27.45°, 27.88°, and 27.32° respectively. The bulk density of (F1-F4) batches prepared by varying concentrations of Konjac Glucomannan as a binder was found to be 0.548, 0.588,0.561 and 0.547 gm/ml, respectively, and tapped density was found to be 0.632, 0.710, 0.696 and 0.695 gm/ml, respectively. The Carr's index of batches (F1-F4) was observed as good for F1, fair for F2 and F3 while passable for F4 with Carr's index of 13.29%, 17.18%, 19.31% and 21.29%, respectively,and Hausner's ratio was found to be good for F1, fair for F2 and F3 and passable for F4 with the ratio of 1.15, 1.21, 1.24 and 1.27 respectively.

Table 3: Pre-compression evaluation of paracetamol granules.

Prefromulation Test	**Formulations**			
	F1	**F2**	**F3**	**F4**
The angle of repose (°)	29.39	27.45	27.88	27.32
Bulk density (g/ml)	0.548	0.588	0.561	0.547
Tapped density (g/ml)	0.632	0.710	0.696	0.695
Carr's Index (%)	13.29	17.18	19.31	21.29
Hausner's Ratio	1.15	1.21	1.24	1.27

Based on Table 3, all four formulations have an angle of repose below 30°, which indicates excellent flowability despite having different concentrations of binders. This study shows that the angle of repose decreases as the binder concentration increases. The angle of repose for all the formulations indicates a free-flowing property of granules. This excellent flowability of granules is essential for acceptable weight variation and content uniformity of tablets [11]. The powder blend's bulk density and tapped density do not differ much, indicating that the powder is not bulky. At 5% and 20% binder concentration, granules prepared with KGM had comparatively lower bulk and tapped density than 10% and 15%. This occurs when the granules occupy larger volumes than smaller granules that occupy the smaller volume [12]. Carr's index and Hausner's ratio are within the acceptable range for all 4 formulations, indicating the free-flowing properties of the granules. A slight difference observed in the flow property results between Carr's index, Hausner's ratio and angle of repose is possibly due to the quality of the measurement and scale [13]. Hence, the pre-compression test results prove that all four KGM granules are suitable for formulating paracetamol tablets.

Evaluation of tablets

Tablet evaluation test	Formulations			
	F1	**F2**	**F3**	**F4**
Weight variation test (mg)	300.4 ± 5.194	302.2 ± 5.896	303.4 ± 5.315	300.6 ± 6.117
Friability test (%)	4.3	1.3	1.2	1.0
Hardness test (kg)	6.205 ± 0.736	6.484 ± 1.018	6.600 ± 1.189	7.287 ± 0.955
Thickness test (mm)	4.199 ± 0.371	4.222 ± 0.128	4.349 ± 0.269	4.300 ± 0.332
Disintegration time test (min)	1.973 ± 0.413	1.157 ± 0.073	1.338 ± 0.146	6.855 ± 2.434

Table 4: Paracetamol tablet evaluation test

A batch of tablets with an average weight within 130 – 324 mg complies with the USP requirement if nomore than two individual weights deviate from ±7.5%. Table 4 shows that all the batches passed the weight variation test; none had two tablets outside the limit. It was indicated that there was no statistically significant difference in the average weight of the tablets between all the formulations ($p>0.05$). The results of the weight variation test are within the limit as stated in USP, which indicates a uniform distribution of active ingredients within each batch of tablets [14]. Besides, the uniform weight of the tablets indicates a uniform filling of the die during tablet compression [15].

The friability value for uncoated tablets should be within 0.5% - 1%. The friability value of formulation 4 lies within the acceptance criteria as stated in USP, while formulations 1,2 and 3 exceed the acceptance criteria (>1.0%). An increase in the concentration of KGM as a binder causes a marked decrease in tablet friability [16]. As the content of KGM in thetablet increases, the tendency of the particles to stick together increases, resulting in more compact,denser granules with reduced porosity [17]. At 20% KGM, the friability of the tablets is at the borderline acceptable limit of 1.0%. To ensure that the tablet remains within acceptable limits and to improve tablet integrity further, it is suggested that higher concentrations of KGM be evaluated. Formulating with 25% and 30% KGM will allow to assess its impact on friability, ensuring a robust formulation with improved mechanical strength. This additional evaluation will help determine the optimal KGM concentration for maintaining tablet integrity and acceptable friability levels [21].

Capping was observed in formulation 1 tablets, as shown in Figure 1, which directly led to a significant increase in tablet friability. The possible reason for capping in formulation 1 is the lower amount of binder [18].

Figure 1: Tablet capping observed in formulation 1

According to USP, the acceptable range of tablet hardness is between 4 - 8 kg for uncoated tablets. Comparatively, the hardness value results in the table show that paracetamol tablets formulated with 20% KGM as the binder produced the highest hardness value than other formulations. This indicatesthat 20% KGM has the highest binding capacity among the 4 concentrations. A previous study reported that an increased concentration of sida acuta gum as a binder causes increased particle bonding, thereby increasing tablet hardness [16]. Therefore, tablets formulated with a higher KGMconcentration would offer greater resistance to shock and abrasion due to the stronger intra-particulate bonding strength of the granules [12].

The thickness test results showed a significant difference for all four tablets ($p < 0.05$). The tablet's thickness varied from 4.199 mm to 4.349 mm with no change in weight due to the pressure difference applied to the tablets and the speed of compression [13]. Besides, tablet thickness is directly related to tablet hardness. When the tablet is too thin, it can easily break, while if it is too thick, it will cause difficulty swallowing. Therefore, maintaining the appropriate amount of pressure applied to the tablet during compression helps to produce tablets with uniform thickness [19].

All the tablets formulated with different concentrations of konjac glucomannan disintegrated within the USP specifications of 15 minutes for uncoated tablets, as shown in Table 4. Although all four formulations disintegrate within the USP specification, the mean disintegration time of F1, F2, and F3 are shorter compared to F4. The longer disintegration time noted in tablets with 20% KGM could be closely linked to decreased liquid penetration into the tablets as tablet hardness increases at higher binder concentrations [16]. Moreover, the disintegration time of tablets formulated with KGM could be influenced by the high swelling index properties of KGM. Besides, a previous study reported that a high swelling index of Melia azedarach gum enables it to break up in the gastrointestinal tract to release the active pharmaceutical ingredient [20]. Hence, the swelling index of KGM makes it a good candidate as a tablet binder.

CONCLUSION

The industry has made great strides in discovering alternatives to non-halal excipients in tablet formulations and will continue expanding rapidly. In recent years, interest in tablet formulations using natural materials has been growing due to their various advantages, such as being readily available, cheaper, less toxic, biodegradable, and biocompatible due to their natural origin.

In conclusion, based on the results obtained by the several quality control tests conducted, among the four different concentrations, good paracetamol tablets can be formulated using 20% KGM, as they show good binding properties. However, 5%, 10%, and 15% KGM may not be recommended as a binder for the formulation of paracetamol tablets because of their high friability. It is also suggested that a higher concentration of KGM be evaluated for its binding properties in future studies.

For future studies, it's recommended to research the use of Konjac glucomannan in formulating orally disintegrating tablets (ODT). As revealed in this research, a lower concentration of Konjac Glucomannan shows a fast disintegration time within 3 minutes; this time range complies with the USP requirement for ODT disintegration time. Hence, using KGM as a disintegrant in formulating ODT would be a great choice. Additionally, conducting a comparative dissolution study of conventional binders such as HPMC and PVP would be beneficial as binding agents significantly influence the dissolution profile. By doing so, we can determine if KGM provides a slower, controlled release or rapid dissolution, influencing bioavailability and therapeutic effectiveness.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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