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 a 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 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 friability test only tablets with 20% KGM passed the test. **Conclusion:** 20% KGM shows good tablet binding properties compared to 5%, 10%, 15% KGM. Hence, paracetamol tablet formulated with higher amount of KGM as binder produces 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 a continuous interest in drug delivery research. This has been widely observed where pharmaceutical companies use novel excipients to formulate an improved version of dosage forms. Dosage forms are 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 as unlawful under Islamic guidelines. Hence, due to the unacceptability of non-halal binders in tablet formulation by certain consumers, including Muslims, Hindus, vegetarians and Jews, there is a growing interest in producing tablets derived from plant sources. 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 interact with water. The adhesive properties are used as fillers, disintegrants, and tablet binders [4]. KGM is a heteropolysaccharide structure consists of a D-mannose and D-glucose backbone linked by β-1, 4 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, 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 hr [7]. The mechanism of action of paracetamol is 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 by wet granulation technique using different concentrations of KGM as binder. Concentration of KGM was varied from 5%, 10%, 15%, 20% (w/w). All ingredients shown in table 1 were mixed at initial blending except for half amount of disintegrant, lubricant and glidant. Distilled water was used as granulating agent to form a wet mass. The wet mass was passed through 12 mesh screen and granules were dried at 50 ºC for 2 hr. The dried granules were sized through 20 mesh screen. Finally, the remaining half amount of disintegrant, lubricant and glidant were added and mixed for further 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 listed in Table 1 to compensate for the mechanical loss [8].

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

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

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].

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

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

Tapped and bulk density

Bulk density of the 20g granules from each batch is measured by pouring the granules into a 100 mL measuring cylinder and recording the granules' 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.

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

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

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 density and bulk density by 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 Electro lab, Dual Drum Friabilator. After 4 minutes, the tablets are weighed again, and any breaks up 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 the ability of tablets to withstand the force applied to them. 10 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. 10 tablets were selected randomly and measured individually using the hardness tester machine (Electro lab, EBT-2PL). 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 uncoated tablets should be within 15 minutes [10].

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 the 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
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 important 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 that of 10% and 15%. Basically, this occurs when the granules occupy larger volumes than smaller granules that occupy the smaller volume [12]. The Carr's index and Hausner's ratio are within the acceptable range for all 4 formulations indicating free-flowing properties of the granules. Slight difference observed in the flow property results between Carr's index, Hausner's ratio and angle of repose is possibly due to their 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

Table 4: Paracetamol tablet evaluation test

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

A batch of tablets with an average weight within 130 – 324 mg comply to USP requirement if no more than two individual weights deviate from ±7.5%. Table 4 shows that all the batches passed the weight variation test; none of the batches had two tablets that were outside the% limit. The results of weight variation test are within the limit as stated in USP, which indicates a uniform distribution of active ingredients within each batch of the tablets [14]. Besides, uniform weight of the tablets indicates a uniform filling of the die during tablet compression [15].

Friability value for uncoated tablets should be within 0.5% - 1% according to the USP. The friability value of formulation 4 lies within the acceptance criteria as per stated in USP, while formulation 1,2, and 3 exceeds the acceptance criteria (>1.0%). Increase in the concentration of KGM as a binder causes a marked decrease in tablet friability [16]. As the content of KGM in the tablet increases, the tendency of the particles to stick together increases, resulting in more compact, denser granules with reduced porosity [17]. 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 due to the lower amount of binder [18].

Figure 1: Tablet capping observed in formulation 1

The acceptable range of tablet hardness is between 4 - 8 kg for uncoated tablets according to USP. Comparatively, the hardness value results in table shows that paracetamol tablets formulated with 20% KGM as the binder produced the highest hardness value than other formulation. This indicates that 20% KGM has the highest binding capacity among the 4 concentrations used. Previous study reported that an increased concentration of sida acuta gum as a binder causes increased particle bonding, thereby increasing tablet hardness [16]. Therefore, tablet formulated with a higher KGM concentration 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 tablets thickness varied from 4.199 mm - 4.349 mm due to the difference in the amount of pressure applied to the tablets during 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 in swallowing. Hence, it is important to follow the thickness limit to produce trouble-free packaging [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, 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 travelled a long way in discovering various alternatives to substitute non halal excipient for formulation of tablets and will continue to expand at a rapid pace. In recent year, the interest in formulation of tablets with the use of natural materials are growing due to its various advantages like 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 it shows good binding properties. However, 5%, 10%, 15% KGM may not be recommended as a binder for formulation of paracetamol tablets because of high friability.

For future studies, its recommended to conduct research on 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 which is within 3 minutes; this range of time complies with the USP requirement for ODT disintegration time. Hence, using KGM as a disintegrant in formulating ODT would be a great choice.

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