Preparation and Evaluation on Paracetamol Tablets Using Goatskin Gelatin as a New Binder

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Abstract

Halal gelatin extracted from goatskin could be used as a new excipient in pharmaceutical dosage forms. This study was to determine the potency of gelatin extracted from goatskin as a binder on paracetamol tablets using wet granulation process with 2, 3 and 4% concentration ranges. As a comparison, tablets were formulated using bovine gelatin at the same concentration level. The results showed that weight variation, thickness uniformity and hardness value have met the requirements. Here, the paracetamol tablets using goatskin gelatin as a binder had better friability value, faster disintegration time and easier dissolution than the comparison ($p < 0.05$). Comparative test result showed increasing the concentration of gelatine caused the hardness value to go up, the disintegration time to take longer, and the tablet friability value to decrease ($p < 0.05$). The best tablets were produced with the 3% concentration of goatskin gelatine with the following evaluation results: the hardness value of 15.07 ± 0.67 Kp, the disintegration time of 3.71 ± 1.00 minutes and the friability value of $0.62\% \pm 0.89$ respectively. The concentration of paracetamol in the 30th-minute dissolution test was equal to $99.78 \pm 0.94\%$. The goatskin gelatin was very promising as a good binder using the wet granulation process.

Introduction

Binder is a main ingredient used in formulating tablets to upgrade powder cohesiveness in order to improve the powder flowability and compaction properties¹. The flowability properties are very significant to produce tablets with consistent weight and uniformity of drug content. The compaction properties are important to produce physical stability and compaction of tablets².

Gelatin was one of binder which was commonly used in pharmaceutical preparations. Gelatin was used as a dry binder for direct compression of tablets or applied as a binding solution for tablets produced by wet granulation process. Here, Gelatin has good dispersion as a binder solution and significant degree of binding. As the result, when it is used as a binder in formulation of paracetamol tablets, it produces the tablets with good hardness and mechanical strength³.

Gelatin can be obtained from mammals, fish and insects. However, the commonly used gelatin generally comes from mammals, bovine and porcine⁴. Porcine gelatin is forbidden (haram) for Muslim consumers. Consequently, any products using such ingredient are also considered haram. At present, halal products (the ones which are allowed for Muslim to consume) are an important concern in pharmaceutical industries, considering that Muslim consumers really take halal products into account. In Indonesia, for instance, the government has even issued the Law on Halal Product Guarantee that requires the products marketed in Indonesia to have already passed halal certification, including the products from pharmaceutical industries such as pharmaceutical products, supplements, vitamins, cosmetics, and traditional/herbal medicine products.

Zilhadia et al. (2018) have discovered a promising finding on gelatin generated from goat skin which is very potential to use as a new halal excipient in pharmaceutical dosage forms⁵. Basically, goat skin

gelatin has physical properties that are not much different from bovine gelatin. Present study an evaluation of paracetamol tablets using goatskin gelatin as a binder prepared by wet granulation process was evaluated as compared to bovine gelatin.

Materials And Methods

Materials.

Goatskin as a source of gelatin purchased at Ciputat Slaughterhouse, distilled water, sodium sulfide (VWR Chemicals, Belgium), calcium hydroxide (Merck, Germany) and Hydrochloride acid (Merck, Germany). The paracetamol tablets were formulated using the following materials: paracetamol (Anqiu Lu'an Pharmaceutical, China), amylum (PIM Pharmaceuticals, Indonesia), lactose monohydrate (DFE Pharma, Germany), goatskin gelatin or bovine gelatin (Rousselot, USA), sodium starch glycolate (Yung Zip Chemical, Taiwan), magnesium stearate (FACI Asia Pacific, Singapore)) and colloidal silicon dioxide (Cabot Blue Star Chemical, China).

Preparing Goatskin Gelatin.

The preparation to extract gelatin from goatskin referred to the method applied by Zilhadia *et al.* (2018)⁵. The hair from the goatskin was removed using a solution of calcium hydroxide and sodium sulfide. The goatskin was then washed up until its pH becomes neutral (6–7). The skin was cut into pieces and hydrolyzed with 4% hydrochloric acid solution at 5° C for 48 hours. After the acid hydrolysis process, the skin was washed again and neutralized with distilled water. The gelatin was extracted from the goatskin using distilled water at 60–70°C for 9 hours. The extract generated from the skin was filtered with vacuum filtration. The filtrate was, in turn, concentrated in the oven at 70° C for 2 hours, and was then cooled down in a refrigerator at 5° C until it formed a gel. Further, the gel was stored in a container to be dried in an oven at 60° C until dried and transparent gelatin sheets were formed. The gelatin sheets were pulverized and weighed as dry weight. At last, their contents including moisture, ash, fat, protein content and pH were evaluated.

The moisture, ash, fat and crude protein contents of gelatin extracted were determined according to Association of Official Analytical Chemists (2000) methods number 927.05, 942.05, 920.39 B and 984.13, respectively⁶. The pH values of gelatin solutions were measured using the British Standard Institution method (1975)⁷. All measurements were performed in triplicate.

Composition of Tablets.

Paracetamol tablets were formulated with 6 formulas consisting of 3 comparison formulas (CF) and 3 test formulas (TF). The formulas to make paracetamol tablets with 650 mg each was presented in Table 1. Each formula was made into 500 tablets.

Table 1
Formulation of paracetamol tablets using goatskin gelatine (test formula) or bovine gelatine (comparison formula) as a binder

Ingredient (mg)	Comparison Formula			Test Formula		
	2%	3%	4%	2%	3%	4%
Paracetamol	500	500	500	500	500	500
Amylum	65	65	65	65	65	65
Lactose Monohydrate	35.75	29.25	22.75	35.75	29.25	22.75
Bovine Gelatin	13	19.5	26	-	-	-
Goat Gelatin	-	-	-	13	19.5	26
Sodium Starch Glycolate	26	26	26	26	26	26
Magnesium Stearate	6.5	6.5	6.5	6.5	6.5	6.5
Colloidal Silicon Dioxide	3.5	3.5	3.5	3.5	3.5	3.5

Preparation of Tablets.

Paracetamol tablets were manufactured using conventional wet granulation process with slight modification^{8,9}. Paracetamol was mixed with amylum and lactose monohydrate in a mortar until the powder was homogenous, then granulated with gelatin solution in hot water. The generated granules were dried at 60°C until they produced moisture at 2.5%. The dried granules were sifted with number 20 sieve (Quadrocomill U5, USA). Some evaluation was made to the granules including their flow rate, angle of repose test, compressibility, moisture and particle size distribution¹⁰. Sodium starch glycolate, magnesium stearate and colloidal silicon dioxide were added to the granules and mixed until they were homogenous. The tablets were at last compressed in single punch tablet press (Manesty F3, United Kingdom).

Evaluation of Tablets.

Paracetamol tablets were evaluated with a suitable method. Weight variation and thickness uniformity were measured with electronic weighing balance (Mettler Toledo, Japan) and callipers (Mitotuyo, Japan), respectively. The hardness tablet testing was measured with hardness tester (Erweka, Germany). Friability testing was conducted using friabilator tester (Erweka, Germany) at the speed of 25 rpm and the

percentage of weight loss was then calculated. Disintegration testing was applied with disintegration test machine (Erweka, Germany).

In vitro drug release study.

Dissolution testing was performed using method described in Indonesian Pharmacopoeia (2014)¹¹. 900 ml phosphate buffer with a pH of 5.8 was placed into the dissolution flask, and the paddle stirrer was set at 50 rpm speed. Tablets were put into six dissolution flasks each and the temperature was maintained at 37°C ± 0.5°C. After 30 minutes, 5 ml sample was taken out and the absorption of paracetamol released was measured with UV-VIS Spectrophotometer (Agilent, USA) at the maximum wavelength (243 nm).

Results

The gelatin from goatskin was successfully extracted with a yield point of 11.72%±1.13. Physically, the goatskin gelatin was coarse powder, was brownish yellow in colour and had very weak odor. Here, the physical properties of the goatskin gelatin were suitable with Indonesian Pharmacopoeia (2014)¹¹. Before using as a binder, the goatskin gelatine contents including pH, moisture, ash, protein, and fat were evaluated. The results of such evaluation were illustrated in Table 2. The table showed the goatskin gelatin met the requirements to be used as excipients, specifically as a binder on tablets preparation.

Tabel 2.

The results of moisture, ash, protein, and fat contents, and pH of goatskin gelatin

Measurement	Result (%)	Requirements	Reference
Moisture	7.61 ± 0.78	8–13	GMIA, 2012
Ash content	0.22 ± 0.42	2.5%	Jones, 1977
Fat content	1.07 ± 0.28	< 5%	Shyni <i>et al.</i> , 2014
Protein content	95.85 ± 1.21	Up to 85%	Shyni <i>et al.</i> , 2014
pH	5.00 ± 0.51	3.8–5.5	Jones, 1977

Formulation of Tablets.

In the previous study, paracetamol tablets using 1% of goatskin gelatine had friability value of 1.29%, and the friability should have reached below 1%¹⁵. Therefore, the concentration of gelatin used was about 2% (Formula I), 3% (Formula II), and 4% (Formula III) in both the test and comparison formulas.

Characteristic of Granules.

Granulation is a process selected by researchers or formulators to prevent the segregation of formulation components in powder mixture, improve the blend flowability, content uniformity, compressibility, and other properties. Therefore, the mass of the granules, before proceeding to the tablet compressing process, must be evaluated to ensure the quality of the product produced, namely flow rate and angle of repose, compressibility, and particle size distribution¹⁵. Based on this evaluation, they met requirement.

Evaluation of Tablets.

The result of testing 20 tablets from all formulas showed that the tablets produced were round, white, bitter, slightly odourless in gelatin, shiny, smooth in texture, uniform in colour, and no defects were detected in the tablets. Besides the physical features, the tablets must have met the requirements for physical specifications and quality standards including criteria for weight variation, content uniformity, thickness, hardness, disintegration, and dissolution. The results of weight variation, thickness uniformity and hardness of tablets were showed met the requirements and described in Table 3.

Table 3
The result of weight variation, thickness uniformity and hardness of tablets.

Formula	Weight variation		Thickness uniformity (mm)	Hardness (kg/cm ²)
	$\bar{X} \pm SD$ (mg)	AV (%)		
CFI	650.37 $\pm$ 1.61	4.234	4.76 $\pm$ 0.02	13.25 $\pm$ 1.03
CFII	650.36 $\pm$ 1.04	2.856	4.73 $\pm$ 0.01	14.30 $\pm$ 1.06
CFIII	650.09 $\pm$ 0.94	2.346	4.75 $\pm$ 0.03	15.24 $\pm$ 0.48
TFI	649.85 $\pm$ 1.31	2.994	4.76 $\pm$ 0.01	13.50 $\pm$ 0.93
TFII	650.16 $\pm$ 1.22	3.088	4.73 $\pm$ 0.03	15.07 $\pm$ 0.67
TFIII	650.62 $\pm$ 1.16	3.404	4.73 $\pm$ 0.01	15.71 $\pm$ 0.66
Requirements		< 15.0%	$\pm$ 5%	< 10 kg/cm ²
CF: Comparison Formula, TF: Test Formula, SD: Standard Deviation, AV: Acceptance Value.				

Table 4.

The result of friability, disintegration and dissolution of tablets

Formula	Friability (%)	Disintegration (minute)	Dissolution (%)
CFI	0.64 ± 1,52	1.93 ± 0.26	96.00 ± 3.96
CFII	0.68 ± 1,73	3.62 ± 0.85	93.08 ± 1.44
CFIII	0.74 ± 0,74	5.75 ± 2.12	95.47 ± 3.06
TFI	1.19 ± 1,25	1.65 ± 0.12	99.43 ± 1.35
TFII	0.62 ± 0,89	3.71 ± 1.00	99.78 ± 0.94
TFIII	0.55 ± 1,03	3.86 ± 0.20	95.98 ± 0.97
Requirements	< 1%	< 15 minutes	> 80%
CF: Comparison Formula, TF: Test Formula			

In vitro drug release study (dissolution testing)

The last evaluation was tablet dissolution testing. The goal of in vitro dissolution testing is to provide reasonable prediction or correlation between products in vivo bioavailability. The result of the evaluation mentioned that all formulas met the dissolution test requirements, i.e. there was no single tablet in which the level was less than 80%¹⁰. However, the paracetamol levels in the test formula were closer to 100% compared to the ones in the comparison formula. The result said that the tablets that used goatskin gelatin were easier to dissolve compared to the ones using bovine gelatin as a binder ($p < 0.05$).

Discussion

Gelatin product demand is increasing in many countries for a variety of functions in life. As per the report published by Fior Markets, the global gelatin market is expected to grow from USD 2.31 Billion in 2017 to USD 4.38 Billion by 2025 at a CAGR of 14.3% during the forecast period 2018-2025¹⁶. Consequently, efforts have been made by researchers to explore various sources of gelatin is mainly derived from animals including buffalo¹⁷, chicken¹⁸ and some fish¹⁹.

The use of gelatin in the pharmaceutical field in drug preparation formulations has long been carried out including as a binder²⁰. The primary role of binders is to provide cohesiveness essential to bond the solid particles under compaction of tablets. Gelatin as a natural polymer can play such function. It has suitable viscosity which will wet the granules and harden after being dried up²¹. The concentration of the gelatin used as a binder was 0.5-3%²². However, the selection of concentration is quite often empirical and depends on the previous experience of the formulator, in conjunction with the evaluation including tablet friability.

The first evaluation focused on the physical features of the tablets including shape, colour, taste, smell, appearance (shiny or dull), surface texture (smooth or rough), and the presence of defects in the tablets. Here, the physical evaluation was important to check the uniformity and defects in the tablets as they could reduce their aesthetic value. In addition, the defects in the tablets could lead to perceptions on poor product and quality⁸.

Evaluation on weight variation aimed at ensuring that each tablet contained active substances assuming homogeneous drug distribution. The requirement for weight variation was the standard deviation of the weight of 10 tablets was not more than 2% and the acceptance value was not more than 15%¹¹. The tablets that are fragile and easily damaged will cause variations in the weight of the tablets and the uniformity of dosage of the active substances²³. Therefore, the friability is needed to ensure the strength and hardness of the tablets. The friability was determined by measuring the weight loss of the tablets in a friabilator. Resistance to loss of weight indicated the ability of the tablets to withstand abrasion in handling, packaging, and shipping. A maximum weight loss of no more than 1% was generally considered acceptable for most products⁸. This study presented the friability of test and comparison formulas met the requirements, except test formula 1 (containing 2% of goat skin gelatin) that had friability up to 1%. Possibly, the solution of the goatskin gelatin had not been able to create strong adhesive power. Consequently, the tablets formulated were fragile²⁴. In the test formula, the result indicated some decrease in the friability value of the tablets with increasing concentration of the goatskin gelatine ($p < 0.05\%$). This was consistent with the statement of mentioned by Wade (1994) that an increase in the concentration of gelatin as a binding agent could improve hardness and reduce friability²⁵.

The thickness uniformity was measured by calculating the tablet thickness. The thickness was related to the fill, die and pressure in compression process and the uniformity of the active ingredients in order for the tablets to be well received by consumers. Therefore, it needed to be controlled to a difference of 5% from the average of 20 tablets⁸. The result indicated all formulas met the requirements of thickness uniformity.

The next evaluation was tablet hardness which aimed at ensuring that the tablets produced had certain strength to be resistant of various mechanical shocks during manufacturing, packaging, and shipping²⁴. The hardness requirement for conventional tablets is lower than 10 kg/cm²¹¹. The result of the hardness evaluation showed that all formulas are greater than the hardness requirement for good tablets. However, the tablet hardness greater than 10 kg/cm² is still acceptable as long as the disintegration time and dissolution have met the requirements. Based on the statistical analysis, there was a significant difference among the concentrations of 2%, 3% and 4% in the hardness value, both in the test and the comparison formulas ($p < 0.05$). The higher the concentration of gelatin solution is, the higher the hardness value of the tablets obtained becomes. However, no significant difference was found at the same concentration, both in the test and comparison formulas ($p > 0.05$).

In order to become available for absorption, the active substances in the tablets must first disintegrate and discharge to the body fluids for dissolution. The tablets must then disintegrate within the time set in the individual monograph. It usually takes 30 minutes. The disintegration test showed that all formulas disintegrated in no more than 15 minutes. The data in table 4 indicated the higher the gelatine concentration was, the longer the disintegration was ($p < 0.05$), both in the test and the comparison formulas. Here, a statistical analysis was also carried out on test and comparison formulas at the same concentration. The results showed that the tablets using goatskin gelatine had faster disintegration compared to the ones with bovine gelatine ($p < 0.05$).

With the development of pharmaceutical technology, the various excipients which provides benefits to drug delivery systems are increasingly being developed and explored so that the resulting pharmaceutical dosage forms that can deliver precise doses of active substances to provide efficacy Present study showed that increase in gelatin concentration caused higher hardness, longer disintegration time and lower friability for paracetamol tablets. The tablets that used goatskin gelatin as a binder had faster disintegration time and were easier to dissolve compared to the ones using bovine gelatin. The ideal concentration of goatskin gelatin as a binder was 3%. In short, the goatskin gelatine was very promising as a binder in pharmaceutical dosage forms, especially tablets.

Declarations

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We thank all study participants for their cooperation in this project.

Author Contribution

Z proposed the study design, analyzed data and prepared the manuscript. Z, SA, YA, VA and YH conducted research, analyzed data and contributed to discussion. All author revised the draft and approved the final version of the manuscript prior to submission.

Competing interests

The author declare no competing interests.

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