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Full Length Article

Physical and Microbiological Characteristics Grain Kefir Tablets in Different Tablet Manufacturing Methods

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Abstract

Kefir grain requires refreshment and cold storage so it needs to be processed into tablets to make it more practical. Three manufacturing methods (wet granulation, dry granulation and direct compression) used in the prepared of kefir grain tablets to see the advantages and disadvantages in the physical characteristics such as size uniformity, weight uniformity, hardness, friability, and disintegration time, also total lactic acid bacteria as a microbiological characteristic. The results showed that wet granulation method had the highest size uniformity, but dry granulation had highest hardness and disintegration time, also had 3.94×10^6 CFU/g in total LAB. The method that produces the best tablets is the dry granulation method. © 2023 Friends Science Publishers

Keywords: Direct compression; Dry granule; Grain kefir; Tablet; Wet granule

Introduction

Fermented product availability is inseparable from the presence of starter culture and substrate (Pendón *et al.* 2022). Kefir is a product that contains various types of microorganisms. The criteria for probiotic products are having a minimum number of live probiotic bacteria of 10^6 CFU/g (Alemneh *et al.* 2021). Currently, fermented products such as kefir are still widely consumed and developed in the food industry due to the presence of probiotics which can have a good health impact on the body.

Microorganisms found in kefir grain include lactic acid bacteria (LAB), acetic acid bacteria (AAB) and yeast. Several families of LAB are found in kefir, including the *Lactobacillus*, *Enterococcus* and *Acetobacter* families (Likotrafiti *et al.* 2015; Garofalo *et al.* 2015; Purutoğlu *et al.* 2020; Romero-Luna *et al.* 2020). One of the species of LAB that plays an essential role in making kefir is *Lactobacillus kefiri*. This species also has a role as a probiotic bacterium, which live in kefir (Kim *et al.* 2016; Purutoğlu *et al.* 2020). Yeast species that grow well on kefir are *Saccharomyces Cerevisiae* and *Kluyveromyces marxianus* (Erdogan *et al.* 2019; Purutoğlu *et al.* 2020). The presence of yeast in kefir that makes kefir have a different taste from other fermented products.

The quality of the kefir starter influences the quality of kefir as a fermented product. A good quality starter should have several living microorganisms so that they can be used in the fermentation of food products. Kefir grain has physical properties in the form of wet granules of various sizes. Inside the granules are multiple microorganisms used in the kefir production process. Kefir grain requires good handling so that it can be used in the kefir production process. Kefir grains must be given a refreshing treatment periodically. Various studies reported that kefir grains are refreshed by inoculating kefir grains in UHT (ultra-high temperature) milk for seven days at 25°C (Demirhan *et al.* 2013). Refreshment is done by inoculating kefir grains in UHT milk at 25°C for five days (Dertli and Con 2017). Refreshment is carried out by inoculating kefir grains in UHT milk at 28°C for three days (Wang *et al.* 2021). Kefir grain refreshment aims to keep the microorganisms in the kefir grain alive. The medium used to grow kefir grains is cow's milk because the lactose content in milk will be used by LAB to support their life (de Lima *et al.* 2018).

The refreshing process of kefir grains is difficult for the general public. A relatively shorter refresh time interval is considered impractical. This is why kefir beverage products are rarely commercialized due to difficulty in handling kefir grains and requiring a longer time. Solving the problem of the complexity of handling kefir starter can be done by making kefir starter into tablets. Tablets are believed to be more effective and efficient because the dose used in the kefir-making process is calculated in one tablet.

Tablets can be made by three methods: direct compression, dry granulation and wet granulation (Arndt *et al.* 2018; Sulaiman and Sulaiman 2020). Direct compression method is carried out by mixing the tablet formulations and followed by compression. The active ingredients and excipients, according to the formulation, are mixed until evenly distributed and then compressed tablets are carried out (Ervasti *et al.* 2015; Eraga *et al.* 2015). Direct compression method is considered more effective and efficient in the process of making tablet preparations because it requires a shorter manufacturing time (Chen *et al.* 2019). The main excipient needed for manufacturing tablets by the direct compression method is in a binder filler (Byl *et al.* 2019).

The dry granulation method is often used in the tablet manufacturing process if the active ingredient is thermolabile or has a high sensitivity to moist and hot conditions (Ma *et al.* 2017; Jaiturong *et al.* 2020). The process of making tablets with the dry granulation method is carried out by molding the powder to obtain large-sized tablets, then milling and sieving to obtain the desired granule size.

The wet granulation method is more suitable for use if the active ingredients used are moist and heat resistant (Hoffmann and Daniels 2019). The process of making tablets with the wet granulation method is carried out by mixing all the ingredients then the binder is dissolved in alcohol and mixed in the powder. The resulting mixture is granules which are dried in an oven (Jassim *et al.* 2018). The dried granules were then continued by grinding and sieving processes to obtain the desired granule size.

The active ingredient used is a kefir starter which has been dried in a freeze dryer. The active ingredient, namely powdered kefir grains, can be damaged during tablet manufacturing. Therefore, this study aims to obtain the best manufacturing method for making kefir grain tablets. This research hypothesizes that the different manufacturing methods will have a significant effect on size uniformity, weight uniformity, hardness, friability, disintegration time and viable count of LAB.

Materials and Methods

Direct compression

The direct compression method for making tablets is carried out by mixing all the ingredients and stirring until evenly distributed, then forming tablets using tablet press machine MKS TBL-55 (Maksindo).

Dry granulation

The preparation of tablets using the dry granulation method was carried out by mixing all the ingredients except for sodium alginate and magnesium stearate. The formation of large tablets was carried out using tablet press machine MKS TBL-55 (Maksindo, Jakarta, Indonesia). The results of tablet formation were crushed and sieved while adding sodium alginate and magnesium stearate. The finished powder is then formed into tablets again using tablet press machine.

Wet granulation

The preparation of tablets using the wet granulation method refers to Lone and Dhole (2013). The active ingredients, hydroxypropyl methyl cellulose (HPMC) and sodium alginate, are mixed and then sieved through a 60-mesh size using sieving machine H-3910FSS60 (Humboldt, CA, USA). Polyvinyl Pyrrolidone (PVP) is dissolved with 70% alcohol (3% w/v). The PVP solution was added slowly to the powder mixture while stirring periodically and baked at 50ºC for 2 h using baking oven 30-1060 (Memmert, Germany). Grinding and sieving were carried out with a size of 44 mesh. Tablets are formed from mixed materials using tablet press machine MKS TBL-55 (Maksindo).

Physical analysis

Size uniformity: Measuring the uniformity of the size of kefir grain tablets was carried out by measuring the sample using a vernier caliper 500 (Monotaro, Japan). The diameter of the tablet shall not exceed 3 and not less than 4/3 of the tablet thickness (Murtini and Elisa 2018).

Weight uniformity: Twenty kefir grain tablets were weighed alternately using an analytical balance ATX224 (Shimadzu, Japan). The weighing results are then seen for the standard deviation (Murtini and Elisa 2018).

Hardness: Measuring the hardness of kefir grain tablets is done by applying pressure to the tablet until the tablet cracks or breaks. The measurement was carried out using a hardness tester YD-1 (Digilab) (Murtini and Elisa 2018).

Friability: Friability testing is done with a tool called a friabilator TFT-1 (Rio). A number of kefir grain tablet samples were put into a plastic tool that rotated at 25 rpm. Tests were conducted to see the effect of scratches and shocks on the quality of the tablet. According to Murtini and Elisa (2018) friability is obtained by the formula:

$$\%\text{friability} = \frac{\text{Initial weight} - \text{Weight after friability}}{\text{Weight after friability}} \text{x } 100\%$$

Disintegration time: Disintegration time testing was carried out on 6 tablets using a disintegration tester BJ-2 (Guoming, China). Time is recorded with a stopwatch (Murtini and Elisa 2018).

Microbial analysis

Analysis of the viable number of LAB: Analysis the viable numbers of LAB by plate count method (Mandang *et al*. 2016). To do this, 1 g of sample was dissolved in 9 mL of 0.85% NaCl and made up until 10^{-6} dilution level. Three levels of last dilution were cultured in MRSA (Merck) then

incubated at 37°C for 48 h. The number of viable colonies will be calculated using the following formula:

$$\Sigma \text{ Colonies} = \frac{1}{\text{dilution factor}}$$

Statistical analysis

Physical parameter data processed with descriptive method. Microbiological parameter data were analyzed using the ANOVA method to determine the effect of treatment. Analysis was performed at 5% significance level. If there is an influence from the treatment, then a further test is carried out with the DMRT method. Data were statistically analyzed using SPSS 26.0 computer software.

Results

Physical analysis

Based on Table 1 shows that different methods in tablet manufacture had a different result in physical characteristics in grain kefir tablets. Grain kefir tablet had a round shape with a white color. Size uniformity of grain kefir tablets in direct compression, dry granule and wet granule respectively were 8.19, 8.24 and 8.34 mm. Weight uniformity in kefir tablets in direct compression, dry granule and wet granule on Table 2 in A column respectively were 0.22–0.25, 0.24–0.28, 0.23–0.26 and B column respectively were 0.20–0.27, 0.22–0.30, and 0.21–0.28 (Table 2). Hardness of grain kefir tablets in direct compression, dry granule and wet granule respectively were 1.58, 1.64 and 1.16 kg. Friability of grain kefir tablets in direct compression, dry granule and wet granule respectively were 0.18, 1.44, 5.86 (Table 1). Disintegration time of grain kefir tablets in direct compression, dry granule and wet granule respectively were 45.45, 45.47, 44.38 min (Table 1).

Microbial analysis

Data showed that the different tablet manufacture of grain kefir tablet had a significant effect ($p<0.05$) on the viable number of LAB (Table 3). Viable amount of LAB in direct compression, dry granule and wet granule method respectively were 1.15×10^6, 3.94×10^6, 5.94×10^3 CFU/g. Dry granulation had higher viable amount of LAB because in tablet manufacture did not used high temperature to make a granule and HPMC can be used to protect LAB in tablet manufacture (Table 3).

Discussion

The results of the size uniformity test showed that all tablet manufacture method meet the requirements, namely, the diameter of the tablet should not be more than three times the thickness of the tablet and not less than 4/3 of the thickness of the tablet (Table 1). Tablets manufactured using the wet granulation method had the highest size uniformity values. This may be due to wet granulation tablets having more compact characteristics. The binder solution added to the powder mixture of active ingredients and excipients will form strong bonds between the powder particles, causing the resulting tablets features to become more compact (Berardi *et al.* 2019; Jin *et al.* 2023). A more compact tablet material produces tablets with a more uniform size (Fitriana *et al.* 2022). Uniform size indicates the amount of material and pressure used to make uniform tablets (Sugiyanto *et al.* 2017).

The results of tablet friability analysis showed that tablets made by direct compression method have the lowest friability compared to dry granulation and wet granulation (Table 1). It is possible for tablets made by the direct compression method to obtain high pressure on the tablet to have the lowest friability value (Indartantri *et al.* 2021). Tablets made by the direct compression method had the lowest friability, while tablets made by the wet granulation method had the highest friability value (Table 1). Based on research conducted by Rori (2016) states that a good tablet has a friability value of less than 1%. The research showed that the manufacture of tablets using the direct compression method has a friability value of 0.18% which is by established standards. Meanwhile, the wet granulation method's tablets produced the highest friability because they had the lowest hardness value. This shows that the tablet friability value has an inverse relationship with the tablet hardness value (Olayemi *et al.* 2016). The tablet friability value correlates with the tablet hardness value because tablet fragility can be interpreted as crushing strength (Solaiman *et al.* 2016). Wet granulated tablets with low hardness values have high crushing strength, making them more brittle and producing high friability values.

Requirements for a good tablet should disintegrate in less than 30 min (Nugroho *et al.* 2020). The three compression methods didn't occupy the requirements of good tablets, the direct compression method had a disintegration time of 45 min 45 sec, dry granulation of 45 min 47 sec and wet granulation of 44 min 38 sec. The difference in disintegration time of the three methods is influenced by the concentration of binder and other compositions used during the tablet manufacturing process (Ambari *et al.* 2019). The use of hygroscopic materials makes the tablet disintegration time longer.

Tablet disintegration time has a relationship with tablet hardness that will be increased in tablet hardness due to an increase in compression force causes tablet disintegration to take longer (Pellett *et al.* 2018). Tablets with a longer disintegration time indicate that the tablet has a higher hardness value and lower friability. The difference in the granulation method makes the water content of each tablet different. According to Kiptiyah *et al.* (2021), the higher the water content that enters the pores of the tablet, so it can make the shorter the disintegration time. The shortest disintegration time of the three methods is wet granulation, where the wet

Table 1: Result of physical quality test for grain kefir tablets with different manufacturing methods

Treatment	Size uniformity (mm)	Hardness (kg)	Friability (%)	Disintegration time (min)
Direct compression	8.19 ± 0.08	1.58±0.27	0.18±0.06	45.45±0.66
Dry granule	8.22 ± 0.06	1.64±0.06	1.44±0.09	45.47±0.89
Wet granule	8.27 ± 0.09	1.16±0.04	5.86±0.54	44.38±0.80

Standard deviation shown 10–15% as the mean value of 7 replicates

Table 2: Result of weight uniformity test for grain kefir tablets with different manufacturing methods

Manufacturing method	Weight uniformity (standard tablet weight)		Deviation of the average weight	
	A	B	A	B
Direct Compression	0.22–0.25	0.20–0.27	7.5	15
Dry Granule	0.24–0.28	0.22–0.30	-	-
Wet Granule	0.23–0.26	0.21–0.28	-	-

Table 3: Analysis of variance (ANOVA) of LAB grain kefir tablets with different manufacturing methods

Treatment	Lactic acid bacteria (CFU/g)
Direct Compression	1.15×10^{6a}
Dry Granule	3.94×10^{6a}
Wet Granule	5.94×10^{3b}

Data are shown as the mean value of 7 replicates

Means labeled with different lowercase superscripts show a significant effect ($p<0.05$)

granulation process goes through the stages of mixing with alcohol and then drying. The drying process that is not maximal can increase the water content in the tablet so that the resulting disintegration time is also faster. The dry granulation method has more stages of formation because it adapts to the requirements of tablet fragility (Sinaga and Manalu 2021). The existence of printing more tablets makes the pores of the tablets tighter so that the resulting disintegration time also gets longer.

The number of LAB that live on tablets with direct compression and dry granulation methods still qualify as probiotic products, namely having a total number of 10^6 LAB (Diza *et al.* 2016). Tablets made by the wet granulation method had the least amount of LAB compared to tablets made by direct compression and dry granulation method because the process of making tablets by wet granulation involved a heating process. The heating process can reduce the viability of LAB cells because they will die at high temperatures (Apriyanto and Frisqila 2016). The decrease in bacterial viability due to heating can be caused by damage to the cell membrane, which is composed of fatty acids and proteins (Dianawati *et al.* 2016).

Tablets made by direct compression and dry granulation methods have a good number of LAB because tablet manufacture is not followed by a heating process, so that the LAB cells tend to be more stable (Govender *et al.* 2016). Making tablets by dry granulation is suitable for tablets with active ingredients that are unstable to high temperatures, one of which is LAB. The optimum temperature for the growth of LAB is 37–42ºC (Anggraini and Ardyati 2017). It is possible that exposure to heat of more than 42ºC can kill LAB cells thereby reducing their viability of lactic acid bacteria cells.

Conclusion

Different tablet manufacture methods gave different physical characteristics in grain kefir tablets. The best treatment is dry granulation method because can provide viable amount of LAB and have a good physical characteristic. The best tablets were found in the dry granulation method. This method produces tablets with good viable number of LAB. However, further research is needed to see the grain kefir tablets resistance when stored at room temperature for several weeks.

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Author Contributions

HR, AML, ASP, RCM, and WAY planned the experiment, interpreted the results, made the write-up, statistically analyzed the data, and made illustrations.

Conflict of Interest

All authors declare no conflict of interest.

Data Availability

Data presented in this study will be available on a fair request to the corresponding author.

Ethics Approval

Not applicable to this paper.

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